The burden of peritoneal metastases

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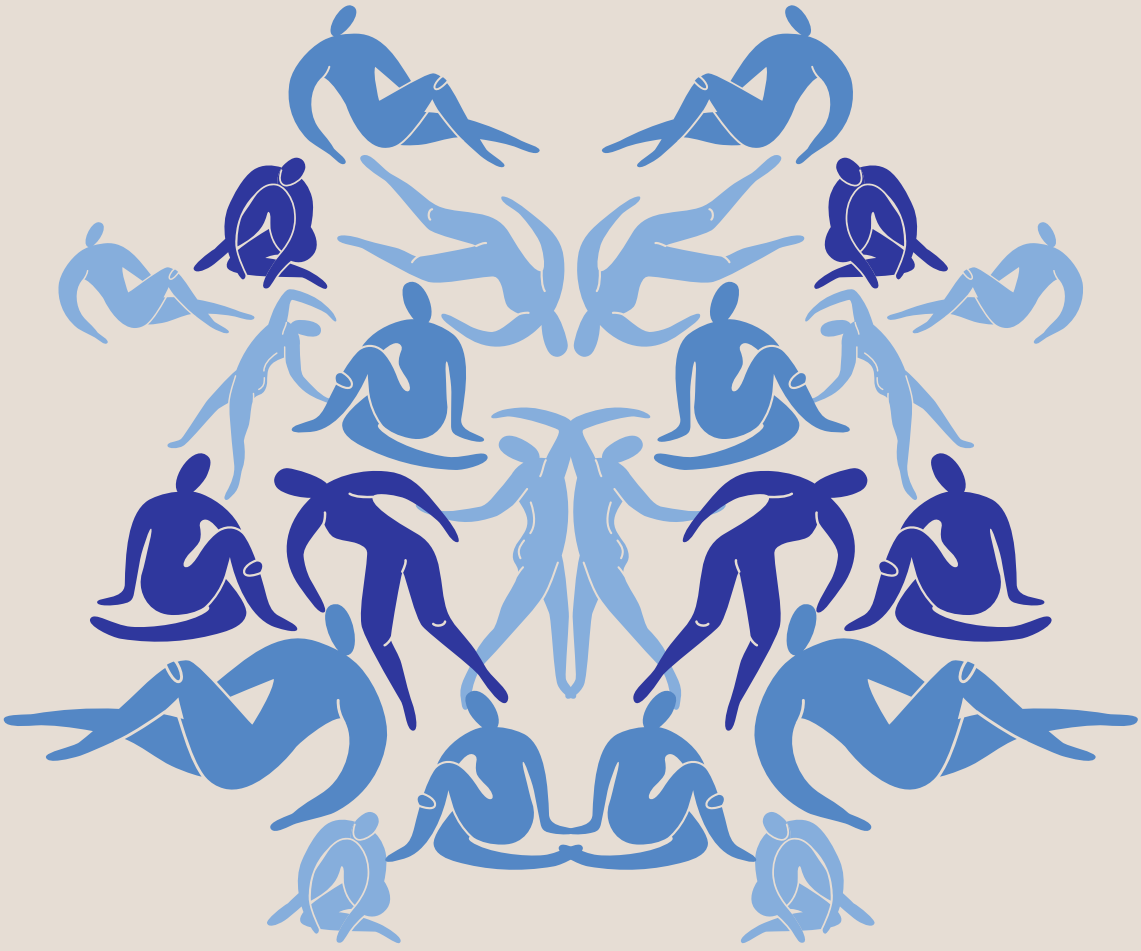
Exploring epidemiological and clinical aspects using population-based data



Anouk Rijken

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Exploring epidemiological and clinical aspects using population-based data

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Exploring epidemiological and clinical aspects using population-based data

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Table of contents

Chapter 1	Introduction	7
Chapter 2	On the origin of peritoneal metastases	19
Chapter 3	Increase in the incidence of synchronous and metachronous peritoneal metastases in patients with colorectal cancer: a nationwide study	25
Chapter 4	The impact of an open or laparoscopic approach on the development of metachronous peritoneal metastases after primary resection of colorectal cancer: results from a population-based cohort study	49
Chapter 5	Treatment strategies and prognosis of patients with synchronous or metachronous colorectal peritoneal metastases: a population-based study	65
Chapter 6	Primary tumor resection or systemic treatment as palliative treatment for patients with isolated synchronous colorectal cancer peritoneal metastases in a nationwide cohort study	91
Chapter 7	The burden of peritoneal metastases from gastric cancer: a systematic review on the incidence, risk factors and survival	115
Chapter 8	Peritoneal metastases from gastric cancer in a nationwide cohort: incidence, treatment and survival	137
Chapter 9	Insights into synchronous peritoneal metastases from hepatobiliary origin: incidence, risk factors, treatment, and survival from a nationwide database	165
Chapter 10	Incidence, treatment, and survival of synchronous peritoneal metastases in pancreatic cancer: update of a nationwide cohort	191
Chapter 11	Synchronous peritoneal metastases from lung cancer: incidence, associated factors, treatment, and survival: a Dutch population-based study	211
Chapter 12	Updated incidence, treatment and survival of a nationwide cohort of patients with peritoneal metastases of unknown origin	233
Chapter 13	Summary and discussion	249
Chapter 14	Impact	267
Chapter 15	Nederlandse samenvatting	273
Chapter 16	Appendices	285
	Appendix 1: Supplementary data	286
	Appendix 2: List of publications	314
	Appendix 3: Curriculum vitae	316
	Appendix 4: Dankwoord	317

Chapter 1

Introduction

Introduction

Peritoneum and peritoneal metastases

The peritoneum is the largest serous membrane of the human body which is formed by two layers: the parietal peritoneum lining the inner surface of the abdominal and pelvic wall and the visceral peritoneum covering the intra-abdominal organs. The peritoneal cavity is located between these two layers and contains a small volume of peritoneal fluid under healthy conditions (*Figure 1*). The peritoneum and peritoneal fluid are of importance in facilitating the movements of the abdominal organs. Besides this, other relevant functions of the peritoneum are regulation of the intraperitoneal homeostasis, fluid transport, inflammation regulation, antigen presentation and tissue repair.

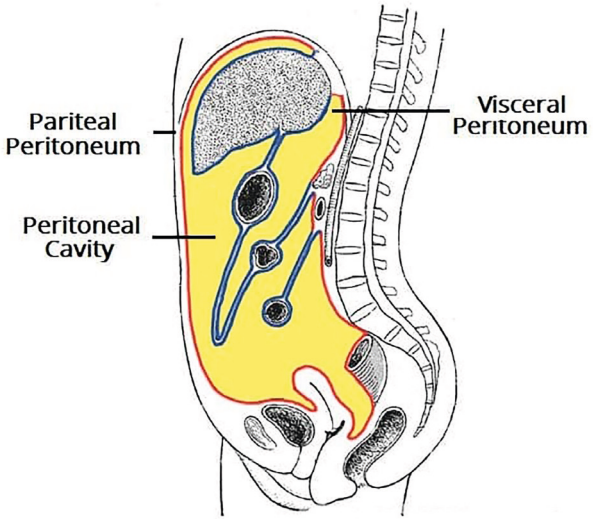

Figure 1. Anatomical location of the peritoneum and peritoneal cavity.

The peritoneum is a preferred location for metastases of several types of malignancies.[1] Peritoneal dissemination is thought to mainly occur by shedding of tumor cells from the surface of the primary tumor which thereafter can spread throughout the abdominal cavity. As a result, metastases to the peritoneum are most frequently arising from primary intraperitoneal tumors such as colorectal, ovarian, pancreatic and gastric cancer. However, it is known that peritoneal metastases can also occur in extraperitoneal cancers such as breast cancer, lung cancer and malignant melanoma.[2] The route of peritoneal dissemination in extra-abdominal tumors is not yet fully understood but some experts hold the opinion that it must involve lymphatic or hematogenous spread.[2]

So far, little has been documented on the incidence and prevalence of peritoneal metastases from various malignancies. One explanation for this may be the difficult detection of peritoneal metastases with the currently available diagnostic imaging techniques. Moreover, some patients with peritoneal metastases can experience symptoms due to mechanic obstruction from large tumor deposits and/or ascites but a considerable number of patients does not report any symptom at all at time of diagnosis.[3] As a result, the diagnosis of peritoneal metastases is challenging.

For long, peritoneal metastases were considered to be a fatal manifestation of cancer and therefore, treatment, diagnostic modalities and adequate epidemiologic information on peritoneal metastases gained little interest from scientific research. However, in the past decades, a renewed interest in peritoneal metastases has been generated which resulted in several clinical trials and retrospective studies and therewith more locoregional and systemic treatment options became available for a selected group of patients.[4]

Aim of this thesis

In concomitance with the arisen proactive attitude towards peritoneal metastases, more reliable and up-to-date epidemiological information on peritoneal metastases and their total impact on current day oncological practice is warranted. Therefore, this thesis aims to provide insight into the burden of peritoneal metastases in a variety of primary malignancies by exploring epidemiological and clinical aspects. This thesis comprises population-based studies using data of the Netherlands Cancer Registry (NCR) and mainly focuses on colorectal, gastric and hepatopancreatobiliary cancer.

Netherlands Cancer Registry

The population-based data that were used in this thesis are derived from the NCR. The NCR registers all patients with newly diagnosed malignancies in the Netherlands. The Netherlands Comprehensive Cancer Organization (also referred to as IKNL) manages the NCR since 1989 and routinely extracts data on patient-, tumor- and treatment characteristics from the medical records by trained data-managers. The anatomical location of the primary tumor and metastases are registered according to the International Classification of Disease for Oncology (ICD-O).[5,6] Every year, data on vital status of all registered patients is checked by linking the NCR data to the Dutch municipal administrative database, which contains information about all present, deceased, and former inhabitants of the Netherlands.

As population-based studies present real-world data from unselected patients in everyday clinical practice, they are important within the scientific research field. Given its adequate external validity, population-based studies provide insight into delivery of care in routine practice for all patients, including elderly and those with comorbidities. Also, by obtaining knowledge on the incidence and risk factors of a variety of malignancies, these studies may guide future scientific research and support future knowledge translation of the assigned malignant disease.[7]

Outline of the thesis

The first chapter of this thesis depicts an overview of all possible primary origins in peritoneal metastases, whereas the following chapters focus on the primary tumors of peritoneal metastases separately. As such, in **Chapter 2,** the different primary tumors with peritoneal metastases were identified from the NCR.

Peritoneal metastases of colorectal origin

Colorectal cancer (CRC) is the third most common cancer diagnosis worldwide with nearly 2 million new cases every year.[8] CRC has already metastasized in 21% of all patients at time of diagnosis and another 20% of patients will develop metastases during follow-up after curative resection.[9,10] After the liver, the peritoneum is the second most common metastatic site in CRC.[9] In spite of their frequent encounter, high-quality studies on peritoneal metastases from colorectal origin are relatively rare as compared to liver metastases.

Peritoneal metastases diagnosed simultaneously with the primary colorectal tumor (i.e., synchronous disease) are present in approximately 5% of all patients with CRC.[11,12] Besides synchronous disease, peritoneal metastases can also develop during follow-up after curative intent therapy, which is defined as metachronous peritoneal metastases. A previous study reported a proportion of 3.5% metachronous peritoneal metastases after curative surgery for patients with CRC, but this study did not included a nationwide cohort and comprised data from more older years (2003-2008).[13] During the past decades there has been an increasing interest towards colorectal peritoneal metastases and together with the improvement of diagnostic imaging techniques, a more up-to-date population-based study on the incidence of peritoneal metastases is warranted. Therefore, **Chapter 3** aims to investigate the incidence of, factors associated with, and differences between synchronous and metachronous colorectal peritoneal metastases in a population-based cohort.

Open or laparoscopic resection of the primary tumor

The type of surgical approach for the resection of the primary tumor in CRC might be associated with the development of metachronous peritoneal metastases. A population-based study reported that synchronous colorectal peritoneal metastases were less frequently diagnosed during a laparoscopic approach than during open resection but yet it is unknown how the surgical approach affects the development of metachronous peritoneal metastases.[14] In order to address this, **Chapter 4** aims to assess the impact of the surgical approach during the primary tumor resection on the incidence of metachronous peritoneal metastases in CRC patients.

Treatment of colorectal peritoneal metastases

Treatment options for patients with peritoneal metastases from colorectal origin have rapidly evolved over the past few decades. A randomized controlled trial, published in 2003, showed that cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) improved survival compared to systemic therapy alone for patients with peritoneal metastases from CRC.[15,16] While the additional benefit of HIPEC after CRS is currently a topic of discussion, it remains the standard treatment for patients with limited peritoneal metastases in the Netherlands.[17,18] Currently, a randomized controlled trial (CAIRO6, NCT02758951) enrolls CRC patients with isolated limited peritoneal metastases to investigate the role of perioperative systemic therapy in addition to CRS-HIPEC.[19] In order to improve both short- and long-term outcome after CRS-HIPEC, patient selection criteria have been increasingly refined over the past years with the extent of peritoneal metastases being the most important factor.[20] The extent of peritoneal metastases is preferably measured with the peritoneal cancer index (PCI) score.[21] However, no previous studies have investigated whether the onset of peritoneal metastases, being synchronous or metachronous, has an impact on outcome. Therefore, **Chapter 5** aims to compare treatment strategies and prognosis of patients with synchronous colorectal peritoneal metastases and patients with metachronous colorectal peritoneal metastases. By presenting these data, an up-to-date basis for future clinical research investigating patients with colorectal peritoneal metastases will be provided.

Palliative primary tumor resection in synchronous colorectal peritoneal metastases

For CRC patients in whom curative intent therapy is not possible due to extensive peritoneal disease, palliative systemic treatment remains the current standard treatment in the Netherlands.[22] Palliative therapies such as pressurized intraperitoneal aerosol chemotherapy (PIPAC) and intraperitoneal

chemotherapy (INTERACT) are still being investigated in randomized controlled trials, and preliminary results seem promising.[23,24]

Whether to perform a palliative primary tumor resection has been a highly debated issue for many years among patients with unresectable systemic metastases and it is currently not recommended in clinical guidelines.[25] However, patients with peritoneal metastases were virtually absent in the randomized controlled trials regarding a palliative primary tumor resection.[26-31] Thus, the effect of a primary tumor resection in this specific patient category remains unknown. In **Chapter 6**, the outcome of palliative primary tumor resection was assessed in patients with CRC and isolated synchronous peritoneal metastases who did not undergo curative intent therapy.

Peritoneal metastases of gastric origin
Gastric cancer is one of the most common cancers worldwide and has high mortality rates with nearly 800.000 deaths each year, probably due to late diagnosis in an advanced stage.[32] Metastases in the peritoneal cavity are common in gastric cancer.[33,34] As hypothesized in CRC, gastric peritoneal metastases may be considered as a locoregional disease entity which has led to several studies investigating the effect of locoregional treatment strategies such as CRS-HIPEC in gastric cancer patients as well. The PERISCOPE II (NCT03348150) study was initiated in the Netherlands, to determine whether CRS-HIPEC provides a potential survival benefit in highly selected patient with limited disease compared to systemic therapy alone.[35] For patients with more extensive disease, studies on palliative intraperitoneal chemotherapy or PIPAC provided encouraging survival results.[36,37] Whilst treatment options for gastric peritoneal metastases are emerging, a clear overview on the total burden of synchronous peritoneal metastases is currently lacking. **Chapter 7** describes a systematic review of available evidence on the incidence, risk factors and survival of patients with gastric cancer and synchronous peritoneal metastases.

The introduction of a diagnostic laparoscopy during the diagnostic work-up of patients with resectable gastric cancer in 2016, probably led to a higher detection rate of metastases. However, a recently published study reported high recurrence rates after curative resection.[38] Yet, only limited epidemiologic data on peritoneal recurrence in gastric cancer is available. Moreover, it is unknown whether the tumor behavior differs between synchronous and metachronous gastric peritoneal metastases. **Chapter 8** aims to investigate the incidence, risk factors, treatment, and survival of synchronous and metachronous peritoneal metastases in gastric cancer.

Peritoneal metastases of hepatopancreatobiliary origin

Hepatopancreatobiliary cancers are a heterogeneous group of cancers originating from the liver, pancreas and biliary tract. The peritoneal cavity is one of the metastatic sites in hepatopancreatobiliary cancer.[39] However, probably due to the lack of curative treatment options and the very poor prognosis of these patients, there has been little scientific interest in patients with peritoneal metastases from hepatopancreatobiliary origin. In spite of emerging experimental treatment options for patients with peritoneal metastases from colorectal- and gastric origin, no large randomized controlled trails are currently investigating curative intent therapies for patients with peritoneal metastases from hepatopancreatobiliary origin.[4] As peritoneal metastases from liver-, pancreatic- and biliary tract cancer are currently not well characterized, the true incidence of peritoneal metastases in these patients remains unknown and the overall burden of peritoneal metastases in hepatopancreatobiliary cancer might be underestimated. Therefore, **Chapter 9** and **Chapter 10** aim to retrieve insight in the incidence, risk factors, treatment, and survival of hepatopancreatobiliary peritoneal metastases.

Peritoneal metastases from lung cancer

With lung cancer being the deathliest type of cancer worldwide, many studies have reported on systemic metastases from this disease entity.[32] However, little is known on the incidence of peritoneal metastases in lung cancer. **Chapter 11** describes the incidence, characteristics, risk factors, treatment strategies and survival of patients with synchronous peritoneal metastases from lung cancer.

Peritoneal metastases of unknown origin

Despite the improvement and increased use of diagnostic tools such as positron emission tomography (PET)- computed tomography (CT), the primary tumor location remains unknown in 2-10% of all cancer diagnoses.[40] Although previous studies have reported on peritoneal metastases where the origin was unknown, these studies are rather outdated, with 2012 being the most recent reported year.[41-43] Moreover, data on the underlying histological subtypes in patients with an unknown primary tumor may provide better insight in the different biological tumor behavior and outcomes of these patients. **Chapter 12** aims to provide an update on incidence, treatment, and survival of patients with peritoneal metastases of unknown origin and to gain more insight into the different histological subtypes of the tumors.

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Chapter

2

On the origin of peritoneal metastases

Letter to the Editor

Anouk Rijken
Felice N. van Erning
Koen P. Rovers
Valery E.P.P. Lemmens
Ignace H.J.T. de Hingh

Eur J Cancer 2023;181:1-2

Dear editor,
For long, peritoneal metastases were considered to be a fatal manifestation of cancer without effective treatment options. However, recent developments in locoregional and systemic therapies have given rise to a more proactive attitude. Cytoreductive surgery, intraperitoneal chemotherapy, and modern systemic therapy are increasingly accepted as, or under evaluation for, the treatment of peritoneal metastases from various malignancies in the palliative or curative intent setting.[1-3]

This paradigm shift emphasizes the need for up-to-date comprehensive epidemiological data regarding the origin of peritoneal metastases and their total impact on current day oncological practice. Therefore, we used the Netherlands Cancer Registry to select a nationwide population-based cohort of all cancer diagnoses in 2019 and 2020: an era of modern diagnostics. Primary tumors from hematopoietic, lymphoid, or peritoneal origin were excluded.

This cohort included 210.496 patients with cancer, of whom 43.408 had synchronous metastases, and 7460 had synchronous peritoneal metastases (i.e. 4% of all cancers, 17% of metastatic cancers). *Figure 1* presents both the total and the sex-stratified distributions of the primary tumor locations of synchronous peritoneal metastases. It reveals that peritoneal metastases may originate from virtually every primary tumor. The 10 primary tumors with the largest proportion of peritoneal metastases in the total cohort are presented individually, and the remaining primary tumor types are combined into 'other'. These 10 most prevalent origins of peritoneal metastases are also presented stratified by sex as applicable. The largest proportion of peritoneal metastases in both sexes combined, as well as in the female group specifically, is caused by ovarian cancer. The largest proportion of peritoneal metastases in the male group originated from colon cancer.

So far, high-quality clinical studies on peritoneal metastases are relatively rare as compared with liver metastases. These studies have mainly focused on peritoneal metastases of ovarian, colorectal, gastric, and appendiceal cancers.[4] However, our data reveal that 40% of synchronous peritoneal metastases arise from other rarely studied primaries, the most frequent being pancreatic-, lung-, endometrial-, biliary tract-, and esophageal cancer.

This unique nationwide cohort reveals that synchronous peritoneal metastases affect a relevant part of cancer patients. In spite of progress that has been achieved for a highly selected subgroup of these patients, prognosis of patients with peritoneal metastases in general remains extremely poor.[4]

The high incidence and poor prognosis of peritoneal metastases should encourage future high-quality clinical research on more effective treatment options for this metastatic entity.

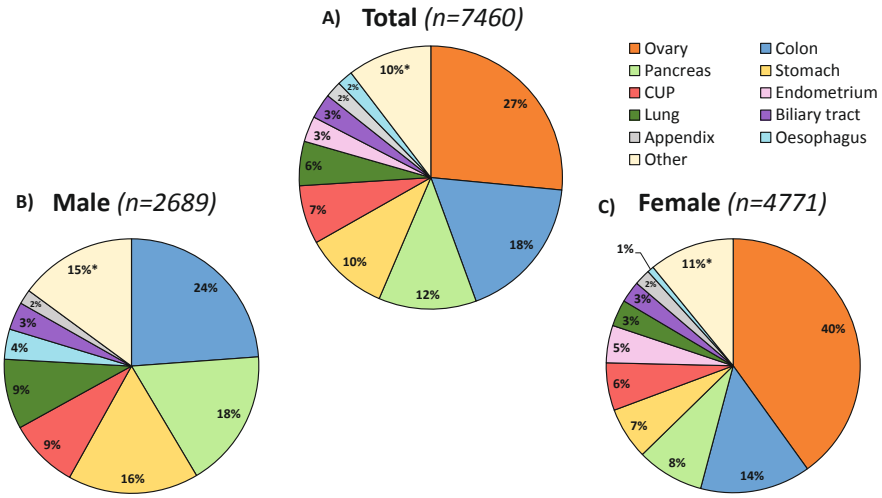

Figure 1. A) Distribution of primary tumor location in 7460 carcinomas with synchronous peritoneal metastases from extraperitoneal origins. **B)** Distribution of primary tumor location in men in 2689 carcinomas with synchronous peritoneal metastases from extraperitoneal origins. **C)** Distribution of primary tumor location in women in 4771 carcinomas with synchronous peritoneal metastases from extraperitoneal origins.
Figure legend: *Other: adrenal gland, anus, bladder, breast, central/peripheral nerve system, cervix, duodenum, ear-nose-throat region, kidney, liver, prostate, soft tissue, small intestine, skin, rectum, testis, thyroid, vagina, vulva and not otherwise specified regions.

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Chapter 3

Increase in the incidence of synchronous and metachronous peritoneal metastases in patients with colorectal cancer: a nationwide study

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Eur J Surg Oncol 2021;47(5):1026-1033.

Abstract

Introduction
To investigate the incidence of, factors associated with, and differences between synchronous and metachronous colorectal peritoneal metastases in a population-based cohort.

Methods
Data from the Netherlands Cancer Registry were used. All patients diagnosed with colorectal cancer (CRC) between 1 January and June 30, 2015 were evaluated for synchronous or metachronous colorectal peritoneal metastases (diagnosis ≤90 or >90 days after surgery for primary CRC), and survival in 2019 (median follow-up 38.4 months).

Results
Of 7233 included patients, 409 (5.7%) were diagnosed with synchronous colorectal peritoneal metastases. Factors associated with synchronous colorectal peritoneal metastases were mucinous (odds ratio [OR] 2.72 [1.90-3.90]) or signet ring cell (SRC) histology (OR 6.58 [3.66-11.81]), T4 (OR 4.82 [3.68-6.32]), N1 (OR 1.66 [1.20-2.30]), or N2 stage (OR 3.27 [2.36-4.52]), and synchronous systemic metastases (OR 3.13 [2.37-4.14]). After surgery for primary CRC, 326 patients developed metachronous colorectal peritoneal metastases after a median time of 14.7 months (3-year cumulative incidence: 5.5%). Factors associated with metachronous colorectal metastases were younger age (hazard ratio [HR] 1.63 [1.10-2.42]), mucinous (HR 1.84 [1.20-2.82]) or SRC histology (HR 2.43 [1.11-5.32]), T4 (HR 2.77 [2.07-3.70]), N1 (HR 2.90 [2.18-3.85]), N2 (HR 3.19 [2.26-4.50]), and synchronous systemic metastases (HR 1.95 [1.43-2.66]).

Conclusions
This population-based study found the highest incidence of colorectal peritoneal metastases currently reported in literature and a strong association between the presence of synchronous systemic metastases and both synchronous and metachronous colorectal peritoneal metastases. These findings may contribute to a tailored approach in the follow-up after primary CRC surgery and guide future clinical trials investigating new strategies regarding risk-reduction or early detection of metachronous colorectal peritoneal metastases.

Introduction

With over a million new cases yearly, colorectal cancer (CRC) is the third most prevalent cancer worldwide.[1] Although the treatment of CRC has evolved into a multimodality approach including surgery, radiotherapy and/or systemic chemotherapy, recurrent disease after curative treatment is common. After the liver, the peritoneum is the second most common metastatic site for CRC spread.[2,3]

For long, CRC with peritoneal metastases was considered a noncurative disease and therefore, its treatment gained little interest from scientific research. However, a randomized controlled trial from 2003 showed that cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) led to a significantly better survival than palliative systemic therapy only.[4] Therewith, a curative treatment option for these patients was introduced. Consequently, this led to an increasing interest in this disease aiming to improve its treatment, which has resulted in the conduction of several large clinical trials.[5,6]

Unfortunately, the majority of patients have extensive, irresectable intraperitoneal disease at time of diagnosis and are only eligible for palliative systemic chemotherapy. In these patients, experimental treatment options like pressurized intraperitoneal aerosol chemotherapy (PIPAC) or prolonged intraperitoneal chemotherapy in addition to palliative systemic therapy are currently being explored in clinical trials.[7,8]

The high proportion of patients presenting with extensive intraperitoneal disease may be explained by the lack of clinical symptoms and poor detection rates of currently available imaging methods.[9,10] To overcome this phenomenon, several clinical trials are investigating new options to reduce the risk of metachronous peritoneal metastases by means of new adjuvant treatment strategies after surgery for primary CRC and to detect metachronous peritoneal metastases in an earlier stage during follow-up.[11-13]

Hence, there is a growing scientific interest in peritoneal metastases of CRC. Reliable, up-to-date epidemiological data are needed to form a basis for future clinical trials and to translate the findings to the impact on current clinical practice, since previously reported incidences are based on older cohorts from 1995 to 2011.[2,3,14-16] The present population-based study aimed to provide insight in the differences between patients with synchronous and metachronous colorectal peritoneal metastases, and the incidence of and

factors associated with the development of synchronous and metachronous colorectal peritoneal metastases.

Methods

Data source

This nationwide population-based cohort study was performed with data from the Netherlands Cancer Registry (NCR), in which all newly diagnosed malignancies in the Netherlands are registered.[17] These data on patient, tumor and treatment characteristics are routinely collected by trained data-managers. The anatomical sites of the primary tumor and metastases are registered according to the International Classification of Disease for Oncology (ICD-O). The primary tumors are staged according to the seventh edition of the Tumor Node Metastasis (TNM) classification. In case of an unknown pathological TNM stadium, the clinical TNM stadium was used. So far, the NCR only provided follow-up information on vital status, which is obtained by annual linkage to the municipal administrative database that registers all deceased and emigrated inhabitants of the Netherlands. However, in 2019, data-managers from the NCR re-evaluated all CRC patients diagnosed between January 1, 2015 and June 30, 2015 to obtain follow-up information regarding local or systemic recurrences and their treatment. For the present study, the latest linkage to the municipal administrative database for vital status was performed in February 2020. Since all data were anonymized, no approval of the medical ethics committee was required for this study.

Patients and characteristics

All patients diagnosed with CRC between January 1, 2015 and June 30, 2015 in the Netherlands were evaluated. Patients were excluded if they had a tumor located in the appendix, a neuroendocrine tumor or a tumor with histology other than adenocarcinoma. In patients with multiple primary colorectal tumors, the firstly diagnosed tumor was included or, if simultaneously diagnosed, the tumor with the highest TNM stage was included. The tumor location was subdivided into three anatomical subsites according to the ICD-O codes: (1) right-sided colon (C18.0, C18.2-18.4: caecum, ascending colon, hepatic flexure, transverse colon); (2) left-sided colon (C18.5-18.7: splenic flexure, descending colon and sigmoid); and (3) rectum (C19.9-20.9: rectosigmoid and rectum). The histology of the primary tumor was divided into adenocarcinoma (8000, 8010, 8020, 8140, 8144, 8210, 8211, 8220 8255, 8261, 8262, 8263, 8560), mucinous adenocarcinoma (8480, 8481) or signet ring cell carcinoma (8490). Data on occurrence, location and timing of colorectal metastases was included, with locations being defined as peritoneal metastases (C16.0-C16.9, C17.0-C17.9, C18.0-C18.9, C19.9, C20.9, C21.8, C23.9,

C26.9, C48.0-C48.8, C49.4-C49.5, C52.9, C53.9, C54.0-C54.9, C55.9, C56.9, C57.0-C57.8, C66.9, C67.0-C67.9, C76.2) or systemic metastases (any other metastatic location). Metastases were defined as synchronous metastases if diagnosed ≤90 days after surgery for primary CRC (or ≤90 days after diagnosis if no surgery for primary CRC was performed) and were defined as metachronous metastases if diagnosed >90 days after surgery for primary CRC. In patients without synchronous peritoneal metastases, only patients who underwent surgery for primary CRC were selected for further analyses (i.e. determining the 1- and 3-year cumulative incidence of metachronous metastases). Patients with a high-risk primary tumor (i.e. T4 tumor or lymph node involvement) were considered to have received adjuvant systemic chemotherapy if they started systemic chemotherapy (a fluoropyrimidine with oxaliplatin, fluoropyrimidine monotherapy, or a not-otherwise-specified chemotherapy regimen) without targeted therapy within 90 days after surgery for primary CRC.

Statistical analyses

The cumulative incidence of metachronous peritoneal metastases at 1- and 3-year after primary surgery for CRC was calculated considering death as competing event, as death may precede the development of metachronous peritoneal metastases. Differences in the cumulative incidence of metachronous peritoneal metastases were compared with the Gray's test according to the presence of synchronous systemic metastases and, in high-risk patients, according to the administration of adjuvant systemic therapy. Baseline characteristics were compared between patients with synchronous and patients with metachronous peritoneal metastases. Differences in continuous variables between patients with synchronous or metachronous peritoneal metastases were compared using unpaired *t*-tests and presented as a mean (± standard deviation [SD]). Differences in categorical variables between groups were compared using chi-squared test and presented as n (%). Missing data were not included in comparative analyses.

Univariable logistic regression analyses were performed to identify factors associated with the presence of synchronous peritoneal metastases. Variables with a $p < 0.10$ were subsequently combined in a multivariable logistic regression model. Similarly, univariable cox competing risk regression analyses considering death as competing event were performed to identify factors associated with the development of metachronous peritoneal metastases, and variables with a $p < 0.10$ were subsequently combined in a multivariable competing risk cox regression model. Dummy variables of missing data were included in the multivariable analyses. Both multivariable regression models were performed with respect to the number of patients

with peritoneal metastases (10 events per degree of freedom) to prevent overfitting of the multivariable model.

The Kaplan-Meier method was used to estimate the interval from surgery for primary CRC to diagnosis of metachronous peritoneal metastases for patients with or without synchronous systemic metastases, given the possibly more aggressive tumor biology which may be associated with a higher metastatic potential.

Finally, a subgroup analysis was performed in patients with an indication for adjuvant systemic therapy according to the Dutch national guideline for the treatment of CRC in 2015 (i.e. T4 tumors and/or lymph node involvement).[18] This subgroup analysis included uni- and multivariable cox competing risk regression analyses, and a calculation of the cumulative incidence of metachronous peritoneal metastases stratified for the administration of adjuvant systemic chemotherapy. All tests were two-sided and $p < 0.05$ was considered statistically significant. All analyses were performed using SAS statistical software (SAS system 9.4, SAS Institute, Cary, NC, United States).

Results

Study population & incidence of synchronous and metachronous peritoneal metastases

The final study population comprised 7233 patients. *Figure 1* contains the study flowchart and provides an overview of the occurrence and onset (i.e. synchronous versus metachronous) of systemic metastases and peritoneal metastases. In total, 409 (5.7%) patients were diagnosed with synchronous peritoneal metastases: 166 (2.3%) had solitary synchronous peritoneal metastases and 243 (3.4%) had both synchronous systemic metastases and peritoneal metastases. Among all patients without synchronous peritoneal metastases who underwent surgery for primary CRC (n=5860), 326 patients were diagnosed with metachronous peritoneal metastases after a median time of 14.7 months (interquartile range [IQR] 9.1-22.4). The median follow-up for the diagnosis of peritoneal metastases or last follow-up was 38.4 (IQR 15.3-45.4) months.

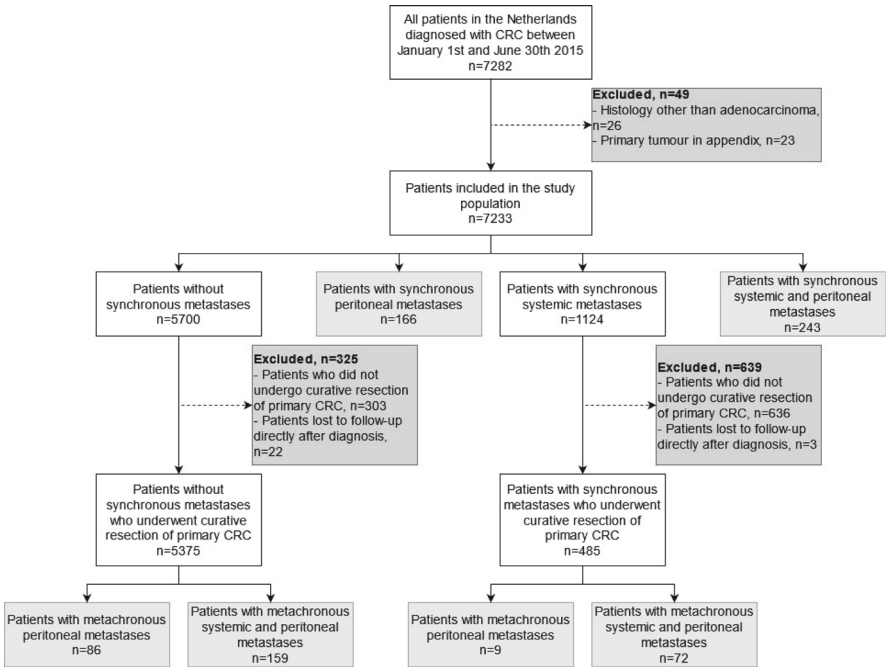
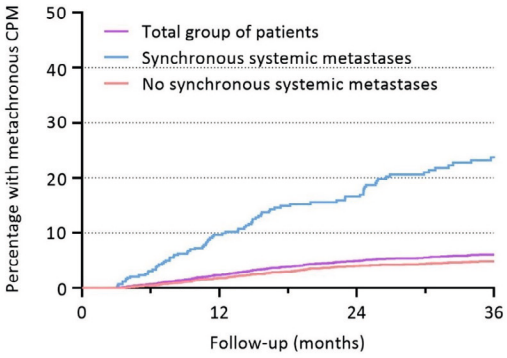


Figure 1. Flowchart of the study population with the incidence and onset of colorectal peritoneal metastases.

The 1- and 3-year cumulative incidence of metachronous peritoneal metastases were 2.2% and 5.5%, respectively. Out of 485 patients with synchronous systemic metastases who underwent surgery for primary CRC, 81 patients developed metachronous peritoneal metastases, which was considerably higher than in the 5375 patients without synchronous systemic metastases who underwent surgery for primary CRC (n=245): 1-year cumulative incidences of 8.2% vs 1.7%, respectively, and 3-year cumulative incidences of 17.0% vs. 4.5%, respectively. Median time from surgery for primary CRC to diagnosis of metachronous peritoneal metastases was 15.0 (IQR 9.7-22.3) months for patients without synchronous systemic metastases and 12.5 (IQR 7.3-23.0) months for patients with synchronous systemic metastases ($p < 0.001$, *Figure 2*).



Number at risk (number censored)

Synchronous systemic metastases	471 (0)	343 (110)	242 (184)	157 (250)
No synchronous systemic metastases	5298 (0)	4821 (492)	4199 (1003)	3680 (1512)

Figure 2. Proportion of patients with metachronous peritoneal metastases after surgery for primary colorectal cancer, according to the presence of synchronous systemic metastases ($p < 0.001$).

Differences between patients developing synchronous and metachronous metastases

Table 1 contains a comparison of baseline characteristics between patients with synchronous and metachronous peritoneal metastases. Patients with metachronous peritoneal metastases more frequently had a well or moderately differentiated tumor and a less advanced tumor and nodal stage (at primary diagnosis), whereas patients with synchronous peritoneal metastases more frequently had synchronous systemic metastases and a primary tumor histology of a mucinous adenocarcinoma or a signet ring cell tumor.

Table 1. Baseline characteristics of patients with colorectal peritoneal metastases.

	Synchronous peritoneal metastases n=409	**Metachronous peritoneal metastases** n=326	*P value*[a]
Age at diagnosis, mean (SD)	69 (12)	67 (11)	0.062
Sex, No. (%)			
Male	225 (55)	180 (55)	0.956
Female	184 (45)	146 (45)	

Table 1. Baseline characteristics of patients with colorectal peritoneal metastases. (continued)

	Synchronous peritoneal metastases n=409	**Metachronous peritoneal metastases** n=326	*P value*[a]
ASA score, No. (%)			
ASA 1	29 (7)	63 (19)	**<0.001**
ASA 2	138 (34)	162 (50)	
ASA ≥3	75 (18)	56 (17)	
Missing data	167 (41)	45 (14)	
Primary tumor location, No. (%)			
Right colon	186 (45)	122 (37)	**<0.001**
Left colon	173 (42)	129 (40)	
Rectum	50 (12)	75 (23)	
Tumor differentiation, No. (%)			
Good/moderate	167 (41)	241 (74)	**<0.001**
Poor/undifferentiated	67 (16)	51 (16)	
Missing data	175 (43)	34 (10)	
Tumor histology, No. (%)			
Adenocarcinoma	313 (77)	282 (86)	**0.001**
Mucinous adenocarcinoma	65 (16)	35 (11)	
Signet ring cell carcinoma	31 (6)	9 (3)	
Tumor stage, No. (%)			
T0-3	117 (29)	207 (63)	**<0.001**
T4	192 (47)	119 (37)	
Missing data	99 (24)	0 (0)	
Nodal stage, No. (%)			
N0	83 (20)	92 (28)	**<0.001**
N1	104 (25)	126 (39)	
N2	165 (40)	106 (32)	
Missing data	57 (14)	2 (1)	
Synchronous systemic metastases, No. (%)			
No	166 (41)	245 (75)	**<0.001**
Yes	243 (59)	81 (25)	

Table 1. Baseline characteristics of patients with colorectal peritoneal metastases. (continued)

	Synchronous peritoneal metastases n=409	**Metachronous peritoneal metastases** n=326	*P value*[a]
Colon perforation, No. (%)			
No	203 (50)	288 (88)	**<0.001**
Yes	24 (6)	20 (6)	
Missing data	182 (44)	18 (6)	

[a]Missing data were not included in comparative analyses; Percentages might not add up to or exceed 100% due to rounding; *SD* standard deviation; *ASA* American society of anesthesiologists score.

Factors associated with synchronous peritoneal metastases

Univariable logistic regression analyses are depicted in *Supplementary Table 3.1*. Multivariable logistic regression analyses identified the following factors to be positively associated with the presence of synchronous peritoneal metastases (*Table 2*): tumor histology of a mucinous adenocarcinoma (odds ratio [OR] 2.72; 95% confidence interval [CI], 1.90-3.90), a signet ring cell carcinoma (OR 6.58; 95% CI, 3.66-11.81), T4 stage (OR 4.82; 95% CI, 3.68-6.32), N1 or (OR 1.66; 95% CI, 1.20-2.30]), N2 stage (OR 3.27; 95% CI, 2.36-4.52), and the presence of synchronous systemic metastases (OR 3.13; 95% CI, 2.37-4.14). The following factors were negatively associated with the presence of synchronous peritoneal metastases: >75 years of age at diagnosis (OR 0.78; 95% CI, 0.60-0.99) and a primary rectal tumor (OR 0.34; 95% CI, 0.24-0.49).

Factors associated with metachronous peritoneal metastases

Univariable cox regression analyses are depicted in *Supplementary Table 3.2*. In multivariable cox competing risk regression analyses, patients having mucinous tumors or signet ring cell tumors were more likely to develop metachronous peritoneal metastases (hazard ratio [HR] 1.84; 95% CI, 1.20-2.82 and HR 2.43; 95% CI, 1.11-5.32, respectively). Also, T4 (HR 2.77; 95% CI, 2.07-3.70), N1 (HR 2.90; 95% CI, 2.18-3.85) or N2 stage (HR 3.19; 95% CI, 2.26-4.50), and the presence of synchronous systemic metastases (HR 1.95; 95% CI, 1.43-2.66) were positively associated with metachronous peritoneal metastases. Metachronous peritoneal metastases did not occur more frequently in patients who presented with tumor perforation (*Table 3*).

Table 2. Multivariable logistic regression analyses for the presence of synchronous peritoneal metastases after primary tumor resection.

	Synchronous peritoneal metastases	**Multivariable logistic regression analysis**		
	n (%)	OR	95% CI	*P value*
Age at diagnosis				
<50 years	27 (9)	1.13	0.69-1.87	0.628
50-74 years	249 (5)	Ref.	Ref.	Ref.
≥75 years	133 (6)	0.78	0.60-0.99	**0.049**
Sex				
Male	225 (5)	-	-	-
Female	184 (6)	-	-	-
ASA score				
ASA 1	29 (3)	0.68	0.43-1.06	0.087
ASA 2	138 (4)	Ref.	Ref.	Ref.
ASA ≥3	75 (6)	1.28	0.92-1.78	0.143
Missing data	167 (10)	0.94	0.70-1.28	0.706
Primary tumor location				
Right colon	186 (8)	1.01	0.79-1.30	0.922
Left colon	173 (6)	Ref.	Ref.	Ref.
Rectum	50 (2)	0.34	0.24-0.49	**<0.001**
Primary tumor differentiation				
Good/moderate	167 (3)	Ref.	Ref.	Ref.
Poor/none	67 (11)	1.25	0.88-1.77	0.212
Missing data	175 (15)	1.84	1.38-2.46	**<0.001**
Tumor histology				
Adenocarcinoma	313 (5)	Ref.	Ref.	Ref.
Mucinous adenocarcinoma	65 (12)	2.72	1.90-3.90	**<0.001**
Signet ring cell carcinoma	31 (38)	6.58	3.66-11.81	**<0.001**

Table 2. Multivariable logistic regression analyses for the presence of synchronous peritoneal metastases after primary tumor resection. (continued)

	Synchronous peritoneal metastases	**Multivariable logistic regression analysis**		
	n (%)	OR	95% CI	*P value*
Tumor stage				
T0-3	118 (2)	Ref.	Ref.	Ref.
T4	192 (19)	4.82	3.68-6.32	**<0.001**
Missing data	99 (27)	3.30	2.25-4.83	**<0.001**
Nodal stage				
N0	83 (2)	Ref.	Ref.	Ref.
N1	104 (6)	1.66	1.20-2.30	**0.002**
N2	165 (15)	3.27	2.36-4.52	**<0.001**
Missing data	57 (15)	2.69	1.75-4.12	**<0.001**
Synchronous systemic metastases				
No	166 (3)	Ref.	Ref.	Ref.
Yes	243 (18)	3.13	2.37-4.14	**<0.001**
Tumor perforation				
No	203 (3)	Ref.	Ref.	Ref.
Yes	24 (10)	1.45	0.88-2.40	0.149
Missing data	182 (16)	2.31	1.75-3.06	**<0.001**

ASA American society of anesthesiologists score; OR odds ratio; CI confidence interval.

Table 3. Multivariable cox regression analyses for the development of metachronous peritoneal metastases after primary tumor resection.

	Metachronous peritoneal metastases	**Multivariable cox regression analysis**		
	n (%)	HR	95% CI	*P value*
Age at diagnosis				
<50 years	24 (9)	1.63	1.10-2.42	**0.015**
50-74 years	221 (5)	Ref.	Ref.	Ref.
≥75 years	81 (4)	0.94	0.72-1.22	0.632
Sex				
Male	180 (5)	-	-	-
Female	146 (5)	-	-	-
ASA score				
ASA 1	63 (6)	-	-	-
ASA 2	162 (5)	-	-	-
ASA ≥3	56 (5)	-	-	-
Missing data	45 (5)	-	-	-
Primary tumor location				
Right colon	122 (7)	1.01	0.78-1.31	0.939
Left colon	129 (6)	Ref.	Ref.	Ref.
Rectum	75 (4)	0.92	0.69-1.23	0.576
Primary tumor differentiation				
Good/moderate	241 (5)	Ref.	Ref.	Ref.
Poor/none	51 (11)	1.15	0.82-1.61	0.426
Missing data	34 (6)	0.79	0.50-1.24	0.303
Tumor histology				
Adenocarcinoma	282 (5)	Ref.	Ref.	Ref.
Mucinous adenocarcinoma	35 (8)	1.84	1.20-2.82	**0.005**
Signet ring cell carcinoma	9 (21)	2.43	1.11-5.32	**0.026**
Tumor stage				
T0-3	207 (4)	Ref.	Ref.	Ref.
T4	119 (19)	2.77	2.07-3.70	**<0.001**

Table 3. Multivariable cox regression analyses for the development of metachronous peritoneal metastases after primary tumor resection. (continued)

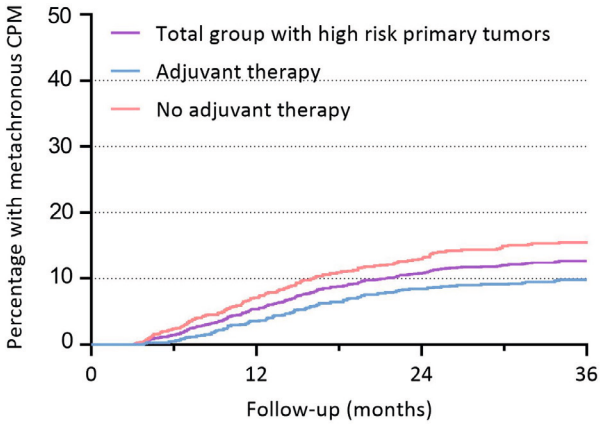
	Metachronous peritoneal metastases	**Multivariable cox regression analysis**		
	n (%)	HR	95% CI	*P value*
Nodal stage				
N0	92 (3)	Ref.	Ref.	Ref.
N1	126 (10)	2.90	2.18-3.85	**<0.001**
N2	106 (15)	3.19	2.26-4.50	**<0.001**
Missing data	2 (1)	0.83	0.19-3.71	0.807
Primary tumor resection margins				
Clear resection margins	286 (6)	Ref.	Ref.	Ref.
No clear resection margins	27 (18)	1.50	0.94-2.39	0.089
Missing data	13 (2)	0.70	0.38-1.29	0.250
Synchronous systemic metastases				
No	245 (5)	Ref.	Ref.	Ref.
Yes	81 (17)	1.95	1.43-2.66	**<0.001**
Tumor perforation				
No	288 (5)	Ref.	Ref.	Ref.
Yes	20 (10)	0.81	0.48-1.35	0.410
Missing data	18 (5)	0.92	0.57-1.49	0.728

ASA American society of anesthesiologists score; *HR* hazard ratio; *CI* confidence interval.

Subgroup analysis in patients with high-risk tumors

In all patients with T4 tumor stage and/or lymph node involvement (n=2242), the cumulative incidence of metachronous peritoneal metastases were 5.0% and 11.2% at 1- and 3- years after surgery for primary CRC, respectively (*Figure 3*). In patients who received adjuvant treatment (n=1024), the 1- and 3-year cumulative incidences of metachronous peritoneal metastases were 3.5% and 9.8%, respectively. In patients who did not receive adjuvant treatment (n=1218), the 1- and 3-year cumulative incidences of metachronous peritoneal metastases were 6.3% and 12.8%, respectively. Uni- and multivariable cox competing risk regression analyses showed that adjuvant treatment was

significantly associated with a lower risk of metachronous peritoneal metastases (HR 0.65; 95% CI, 0.48-0.88) and that no clear resection margins of the primary tumor were associated with a significantly higher risk of metachronous peritoneal metastases (HR 1.75; 95% CI, 1.12-2.75). The associations between the other factors and metachronous peritoneal metastases remained similar to those in the total study population (*Supplementary Table 3.3 [univariable cox regression] and Table 4 [multivariable cox regression]*).



Number at risk (number censored)

Adjuvant therapy	1017 (0)	946 (44)	824 (116)	746 (187)
No adjuvant therapy	1181 (0)	943 (210)	743 (347)	592 (480)

Figure 3. Proportion of patients with high-risk primary tumors with metachronous peritoneal metastases after surgery for primary colorectal cancer, stratified for adjuvant systemic therapy.

Table 4. Multivariable cox regression analyses in high-risk primary tumors for the likelihood of metachronous peritoneal metastases after primary tumor resection.

	Metachronous peritoneal metastases	**Multivariable cox regression analysis**		
	n (%)	HR	95% CI	*P value*
Age at diagnosis				
<50 years	24 (18)	1.91	1.24-2.94	**0.003**
50-74 years	168 (11)	Ref.	Ref.	Ref.
≥75 years	65 (11)	0.84	0.62-1.15	0.275
Sex				
Male	139 (11)	-	-	-
Female	118 (12)	-	-	-
ASA score				
ASA 1	47 (12)	-	-	-
ASA 2	131 (11)	-	-	-
ASA ≥3	41 (10)	-	-	-
Missing data	38 (14)	-	-	-
Primary tumor location				
Right colon	105 (14)	1.11	0.84-1.47	0.481
Left colon	105 (12)	Ref.	Ref.	Ref.
Rectum	47 (8)	0.56	0.38-0.82	**0.003**
Primary tumor differentiation				
Good/moderate	182 (11)	Ref.	Ref.	Ref.
Poor/none	46 (16)	1.29	0.93-1.80	0.133
Missing data	29 (13)	0.82	0.49-1.36	0.435
Tumor histology				
Adenocarcinoma	218 (11)	Ref.	Ref.	Ref.
Mucinous adenocarcinoma	30 (15)	1.83	1.15-2.92	**0.010**
Signet ring cell carcinoma	9 (31)	3.59	1.59-8.11	**0.002**

Table 4. Multivariable cox regression analyses in high-risk primary tumors for the likelihood of metachronous peritoneal metastases after primary tumor resection. (continued)

	Metachronous peritoneal metastases	**Multivariable cox regression analysis**		
	n (%)	HR	95% CI	*P value*
Primary tumor resection margins				
Clear resection margins	227 (11)	Ref.	Ref.	Ref.
No clear resection margins	24 (21)	1.75	1.12-2.75	**0.015**
Missing data	6 (8)	0.80	0.34-1.84	0.594
Synchronous systemic metastases				
No	191 (10)	Ref.	Ref.	Ref.
Yes	66 (18)	1.52	1.11-2.07	**0.009**
Tumor perforation				
No	225 (11)	-	-	-
Yes	17 (12)	-	-	-
Missing data	15 (12)	-	-	-
Adjuvant treatment				
No	154 (13)	Ref.	Ref.	Ref.
Yes	103 (10)	0.65	0.48-0.88	**0.005**

ASA American society of anesthesiologists score; *HR* hazard ratio; *CI* confidence interval.

Discussion

The present study showed that synchronous peritoneal metastases were diagnosed in 5.7% of CRC patients. The 3-year cumulative incidence of metachronous peritoneal metastases was 5.5%, which developed after a median time of 14.7 months after surgery for primary CRC. This is the highest incidence of colorectal peritoneal metastases reported to date in population-based studies[2,3,14-16] and therefore provides an up-to-date overview of the incidence of and factors associated with colorectal peritoneal metastases in a population-based cohort in which modern diagnostic and treatment strategies were applied. As such, this study will be of additional value to

previously published studies and provides a basis for future clinical research regarding the prevention, detection, and treatment of this severe disease.

Previously published population-based studies reported an incidence of 4.7% and 4.8% for synchronous peritoneal metastases (patients diagnosed between 1995 and 2011)[3,15] and 3.5%, and 4.9% for metachronous peritoneal metastases (patients diagnosed between 1995 and 2008).[14,16] The higher incidence found in the present study, which comprised patients who were diagnosed with CRC in 2015, may be due to the expansion of both knowledge and awareness of this disease during follow-up after primary CRC surgery (especially in patients with high-risk tumors), accompanied by improvements in diagnostic imaging techniques.

Besides T4 stage, lymph node involvement and mucinous or signet ring cell histology, which have previously been identified as high-risk features for peritoneal metastases[14,16,19,20], the presence of synchronous systemic metastases was strongly associated with both synchronous and metachronous peritoneal metastases compared to patients without synchronous systemic metastases. This suggests that a more intensive follow-up of the peritoneal cavity is designated in patients with curatively treated synchronous systemic metastases, and it may also guide future patient selection for clinical trials investigating new approaches to prevent or detect metachronous peritoneal disease after primary surgery for CRC in an early stage.

In the subgroup of patients with high-risk tumors (i.e. T4 tumor stage, lymph node involvement), adjuvant systemic therapy after surgery for primary CRC was associated with a lower risk to develop metachronous peritoneal metastases. Nevertheless, still 10% of patients being treated with adjuvant systemic chemotherapy developed metachronous peritoneal metastases. This stresses the need to further improve adjuvant treatment regimens to further lower the incidence of metachronous peritoneal metastases. Furthermore, two recently published studies investigated new strategies to lower the risk on metachronous peritoneal metastases, but both showed negative results: the PROPHYLOCHIP trial did not show a benefit in disease-free survival of an additional systematic second-look surgery plus oxaliplatin-HIPEC in 150 patients with perforated CRC, or non-perforated CRC with synchronous ovarian metastases or peritoneal metastases, who all underwent extensive adjuvant oxaliplatin-based systemic chemotherapy.[11] The COLOPEC trial, in which 204 patients with perforated or T4 colon cancer were included, also concluded that adjuvant oxaliplatin-HIPEC shortly after surgery did not improve peritoneal metastases free survival over adjuvant systemic chemotherapy alone.[12] Hence, the currently available treatment

strategies aiming to minimize the risk of metachronous peritoneal metastases in patients with high-risk colon cancer are insufficient, emphasizing the need for future research.

As the clinical diagnosis of peritoneal metastases is complicated due to limited sensitivity of currently available imaging techniques, as well as the lack of symptoms in most patients before advanced disease stages, the COLOPEC II trial was conducted. This currently recruiting trial investigates second- and third-look surgeries (without HIPEC) after primary surgery (with or without adjuvant systemic therapy) for T4 stage CRC with or without lymph node involvement.[13] However, patients presenting with synchronous systemic metastases are excluded from this trial. Considering the results of the present study, future research focusing on different strategies for the prevention and treatment of metachronous peritoneal metastases should also consider to include patients with synchronous systemic metastases given their high risk of metachronous peritoneal metastases.

Although the present study provides new insights in both synchronous and metachronous peritoneal metastases, it has some potential drawbacks. Firstly, given its retrospective design, it was unknown whether all primary tumor resections were performed with curative intent, especially in the subgroup of patients with synchronous systemic metastases. Palliative tumor resection could have been a treatment strategy in case of obstructive disease without aiming for curation in some patients. In these patients undergoing treatment with palliative intent, a higher incidence rate of metachronous peritoneal metastases could have been the case. Finally, data on the extent of intraperitoneal disease (peritoneal cancer index) was lacking, which may also have been associated with the patient characteristics included in this study.

In conclusion, the present study provides updated and new insights into the incidence of and factors associated with synchronous and metachronous peritoneal metastases, based on an up-to-date nationwide cohort. Besides well-known risk factors for metastatic disease in CRC (i.e. T4 tumors, lymph node involvement), the presence of synchronous systemic metastases was strongly correlated with the development of metachronous peritoneal metastases. Although adjuvant treatment lowered the risk of metachronous peritoneal metastases in patients with high-risk tumors, the incidence of metachronous peritoneal metastases was still remarkably higher than in the general cohort, suggesting that particularly in these patients, currently available treatment strategies may be insufficient and new treatment strategies are designated. These findings may contribute to a tailored approach in the follow-up of patients after primary CRC surgery and guide

future clinical trials investigating new strategies for the risk-reduction and early detection of metachronous peritoneal metastases after colorectal surgery.

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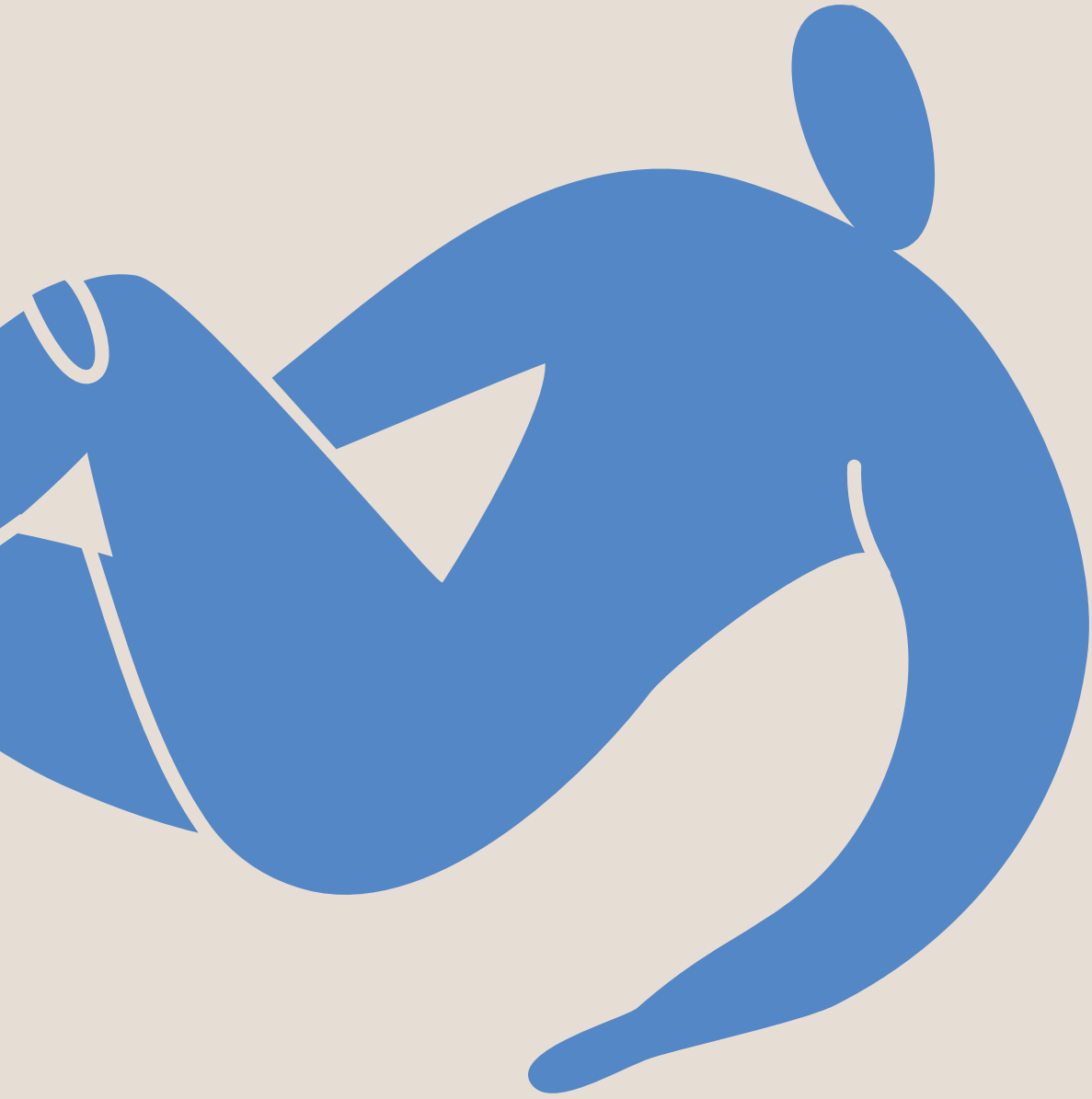

Chapter

4

The impact of an open or laparoscopic approach on the development of metachronous peritoneal metastases after primary resection of colorectal cancer: results from a population-based cohort study

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Abstract

Introduction
This study aimed to assess the impact of open or laparoscopic resection of primary colorectal cancer (CRC) on the development of metachronous colorectal peritoneal metastases in a population-based cohort.

Methods
This was a retrospective, population-based study of CRC patients who underwent open or laparoscopic resection of the primary tumor in the Netherlands between January 1st and June 30th 2015. Patients with synchronous metastases were excluded. Colorectal peritoneal metastases were considered metachronous if diagnosed ≥ 90 days after resection of primary CRC. Multivariable cox regression analysis was performed to correct for tumor location, histology, differentiation, tumor stage, nodal stage, tumor perforation, primary surgery type, and unclear resection margins.

Results
In total, 1516 CRC patients underwent open resection and 3236 CRC patients underwent laparoscopic resection, with a 3-year cumulative incidence of metachronous colorectal peritoneal metastases of 7.3% and 3.7%, respectively ($p < 0.001$), after median follow-up of 42 months. Open surgical approach was significantly associated with the development of metachronous colorectal peritoneal metastases: hazard ratio (HR) 1.4 [95% CI 1.1–1.8]. Other prognostic factors were mucinous adenocarcinoma histology (HR 1.6, 95% CI 1.0–2.5), T4 stage (HR 3.2, 95% CI 2.3–4.5), N1 stage (HR 2.9, 95% CI 2.1–4.0), and N2 stage (HR 4.2, 95% CI 2.9–6.1).

Conclusions
Patients treated with open resection had a significantly higher risk to develop metachronous colorectal peritoneal metastases than patients treated with laparoscopic resection. The mechanisms underlying this phenomenon remain unknown but might be related to differences in per-operative specimen handling, tumor spill, surgical trauma and pro-inflammatory response. This finding might imply the need for a personalized follow-up after primary resection of CRC.

Introduction

Colorectal cancer (CRC) is the second most prevalent cancer worldwide, with an incidence of nearly two million patients in 2020.[1] Despite the improvement of curative treatment options, recurrent disease occurs frequently. In CRC, the peritoneum is the second most prevalent metastatic site, after the liver.[2–4]

Considering that curative-intent cytoreductive surgery for limited colorectal peritoneal metastases is associated with a more favorable prognosis, timely detection of colorectal peritoneal metastases is of utmost importance.[5–7] Unfortunately, colorectal peritoneal metastases are difficult to detect on conventional imaging during normal follow-up and subsequently patients often present with advanced disease. Several factors, such as an advanced TNM stage at diagnosis, and mucinous or signet ring cell tumor histology have been found to be associated with an increased incidence of metachronous colorectal peritoneal metastases. Thus, these parameters can be used to optimize follow-up for early detection of colorectal peritoneal metastases.[4]

In a previous population-based study we showed that synchronous colorectal peritoneal metastases were less frequently diagnosed during laparoscopic resection than during open resection.[8] It was hypothesized that colorectal peritoneal metastases might have been overlooked during laparoscopy due to an insufficient overview of the peritoneal cavity and the lack of tactile feedback. If this were true, this should result in an increased number of patients in whom peritoneal metastases are diagnosed during follow-up (i.e. metachronous colorectal peritoneal metastases). A single-center retrospective cohort study in patients with T4 colon cancer seemed to confirm this hypothesis, as they found a greater incidence of metachronous colorectal peritoneal metastases after laparoscopic resection.[9] Such a finding could have serious consequences for the treatment of CRC, since laparoscopic resection has been increasingly applied given the lower complication rate, lower mortality rate, less major morbidity and a shorter hospital stay than open resection.[10, 11]

Therefore, this study aimed to assess the impact of an open or laparoscopic approach on the incidence of metachronous peritoneal metastases in patients who underwent surgical treatment for CRC in a population-based cohort.

Methods

Data source

Data from the Netherlands Cancer Registry (NCR), which registers all newly diagnosed malignancies in the Netherlands, were used for this nationwide population-based cohort study. Trained data-managers routinely collect these data from hospital records. The International Classification of Disease for Oncology (ICD-O) was used to register the anatomical sites of the primary tumor and metastases, and the seventh edition of the Tumor Node Metastasis (TNM) classification was used to classify the tumor and nodal status. The clinical TNM stage was used when the pathological TNM stage was not available. Normally, the NCR contains information on the primary tumor, metastases diagnosed at the time of diagnosis of the primary tumor, and primary treatment, after which a yearly update of the vital status is performed by linkage to the Dutch municipal administrative database. In 2019, the NCR data-managers performed a re-evaluation of all CRC patients diagnosed between January 1st 2015 and June 30th 2015, aiming for follow-up information on local or systemic recurrences and their treatment. All data were anonymized. No approval of a medical ethics committee was required.

Patients and characteristics

All patients diagnosed with CRC between January 1st and June 30th 2015 in the Netherlands were included in the current study. If more than one primary colorectal tumor was diagnosed in the same patient, only the firstly diagnosed tumor was included, or, if simultaneously diagnosed, the tumor with the highest TNM stage was included. The location of the primary tumor was categorized into three anatomical subsites: (1) right-sided colon (C18.0, C18.2–18.4: cecum, ascending colon, hepatic flexure, transverse colon); (2) left-sided colon (C18.5–18.7: splenic flexure, descending colon and sigmoid); and (3) rectum (C19.9–20.9: rectosigmoid and rectum). Primary tumor histology was categorized into three subtypes: (1) adenocarcinoma (8000, 8010, 8020, 8140, 8144, 8210, 8211, 8220 8255, 8261, 8262, 8263, 8560); (2) mucinous adenocarcinoma (8480, 8481); and (3) signet ring cell carcinoma (8490). Patients were excluded if they had a primary tumor located in the appendix, a neuroendocrine primary tumor, a non-adenocarcinoma tumor histology, or synchronous metastases. The following ICD-O codes were considered peritoneal metastases: C16.0–C16.9, C17.0–C17.9, C18.0–C18.9, C19.9, C20.9, C21.8, C23.9, C26.9, C48.0–C48.8, C49.4–C49.5, C52.9, C54.3–C54.9, C55.9, C56.9, C57.0–C57.8, C66.9, C67.0–C67.9, C76.2. Among patients who underwent open or laparoscopic resection of primary CRC, follow-up data was used to assess the occurrence of metachronous peritoneal metastases (≥ 90 days after surgery for primary CRC). Patients in whom a

laparoscopic resection was converted to open resection were considered to have undergone open resection.

Statistical analyses

The 1- and 3-year cumulative incidence of metachronous colorectal peritoneal metastases after open and laparoscopic resection of primary CRC was calculated considering death as competing event. Time to event was calculated from the date of surgery to the date of last follow-up (censor), diagnosis of metachronous colorectal peritoneal metastases (event of interest), or death (competing event). The Gray's test was used to compare differences in the cumulative incidence of metachronous colorectal peritoneal metastases. Baseline characteristics were compared between patients who underwent open or laparoscopic resection of primary CRC. Differences in continuous variables were compared with the unpaired *t*-test and presented as a mean (± standard deviation [SD]), and differences in categorical variables were compared using chi-squared tests and presented as n (%). Missing data were excluded from comparative analyses. Univariable cox regression analyses with death as competing event were performed to identify factors associated with the development of metachronous colorectal peritoneal metastases. Time to event was calculated from the date of surgery to the date of last follow-up (censor), diagnosis of metachronous colorectal peritoneal metastases (event of interest), or death (competing event). Variables with a $p < 0.10$ were combined in a multivariable cox regression model with respect to the number of patients developing metachronous colorectal peritoneal metastases (10 events per degree of freedom) to prevent overfitting of the multivariable model. Dummy variables of missing data were included in the regression analyses. All tests were two-sided and $p < 0.05$ was considered statistically significant. All analyses were performed using SAS statistical software (SAS system 9.4, SAS Institute, Cary, NC, United States).

Results

Study population

The final study population comprised 4752 patients with CRC without synchronous metastases of whom 1516 underwent open resection (31.9%) and 3236 underwent laparoscopic resection (68.1%) of the primary CRC tumor (*Figure 1*). *Table 1* contains an overview of the study population, stratified for surgical approach. Patients who underwent laparoscopic resection were younger, more often had a lower American society of anesthesiologists score (ASA classification), a primary tumor located in the rectum, an adenocarcinoma histology, good or moderate tumor differentiation, a T0-3 tumor stage, an

No nodal stage, clear resection margins, and a non-perforated colon than patients who underwent open resection.

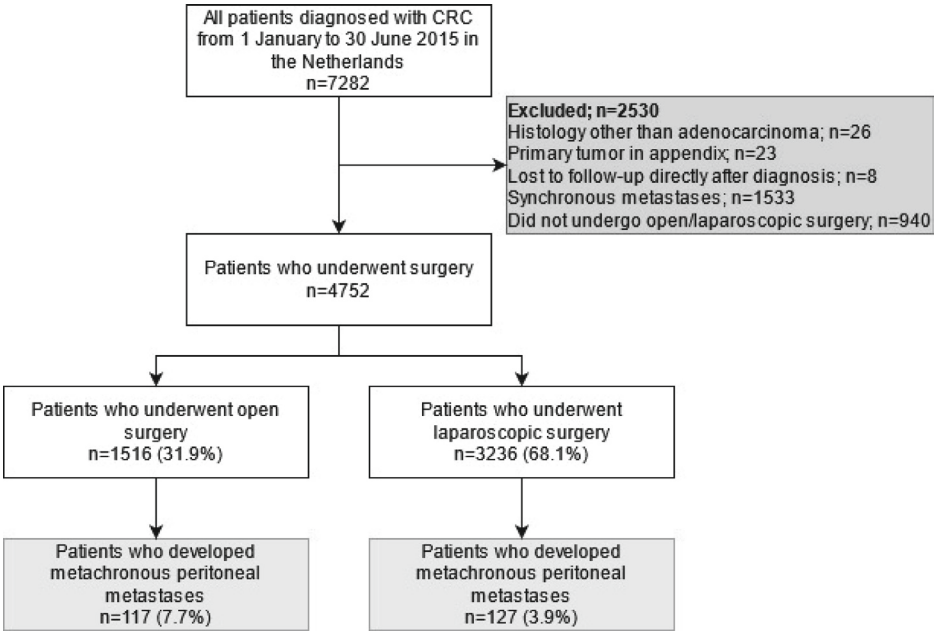


Figure 1. Study flowchart.
CRC colorectal cancer.

Table 1. Baseline characteristics

	Open surgery n=1516	**Laparoscopic surgery** n=3236	*P value*[a]
Sex, No (%)			0.551
Male	882 (58)	1853 (57)	
Female	634 (42)	1383 (43)	
Age at diagnosis, mean (SD)	70 (11)	68 (9)	**<0.001**
ASA score, No (%)			**<0.001**
ASA 1	174 (11)	631 (20)	
ASA 2	746 (49)	1789 (55)	
ASA 3-4	388 (26)	517 (16)	
Missing data	208 (14)	299 (9)	

Table 1. Baseline characteristics (continued)

	Open surgery n=1516	**Laparoscopic surgery** n=3236	*P value*[a]
Primary tumor location, No (%)			**<0.001**
Right colon	618 (41)	950 (29)	
Left colon	575 (38)	1220 (38)	
Rectum	323 (21)	1066 (33)	
Primary tumor histology, No (%)			**0.006**
Adenocarcinoma	1345 (89)	2964 (92)	
Mucinous adenocarcinoma	155 (10)	248 (8)	
Signet ring cell carcinoma	16 (1)	24 (1)	
Primary tumor differentiation, No (%)			**<0.001**
Good/moderate	1179 (78)	2704 (84)	
Poor/none	160 (11)	218 (7)	
Missing data	177 (12)	314 (10)	
Tumor stage, No (%)			**<0.001**
T0-3	1239 (82)	3013 (93)	
T4	276 (18)	222 (7)	
Missing data	1 (0)	1 (0)	
Nodal stage, No (%)			**<0.001**
N0	933 (62)	2183 (67)	
N1	375 (25)	730 (23)	
N2	208 (14)	322 (10)	
Missing data	0 (0)	1 (0)	
Colon perforation, No (%)			**<0.001**
No	1320 (87)	3068 (95)	
Yes	112 (7)	49 (2)	
Missing data	84 (6)	119 (4)	

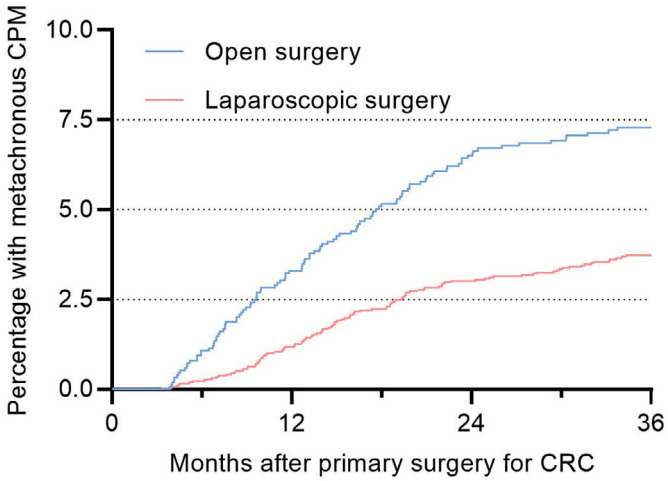
Table 1. Baseline characteristics (continued)

	Open surgery n=1516	**Laparoscopic surgery** n=3236	*P value*[a]
Resection margins, No (%)			**<0.001**
Not clear	54 (4)	52 (2)	
Clear	1446 (95)	3169 (98)	
Missing data	16 (1)	15 (0)	

[a]Missing data were not included in the comparative analyses; Percentages might not add up to or exceed 100% due to rounding; *SD* standard deviation; *ASA* American society of anesthesiologists score.

Metachronous colorectal peritoneal metastases

A total of 244 patients were diagnosed with metachronous colorectal peritoneal metastases after a median follow-up of 42.4 months (interquartile range [IQR] 30.3–46.3). After open resection, 117 out of 1516 patients developed metachronous colorectal peritoneal metastases, with a 1- and 3-year cumulative incidence of metachronous colorectal peritoneal metastases of 3.3% (95% cumulative incidence [CI] 2.5–4.3) and 7.3% (95% CI 6.1–8.7), respectively. After laparoscopic resection, 127 out of 3235 patients developed metachronous colorectal peritoneal metastases, with a 1- and 3-year cumulative incidence of metachronous colorectal peritoneal metastases of 1.2% (95% CI 0.8–1.6) and 3.7% (95% CI 3.1–4.5), respectively ($p < 0.001$) (*Figure 2*). In multivariable cox competing risk regression analysis (*Table 2; univariable cox competing risk analyses in Supplementary Table 4.1*), a statistically significant association between open resection and the development of metachronous colorectal peritoneal metastases (hazard ratio [HR] 1.4; 95% CI, 1.1–1.8) was observed. Furthermore, the following factors were also associated with the development of metachronous colorectal peritoneal metastases: histology of a mucinous adenocarcinoma (HR 1.6; 95% CI, 1.0–2.5), T4 tumor stage (HR 3.2; 95% CI, 2.3–4.5), N1 nodal stage (HR 2.9; 95% CI, 2.1–4.0), and N2 nodal stage (HR 4.2; 95% CI, 2.9–6.1).



Number at risk				
Open surgery	1516	1286	1103	951
Laparoscopic surgery	3236	2983	2680	2402

Figure 2. Cumulative incidence of metachronous peritoneal metastases after open or laparoscopic resection.
CPM colorectal peritoneal metastases; *CRC* colorectal cancer.

Table 2. Multivariable cox competing risk regression analysis for the development of metachronous peritoneal metastases.

	Metachronous peritoneal metastases	**Multivariable cox regression analysis**		
	n (%)	HR	95% CI	*P value*
Primary surgery type				
Laparoscopic	127 (4)	Ref.	Ref.	Ref.
Open	117 (8)	1.4	1.1-1.8	**0.016**
Sex				
Male	132 (5)	-	-	-
Female	112 (6)	-	-	-
Age				
<50	16 (8)	**-**	**-**	**-**
50-74	158 (5)	-	-	-
≥75	70 (5)	-	-	-

Table 2. Multivariable cox competing risk regression analysis for the development of metachronous peritoneal metastases. (continued)

	Metachronous peritoneal metastases	**Multivariable cox regression analysis**		
	n (%)	HR	95% CI	*P value*
ASA score				
ASA 1	40 (5)	-	-	-
ASA 2	128 (5)	-	-	-
ASA ≥3	46 (5)	-	-	-
Missing data	30 (6)	-	-	-
Primary tumor location				
Right colon	108 (7)	1.2	0.9-1.6	0.188
Left colon	87 (5)	Ref.	Ref.	Ref.
Rectum	49 (4)	1.0	0.7-1.4	0.848
Tumor histology				
Adenocarcinoma	204 (5)	Ref.	Ref.	Ref.
Mucinous adenocarcinoma	31 (8)	1.6	1.0-2.5	**0.042**
Signet ring cell carcinoma	9 (23)	2.3	0.9-5.4	0.053
Primary tumor differentiation				
Good/moderate	176 (5)	Ref.	Ref.	Ref.
Poor/none	39 (10)	1.2	0.9-1.8	0.247
Missing data	29 (6)	0.8	0.5-1.3	0.329
Tumor stage				
T0-3	149 (4)	Ref.	Ref.	Ref.
T4	95 (19)	3.2	2.3-4.5	**<0.001**
Nodal stage				
N0	72 (2)	Ref.	Ref.	Ref.
N1	91 (8**)**	2.9	2.1-4.0	**<0.001**

Table 2. Multivariable cox competing risk regression analysis for the development of metachronous peritoneal metastases. (continued)

	Metachronous peritoneal metastases	**Multivariable cox regression analysis**		
	n (%)	HR	95% CI	*P value*
N2	81 (15)	4.2	2.9-6.1	**<0.001**
Tumor perforation				
No	215 (5)	Ref.	Ref.	Ref.
Yes	17 (11)	1.0	0.5-1.8	0.960
Missing data	12 (6)	1.0	0.6-1.8	0.901
Resection margins				
Clear	223 (5)	Ref.	Ref.	Ref.
Not clear	18 (17)	1.3	0.7-2.3	0.370
Missing data	3 (10)	0.8	0.2-2.6	0.688

ASA American society of anesthesiologists score; *HR* Hazard Ratio; *CI* confidence interval; *OS* overall survival.

Discussion

This population-based study aimed to assess the impact of open or laparoscopic approach for CRC on the development of metachronous peritoneal metastases. Patients who underwent open resection of the primary tumor had a significantly higher risk of developing metachronous colorectal peritoneal metastases than patients who underwent laparoscopic resection. This finding contributes to the growing support of the laparoscopic approach given its superior short-term outcomes (i.e. shorter hospital stay, lower complication rate, lower mortality, less major morbidity).[10,11]

Previously, we reported a lower rate of synchronous colorectal peritoneal metastases detected during laparoscopic resection than during open resection.[8] It was hypothesized that the limited overview of the entire peritoneal cavity and the lack of tactile feedback during laparoscopic surgery increased the risk of overlooking peritoneal deposits, resulting in a lower rate of colorectal peritoneal metastases diagnosed during surgery. Eventually, after being overlooked during primary laparoscopic resection, this would subsequently have to lead to a greater number of patients diagnosed with

'metachronous' colorectal peritoneal metastases. This phenomenon would be similar to that of the surgical assessment of the peritoneal cancer index, which is also often underestimated during laparoscopic surgery as compared to open surgery.[12] However, this hypothesis was not confirmed by the current study. Instead, the opposite appeared to be true with patients undergoing laparoscopic resection of primary CRC being less frequently diagnosed with metachronous colorectal peritoneal metastases than those who underwent open resection of primary CRC.

The explanation for this phenomenon remains to be elucidated. A possibility may be a difference in surgical trauma as open surgery is known to result in a larger trauma and subsequently a more pronounced pro-inflammatory response.[13, 14] This may result in higher levels of cytokines and growth factors intraperitoneally which may promote the survival and outgrowth of spilled malignant cells into peritoneal metastases. Another reason might be that the embryological planes of dissection are better preserved with subsequent less tumor spill in laparoscopic resection.

However, the differences may also be caused by patient selection. Indeed, patients who underwent open resection more frequently had a T4 tumor stage, nodal involvement, and poorer tumor differentiation. After multivariable regression analyses for these confounders, open resection was still associated with a significantly higher incidence of metachronous colorectal peritoneal metastases. Nevertheless, residual confounding may be present since not all variables that express a poorer tumor biology (e.g. KRAS and/or BRAF mutations, presence of vascular invasion) or factors that complicate laparoscopic surgery (e.g. abdominal wall involvement, acute setting, colonic obstruction) were included in the current analyses, as these were not available for the majority of patients. Adding these factors to the analyses could increase the accurateness of the multivariable model.

The current finding that open resection is associated with an increased incidence of metachronous colorectal peritoneal metastases should not be taken as an argument that all primary CRC resections should be performed by a laparoscopic approach, as it remains unclear whether the surgical approach itself is causing the difference in the incidence of metachronous colorectal peritoneal metastases. In several clinical situations, an open approach may still be preferred, such as an acute setting, colon perforation, T4 tumor, or a history of extensive abdominal surgery.[15]

Besides the identification of additional risk factors for metachronous colorectal peritoneal metastases, research should also focus on its

prevention. In theory, adjuvant (intraperitoneal) chemotherapy could reduce the risk of metachronous colorectal peritoneal metastases. Nevertheless, two randomized controlled trials were not able to detect a clinical benefit of adjuvant, mainly oxaliplatin-based, intraperitoneal chemotherapy.[16, 17] However, this could also be related to the choice of cytostatic agent, since peritoneal metastases predominantly consist of the consensus molecular subtype 4 (CMS-4), which is considered generally resistant to oxaliplatin.[18–20] The introduction of colorectal peritoneal metastases derived organoids could allow for a personalized selection of adjuvant (intraperitoneal) chemotherapy[21], aiming to prevent the development of metachronous colorectal peritoneal metastases or to improve their treatment if they develop despite adjuvant therapy.

A limitation of the current study is that residual confounding may still be present because some variables (e.g. KRAS and/or BRAF mutations, presence of vascular invasion) were not available from the NCR. Future studies should focus on the impact of these potentially prognostic factors.

This study also has several merits; it is the first large population-based cohort to investigate the impact of open versus laparoscopic approach on the incidence of metachronous colorectal peritoneal metastases. Also, the NCR is characterized by highly accurate and complete data registration rates, contributing to the interpretability of the results.[22] Finally, all patients in the current cohort were diagnosed in 2015 and thus treated according to the same national guideline for CRC, reducing the chance of bias due to changes in recommended treatments over time.

Results of the current study add further insight into the factors being associated with the development of metachronous colorectal peritoneal metastases. Combined, these can further assist health care providers to select patients who might benefit from intensified follow-up or adjuvant treatment, aiming to reduce the development of metachronous colorectal peritoneal metastases and to increase its detection in an early stage.

In conclusion, patients treated with open resection had a significantly higher risk to develop metachronous colorectal peritoneal metastases than patients treated with laparoscopic resection. The mechanisms underlying this phenomenon remain to be elucidated. However, this finding may further contribute to the development of a personalized follow-up and treatment of patients after primary resection of CRC, aiming to reduce the development of metachronous peritoneal metastases or to detect and treat it as early as possible.

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Chapter 5

Treatment strategies and prognosis of patients with synchronous or metachronous colorectal peritoneal metastases: a population-based study

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Abstract

Introduction
This study aimed to compare treatment strategies and survival of patients with synchronous colorectal peritoneal metastases and patients with metachronous colorectal peritoneal metastases in a nationwide cohort.

Methods
All patients from the Netherlands Cancer Registry with synchronous or metachronous colorectal peritoneal metastases whose primary colorectal cancer (CRC) was diagnosed between 1 January and 30 June 2015 were included in the study. Treatments were categorized as (A) cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC); (B) palliative treatment; or (C) best supportive care. Overall survival (OS) for all the patients and disease-free survival (DFS) for those who underwent CRS-HIPEC were compared between the two groups.

Results
Of 7233 patients, 743 had a diagnosis of colorectal peritoneal metastases, including 409 patients with synchronous colorectal peritoneal metastases and 334 patients with metachronous colorectal per. The median OS was 8.1 months for the patients with synchronous colorectal peritoneal metastases versus 12 months for the patients with metachronous colorectal peritoneal metastases (p = 0.003). After multivariable correction, OS no longer differed between the patients with synchronous colorectal peritoneal metastases and those with metachronous colorectal peritoneal metastases (HR 1.03 [0.83–1.27]). The patients with metachronous colorectal peritoneal metastases more often underwent CRS-HIPEC than the patients with synchronous colorectal peritoneal metastases (16% vs 8%; p = 0.001). The two groups did not differ statistically in terms of DFS and OS (median DFS, 21.5 vs 14.1 months, respectively; p = 0.094; median OS, 37.8 vs. 35.8 months, respectively; p = 0.553).

Conclusions
This population-based study showed that survival for the patients with synchronous colorectal peritoneal metastases and patients with metachronous colorectal peritoneal metastases did not significantly differ. This suggests that a similar prognosis may be expected for patients selected for treatment regardless of the onset of colorectal peritoneal metastases.

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide.[1] Approximately one third of patients are confronted with metastatic disease, either at the time of diagnosis or later during follow-up evaluation after curative treatment.[2] After the liver, the peritoneum is the second most common metastatic site of CRC.[3,4] Colorectal peritoneal metastases, occurring in about 10% of CRC patients, are diagnosed during the initial treatment of the primary tumor (synchronous peritoneal metastases) or during follow-up evaluation (metachronous peritoneal metastases).[2]

Although the risk factors for synchronous and metachronous colorectal peritoneal metastases are alike,[2] it is unknown whether the tumor behavior differs between synchronous peritoneal metastases and metachronous peritoneal metastases. A different tumor behavior may result in a different prognosis and therefore require adjusted treatment strategies.[5,6]

Recently, an Italian society of experts in peritoneal surface malignancies defined and approved different diagnostic and therapeutic algorithms for synchronous peritoneal metastases and metachronous peritoneal metastases.[7] However, most international guidelines do not take the presentation of colorectal peritoneal metastases into account in recommendations regarding treatment.[8–11] Also, in some randomized trials, the synchronous or metachronous presentation of colorectal peritoneal metastases is used as a stratification factor.[12] Still, it remains unclear whether any differences exist between synchronous colorectal peritoneal metastases and metachronous colorectal peritoneal metastases and, if so, how this affects prognosis in an unselected population.

This population-based study aimed to provide insight into the treatment strategies and prognosis of patients with synchronous colorectal peritoneal metastases and those with metachronous colorectal peritoneal metastases and to identify characteristics associated with prognosis, providing an up-to-date basis for future clinical research investigating patients with synchronous colorectal peritoneal metastases and those with metachronous colorectal peritoneal metastases.

Methods

Data Source

Data from the Netherlands Cancer Registry (NCR) were used for the performance of the current nationwide population-based cohort study. The NCR registers all newly diagnosed malignancies in the Netherlands, and trained data managers from the NCR routinely collect patient, tumor, and treatment characteristics. Each year, the vital status of all patients is checked by linkage to the municipal administrative database, in which all deaths of Dutch inhabitants are registered.

For the current study, the latest linkage to the municipal administrative database was performed in February 2020. In 2019, all patients with a diagnosis of CRC determined between 1 January and 30 June 2015 were reassessed to obtain follow-up information on locoregional and/or systemic recurrences and their treatment. All data were rendered anonymous, obviating approval for the study by the medical ethics committee.

Patients and characteristics

The study excluded patients with an appendiceal tumor, a neuro-endocrine tumor, or a tumor with histology other than adenocarcinoma. For the analyses, the study included only patients who experienced synchronous or metachronous peritoneal metastases, defined as present in any of the following metastatic locations according to the International Classification of Disease for Oncology (ICD-O): C16.0–C16.9, C17.0–C17.9, C18.0–C18.9, C19.9, C20.9, C21.8, C23.9, C26.9, C48.0–C48.8, C49.4–C49.5, C52.9, C53.9, C54.0–C54.9, C55.9, C56.9, C57.0–C57.8, C66.9, C67.0–C67.9, or C76.2. All metastases in other locations were registered as systemic metastases. Metastases were considered synchronous if diagnosed 90 days or less after surgery for primary CRC or 90 days or less after diagnosis if no surgery for primary CRC was performed. Among the patients without synchronous peritoneal metastases, only those who underwent surgery for primary CRC were evaluated for the development of metachronous metastases. Metastases were considered metachronous if diagnosed longer than 90 days after surgery for primary CRC.

The primary tumor location was subcategorized according to the ICD-O as (1) right-sided colon (C18.0, C18.2–18.4): cecum, ascending colon, hepatic flexure, transverse colon; (2) left-sided colon (C18.5–18.7): splenic flexure, descending colon and sigmoid; or (3) rectum (C19.9–20.9): rectosigmoid and rectum. The primary tumor histology was defined as adenocarcinoma (8000, 8010,

8020, 8140, 8144, 8210, 8211, 8220 8255, 8261, 8262, 8263, 8560), mucinous adenocarcinoma (8480, 8481), or signet ring cell carcinoma (8490).

The treatment of peritoneal metastases was defined as (1) cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) with or without systemic chemotherapy and/or radiotherapy; (2) palliative treatment: systemic chemotherapy, metastasectomy, and/or radiotherapy without curative intent; or (3) no tumor-directed treatment, only best supportive care (BSC).

Statistical analyses

The baseline characteristics of the patients with synchronous peritoneal metastases were compared with those of patients with metachronous peritoneal metastases. Continuous variables are presented as mean ± standard deviation and were compared using the unpaired *t*-test. Categorical variables are presented as number (%) and were compared with the chi-squared test. Different treatment strategies between the patients with synchronous and those with metachronous peritoneal metastases were compared using the chi-squared test. All the tests were two-sided, and a p-value lower than 0.05 was considered statistically significant. Median overall survival (OS) was determined with the Kaplan-Meier method and compared between the patients with synchronous colorectal peritoneal metastases and those with metachronous colorectal peritoneal metastases as well as between the patients treated with different treatment strategies using the Log-rank test. The median OS was calculated from the first diagnosis of peritoneal metastases until death or loss to follow-up evaluation. Disease free survival (DFS) was determined only for the patients who underwent CRS-HIPEC and was calculated from the date of CRS-HIPEC until the diagnosis of metastases (locoregional and/or systemic metastases) thereafter.

Univariable cox regression analyses were performed for the patients with peritoneal metastases (as one group) and for the patients with synchronous or metachronous peritoneal metastases (as two groups) to identify risk factors affecting OS. To prevent overfitting, variables with a p-value lower than 0.10 were subsequently combined in multivariable cox regression models with respect to the number of deaths in each group (10 deaths per degree of freedom). Dummy variables of missing data were included in the multivariable analyses. All analyses were performed using SAS statistical software (SAS system 9.4, SAS Institute, Cary, NC, USA).

Results

Study population

Between 1 January and 30 June 2015, CRC was diagnosed for 7233 patients. Of these patients, 409 (5.7%) presented with synchronous peritoneal metastases. During follow-up evaluation, metachronous peritoneal metastases was diagnosed for 334 (5.7%) of 5860 patients without synchronous peritoneal metastases who underwent surgery for primary CRC. The median follow-up period after surgery was 38.4 months (interquartile range [IQR], 15.3–45.4 months). The baseline characteristics of the patients with synchronous colorectal peritoneal metastases and those with metachronous colorectal peritoneal metastases are presented in *Table 1*. Poorly differentiated or undifferentiated tumor, T4 tumor stage, and synchronous systemic metastases were more frequently diagnosed for the patients with synchronous peritoneal metastases than for those with metachronous peritoneal metastases.

Table 1. Baseline characteristics.

	Synchronous peritoneal metastases n=409	**Metachronous peritoneal metastases** n=334	*P value*[a]
Age at diagnosis, mean (SD)	69 (12)	67 (11)	0.062
Sex, No. (%)			
Male	225 (55)	185 (55)	0.918
Female	184 (45)	149 (45)	
ASA score, No. (%)			
ASA 1	29 (7)	63 (19)	**<0.001**
ASA 2	138 (34)	165 (49)	
ASA ≥3	75 (18)	57 (17)	
Missing data	167 (41)	49 (15)	
Primary tumor location, No. (%)			
Right-sided colon	186 (45)	126 (38)	**<0.001**
Left-sided colon	173 (42)	132 (39)	
Rectum	50 (12)	76 (23)	

Table 1. Baseline characteristics. (continued)

	Synchronous peritoneal metastases n=409	**Metachronous peritoneal metastases** n=334	*P value*[a]
Tumor differentiation, No. (%)			
Good/moderate	167 (41)	248 (74)	**0.002**
Poor/undifferentiated	67 (16)	52 (16)	
Missing data	175 (43)	34 (10)	
Tumor histology, No. (%)			
Adenocarcinoma	313 (77)	282 (86)	**0.001**
Mucinous adenocarcinoma	65 (16)	35 (11)	
Signet ring cell carcinoma	31 (6)	9 (3)	
Tumor stage, No. (%)			
T0-3	118 (29)	210 (63)	**<0.001**
T4	192 (47)	124 (37)	
Missing data	99 (24)	0 (0)	
Nodal stage, No. (%)			
N0	83 (20)	97 (29)	**<0.001**
N1	104 (25)	126 (38)	
N2	165 (40)	109 (32)	
Missing data	57 (14)	2 (1)	
Synchronous systemic metastases, No. (%)			
No	166 (41)	252 (75)	**<0.001**
Yes	243 (59)	82 (25)	
Colon perforation, No. (%)			
No	203 (50)	293 (88)	0.106
Yes	24 (6)	21 (6)	
Missing data	182 (44)	20 (6)	

[a]Missing data were not included in the comparative analyses; Percentages might not add up to 100% due to rounding; *SD* standard deviation; *ASA* American society of anesthesiologists score.

Treatments

Figure 1 provides an overview of the treatment strategies applied for the patients with synchronous or metachronous peritoneal metastases. Overall, the distribution of applied treatment strategies differed significantly between patients with synchronous peritoneal metastases and those with metachronous peritoneal metastases ($p < 0.001$). The patients with metachronous peritoneal metastases more frequently underwent CRS-HIPEC (16 % vs. 8%; $p = 0.001$) and less frequently underwent palliative treatment (55 % vs. 69 %; $p < 0.001$) than the patients with synchronous peritoneal metastases. The number of patients who received BSC was similar between the metachronous peritoneal metastases group and synchronous peritoneal metastases group (29 % vs. 23 %; $p = 0.051$).

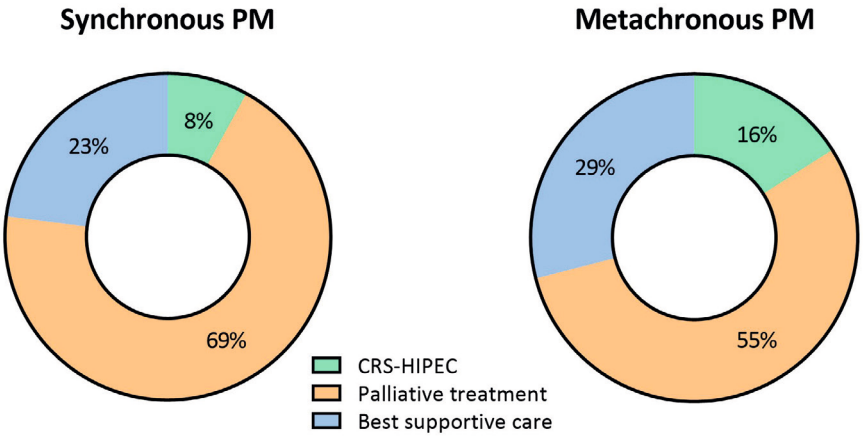
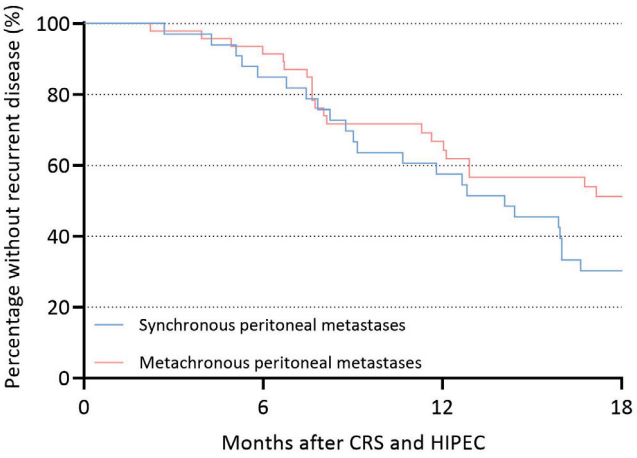


Figure 1. Treatment strategies for patients with synchronous or metachronous colorectal peritoneal metastases.
PM peritoneal metastases; *CRS-HIPEC* cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Disease-free survival

The DFS of the patients with synchronous or metachronous peritoneal metastases who underwent CRS-HIPEC is shown in *Figure 2*. The median DFS was 14.1 months (IQR, 8.2–29.2 months) for the patients with synchronous peritoneal metastases and 21.5 months (IQR, 8.0, not reached) for the patients with metachronous peritoneal metastases, but the difference was not significant ($p = 0.094$). The site or sites of first recurrence after CRS-HIPEC in the patients with synchronous or metachronous peritoneal metastases are shown in *Figure 3*. No differences in the pattern of recurrence were observed

between the patients with synchronous peritoneal metastases and those with metachronous peritoneal metastases (p = 0.950).



Number at risk				
Synchronous PM	34	31	20	10
Metachronous PM	54	43	29	20
Number censored				
Syncronous PM	0	1	0	0
Metachronous PM	0	8	4	2

Figure 2. Disease-free survival of patients with synchronous or metachronous colorectal peritoneal metastases after CRS-HIPEC.
PM peritoneal metastases; *CRS-HIPEC* cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

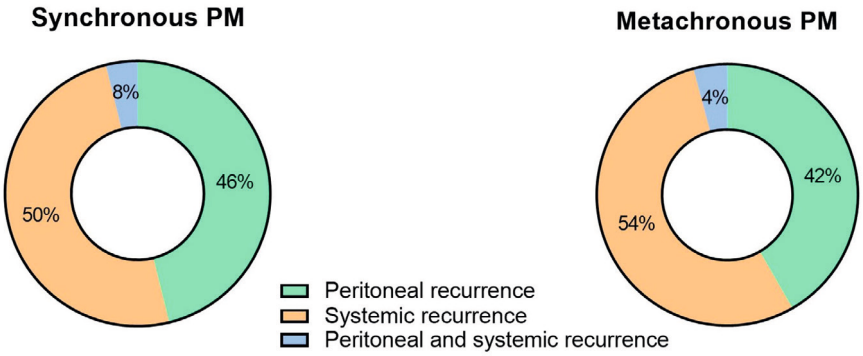


Figure 3. Sites of recurrent disease after CRS-HIPEC in patients with synchronous or metachronous colorectal peritoneal metastases.
PM peritoneal metastases.

Overall survival

The median OS of all the patients with peritoneal metastases was 9.1 months (IQR, 2.6–22.5 months), with a 1-year OS of 44% and a 3-year OS of 13%. The patients with synchronous peritoneal metastases had a worse OS (median, 8.1 months; IQR, 2.0–20.5 months) than the patients with metachronous peritoneal metastases (12.0 months; IQR, 3.5–25.5 months) (p = 0.003; *Figure 4a*). However, after multivariable cox regression analysis, the presentation of peritoneal metastases did not affect OS significantly (metachronous peritoneal metastases vs synchronous peritoneal metastases: hazard ratio [HR], 1.03; 95 % CI 0.83–1.27) (*Supplementary Table 5.1 [univariable cox regression analyses] and Table 2 [multivariable cox regression analyses]).*

Table 2. Multivariable cox regression analyses for overall survival of the entire study cohort.

	Median OS (months)	**Multivariable cox regression analyses**		
		HR	95% CI	*P value*
Age at diagnosis				
<50 years	15.6	0.84	0.61-1.15	0.283
50-74 years	11.9	Ref.	Ref.	Ref.
≥75 years	4.2	1.05	0.86-1.26	0.654

Table 2. Multivariable cox regression analyses for overall survival of the entire study cohort. (continued)

	Median OS (months)	**Multivariable cox regression analyses**		
		HR	95% CI	*P value*
Sex				
Male	9.4	-	-	-
Female	8.7	-	-	-
ASA score				
ASA 1	17.6	0.92	0.69-1.22	0.571
ASA 2	12.1	Ref.	Ref.	Ref.
ASA ≥3	5.7	1.16	0.93-1.45	0.202
Missing data	4.6	1.26	1.02-1.56	0.034
Primary tumor location				
Right colon	7.3	Ref.	Ref.	Ref.
Left colon	11.4	0.87	0.73-1.05	0.141
Rectum	9.7	1.12	0.88-1.44	0.356
Primary tumor differentiation				
Good/moderate	14.2	Ref.	Ref.	Ref.
Poor/undifferentiated	3.6	2.00	1.57-2.52	**<0.001**
Missing data	5.3	1.21	0.97-1.51	0.096
Tumor histology				
Adenocarcinoma	9.5	Ref.	Ref.	Ref.
Mucinous adenocarcinoma	9.1	0.83	0.64-1.07	0.148
Signet ring cell carcinoma	3.8	1.51	1.06-2.15	**0.024**
Tumor stage				
T0-3	9.5	Ref.	Ref.	Ref.
T4	11.7	1.12	0.92-1.35	0.257
Missing data	3.7	1.20	0.90-1.60	0.220
Nodal stage				
N0	12.8	0.82	0.66-1.03	0.087
N1	10.8	1.01	0.83-1.23	0.937
N2	8.3	Ref.	Ref.	Ref.

Table 2. Multivariable cox regression analyses for overall survival of the entire study cohort. (continued)

	Median OS (months)	**Multivariable cox regression analyses**		
		HR	95% CI	*P value*
Missing data	2.8	1.74	1.27-2.38	<0.001
Synchronous systemic metastases				
No	12.1	Ref.	Ref.	Ref.
Yes	6.7	1.22	1.02-1.47	**0.034**
Tumor perforation				
No	12.2	Ref	Ref	Ref
Yes	9.4	0.99	0.69-1.41	0.958
Missing data	8.2	1.06	0.86-1.31	0.593
Presentation of peritoneal metastases				
Synchronous	8.1	Ref.	Ref.	Ref.
Metachronous	12.0	1.03	0.83-1.27	0.813
Treatment of peritoneal metastases				
Best supportive care	1.8	4.44	3.57-5.52	**<0.001**
Palliative treatment	12.2	Ref.	Ref.	Ref.
CRS-HIPEC	36.0	0.40	0.29-0.55	**<0.001**

ASA American association of anesthesiologists score; *OS* overall survival; *HR* hazard ratio; *CI* confidence interval; *CRS* cytoreductive surgery; *HIPEC* hyperthermic intraperitoneal chemotherapy.

For the patients who underwent CRS-HIPEC, the median OS of the entire cohort was 36 months (IQR, 22.5 months, not reached). The median OS did not differ significantly between the patients with synchronous peritoneal metastases (35.8 months; IQR, 26.2 months, not reached) and those with metachronous peritoneal metastases (37.8 months; IQR, 17.3 months, not reached) (p = 0.553; *Figure 4b*).

For the patients who received palliative treatment, the median OS of the entire cohort was 12.2 months (IQR 4.9–22.7 months). The OS was worse for the patients with synchronous peritoneal metastases (median, 10.0 months; IQR

3.6–20.6 months) than for those with metachronous peritoneal metastases (15.4 months; IQR, 6.8–25.6 months; $p < 0.001$ (*Figure 4c*).

For the patients who received only BSC, the median OS of the entire cohort was 1.8 months (IQR, 0.9–3.9 months). The OS was worse for the patients with synchronous peritoneal metastases (1.3 months; IQR, 0.6–3.2 months) than for the patients with metachronous peritoneal metastases (2.1 months; IQR, 1.0–4.6 months; $p = 0.021$) (*Figure 4d*).

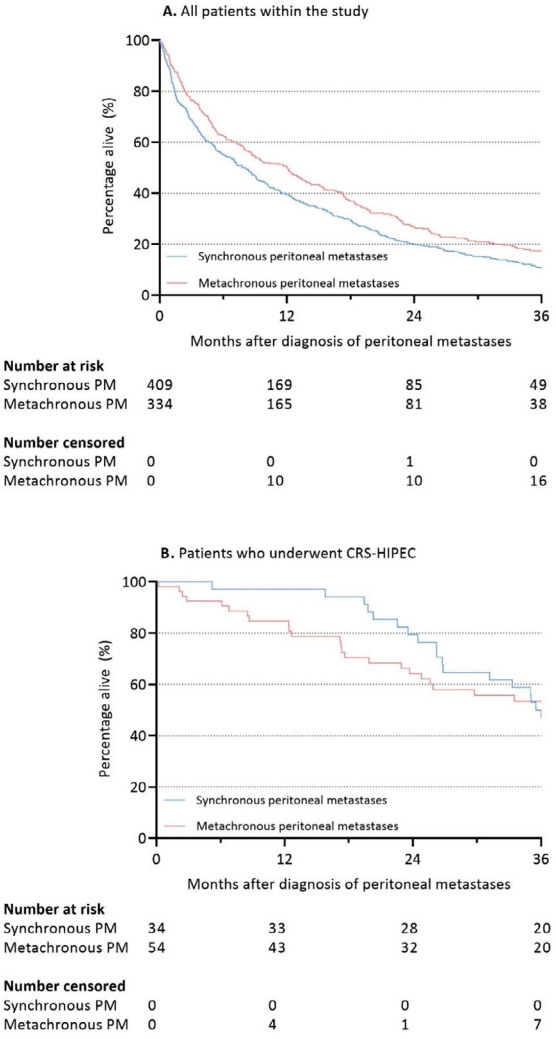
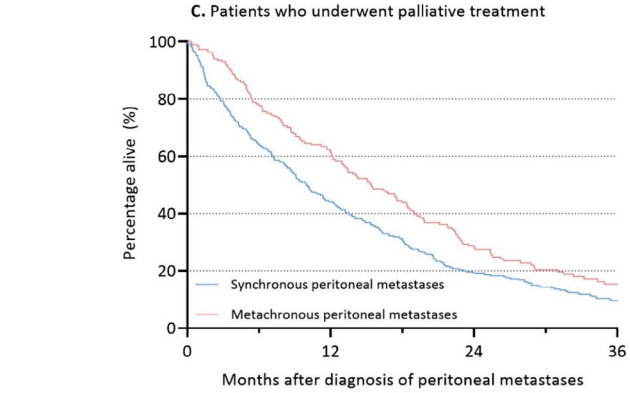
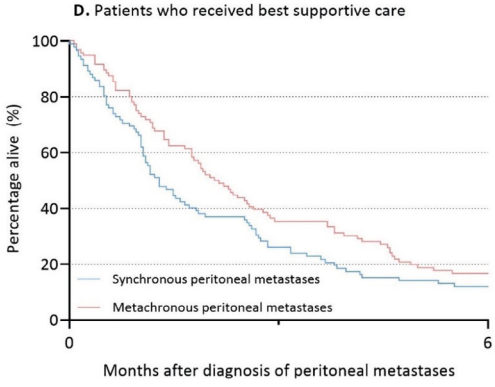


Figure 4a-b. Overall survival of patients with synchronous or metachronous peritoneal metastases.
PM peritoneal metastases



Number at risk				
Synchronous PM	283	132	57	29
Metachronous PM	184	114	47	18
Number censored				
Synchronous PM	0	0	1	0
Metachronous PM	0	5	8	9



Number at risk		
Synchronous PM	92	13
Metachronous PM	96	18
Number censored		
Synchronous PM	0	0
Metachronous PM	0	0

Figure 4c-d. Overall survival of patients with synchronous or metachronous peritoneal metastases.
PM peritoneal metastases

Factors associated with overall survival

The results of the univariable cox regression analyses for the OS of the patients with synchronous and those with metachronous peritoneal metastases are shown in *Supplementary Table 5.2 and 5.3,* respectively. The results of the multivariable cox regression analyses of the patients with synchronous and those with metachronous peritoneal metastases are shown in *Table 3 and 4*. For the patients with synchronous peritoneal metastases, a worse OS was significantly associated with an American society of anesthesiologists score (ASA classification) of 3 or higher (adjusted hazard ratio [HR] 1.43; 95% confidence interval [CI], 1.05–1.94), a primary tumor located in the rectum (HR 1.63; 95% CI, 1.15–2.31]), and a poorly differentiated or undifferentiated primary tumor (HR 2.06; 95% CI, 1.48–2.85). Treatment with CRS-HIPEC was significantly associated with better OS than palliative treatment (HR 0.35; 95% CI, 0.22–0.57). BSC was significantly associated with worse OS than palliative treatment (HR 4.11; 95% CI, 3.00–5.63).

For the patients with metachronous peritoneal metastases, a worse OS was significantly associated with a poorly differentiated or undifferentiated primary tumor (HR 2.00; 95% CI 1.42–2.80) and signet ring cell carcinoma (HR 2.70; 95% CI, 1.24–5.88). An N0 status was significantly associated with a better OS (HR 0.64; 95% CI, 0.45–0.92). Treatment with CRS-HIPEC was significantly associated with a better OS than palliative treatment (HR 0.43; 95% CI, 0.28–0.67). BSC was significantly associated with a worse OS than palliative treatment (HR 4.95; 95% CI, 3.60–6.81).

Table 3. Multivariable cox regression analyses for overall survival in patients with synchronous peritoneal metastases.

	Median OS (months)	**Multivariable cox regression analysis**		
		HR	95% CI	*P value*
Age at diagnosis				
<50 years	15.9	0.86	0.56-1.32	0.494
50-74 years	10.0	Ref.	Ref.	Ref.
≥75 years	3.8	0.95	0.75-1.21	0.672
Sex				
Male	8.4	-	-	-
Female	7.3	-	-	-

Table 3. Multivariable cox regression analyses for overall survival in patients with synchronous peritoneal metastases. (continued)

	Median OS (months)	**Multivariable cox regression analysis**		
		HR	95% CI	*P value*
ASA score				
ASA 1	18.6	0.88	0.55-1.38	0.567
ASA 2	11.3	Ref.	Ref.	Ref.
ASA ≥3	5.2	1.43	1.05-1.94	**0.023**
Missing data	3.8	1.31	1.01-1.72	0.049
Primary tumor location				
Right-sided colon	7.0	Ref.	Ref.	Ref.
Left-sided colon	9.9	0.93	0.74-1.17	0.545
Rectum	6.3	1.63	1.15-2.31	**0.006**
Primary tumor differentiation				
Good/moderate	14.9	Ref.	Ref.	Ref.
Poor/none	3.7	2.06	1.48-2.85	**<0.001**
Missing data	5.3	1.23	0.94-1.59	0.130
Tumor histology				
Adenocarcinoma	8.2	Ref.	Ref.	Ref.
Mucinous adenocarcinoma	9.9	0.81	0.59-1.11	0.191
Signet ring cell carcinoma	4.2	1.32	0.87-2.01	0.192
Tumor stage				
T0-3	7.8	Ref.	Ref.	Ref.
T4	12.0	1.19	0.91-1.56	0.203
Missing data	3.7	1.25	0.91-1.71	0.163
Nodal stage				
N0	8.4	0.96	0.71-1.31	0.802
N1	9.0	0.97	0.73-1.28	0.812
N2	10.9	Ref.	Ref.	Ref.
Missing data	2.8	1.70	1.21-2.39	0.002

Table 3. Multivariable cox regression analyses for overall survival in patients with synchronous peritoneal metastases. (continued)

	Median OS (months)	**Multivariable cox regression analysis**		
		HR	95% CI	*P value*
Synchronous systemic metastases				
No	10.6	Ref.	Ref.	Ref.
Yes	5.5	1.18	0.93-1.49	0.174
Tumor perforation				
No	12.6	Ref.	Ref.	Ref.
Yes	13.3	0.80	0.49-1.30	0.366
Missing data	7.0	1.24	0.96-1.59	0.100
Treatment of peritoneal metastases				
Best supportive care	1.3	4.11	3.00-5.63	**<0.001**
Palliative treatment	10.0	Ref.	Ref.	Ref.
CRS-HIPEC	35.8	0.35	0.22-0.57	**<0.001**

ASA American association of anesthesiologists score; *OS* overall survival; *HR* hazard ratio; *CI* confidence interval; *CRS* cytoreductive surgery; *HIPEC* hyperthermic intraperitoneal chemotherapy.

Table 4. Multivariable cox regression analyses for overall survival in patients with metachronous peritoneal metastases.

	Median OS (months)	**Multivariable cox regression analysis**		
		HR	95% CI	*P value*
Age at diagnosis				
<50 years	14.5	0.84	0.52-1.35	0.472
50-74 years	14.3	Ref.	Ref.	Ref.
≥75 years	4.6	1.19	0.86-1.64	0.294
Sex				
Male	12.2	Ref.	Ref.	Ref.
Female	10.4	1.01	0.78-1.30	0.969
ASA score				
ASA 1	16.4	0.95	0.65-1.38	0.775
ASA 2	12.2	Ref.	Ref.	Ref.
ASA ≥3	6.1	0.87	0.62-1.23	0.420
Missing data	10.4	1.15	0.80-1.67	0.457
Primary tumor location				
Right-sided colon	8.5	-	-	-
Left-sided colon	13.5	-	-	-
Rectum	12.4	-	-	-
Primary tumor differentiation				
Good/moderate	14.1	Ref.	Ref.	Ref.
Poor/none	3.2	2.00	1.42-2.80	**<0.001**
Missing data	12.1	0.75	0.43-1.30	0.301
Tumor histology				
Adenocarcinoma	13.0	Ref.	Ref.	Ref.
Mucinous adenocarcinoma	6.6	1.22	0.74-2.01	0.434
Signet ring cell carcinoma	3.2	2.70	1.24-5.88	**0.012**
Tumor stage				
T0-3	12.4	-	-	-
T4	11.2	-	-	-

Table 4. Multivariable cox regression analyses for overall survival in patients with metachronous peritoneal metastases. (continued)

	Median OS (months)	**Multivariable cox regression analysis**		
		HR	95% CI	*P value*
Nodal stage				
N0	17.9	0.64	0.45-0.92	**0.015**
N1	12.2	1.08	0.80-1.46	0.622
N2	5.3	Ref.	Ref.	Ref.
Missing data	10.5	2.06	0.49-8.64	0.323
Synchronous systemic metastases				
No	12.7	-	-	-
Yes	8.7	-	-	-
Tumor perforation				
No	12.0	-	-	-
Yes	7.6	-	-	-
Missing data	13.1	-	-	-
Adjuvant treatment after primary surgery for colorectal cancer				
No	9.0	Ref.	Ref.	Ref.
Yes	17.4	0.84	0.63-1.13	0.250
Treatment of peritoneal metastases				
Best supportive care	2.1	4.95	3.60-6.81	**<0.001**
Palliative treatment	15.4	Ref.	Ref.	Ref.
CRS- HIPEC	37.8	0.43	0.28-0.67	**<0.001**

ASA American association of anesthesiologists score; *OS* overall survival; *HR* hazard ratio; *CI* confidence interval; *CRS* cytoreductive surgery; *HIPEC* hyperthermic intraperitoneal chemotherapy.

Discussion

To the best of our knowledge, the current study was the first to compare treatment strategies and survival between patients with synchronous colorectal peritoneal metastases and those with metachronous colorectal peritoneal metastases in a nationwide cohort. Overall survival did not differ significantly between the patients with synchronous peritoneal metastases and those with metachronous peritoneal metastases after correction for covariables, although the patients with metachronous peritoneal metastases were more often treated with CRS-HIPEC than the patients with synchronous peritoneal metastases. Moreover, neither OS nor DFS differed significantly the between patients with synchronous peritoneal metastases and those with metachronous peritoneal metastases who underwent CRS-HIPEC.

Although the OS for the patients with synchronous peritoneal metastases and those with metachronous peritoneal metastases did not differ significantly after correction for covariables, the more favorable crude OS of the patients with metachronous peritoneal metastases could be explained in different ways. First, the late presentation of metachronous peritoneal metastases may itself suggest a less aggressive tumor behavior, thus resulting in better OS. However, metachronous peritoneal metastases occur primarily in patients with high-risk tumors, who are designated for adjuvant systemic therapy after primary surgery according to most national and international guidelines to minimize the risk of metastatic recurrence.[10,13] Therefore, if metachronous peritoneal metastases occur regardless of adjuvant systemic therapy, it may instead suggest a more aggressive tumor biology.

Second, the better crude OS for patients with metachronous peritoneal metastases may have been related to lead-time bias. After primary treatment for CRC, these patients underwent standardized follow-up evaluation for several years, which may have resulted in the early diagnosis of less advanced metachronous peritoneal metastases. On the other hand, the patients with synchronous peritoneal metastases may have remained unnoticed until an advanced stage of disease given the absence of clinical symptoms in most of these patients.[14] The higher number of patients with metachronous peritoneal metastases treated with CRS-HIPEC compared with the number of patients who had synchronous peritoneal metastases treated with CRS-HIPEC in the current study supports this hypothesis. Furthermore, synchronous colorectal peritoneal metastases are frequently discovered (in an emergency setting) in non-academic hospitals that are not specialized HIPEC centers, which is known to affect the likelihood of a patient eventually undergoing CRS-HIPEC.[15]

In the current study, DFS and OS for the patients with synchronous peritoneal metastases and those with metachronous peritoneal metastases who underwent CRS-HIPEC were non-significantly different. Another comparative study, which included patients from two Dutch HIPEC centers, showed a significantly longer DFS (15 months) for 231 patients with synchronous peritoneal metastases compared with 11 months for 202 patients who had metachronous peritoneal metastases, without a difference in OS.[16] Recently, Min Wong et al.[5] demonstrated no differences in DFS, but showed a better OS for patients with metachronous peritoneal metastases (45 months) than for patients with synchronous peritoneal metastases (27 months). A similar trend was observed in a third study, with no difference in DFS but a better OS for patients with metachronous peritoneal metastases (28 months) than for patients with synchronous peritoneal metastases (7 months). However, in the latter study, survival was calculated from the diagnosis of primary CRC instead of from the diagnosis of peritoneal metastases, explaining the much longer survival of patients with metachronous colorectal peritoneal metastases.[6]

Other population-based studies that reported the survival of all patients with synchronous peritoneal metastases demonstrated a median OS of 8 to 9 months (diagnosis in 2002–2011),[4,17] similar to that of the current study. For metachronous peritoneal metastases, a median OS of 6 months was reported (diagnosis of primary CRC in 2003–2008),[18] which is lower than the OS for the patients in the current study. This improvement over time for patients with metachronous peritoneal metastases may be due to improved diagnostic methods and better follow-up evaluation, with higher awareness for metachronous peritoneal metastases after primary surgery for CRC, especially because no improvement was found in patients with synchronous peritoneal metastases. However, currently available data on the association between the intensity of follow-up evaluation after primary CRC treatment and OS is rather contradictory to two meta-analyses conducted in 2019[19] and 2016[20] concluding that the intensified surveillance of CRC patients does not result in a cancer-specific survival benefit. Furthermore, a systematic review from 2017 concluded that although patients with stages 1 to 3 CRC may experience a survival benefit, the existence of this benefit is questionable for patients with stage 4 CRC.[21] In addition, a randomized controlled trial concluded that intensified carcinoembryonic antigen (CEA) measurements resulted in earlier recurrence detection and a higher proportion of patients who could be treated with curative intent. However, this did not result in a survival benefit.[22,23] As previously noted, patients with synchronous colorectal peritoneal metastases were less likely to be treated with CRS-HIPEC, which may be responsible for this phenomenon.

The extent of peritoneal metastases (peritoneal cancer index [PCI]) was unknown for the patients included in the current study because this is not registered by the NCR. The PCI is known to affect prognosis[24] and, hypothetically, the patients with metachronous peritoneal metastases may have had a lower PCI than the patients with synchronous peritoneal metastases, explaining the higher percentage of patients who had metachronous colorectal peritoneal metastases treated with CRS-HIPEC. However, such a difference was not observed in previous studies.[5,16] Furthermore, the primary tumor being in situ in patients with synchronous peritoneal metastases may have had a negative impact on treatment and prognosis. Moreover, some patients with metachronous peritoneal metastases were excluded from this analysis if they had not undergone surgery for primary CRC. These patients may have had a worse prognosis because they were not able to undergo surgery. The exclusion of patients who did not undergo surgery may have led to an overestimation of the OS in the group of patients with metachronous peritoneal metastases. Also, selection bias likely will have influenced the received treatment, possibly resulting in overestimation of the beneficial effect of CRS-HIPEC and, to a lesser extent, palliative treatment because patients who are fit enough to receive treatment are more likely to actually undergo treatment than patients with a poor clinical condition. Unfortunately, the NCR does not register the reason for the choosing or not choosing of a certain treatment. Still, all patients were treated according to the national guideline for CRC, which defines the selection criteria for eligibility to receive CRS-HIPEC (e.g., PCI <20, limited small bowel involvement, absence of systemic metastases).

In conclusion, the OS did not differ significantly between the synchronous colorectal peritoneal metastases and metachronous colorectal peritoneal metastases patients. Also, within the subgroup of patients treated with CRS-HIPEC, DFS and OS as well as the pattern of recurrence were comparable. This suggests that a similar prognosis may be expected for patients selected to undergo treatment regardless of the onset of colorectal peritoneal metastases.

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Chapter

6

Primary tumor resection or systemic treatment as palliative treatment for patients with isolated synchronous colorectal cancer peritoneal metastases in a nationwide cohort study

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Abstract

Introduction
Limited data are available to guide the decision-making process for clinicians and their patients regarding palliative treatment options for patients with isolated synchronous colorectal peritoneal metastases. Therefore, the aim of this study is to analyze the outcome of the different palliative treatments for these patients.

Methods
All patients diagnosed with isolated synchronous colorectal peritoneal metastases between 2009 and 2020 (Netherlands Cancer Registry) who underwent palliative treatment were included. Patients who underwent emergency surgery or curative intent treatment were excluded. Patients were categorized into upfront palliative primary tumor resection (with or without additional systemic treatment) or palliative systemic treatment only. Overall survival (OS) was compared between both groups and multivariable cox regression analysis was performed.

Results
Of 1031 included patients, 364 (35%) patients underwent primary tumor resection and 667 (65%) patients received systemic treatment only. Sixty-day mortality was 9% in the primary tumor resection group and 5% in the systemic treatment group ($p = 0.007$). OS was 13.8 months in the primary tumor resection group and 10.3 months in the systemic treatment group ($p < 0.001$). Multivariable analysis showed that primary tumor resection was associated with improved OS (HR 0.68; 95% CI 0.57–0.81; $p < 0.001$).

Conclusions
Palliative primary tumor resection appeared to be associated with improved survival compared to palliative systemic treatment alone in patients with isolated synchronous colorectal peritoneal metastases despite a higher 60-day mortality. This finding must be interpreted with care as residual bias probably played a significant role. Nevertheless, this option may be considered in the decision-making process by clinicians and their patients.

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide, with a yearly incidence of almost two million cases.[1] Frequently, CRC has already metastasized at the time of diagnosis, with the peritoneum as the second most affected organ being present in approximately 23% of patients with metastatic CRC.[2] In one third of these patients these metastases are confined to the peritoneum.[3,4]

Treatment of CRC patients presenting with peritoneal metastases is challenging and depends on various factors including the condition of the patient, the presence of systemic metastases, symptoms of the primary tumor and extend of the peritoneal disease.[5,6] A selected group of fit patients with limited peritoneal disease may undergo curative intent treatment such as cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (CRS-HIPEC).[7] Patients with a symptomatic primary tumor (e.g., obstruction or perforation) are usually treated with surgery in an emergency setting.[8]

For fit patients that do not require emergency surgery and in whom curative intent treatment is not possible due to extensive disease, two palliative treatment options may be considered: resection of the primary tumor (with or without additional systemic treatment) or palliative systemic treatment only. Whether to resect an asymptomatic primary colorectal tumor in patients presenting with unresectable systemic metastases has been a highly debated issue for many years with various retrospective studies and recently published randomized trials reporting conflicting results.[9-21]

However, it should be noted that both in these prospective trials and retrospective studies the vast majority of included patients suffered from liver metastases and/or lung metastases.[9-21] Patients with peritoneal metastases were either absent or represented only a very small proportion of the study population. Thus, these studies give no guidance regarding the treatment of patients with CRC and isolated peritoneal metastases. This is relevant as patients with colorectal peritoneal metastases are known to have a different clinical outcome as compared to CRC patients with liver metastases or lung metastases with a markedly shorter survival.[22] This may be due to the observation that peritoneal metastases seem to respond less to systemic treatment as compared to other systemic metastases.[23,24,25] Therefore, the aim of the current study was to analyze the outcome of palliative primary tumor resection (with or without additional systemic treatment) and palliative systemic treatment only specifically in CRC patients with isolated synchronous

peritoneal metastases who did not undergo emergency surgery or curative intent treatment.

Methods

Data source

Data were extracted from the Netherlands Cancer Registry (NCR). The NCR registers all newly diagnosed malignancies in the Netherlands. Specially trained data managers of the NCR extract data on patient, tumor and treatment characteristics from the medical records. A yearly update of the vital status of patients is performed by linking the registry to the Dutch municipal administrative database, which contains information about all present, deceased and former inhabitants of the Netherlands. For the present study, the latest update was performed on January 31st, 2022. The International Classification of Diseases for Oncology (ICD-O) was used for the specification of the primary tumor location, location of synchronous metastases and for histological subtypes. The tumor node metastasis (TNM) classification was used for stage classification of the primary tumor, according to the edition valid at diagnosis. If pathological T or N stage was unknown, clinical T or N stage was used. The study is approved by the privacy review board of the NCR as well as the combined scientific committee of the NCR and Prospective Dutch ColoRectal Cancer Cohort (PLCRC) study of the Dutch Colorectal Cancer Group (DCCG).

Study population

All CRC patients with synchronous metastases diagnosed between 2009 and 2020 were evaluated. In patients with multiple primary tumors, the tumor which was first diagnosed was included or, if simultaneously diagnosed, the tumor with the highest TNM stage was included. Patients with extraperitoneal metastases were excluded. Patients were also excluded if they had a primary tumor in the appendix or a neuroendocrine primary tumor. In addition, patients were excluded if they had undergone curative intent treatment such as CRS-HIPEC, debulking surgery or metastasectomy, if they had only received best supportive care (BSC), if the primary tumor was resected after initial systemic treatment or neo-adjuvant chemoradiotherapy or if the treatment was unknown. The NCR records whether the primary tumor resection was performed in an elective setting or in an emergency setting. Patients who underwent an emergency resection were excluded. If no data regarding the clinical indication for surgery was registered, patients who had undergone surgery within 5 days after their initial diagnosis were considered to be emergency resection rather than primary tumor resection and were excluded.

Treatment allocation

For all analyses, treatment strategies were categorized as follows:

1. Upfront palliative primary tumor resection with or without additional systemic treatment, comprising different types of resections(i.e., hemicolectomy, ileocecal resection, transverse colon resection, sigmoid resection, (sub)total colectomy, low anterior resection and rectum amputation).
2. Palliative systemic treatment only.

Primary outcome

The primary outcome was overall survival (OS), compared between patients in the palliative primary tumor resection group and patients in the palliative systemic treatment group. Median OS was defined as the interval between date of diagnosis of CRC until date of death or loss to follow-up. Patients were censored if they were alive on January 31st, 2022.

Patient- and tumor characteristics

The location of the primary tumor was categorized according to the following sites: (1) right-sided colon (C18.0, C18.2-18.4: cecum, ascending colon, hepatic flexure, transverse colon); (2) left-sided colon (C18.5-18.7: splenic flexure, descending colon and sigmoid); and(3) rectum (C19.9-20.9: rectosigmoid and rectum). Primary tumor histology was categorized into the following subtypes: (1)adenocarcinoma (8000, 8010, 8020, 8140, 8144, 8210, 8211, 8220 8255, 8261, 8262, 8263, 8560); (2) mucinous adenocarcinoma (8480,8481); and (3) signet ring cell carcinoma (8490). The following ICD-O codes were considered peritoneal metastases: C16.0-C16.9, C17.0-C17.9, C18.0-C18.9, C19.9, C20.9, C21.8, C23.9, C26.9, C48.0-C48.8, C49.4-C49.5, C52.9, C54.3-C54.9, C55.9, C56.9, C57.0-C57.8, C66.9, C67.0-C67.9, C76.2. Any other ICD-O code was considered to reflect extraperitoneal metastases. Patient- and tumor characteristics included in this study are sex, age, primary tumor location, tumor histology, differentiation of primary tumor, tumor stage, nodal stage and period of diagnosis.

Statistical analysis

Baseline characteristics of patients in the primary tumor resection group were compared to patients in the palliative systemic treatment group. Categorical variables were compared using chi-squared test and presented as a No. (%), and continuous variables were compared with the unpaired *t*-tests and presented as mean (± standard deviation [SD]). Missing data were excluded from comparative analyses. Sixty-day mortality was compared between patients in the palliative primary tumor resection group and the palliative systemic treatment group by using the chi-squared test. Median OS of

patients in the palliative primary tumor resection group and patients in the palliative systemic treatment group was estimated with the Kaplan-Meier method and compared with the Log-rank test.

Univariable cox regression analyses were performed to assess the association between palliative primary tumor resection and OS and to identify whether the following factors were associated with OS: sex, age, primary tumor location, tumor histology, tumor differentiation, tumor stage, nodal stage, period of diagnosis and the presence of a stoma. Subsequently, variables with a p-value lower than 0.10 in the univariable analyses, were combined in a multivariable cox regression model. To prevent overfitting, a minimum of 10 events per degree of freedom was used as limit for the number of variables of the multivariable model.

Finally, a subgroup analysis was performed in patients who underwent primary tumor resection. This subgroup analysis included uni- and multivariable cox regression analyses to identify factors associated with OS within this subgroup.

All tests were two-sided and a p-value lower than 0.05 was considered statistically significant. All analyses were performed with SAS statistical software (SAS system 9.4, SAS Institute, Cary, NC, United States).

Results

Study population

In total, 33.979 patients were diagnosed with metastasized CRC between 2009 and 2020. Of these patients, 8492 (25%) had synchronous peritoneal metastases of whom 3601 (11%) without concurrent extraperitoneal metastases. Of this latter group, 2215 (62%) patients were excluded because they had undergone curative treatment, BSC or an unknown treatment modality. An additional 328 patients undergoing primary tumor resection within five days of diagnosis of their primary CRC were excluded and 27 patients were excluded because their primary tumor was resected after initial systemic treatment or neo-adjuvant chemoradiotherapy. The remaining 1031 patients were included in this study, of whom 364 (35%) underwent primary tumor resection. In the palliative systemic treatment group (n=667/1031, 65%), patients were exclusively treated with palliative systemic treatment. The primary tumor resection group (n=364) comprised of 220 (60%) patients who underwent primary tumor resection only and 144 (40%) patients who underwent primary tumor resection followed by additional systemic treatment (*Figure 1*).

In patients who underwent a primary tumor resection followed by additional systemic treatment (n=144), 126 patients (88%) received chemotherapy only and 18 patients (12%) received both chemotherapy and targeted therapy. Details regarding the prescribed regimens were registered in 46 patients (32%). In these patients, capecitabine with oxaliplatin (CAPOX) (n=20) and capecitabine monotherapy (n=17) were the most used chemotherapeutic regimens.

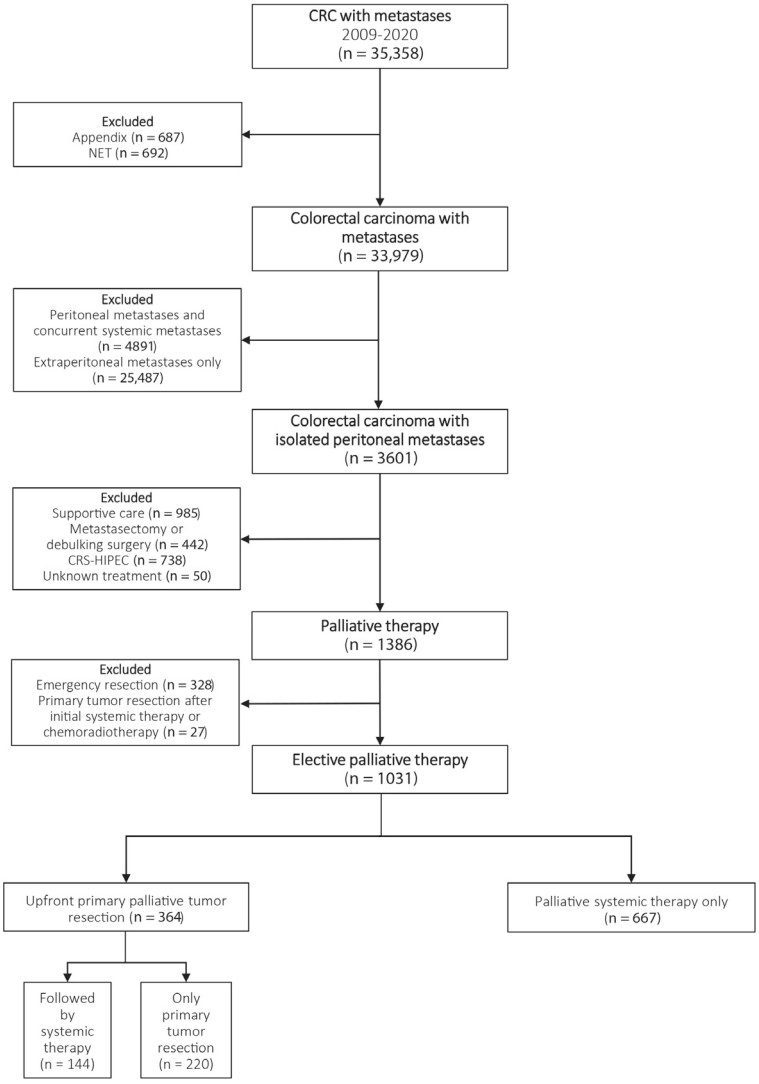


Figure 1. Patient selection and treatment allocation.
CRC colorectal cancer; *NET* neuroendocrine tumor; *CRS-HIPEC* cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

In the palliative systemic treatment group (n=667), 549 patients (82%) received chemotherapy only, 5 patients (1%) received targeted therapy only and 113 patients (17%) received both chemotherapy and targeted therapy. Details regarding the prescribed regimens were registered in 345 patients (52%), capecitabine with oxaliplatin (CAPOX) (n=169), capecitabine monotherapy (n= 89) and 5-fluorouracil/leucovorin with oxaliplatin (FOLFOX) (n=58) being the most used chemotherapeutic regimens. Panitumumab (n=19) was the most used targeted therapy in these patients.

Older age, a right-sided tumor, a T4 tumor stage, N+ stage and primary tumor diagnosis between 2009 and 2012 were more frequently present in patients who underwent palliative primary tumor resection than in those who received palliative systemic treatment (*Table 1*).

Table 1. Comparison of baseline characteristics between treatment groups.

	Palliative primary tumor resection n=364	**Palliative systemic therapy** n=667	*P value*[a]
Sex, No. (%)			
Male	186 (51)	384 (58)	0.05
Female	178 (49)	283 (42)	
Age at diagnosis, mean (SD)	72 (11)	65 (12)	**<0.001**
Primary tumor location, No. (%)			
Right colon	234 (60)	325 (49)	**<0.001**
Left colon	114 (31)	257 (39)	
Rectum	16 (4)	85 (13)	
Tumor histology, No. (%)			
Adenocarcinoma	230 (63)	389 (58)	0.19
Mucinous adenocarcinoma	94 (26)	181 (27)	
Signet ring cell carcinoma	40 (11)	97 (15)	
Tumor differentiation, No. (%)			
Well/moderately	165 (45)	119 (18)	0.17
Poor/undifferentiated	140 (38)	128 (19)	
Missing data	59 (16)	420 (63)	

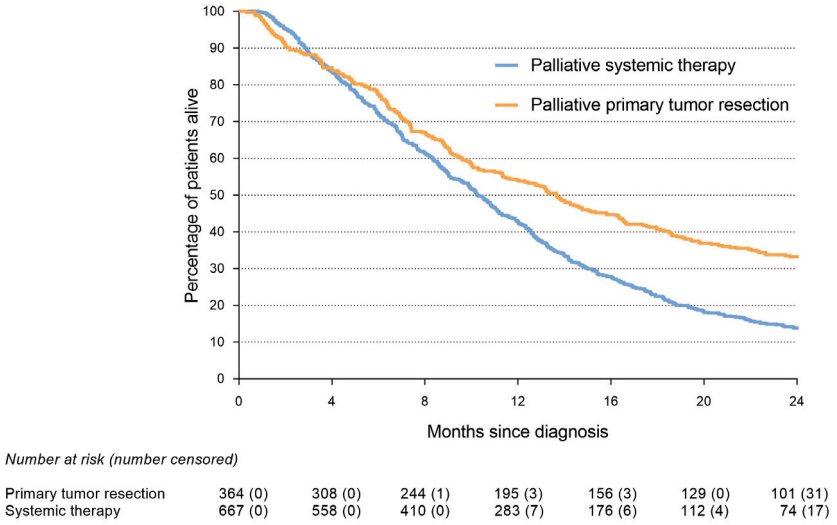
Table 1. Comparison of baseline characteristics between treatment groups. (continued)

	Palliative primary tumor resection n=364	**Palliative systemic therapy** n=667	*P value*[a]
Tumor stage, No. (%)			
T1 – T3	138 (38)	173 (26)	**0.01**
T4	224 (62)	192 (29)	
Missing data	2 (1)	302 (45)	
Nodal stage, No. (%)			
N0	51 (14)	214 (32)	**<0.001**
N1/N2	311 (85)	251 (38)	
Missing data	2 (1)	202 (30)	
Period of diagnosis, No. (%)			
2009 – 2012	192 (53)	212 (32)	**<0.001**
2013 – 2016	109 (30)	246 (37)	
2017 – 2020	63 (17)	209 (31)	
Stoma, No. (%)			
Yes	83 (23)	140 (21)	0.50
No	281 (77)	527 (79)	

[a]Missing data were not included in the comparative analyses; percentage might not add up to 100% due to rounding; *SD* standard deviation.

Survival

Sixty-day mortality was 9% in the primary tumor resection group and 5% in the palliative systemic treatment group ($p = 0.007$). Two-year survival was 32% in the primary tumor resection group and 14% in the palliative systemic treatment group ($p < 0.001$). The median OS was 13.7 (interquartile range [IQR] 6.4–29.4) months in the primary tumor resection group and 10.3 (IQR 5.5–17.0) months in the palliative systemic treatment group ($p < 0.001$) (*Figure 2*). If a primary tumor resection was followed by systemic therapy, median OS was 18.0 months (IQR 8.9–33.4).



Number at risk (number censored)

Primary tumor resection	364 (0)	308 (0)	244 (1)	195 (3)	156 (3)	129 (0)	101 (31)
Systemic therapy	667 (0)	558 (0)	410 (0)	283 (7)	176 (6)	112 (4)	74 (17)

Figure 2. Overall survival of palliative primary tumor resection group and palliative systemic therapy group (Log-rank: <0.001).
PTR primary tumor resection; *ST* systemic therapy.

Uni- and multivariable analysis showed that primary tumor resection was significantly associated with improved OS (adjusted hazard ratio [HR] 0.68; 95% CI, 0.57–0.81; $p < 0.001$). Factors that were associated with worse OS included a signet ring cell carcinoma histology (HR 1.38; 95% CI, 1.13–1.68; $p = 0.001$), a poor differentiated tumor (HR 1.49; 95% CI, 1.24–1.78; $p < 0.001$), a T4 tumor stage (HR 1.25; 95% CI, 1.07–1.46; $p = 0.005$) and nodal involvement (HR 1.28; 95% CI, 1.09–1.51; $p < 0.001$]) (*Table 2*).

Table 2. Uni- and multivariable cox regression analyses for overall survival of the entire study cohort.

	Total group n=1031	**Median OS (months)**	**Univariable cox regression analyses**			**Multivariable cox regression analysis**		
			HR	95% CI	*P value*	HR	95% CI	*P value*
Palliative therapy					**<0.001**			
Primary tumor resection	364	13.7	0.61	0.53-0.70		0.68	0.57-0.81	**<0.001**
Systemic therapy	667	10.3	Ref.	Ref.		Ref.	Ref.	Ref.
Sex					0.30			
Male	570	10.7	Ref.	Ref.		-	-	-
Female	461	11.3	0.94	0.82-1.06		-	-	-
Age at diagnosis	-	-	1.00	1.00-1.01	0.64	-	-	-
Primary tumor location					0.40			
Right colon	559	11.0	Ref.	Ref.		-	-	-
Left colon	371	11.5	0.9	0.86-1.13		-	-	-
Rectum	101	10.4	1.14	0.93-1.41		-	-	-
Tumor histology					**<0.001**			
Adenocarcinoma	619	12.2	Ref.	Ref.		Ref.	Ref.	Ref.
Mucinous adenocarcinoma	275	10.0	1.14	0.98-1.35		1.08	0.93-1.26	0.32
Signet ring cell carcinoma	137	9.1	1.53	1.28-1.82		1.38	1.13-1.68	**0.001**

Table 2. Uni- and multivariable cox regression analyses for overall survival of the entire study cohort. (continued)

	Total group n=1031	**Median OS (months)**	**Univariable cox regression analyses**			**Multivariable cox regression analysis**		
			HR	95% CI	*P value*	HR	95% CI	*P value*
Tumor differentiation					**<0.001**			
Good/moderately	284	15.8	Ref.	Ref.		Ref.	Ref.	Ref.
Poor/undifferentiated	268	8.1	1.64	1.36-1.99		1.49	1.24-1.78	**<0.001**
Missing data	479	10.5	1.68	1.46-1.95		1.24	1.03-1.48	0.02
Tumor stage					**<0.001**			
T1-T3	311	13.1	Ref.	Ref.		Ref.	Ref.	Ref.
T4	416	11.0	1.24	1.06-1.45		1.25	1.07-1.46	**0.005**
Missing data	304	9.0	1.74	1.48-2.04		1.42	1.18-1.71	**<0.001**
Nodal stage					**<0.001**			
N0	265	12.7	Ref.	Ref.		Ref.	Ref.	Ref.
N1/N2	562	10.8	1.08	0.92-1.25		1.28	1.09-1.51	**0.003**
Missing data	204	8.9	1.55	1.29-1.85		1.32	1.09-1.60	**0.005**
Period of diagnosis					0.35			
2009 – 2012	404	10.7	Ref.	Ref.		-	-	-
2013 – 2016	355	10.7	1.07	0.93-1.24		-	-	-
2017 – 2020	272	11.3	0.95	0.81-1.12		-	-	-

Table 2. Uni- and multivariable cox regression analyses for overall survival of the entire study cohort. (continued)

	Total group n=1031	**Median OS (months)**	**Univariable cox regression analyses**			**Multivariable cox regression analysis**		
			HR	95% CI	*P value*	HR	95% CI	*P value*
Stoma					0.53			
Yes	223	10.3	Ref.	Ref.		-	-	-
No	808	11.2	0.95	0.82-1.11		-	-	-

OS overall survival; *HR* hazard ratio; *CI* confidence interval.

Subgroup analyses in primary tumor resection group

In subgroup analyses of patients who underwent primary tumor resection, multivariable analysis showed that older age (HR 1.02; 95% CI, 1.01–1.03; $p = 0.002$), a signet ring cell carcinoma histology (HR 1.58; 95% CI, 1.08–2.31; $p = 0.02$), a poor differentiated tumor(HR 1.68; 95% CI, 1.31–2.15; $p < 0.001$), a T4 tumor stage (HR 1.46; 95% CI, 1.15–1.85; $p = 0.002$), nodal involvement (HR 1.87; 95% CI, 1.33–2.63; $p < 0.001$) and having a stoma (HR 0.67; 95% CI, 0.51–0.85; $p = 0.002$) were associated with worse OS (*Table 3*).

Table 3. Uni- and multivariable cox regression analyses for overall survival of patients who have undergone a palliative primary tumor resection

	Total group n=364	**Median OS (months)**	**Univariable cox regression analyses**			**Multivariable cox regression analysis**		
			HR	95% CI	*P value*	HR	95% CI	*P value*
Sex					0.15			
Male	186	13.0	Ref.	Ref.		-	-	-
Female	178	14.6	0.85	0.69-1.06		-	-	-
Age	-	-	1.01	1.00-1.02	**0.05**	1.02	1.01-1.03	**0.002**
Primary tumor location					0.63			
Right colon	234	12.2	Ref.	Ref.		-	-	-
Left colon	114	16.6	0.90	0.72-1.12		-	-	-
Rectum	16	14.0	0.94	0.57-1.54		-	-	-
Tumor histology					**0.003**			
Adenocarcinoma	230	14.4	Ref.	Ref.		Ref.	Ref.	Ref.
Mucinous adenocarcinoma	94	14.0	1.13	0.89-1.45		1.15	0.88-1.50	0.31
Signet ring cell carcinoma	40	8.6	1.80	1.28-2.52		1.58	1.08-2.31	**0.02**
Tumor differentiation					**<0.001**			
Good/moderate	165	20.3	Ref.	Ref.		Ref.	Ref.	Ref.
Poor/undifferentiated	140	8.5	1.71	1.32-2.21		1.68	1.31-2.15	**<0.001**
Missing data	59	11.7	1.54	1.15-2.07		1.41	1.00-1.99	**0.05**

Table 3. Uni- and multivariable cox regression analyses for overall survival of patients who have undergone a palliative primary tumor resection (continued)

	Total group n=364	**Median OS (months)**	**Univariable cox regression analyses**			**Multivariable cox regression analysis**		
			HR	95% CI	*P value*	HR	95% CI	*P value*
Tumor stage					**<0.001**			
T1-T3	138	16.5	Ref.	Ref.		Ref.	Ref.	Ref.
T4	224	11.7	1.39	1.11-1.75		1.46	1.15-1.85	**0.002**
Missing data	2	3.7	8.47	3.40-21.10		7.18	0.44-118.06	0.17
Nodal stage					**<0.001**			
N0	51	25.8	Ref.	Ref.		Ref.	Ref.	Ref.
N1/N2	311	13.2	1.72	1.26-2.36		1.87	1.33-2.63	**<0.001**
Missing data	2	4.4	9.05	4.99-16.41		3.13	0.19-51.14	0.42
Period of diagnosis					0.36			
2009-2012	192	13.7	Ref.	Ref.		-	-	-
2013-2016	109	12.3	1.14	0.90-1.46		-	-	-
2017-2020	63	16.6	0.91	0.66-1.24		-	-	-
Stoma					**0.05**			
Yes	83	9.5	Ref.	Ref.		Ref.	Ref.	Ref.
No	281	14.6	0.77	0.59-1.00		0.67	0.51-0.85	**0.002**

OS overall survival; *HR* hazard ratio; *CI* confidence interval.

Discussion

In this nationwide observational cohort study of patients with isolated synchronous colorectal peritoneal metastases, primary tumor resection was associated with an improved OS when compared to palliative systemic treatment only (median 13.7 months vs. 10.3 months). However, primary tumor resection was associated with an increase in sixty-day mortality. Patients undergoing treatment with curative intent, patients undergoing BSC only and patients requiring emergency surgery were excluded in this study and therefore, the results from the current study apply to those in whom the choice whether to perform a palliative resection of the primary tumor could be considered in a non-emergency setting.

The role of primary tumor resection in the treatment of patients with unresectable synchronous metastatic CRC with an asymptomatic primary tumor has been a highly debated issue for many years.[21,26-28] Various retrospective studies seem to suggest a survival benefit after primary tumor resection.[9-15] However, selection bias may be an important explanation for this finding with younger and fitter patients usually tending to undergo surgery instead of systemic treatment. To address this issue in a prospective manner, several randomized trials have been conducted over the recent past. The recently published randomized controlled iPACs trial (JCOG1007)showed that the OS of systemic metastatic CRC patients who underwent primary tumor resection followed by systemic treatment was comparable to that of patients treated with systemic treatment only (26.4 months versus 25.9 months, respectively), which was in line with recently presented results from the SYNCHRONOUS trial.[19,29,30] Also, the CAIRO4 trial (NCT01606098) recently published the short-term results and reported a significantly higher mortality after primary tumor resection as compared to systemic treatment only (11%vs. 3% respectively) in the first 60 days after randomization.[18] As such, both trials provide valid arguments for no longer removing the primary tumor in CRC patients with widespread systemic disease.[27] As a result, resection of an asymptomatic primary colorectal tumor in patients with systemic metastases is no longer advised in most clinical guidelines such as the National Comprehensive Cancer Network.[31]

Up to 10% of patients with CRC will be diagnosed with peritoneal metastases during the course of their disease.[3] As such, the peritoneum is a very relevant metastatic site in CRC. In spite of this, patients with peritoneal metastases are usually underrepresented in clinical trials as peritoneal metastases are often not visible on radiological imaging that is required for response evaluation to treatment.[32,33] Also, in both previously mentioned retrospective

and prospective trials investigating the effect of primary tumor resection, patients with peritoneal metastases were virtually absent.[9-15, 18-21]

As recent data suggests that peritoneal metastases almost exclusively derive from a specific molecular subtype of CRC, it is probably not appropriate to translate knowledge that has been obtained in trials, performed in patients with liver metastases and lung metastases, to clinical scenarios in which peritoneal metastases are involved.[34] One reason may be that the subtype that causes peritoneal metastases is known to be less sensitive to systemic treatment.[23,25] Together with the typical clinical presentation of peritoneal metastases with frequent bowel obstructions resulting in malnourishment, this probably explains that the prognosis of patients with peritoneal metastases is markedly worse as compared to other metastatic sites. Therefore, it can be argued that surgical treatment may indeed be more effective in alleviating clinical symptoms in this specific patient category than treating chemo-resistant metastases with systemic treatment.

The present study reported a higher sixty-day mortality for patients in the primary tumor resection group (9%) than for patients in the palliative systemic treatment group (5%). This finding is in line with a recently published randomized controlled trial on this topic for patients with CRC and systemic metastases.[18] This increase in early mortality confirms that primary tumor resection in patients with systemic disease does not come without substantial risk in the early postoperative period. Regarding OS, older age, a signet ring cell carcinoma histology, a poor tumor differentiation, a T4 tumor stage, nodal involvement and having a stoma were associated with a worse survival within the primary tumor resection group. Early postoperative mortality and risk factors for decreased OS after surgical treatment should be taken into account when discussing treatment options in these patients.

Construction of a stoma was necessary in 21% of patients treated with systemic treatment. No significant difference in the number of stomas was observed as compared to the primary tumor resection group. This is important in the decision-making process as fear for a stoma may deter patients from undergoing primary tumor resection.

In this study, the proportion of patients who received chemotherapy alone or in combination with targeted therapy was comparable between the systemic treatment group and the primary tumor resection group. In both groups, CAPOX was the most frequently used chemotherapy regimen. Therefore, treatment with systemic chemotherapy is not expected to result in a significant difference in survival.

Patients who underwent primary tumor resection in the present study were significantly older, more frequently had a right-sided tumor and nodal involvement as compared to patients that received systemic treatment only. Although multivariable cox regression analyses aimed to correct for these confounders after which primary tumor resection remained associated with an improved OS, residual selection bias probably still plays an important role. Relevant in this respect is the fact that the extent of peritoneal disease was not known. It may be that patients with less extensive peritoneal disease were more prone to undergo a primary tumor resection, which may explain the more favorable outcome in these patients.

To our knowledge, this is the first nationwide population-based study to investigate the role of primary tumor resection in patients with isolated synchronous colorectal peritoneal metastases. The NCR provides highly accurate data on tumor and patients characteristics, strengthening the generalizability of the results.[35] However, the retrospective design is clearly a drawback of the current study as no data on extent of peritoneal disease, tumor biology (e.g., CMS subtype), mutational status, performance status, postoperative complications or toxicity of systemic therapy and clinical symptoms were available. The addition of these factors would have increased the accurateness of the multivariable model.

It is not likely that a randomized controlled trial will address the issue of primary tumor resection in CRC patients with peritoneal metastases in the near future. Therefore, in spite of its retrospective nature, we believe that the current study provides valuable information to guide decision making in current day clinical practice in this distinct and relevant category of metastatic patients.

In this retrospective nationwide cohort of patients with isolated synchronous colorectal peritoneal metastases, primary tumor resection appeared to be associated with an improved OS in comparison to those who received only systemic treatment, despite an increased sixty-day mortality rate after surgery. These findings must be interpreted with care as residual bias is likely to have played a significant role. Nevertheless, this finding may be considered in the decision-making process by clinicians and their patients regarding the different palliative treatment options in this specific patient category.

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Chapter 7

The burden of peritoneal metastases from gastric cancer: a systematic review on the incidence, risk factors and survival

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Abstract

Introduction
The peritoneum is a common metastatic site in gastric cancer. This systematic review provides an overview of the incidence, risk factors and survival of synchronous peritoneal metastases from gastric cancer.

Methods
A systematic search was performed to identify studies wherein the incidence, risk factors and survival of gastric cancer with peritoneal metastases were investigated.

Results
Of all 38 potentially eligible studies, 17 studies were included based on the eligibility criteria. The incidence of synchronous gastric peritoneal metastases was reviewed for population-based studies (10-21%), for observational cohort studies (2-15%) and for surgical cohort studies (13-40%). Potential risk factors for synchronous gastric peritoneal metastases were younger age, non-cardia gastric cancer, female sex, signet ring cell carcinoma, diffuse type histology or linitis plastic, T4 tumor stage, Hispanic ethnicity and more than one metastatic location.

Conclusions
Synchronous peritoneal metastases are commonly diagnosed in patients with gastric cancer with an incidence up to 21% in recent population-based studies. Furthermore, prognosis of patients with gastric peritoneal metastases is poor with median overall survival ranging from 2 to 9 months. The high incidence and poor prognosis require intensive research on diagnostic features and effective treatment options to improve survival.

Introduction

Gastric cancer is one of the most common cancers worldwide with an incidence of over one million cases in 2020. It is the third most common cause of cancer-related death in the world, with almost 800.000 deaths a year.[1] Among Asian men, gastric cancer is even the most commonly diagnosed cancer and the leading cause of cancer death.[2] Due to the lack of early symptoms, patients with gastric cancer are often diagnosed in an advanced stage, which generally leads to a poor prognosis.[3]

The peritoneal cavity is a well-known metastatic site in gastric cancer. For a long time, patients with isolated peritoneal metastases regardless of their origin had a dismal prognosis, and therapeutic options were scarce. However, several studies investigating the effect of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with gastric, colorectal and ovarian peritoneal metastases have suggested an improvement in survival in carefully selected patients.[4-7] A randomized controlled trial (PERISCOPE II, NCT03348150) currently enrolls gastric cancer patients with isolated limited peritoneal metastases to investigate whether CRS-HIPEC provides a survival benefit compared to systemic chemotherapy alone.[8,9] For patients with more extensive disease, new therapeutic options such as pressurized intraperitoneal aerosol chemotherapy (PIPAC) or normothermic intraperitoneal chemotherapy are being studies in clinical trials.[10,11] Awaiting the results of these trials, the current standard treatment in the Netherlands for this patient group remains palliative systemic chemotherapy, although the beneficial effect of current chemotherapeutic regimens is probably limited.[12] In patients with HER2-positive gastric cancer, the addition of trastuzumab may be considered as the randomized controlled ToGa-trial showed that this prolonged survival in advanced gastric cancer as compared to systemic chemotherapy alone.[13]

The evolution and refinement of new techniques such as CRS-HIPEC, PIPAC and normothermic intraperitoneal chemotherapy have generated a renewed interest in the treatment of gastric peritoneal metastases. However, the burden of peritoneal metastases from gastric cancer is currently not well described. Detailed information on this topic will be helpful in counselling of patients and will guide future research directions. Especially, knowledge about risk factors for peritoneal metastases and the impact on survival may contribute to a tailored approach in treatment of patients with gastric cancer. The aim of this systematic review was to provide an overview of the incidence, risk factors, and survival of gastric cancer with peritoneal metastases.

Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement.[14] Two researchers (A.R. and R.J.L.) independently performed the literature search, study selection, data collection, risk of bias assessment and data synthesis. Inter-reviewer disagreements were resolved by achieving consensus between the two researchers.

Eligibility criteria

Studies were considered potentially eligible if (1) patients with gastric cancer were included and (2) the incidence, risk factors and/or survival of synchronous peritoneal metastases were analyzed in the setting of a population-based or observational cohort. Furthermore, in a specific subgroup, studies were considered potentially eligible if patients who underwent diagnostic laparoscopy for staging of gastric cancer were investigated. Studies reporting on incidence were considered eligible if synchronous peritoneal metastases were reported as the proportion of all patients with gastric cancer. Studies reporting on risk factors were considered eligible if: (1) multivariable regression analyses were performed and (2) an odds ratio or relative risk were reported as outcome measure. Furthermore studies reporting exclusively on patients with gastro-esophageal junction cancer, case-reports, systematic reviews and studies with a publication year before 2000 were excluded. No language restrictions were applied.

Search strategy

On 15 August 2021, PubMed/MEDLINE, EMBASE and Cochrane were systematically searched with a date restriction from 2000 to 2021. Full search queries are presented in *Supplementary results 7.1*. The references of all eligible manuscripts were search for additional eligible studies.

Study selection

Titles and abstracts were screened for potentially eligible studies based on the predefined eligibility criteria. Afterwards, all potentially eligible studies were thoroughly read screened for final inclusion.

Data collection

Data were collected by two researchers (A.R. and R.J.L.) using a standardized form that contained the following items: year of publication, study design, study setting, country, enrolment period, total number of patients, study population and the three outcomes under investigation (incidence, risk factors and survival).

Synthesis of results
Results of all studies considered eligible were descriptively presented. Due to the high degree of heterogeneity across the included studies (i.e., study design, differences in study population), no meta-analysis was performed.

Results

Study Selection
After title and abstract screening, 38 studies were considered potentially eligible. After full text screening, seventeen studies were included.[12,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30] The study flowchart and reasons for exclusion are shown in *Figure 1* and *Supplementary results 7.2*. In sixteen studies, information on incidence numbers of synchronous gastric peritoneal metastases was provided.[12,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30] Risk factors for gastric peritoneal metastases were reported in four studies.[15,16,17,18] Survival was also reported in four studies.[12,15,16,28,29]

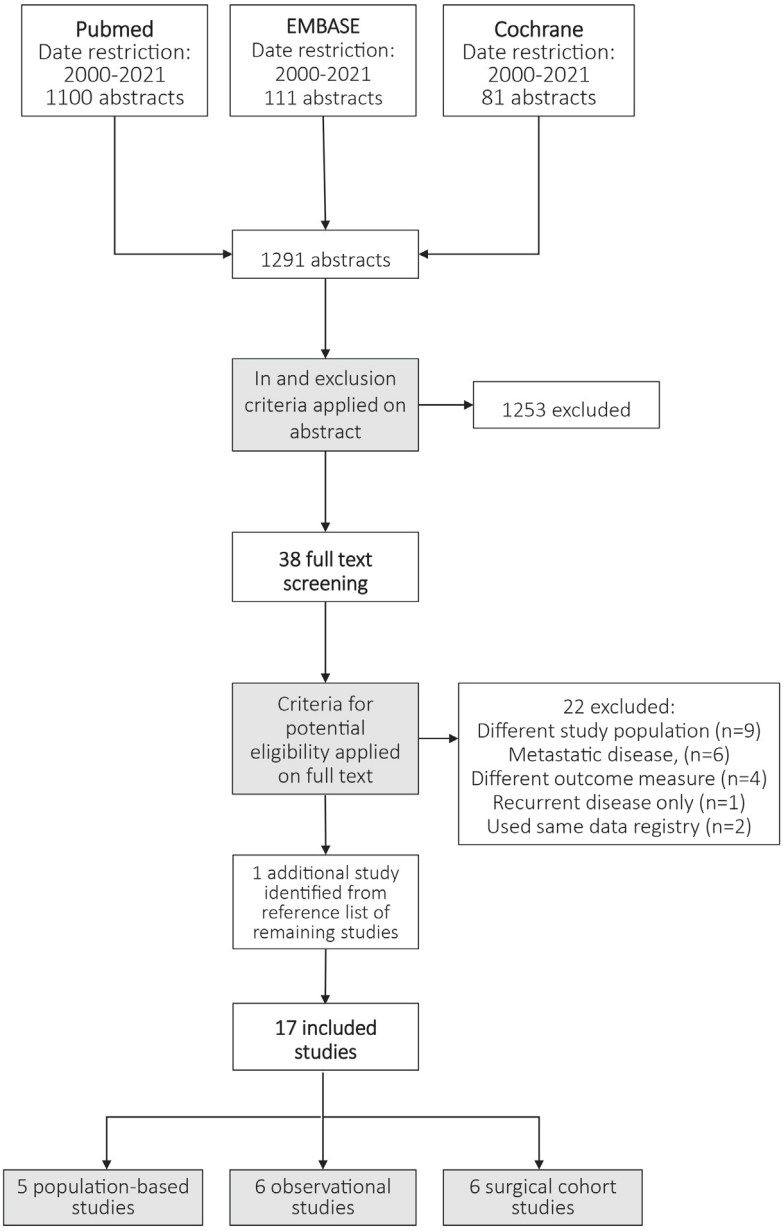

Figure 1. Literature search and study selection. Details of the literature search and study selection are presented in the Supplementary attachment.

Study Characteristics

Of all included studies, five studies were population-based studies[12,15,16,17,18], six studies were observational cohort studies[19,20,21,22,23,24] and six studies reported surgical cohorts of patients who underwent a staging laparoscopy.[25,26,27,28,29,30] Study characteristics and outcome measures of all studies are presented in *Table 1A, B and Table 2*. The five population-based studies were published between 2013 and 2021.[12,15,16,17,18] The number of included patients ranged from 5220 to 34.943 (*Table 1A*). The risk factors reported in these studies are reported in *Supplementary table 7.1*. The six observational cohort studies were published between 2003 and 2015 and the number of included patients ranged from 1108 to 4559 (*Table 1B*).[19,20,21,22,23,24] The six studies that reported the incidence of gastric peritoneal metastases of patients who underwent staging laparoscopy were published between 2013 and 2020, and the number of included patients ranged from 89 to 867 (*Table 2*).[25,26,27,28,29,30] The inclusion criteria for patients in these surgical cohort studies are reported in *Supplementary table 7.2*.

Incidence

Population-Based Studies

Incidence of synchronous gastric peritoneal metastases was reported in five population-based studies from Sweden[17], the United States[18] and the Netherlands.[12,15,16] The proportions of patients presenting with peritoneal metastases from gastric cancer ranged from 10% to 21%.

Observational Cohort Studies

Incidence of synchronous gastric peritoneal metastases was reported in six observational cohort studies from Germany[19], South-Korea[20,22], Japan[21,24], China[21] and the United States[23]. The proportion of patients with gastric peritoneal metastases ranged from 2% to 15%.

Surgical Cohort Studies

Six studies reported the incidence of synchronous gastric peritoneal metastases of patients who underwent a staging laparoscopy. Patient in these studies were eligible for curative intent surgery and no systemic metastases after radiological staging.[25,26,27,28,29,30] The studies in this subgroup were conducted in the United States[25], China[26,27], Pakistan[28] and the United Kingdom.[29,30] The reported incidence ranged from 13% to 40%.

Table 1. Study characteristics of A) Population-based studies B) Observational cohort studies

A	Design				Outcomes		
First author Year	Enrolment period	Country	Setting	Total patients (n)	Incidence of GPM		
					Reported	*n*	*%*
Koemans[12, a] 2021	2008-2017	The Netherlands	Nationwide register	12 504	Yes	2607	21%
Koemans[15, a] 2020	1999-2017	The Netherlands	Nationwide register	34 943	No		
Thomassen[16] 2013	1995-2012	The Netherlands	Regional register of southern part of the Netherlands	5 220	Yes	706	14%
Riihimäki[17] 2016	2002-2012	Sweden	Nationwide register	7 559	Yes	936	12%
Choi[18] 2020	2004-2014	United States	State register of California	16 275	Yes	1691	10%
B	Design				Outcomes		
Seyfried[19] 2015	1986-2013	Germany	Single center	1108	Yes	158	14%
Park[20] 2010	2000-2005	Korea	Single center	3193	Yes	104	3%
Yu[21] 2010	1993-2006 1980-2003	Japan China	Multicenter	2063 2496	Yes	42 324	2% 13%

Table 1. Study characteristics of A) Population-based studies B) Observational cohort studies (continued)

A	Design				Outcomes		
First author Year	Enrolment period	Country	Setting	Total patients (n)	Incidence of GPM		
					Reported	*n*	*%*
Kim[22] 2003	1988-1998	Korea	Single center	1833	Yes	267	15%
Yao[23] 2005	1985-1999	United States	Single center	1897	Yes	200	11%
Isobe[24] 2013	1977-2006	Japan	Single center	3818	Yes	447	12%

GPM gastric peritoneal metastases.

Table 2. Study characteristics of studies on gastric cancer and staging laparoscopy.

	Design				Outcomes		
First author Year	Enrolment period	Country	Setting	Total patients (n)	Incidence of GPM		
					Reported	*n*	*%*
Allen[25] 2020	1995-2018	United States	Single center	867	Yes	175	20%
Hu[26] 2016	2004-2014	China	Single center	582	Yes	118	20%
Yang[27] 2020	2014-2019	China	Single center	672	Yes	89	13%
Bhatti[28] 2014	2005-2012	Pakistan	Single center	89	Yes	36	40%
Convie[29] 2015	2007-2013	United Kingdom	Single center	159	Yes	36	23%
Munasinghe[30] 2013	2006-2010	United Kingdom	Single center	142	Yes	19	13%

GPM gastric peritoneal metastases; *SL* staging laparoscopy.

Risk Factors

Risk factors for synchronous gastric peritoneal metastases were reported in four studies.[15,16,17,18] Younger age[15,16,17], non-cardia cancer[15,16,17], female sex[15,16,17], signet ring cell carcinoma[16,17], diffuse type histology or linitis plastica[15,16], T4 tumor stage[16], Hispanic ethnicity[18] and more than one location of metastases[15] were associated with an increased risk of gastric peritoneal metastases. Contradicting results were published regarding the association of synchronous peritoneal metastases with positive lymph node status.[15,16] Details on risk factors are presented in *Table 3*.

Table 3. Risk factors for synchronous gastric peritoneal metastases.

Study	Groups	OR	95% CI
Age			
Koemans et al. (2020)[15]	<45 years	Ref.	Ref.
	46-60 years	0.74	0.6-0.9
	61-75 years	0.62	0.5-0.8
	>75 years	0.52	0.4-0.7
Thomassen et al. (2013)[16]	<60 years	Ref.	Ref.
	60-69 years	0.7	0.5-0.9
	70-79 years	0.5	0.4-0.6
	>80 years	0.3	0.2-0.3
Riihimaki et al. (2015)[17]			
Single metastasis	<60 years	Ref.	Ref.
	70-79 years	0.5	0.4-0.7
	>79 years	0.3	0.2-0.4
Multiple metastases	<60 years	Ref.	Ref.
	60-69 years	0.8	0.7-1.0
	70-79 years	0.5	0.4-0.6
	>79 years	0.2	0.2-0.3

Table 3. Risk factors for synchronous gastric peritoneal metastases. (continued)

Study	Groups	OR	95% CI
Location of primary gastric tumor			
Koemans et al. (2020)[15]	OGJ/cardia	Ref.	Ref.
	Proximal/Middle stomach	2.4	2.1-2.8
	Distal stomach	2.7	2.3-3.1
	Overlapping location	3.6	3.1-4.1
Thomassen et al. (2013)[16]	Non-cardia	Ref.	Ref.
	Cardia	0.4	0.3-0.5
	Overlapping lesions/ NOS	1.3	1.0-1.6
Riihimaki et al. (2015)[17]			
Single metastasis	Cardia	Ref.	Ref.
	Fundus/Corpus	1.7	1.3-2.2
	Antrum/Pylorus	1.8	1.3-2.3
Multiple metastases	Cardia	Ref.	Ref.
Sex			
Koemans et al. (2020)[15]	Male	Ref.	Ref.
	Female	1.5	1.3-1.6
Thomassen et al. (2013)[16]	Male	Ref.	Ref.
	Female	1.2	1.0-1.5
Riihimaki et al. (2015)[17]			
Single metastasis	Male	Ref.	Ref.
	Female	1.1	1.0-1.4
Multiple metastases	Male	Ref.	Ref.
	Female	1.3	1.1-1.5

Table 3. Risk factors for synchronous gastric peritoneal metastases. (continued)

Study	Groups	OR	95% CI
Histology			
Koemans et al. (2020)[15]	Intestinal type	Ref.	Ref.
	Diffuse type	2.8	2.5-3.1
	Mixed type	2.1	1.7-2.7
Thomassen et al. (2013)[16]	Adenocarcinoma	Ref.	Ref.
	Signet ring cell carcinoma	1.7	1.4-2.2
	Linitis plastica	2.0	1.5-2.8
Riihimaki et al. (2015)[17]			
Single metastases	Adenocarcinoma	Ref.	Ref.
	Signet ring cell carcinoma	2.5	2.0-3.1
Multiple metastases	Adenocarcinoma	Ref.	Ref.
	Signet ring cell carcinoma	2.3	1.9-2.7
Tumor stage			
Koemans et al. (2020)[15]	T1	Ref.	Ref.
	T2-3	2.1	1.3-3.2
	T4	3.0	1.9-4.7
Thomassen et al. (2013)[16]	T1-2	Ref.	Ref.
	T3	2.4	1.7-3.3
	T4	2.9	2.1-4.0
Nodal stage			
Koemans et al. (2020)[15]	N0	Ref.	Ref.
	N1-2	0.4	0.3-0.4
	N3	0.3	0.2-0.3
Thomassen et al. (2013)[16]	N0	Ref.	Ref.
	N+	4.0	2.2-7.3

Table 3. Risk factors for synchronous gastric peritoneal metastases. (continued)

Study	Groups	OR	95% CI
Ethnicity			
Choi et al. (2020)[18]			
Non-Hispanic white vs. Hispanic	Non-Hispanic white	Ref.	Ref.
	Hispanic	1.9	1.6-2.1
Asian/other vs. Hispanic	Asian/other	Ref.	Ref.
	Hispanic	1.5	1.3-1.7
Number of metastatic locations			
Koemans et al. (2020)[15]	1 metastasis	Ref.	Ref.
	> 1 metastases	1.6	1.5-1.8

Survival

Survival was reported in three population-based studies and in one surgical cohort study.[12,15,16,29] One study reported a median overall survival (OS) of 4.0 months in patients with peritoneal metastases.[16] Another study reported survival of gastric peritoneal metastases by histological subtype with a median OS of 4.6 months for diffuse type gastric cancer with peritoneal metastases versus 5.1 months for intestinal type gastric cancer with peritoneal metastases.[15] Furthermore, a study on gastric peritoneal metastases reported a median OS of 2.1 months in patients who did not receive systemic therapy versus 9.4 months in patients who received systemic therapy.[12] A study documented a median OS of 7 months in a cohort with gastric cancer patients that underwent staging laparoscopy.[29]

Discussion

In this systematic review, the proportion of patients with synchronous peritoneal metastases from gastric cancer origin ranged from 10–21% in population-based studies[12,16,17,18], from 2–15% in observational cohort studies[19,20,21,22,23,24] and from 13–40% in surgical cohort studies.[25,26,27,28,29,30] Interestingly, the highest incidence of synchronous peritoneal metastases (21%) was reported in the most recent population-based study.[12] This may be attributable to the improvement of imaging techniques resulting in a higher detection rate of the typically small peritoneal lesions as well as a higher awareness towards peritoneal metastases amongst radiologists. Moreover,

the introduction of a standard diagnostic laparoscopy in the staging guidelines of operable patients with resectable gastric cancer will have contributed to the increased documentation of peritoneal metastases. Identified risk factors for gastric peritoneal metastases were younger age, non-cardia cancer, female sex, signet ring cell carcinoma, diffuse type histology or linitis plastica, T4 tumor stage and Hispanic ethnicity.[15,16,17,18] Median OS in patients with gastric peritoneal metastases ranged from 2 to 9 months.[12,15,16,29]

To the best of our knowledge, this is the first comprehensive systematic review providing an overview on incidence, risk factors and survival for synchronous gastric peritoneal metastases. Previous studies have performed a systematic review on gastric cancer in general but reported very limited information about peritoneal metastases with none of these studies focusing specifically on the incidence of synchronous peritoneal metastases.[31,32] From these studies, it can be concluded that the proportion of patients presenting with metastases at any location increased over time from 24% in 1990 to 44% in 2011. The peritoneum is recognized as one of the most common metastatic sites in gastric cancer patients, ranking second after the liver.[3,17] Again, improved radiologic and staging techniques probably explain the stage migration towards more patients with metastatic disease. One review on gastric cancer confirmed the striking difference of a much higher incidence of gastric cancer in Asian countries than in Western countries, as well as a less advanced stage at the time of diagnosis.[33] The latter may be explained by the mass screening programs for gastric cancer in high-incidence regions such as Japan and Korea, aiming to diagnose the cancer at an early stage.[34]

In the current review, several risk factors associated with peritoneal metastases were identified, among which are a younger age. Interestingly, a meta-analysis on young patients with gastric cancer also reported that these patients were more often females with diffuse type gastric cancer and signet ring cell carcinoma and were more often diagnosed with peritoneal metastases.[35] Therefore, young patients may have a poorer tumor biology and subsequently may be more at risk for peritoneal metastases. On the other hand, younger patients are usually in a good condition and are thus more likely to receive a thorough diagnostic work-up which increases the chance of discovering peritoneal metastases. Therefore, it remains unknown whether the higher incidence of peritoneal metastases in younger patients reflects a more aggressive tumor biology or whether this finding is biased by an intensified diagnostic workup.

Other risk factors, such as a T4 tumor stage and signet ring cell differentiation, were previously identified to be associated with an increased incidence of

peritoneal metastases from colorectal cancer.[36] Furthermore, linitis plastica, positive lymph node status and a primary tumor not located in the cardia were previously reported as risk factors for metastases in gastric cancer patients.[37] This highlights the role of a more advanced tumor stage in the development of peritoneal metastases. Remarkably, in one study, positive lymph node status were associated with a higher rate of systemic metastases but with a lower risk of peritoneal metastases.[15] At first, this may seem contradictory, but this can be explained by the fact that this study was performed in patients presenting with metastatic disease only. Patients with lymph node involvement and systemic metastases on computed tomography (CT) probably have not undergone a staging laparoscopy since they are already considered to have unresectable disease. As a result, peritoneal metastases may have been missed in many patients as they are usually hard to diagnose by radiologic imaging alone.

Staging laparoscopy is frequently carried out in patients with (advanced) gastric cancer eligible for curative intent surgery and without metastases after radiology staging. In this systematic review, studies on patients who underwent staging laparoscopy generally reported a higher incidence of gastric peritoneal metastases compared to the other studies, up to 40%. This proportion is comparable to the numbers of a recent review specifically on gastric cancer patients undergoing staging laparoscopy.[38] This emphasizes the importance of a staging laparoscopy in patients with gastric cancer. Less invasive diagnostic modalities, such as (positron emission tomography) CT and magnetic resonance imaging, need to be further improved to increase their accuracy for diagnosing peritoneal metastases.

As shown in this review, survival of gastric peritoneal metastases is poor, ranging from 2 to 9 months, depending on systemic therapy or histological subtype. Similar poor survival outcomes for patients receiving best supportive care, or systemic therapy only, were previously reported for peritoneal metastases of other primary tumors, such as colorectal and pancreatic cancer, which emphasizes the need for new treatment options for patients with peritoneal metastases, regardless of the origin of the tumor.[39,40,41] In gastric cancer with peritoneal metastases, experimental treatment options such as CRS-HIPEC or PIPAC are currently being investigated.[8,10] Although limited literature is available about this experimental treatment, preliminary results seem promising.[6,7,42] Furthermore, it needs to be investigated whether patients with peritoneal metastases may also benefit from new systemic treatment strategies such as docetaxel-based triplet FLOT therapy (fluorouracil plus leucovorin, oxaliplatin and docetaxel) that has been shown

to improve survival in patients with locally advanced resectable gastric cancer.[43]

This review has several limitations. Firstly, some population-based studies used the same data registries which results in overlapping use of patient characteristics.[12,15] However, these studies reported on different outcomes and therefore did not result in duplication of data. Secondly, the population-based studies were performed in western countries, whereas the observational cohort studies were mostly performed in Asian countries. The prevalence of gastric cancer in western countries is low compared to the prevalence in Asian countries, and types of histology vary among these different parts of the world whereas diffuse type gastric cancer is more common in Asian countries.[1,2,43,44,45] The observational cohort studies revealed large heterogeneity within and across these studies. This may lead to an incomplete overview of patients diagnosed with synchronous gastric peritoneal metastases in non-western countries. Finally, this systematic review focused on synchronous peritoneal metastases only, whereas it is known that metachronous peritoneal metastases frequently occur after curative treatment for gastric cancer. Recent literature showed that the peritoneum (36%) was the most common initial site of recurrence after potentially curative gastric cancer surgery.[46] Population-based studies with adequate follow-up to include metachronous peritoneal metastases are therefore designated to provide a more accurate overview of the total burden of peritoneal metastases from gastric cancer.

To conclude, in this systematic review, synchronous peritoneal metastases were frequently diagnosed in patients with gastric cancer with an incidence up to 21% in most recent population-based studies. Furthermore, prognosis of patients with gastric peritoneal metastases is poor. Given the high incidence and poor prognosis, this patient category is an important focus for future research on diagnostic features and effective treatment options to improve survival.

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Chapter

8

Peritoneal metastases from gastric cancer in a nationwide cohort: incidence, treatment and survival

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Abstract

Introduction
The aims of this study were to investigate incidence, risk factors and treatment of synchronous or metachronous peritoneal metastases from gastric cancer and to estimate survival of these patients using population-based data.

Methods
Patients diagnosed with gastric cancer in 2015-2016 were selected from the Netherlands Cancer Registry. The incidence of synchronous and metachronous peritoneal metastases were calculated. Multivariable regression analyses were performed to identify factors associated with the occurrence of peritoneal metastases. Treatment and survival were compared between patients with synchronous and metachronous peritoneal metastases.

Results
Of 2206 patients with gastric cancer, 741 (34%) were diagnosed with peritoneal metastases. Of these, 498 (23%) had synchronous peritoneal metastases. The cumulative incidence of metachronous peritoneal metastases in patients who underwent potentially curative treatment (n=675) was 22.8% at 3 years. A factor associated with synchronous and metachronous peritoneal metastases was diffuse type histology. Patients diagnosed with synchronous peritoneal metastases more often received systemic treatment than patients with metachronous peritoneal metastases (35% vs. 18% respectively, $p < 0.001$). Median overall survival was comparable between synchronous and metachronous peritoneal metastases (3.2 vs. 2.3 months respectively, $p = 0.731$).

Conclusions
Approximately one third of all patients with gastric cancer are diagnosed with peritoneal metastases, either at primary diagnosis or during 3-year follow-up after potentially curative treatment. Patients with metachronous peritoneal metastases less often received systemic treatment than those with synchronous peritoneal metastases but survival was comparable between both groups. Future trials are warranted to detect gastric cancer at an earlier stage and to examine strategies that lower the risk of peritoneal dissemination. Also, specific treatment options for patients with gastric peritoneal metastases should be further investigated.

Introduction

With over a million new cases yearly, gastric cancer is the sixth most prevalent cancer worldwide.[1] Prognosis of gastric cancer is known to be poor with a 5-year overall survival (OS) of 18% because it is frequently detected at an advanced stage.[2,3] Although the introduction of a diagnostic laparoscopy in the diagnostic work-up of patients with resectable gastric cancer will have contributed to a higher detection rate of peritoneal metastases, recurrence of disease after potentially curative treatment is common.[4] Of all patients with gastric cancer, 21% have metastases to the peritoneum at primary diagnosis.[5]

Recently, peritoneal metastases from gastric cancer have been increasingly considered as a locoregional disease entity which has led to more scientific interest regarding suitable treatment strategies for these patients. A randomized controlled trial (RCT) described cytoreductive surgery in combination with intraperitoneal hyperthermic chemotherapy (CRS-HIPEC) in patients with peritoneal metastases from gastric cancer.[6] However, further clinical evaluation of CRS-HIPEC is warranted, due to the very small number of included patients in the above mentioned trial.[6] Currently, the phase III PERISCOPE II trial (NCT03348150) is carried out to investigate whether CRS-HIPEC has additional value as compared to systemic treatment alone in patients with gastric cancer and isolated limited synchronous peritoneal metastases.[7] However, a high number of patients with gastric peritoneal metastases is not eligible to participate in this trial due to extensive peritoneal disease. For these patients, experimental palliative treatment options like pressurized intraperitoneal aerosol chemotherapy (PIPAC) or prolonged/direct intraperitoneal chemotherapy are being studied in clinical trials.[8,9] In the meantime, palliative systemic treatment remains the current standard of care for all patients with gastric peritoneal metastases in the Netherlands.

These ongoing clinical trials have led to an increasing interest in the treatment of gastric peritoneal metastases. However, until now, nationwide cohort studies only focused on synchronous peritoneal metastases from gastric cancer and comprehensive epidemiologic data on metachronous peritoneal metastases in gastric cancer patients is currently lacking.[10-13] Therefore, the overall burden of peritoneal metastases and details on peritoneal recurrence in gastric cancer patients at population-based level remain unknown. Reliable, nationwide data on peritoneal metastases from patients in everyday clinical practice is needed to form a basis for future clinical trials.

Hence, the aim of this present population-based study was to investigate incidence, risk factors and treatment of synchronous or metachronous

peritoneal metastases in patients with gastric cancer and to describe possible differences between synchronous and metachronous peritoneal metastases. Also, this study aims to estimate survival of patients with gastric peritoneal metastases.

Methods

Data source

Data from the Netherlands Cancer Registry (NCR) were used to perform this population-based study. Specially trained data managers of the NCR register all newly diagnosed malignancies in the Netherlands. Data on patient, tumor and treatment characteristics are routinely extracted from medical records. The anatomical location of the primary tumor and metastases are registered according to the International Classification of Disease for Oncology (ICD-O).[14] The 7th edition of the Tumor Node Metastasis (TNM) was used for staging of the primary tumor.[15] In order to preserve a homogenous study cohort, only the clinical T or N stage (instead of pathological stage) was presented. The medical records of all gastric cancer patients diagnosed in 2015 and 2016 were re-evaluated by trained data managers in the second half of 2019 to obtain follow-up information on disease recurrence and progression, including the presence of peritoneal metastases. Each year, the vital status of all patients is updated through linkage of the NCR data with the Dutch Personal Records Database, which contains information about all present, deceased and former inhabitants of the Netherlands. Follow-up on vital status was complete until February 2022.

Study population

All patients diagnosed with gastric cancer in 2015 and 2016 in the Netherlands were evaluated (ICD-O: C16). Synchronous metastases were defined as metastases diagnosed before or within the first 5 days after start of either systemic treatment or primary surgery. For patients receiving best supportive care (BSC), synchronous metastases were defined as metastases diagnosed within six weeks from primary diagnosis. Metachronous metastases were defined as metastases diagnosed more than five days after primary tumor resection for non-metastatic disease (i.e. endoscopic resection or (sub)total gastrectomy), to account for delay in pathological confirmation.
Patients with an unknown date of metastases were excluded (*Figure 1*). Patients receiving BSC with metastases diagnosed more than six weeks after primary diagnosis, patients with interval metastases (i.e., diagnosed more than five days after the start of neoadjuvant chemotherapy (if applicable) until the date of gastric cancer surgery) and patients with gastric cancer and no metastases (M0) at primary diagnosis who did not receive curative

intent surgery for the gastric tumor were considered as having an undefined onset in detection of metastases (neither synchronous or metachronous) and these patient groups were excluded from further analyses.[16] The amount of peritoneal metastases in these patient groups are demonstrated in *Figure 1*.

Patient- and tumor characteristics

The location of the primary tumor was categorized according to the following sites: 1) proximal stomach (C16.0-16.2, C16.5, C16.6: cardia, fundus, body, lesser- and greater curvature); 2) distal stomach (C16.3-16.4: antrum, pylorus); 3) overlapping sites in the stomach (C16.8); and 4) not otherwise specified location in the stomach (C16.9). The following ICD-O codes were considered peritoneal metastases: C17.0-C17.9, C18.0-C18.9, C19.9, C20.9, C21.8, C23.9, C26.9, C48.0-C48.8, C49.4-C49.5, C52.9, C54.3-C54.9, C55.9, C56.9, C57.0-C57.8, C66.9, C67.0-C67.9, C76.2.[14] Any other ICD-O code was considered as extraperitoneal metastases.

Patient- and tumor characteristics included in this study were sex, age, primary tumor location, performance status, differentiation of primary tumor, Lauren classification for the histology of primary tumor[17], HER2 status, clinical tumor stage and nodal stage. T1 stage and T2 stage were combined for further analyses, due to a very small number of patients with T1 stage. Information on type of gastric resection and perioperative therapy (i.e., resection only, neoadjuvant chemotherapy and resection, or resection and both neoadjuvant and adjuvant chemotherapy (the latter being the perioperative chemotherapy group) were displayed at time of potentially curative treatment (only for patients who underwent potentially curative treatment).

Treatment

Treatment in patients with synchronous or metachronous peritoneal metastases from gastric cancer in this cohort was categorized as follows:

1) Systemic treatment, defined as tumor-directed treatment, that may include chemotherapy, immunotherapy and/or targeted therapy.
2) Surgery, defined as tumor-directed treatment, that may include palliative resection of the primary tumor (only applicable for synchronous peritoneal metastases), and/or CRS-HIPEC, and/or metastasectomy as only treatment or a combination of surgery and systemic treatment.
3) BSC defined as no tumor-directed treatment that may include palliative interventions for symptom control (e.g., stent placement or radiotherapy at the site of the gastric tumor or metastatic lesion) or no treatment at all.

Statistical analysis

Patient- and tumor characteristics were depicted for the total study population (stratified by synchronous peritoneal metastases) and for the subgroup of patients who underwent potentially curative treatment (stratified by metachronous peritoneal metastases). Patients with synchronous or metachronous peritoneal metastases were compared to patients without synchronous or metachronous peritoneal metastases and analyzed using chi-squared test in categorical variables (number [%]) and using Mann-Whitney U test in continuous variables (interquartile range [IQR]). Missing data were described but excluded from comparative analyses for each separate variable. For patients who underwent potentially curative primary surgery, cumulative incidence of metachronous peritoneal metastases at 1- and 3-years was calculated with death as competing event. Time to event was calculated from 5 days after potentially curative surgery until date of diagnosis of metachronous peritoneal metastases (event of interest), last follow-up (censor) or death (competing event), depending on whichever came first. Uni- and multivariable logistic regression analyses were performed to identify factors associated with the presence of synchronous peritoneal metastases from gastric cancer. Uni- and multivariable cox regression analyses were performed to identify factors associated with the development of metachronous peritoneal metastases after potentially curative surgical resection of non-metastatic gastric cancer and with death as competing event. Time to event was calculated the same as in cumulative incidence analyses. Variables with a p-value < 0.10 in univariable regression analyses, were included in the multivariable regression models. Treatment strategies for patients with synchronous peritoneal metastases and metachronous peritoneal metastases were compared using chi-squared test. Median OS from the date of diagnosis of peritoneal metastases until death or loss to follow-up was estimated with the Kaplan-Meier method and compared for patients with synchronous peritoneal metastases and metachronous peritoneal metastases, as well as stratified by treatment strategies using Log-rank test. A power analysis was executed to determine the minimal number of cases for performing survival analyses with an α of < 0.05 and a β of 0.2.[18] With a minimum required amount of 228 cases, the survival analyses in this study were sufficiently powered. Median OS was also estimated for the subgroup of patients with early versus late metachronous peritoneal metastases. Early metachronous peritoneal metastases was defined as peritoneal metastases detected ≤6 months after primary diagnosis, while peritoneal metastases detected >6 months after primary diagnosis was defined as late metachronous peritoneal metastases. Univariable cox regression analyses were performed in patients with peritoneal metastases (synchronous and

metachronous as one group) to identify risk factors affecting OS. Variables with a $p < 0.10$ were combined in the multivariable cox regression analysis.

Results

Study population

In total, 2217 patients were diagnosed with gastric cancer in the Netherlands in 2015 and 2016. After exclusion of 11 patients in whom the data of metastases were unknown, 2206 patients were included in the study. Patients without synchronous metastases (M0) who did not underwent curative intent surgery (n=541), patients with interval metastases (n=38) and patients receiving BSC with metastases diagnosed more than six weeks after primary diagnosis (n=21) were considered as having an undefined onset of metastases and were excluded from further analyses. In total, 741 patients (34%) were diagnosed with either synchronous peritoneal metastases, metachronous peritoneal metastases or peritoneal metastases with an unknown unset. The incidence of synchronous peritoneal metastases in this series was 23% (498 out of 2147 patients).

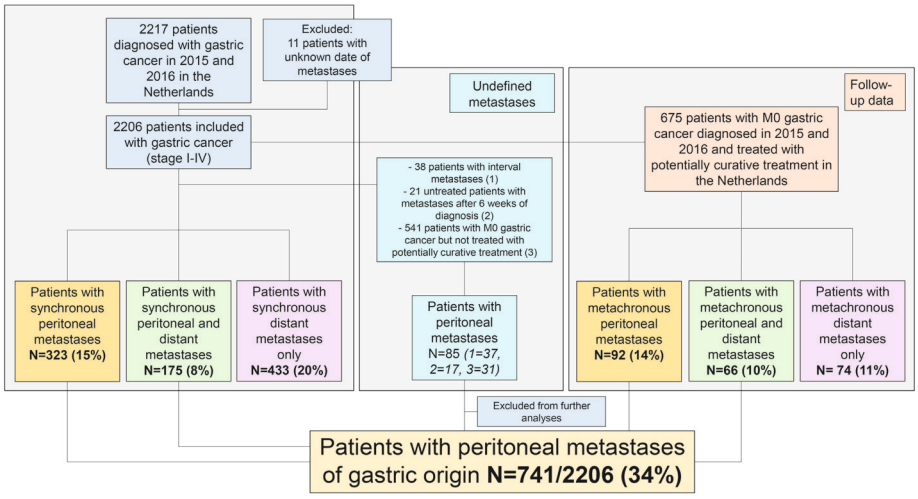


Figure 1. Flowchart of the study population.

Among all 675 patients who underwent potentially curative treatment for non-metastatic gastric cancer, 158 (24%) developed metachronous peritoneal metastases during the follow-up period. The median time until diagnosis of metachronous peritoneal metastases was 12.4 months (IQR 6.5-21.9). The 1- and 3-year cumulative incidence of metachronous peritoneal metastases

was 11.4% (95% confidence interval [CI] 9.2-14.0) and 22.8% (95% CI 19.6-26.2), respectively (*Figure 2*).

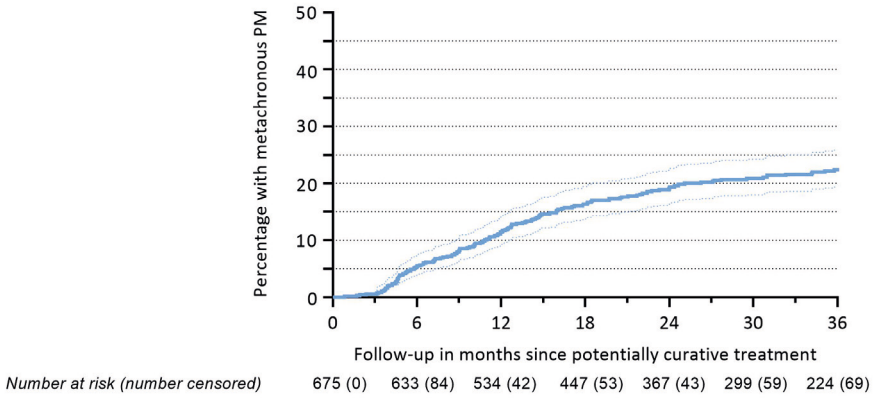


Figure 2. Cumulative incidence of metachronous peritoneal metastases among patients treated with potentially curative treatment (n=675).

Synchronous peritoneal metastases were pathologically confirmed in 205 (41%) patients, cytologically confirmed in 88 (18%) patients and radiologically confirmed in 205 (41%). In 1 (<1%) patient, the basis of diagnosis (radiological, cytological or pathological examination) was unknown. Metachronous peritoneal metastases were pathologically confirmed in 62 (39%) patients, cytologically confirmed in 33 (21%) patients and radiologically confirmed in 63 (40%).

Comparison of patient- and tumor characteristics (at primary gastric cancer diagnosis) between patients with synchronous peritoneal metastases and patients without synchronous peritoneal metastases and between patients with metachronous peritoneal metastases and patients without metachronous peritoneal metastases are depicted in *Table 1*.

Table 1. Patient- and tumor characteristics of the total study population.

	Total study population n=2147			**Patients treated with potentially curative treatment** n=675		
	No synchronous PM *(n=1649)*	Synchronous PM *(n=498)*	*P value*[a]	No metachronous PM *(n=517)*	Metachronous PM *(n=1158)*	*P value*[a]
Sex, No. (%)						
Male	999 (61)	276 (55)	***0.040***	319 (62)	86 (54)	*0.103*
Female	650 (39)	222 (45)		198 (38)	72 (46)	
Age at diagnosis, median (IQR)	74 (67-81)	69 (60-77)	***<0.001***	72 (64-78)	69 (59-75)	***0.002***
Primary tumor location, No. (%)						
Proximal	503 (30)	135 (27)	***<0.001***	163 (32)	51 (32)	***0.010***
Distal	670 (41)	139 (28)		250 (48)	65 (41)	
Overlapping sites	338 (21)	183 (37)		70 (14)	37 (23)	
NOS	138 (8)	41 (8)		34 (7)	5 (3)	
WHO Performance status						
0-1	702 (43)	198 (40)	*0.070*	312 (60)	98 (62)	*0.690*
≥2	200 (12)	75 (15)		42 (8)	15 (9)	
Unknown[a]	747 (45)	225 (45)		163 (32)	45 (28)	

Table 1. Patient- and tumor characteristics of the total study population. (continued)

	Total study population n=2147			**Patients treated with potentially curative treatment** n=675		
	No synchronous PM *(n=1649)*	Synchronous PM (*n=498)*	*P value*[a]	No metachronous PM *(n=517)*	Metachronous PM (*n=1158)*	*P value*[a]
Tumor differentiation						
Good/moderate	364 (22)	50 (10)	***<0.001***	181 (35)	20 (13)	***<0.001***
Poor/undifferentiated	722 (44)	221 (44)		258 (50)	107 (68)	
Unknown[a]	563 (34)	227 (46)		78 (15)	31 (20)	
Lauren classification						
Intestinal	534 (32)	83 (17)	***<0.001***	254 (49)	34 (22)	***<0.001***
Diffuse	596 (36)	292 (59)		168 (33)	100 (63)	
Mixed/indeterminate	81 (5)	20 (4)		27 (5)	11 (7)	
Unknown[a]	438 (27)	103 (21)		68 (13)	13 (8)	
HER2 status						
Positive	82 (5)	27 (5)	*0.076*	21 (4)	5 (3)	*0.518*
Negative	477 (29)	238 (48)		156 (30)	52 (33)	
Unknown/not tested[a]	1090 (66)	233 (47)		340 (66)	101 (64)	

Table 1. Patient- and tumor characteristics of the total study population. (continued)

	Total study population n=2147			**Patients treated with potentially curative treatment** n=675		
	No synchronous PM *(n=1649)*	Synchronous PM *(n=498)*	*P value*[a]	No metachronous PM *(n=517)*	Metachronous PM *(n=1158)*	*P value*[a]
Clinical tumor stage						
T1-T2	636 (39)	154 (31)	***<0.001***	259 (50)	77 (49)	***0.003***
T3	285 (17)	88 (18)		106 (21)	47 (30)	
T4	182 (11)	111 (22)		19 (4)	11 (7)	
Tx	546 (33)	145 (29)		133 (26)	23 (15)	
Clinical nodal stage						
N0	760 (46)	178 (36)	***<0.001***	336 (65)	92 (58)	*0.471*
N1	365 (22)	103 (21)		106 (21)	37 (23)	
N2/N3	289 (18)	125 (25)		46 (9)	18 (12)	
Nx	235 (14)	92 (18)		29 (6)	11 (7)	
Perioperative chemotherapy						
None	N.A.	N.A.		274 (53)	64 (41)	***0.022***
Neoadjuvant chemotherapy	N.A.	N.A.		93 (18)	36 (23)	
Perioperative chemotherapy	N.A.	N.A.		150 (29)	58 (37)	

Table 1. Patient- and tumor characteristics of the total study population. (continued)

	Total study population n=2147			**Patients treated with potentially curative treatment** n=675		
	No synchronous PM *(n=1649)*	Synchronous PM (*n=498)*	*P value*[a]	No metachronous PM *(n=517)*	Metachronous PM (*n=1158)*	*P value*[a]
Type of curative PTR						
Total gastrectomy	N.A.	N.A.		170 (33)	79 (50)	***0.002***
Partial gastrectomy	N.A.	N.A.		321 (62)	77 (49)	
Endoscopic resection	N.A.	N.A.		26 (5)	2 (1)	
Distant metastases at primary diagnosis						
Yes	433 (26)	175 (35)	***<0.001***	N.A.	N.A.	
No	1216 (74)	323 (65)		N.A.	N.A.	

All characteristics are presented at baseline (primary diagnosis), being non-metastatic disease in patients who underwent potentially curative treatment. *Information on type of gastric resection and perioperative therapy (i.e., resection only, neoadjuvant chemotherapy and resection, or resection and both neoadjuvant and adjuvant chemotherapy) were displayed at time of potentially curative treatment. [a]Missing data were not included in comparative analyses. Percentages may not add up to 100 due to rounding. *PM* indicates peritoneal metastases, *NOS* indicates no other specified tumor location, *PTR* indicates primary tumor resection, N.A.: not applicable.

Factors associated with synchronous or metachronous peritoneal metastases

Univariable logistic- and cox regression analyses are depicted in *Supplementary Table 8.1* and multivariable logistic- and cox regression analyses are presented in *Table 2*. The following factors were associated with the presence of synchronous peritoneal metastases in gastric cancer: overlapping primary tumor sites versus proximal primary tumor location (adjusted odds ratio [OR] 1.51; 95% CI, 1.14-2.00), unknown tumor differentiation versus good/moderate tumor differentiation (OR 1.66; 95% CI, 1.15-2.42), diffuse type histology versus intestinal type histology (OR 2.10; 95% CI, 1.53-2.87), T4 stage versus T1-T2 stage (OR 2.18; 95% CI, 1.59-2.98), N2/N3 stage (OR 1.44; 95% CI, 1.06-1.94) and Nx (OR 1.63; 95% CI, 1.18-2.25) versus N0 stage and the absence of distant metastases at diagnosis (OR 0.75; 95% CI, 0.59-0.96). Also, having a younger age (<65 years) at diagnosis versus 65-75 years (OR 0.73; 95% CI, 0.55-0.95) and >75 years (OR 0.45; 95% CI, 0.35-0.59) was associated with the presence of synchronous peritoneal metastases.

Factors associated with the development of metachronous peritoneal metastases after potentially curative treatment for non-metastatic gastric cancer were: poor/undifferentiated tumor differentiation (adjusted hazard ratio [HR] 1.85; 95% CI 1.11-3.07), diffuse type histology (HR 2.62; 95% CI, 1.74-3.96) or a mixed/indeterminate type histology (HR 2.31; 95% CI, 1.16-4.60) versus intestinal type histology and Tx stage versus T1-T2 stage (HR 0.62; 95% CI, 0.38-0.99).

Table 2. Multivariable logistic regression analyses for the presence of synchronous peritoneal metastases and multivariable cox regression analyses for the development of metachronous peritoneal metastases after potentially curative treatment.

	Synchronous PM	**Multivariable logistic regression analysis**			**Metachronous PM**	**Multivariable cox regression analysis**		
	n (%)	OR	95% CI	*P value*	n(%)	OR	95% CI	*P value*
Sex								
Male	276 (55)	Ref.	Ref.	Ref.	86 (54)	N.A.	N.A.	N.A.
Female	222 (45)	1.20	0.96-1.49	0.108	72 (46)	N.A.	N.A.	N.A.
Age at diagnosis								
< 65 years	178 (36)	Ref.	Ref.	Ref.	56 (35)	Ref.	Ref.	Ref.
65 - 75 years	161 (32)	0.73	0.55-0.95	**0.019**	58 (37)	1.03	0.71-1.49	0.889
> 75 years	159 (32)	0.45	0.35-0.59	**<0.001**	44 (28)	0.80	0.51-1.27	0.343
Primary tumor location								
Proximal	135 (27)	Ref.	Ref.	Ref.	51 (32)	Ref.	Ref.	Ref.
Distal	139 (28)	0.79	0.60-1.05	0.100	65 (41)	0.80	0.56-1.14	0.217
Overlapping sites	183 (37)	1.51	1.14-2.00	**0.004**	37 (23)	1.04	0.67-1.62	0.861
NOS	41 (8)	1.13	0.74-1.73	0.563	5 (3)	0.72	0.27-1.90	0.502
Tumor differentiation								
Good/moderate	50 (10)	Ref.	Ref.	Ref.	20 (13)	Ref.	Ref.	Ref.
Poor/undifferentiated	221 (44)	1.26	0.87-1.83	0.226	107 (68)	1.85	1.11-3.07	**0.018**
Unknown	227 (46)	1.66	1.15-2.42	**0.007**	31 (20)	1.66	0.93-2.94	0.085

Table 2. Multivariable logistic regression analyses for the presence of synchronous peritoneal metastases and multivariable cox regression analyses for the development of metachronous peritoneal metastases after potentially curative treatment. (continued)

	Synchronous PM	**Multivariable logistic regression analysis**			**Metachronous PM**	**Multivariable cox regression analysis**		
	n (%)	OR	95% CI	*P value*	n(%)	OR	95% CI	*P value*
Lauren classification								
Intestinal	83 (17)	Ref.	Ref.	Ref.	34 (22)	Ref.	Ref.	Ref.
Diffuse	292 (59)	2.10	1.53-2.87	**<0.001**	100 (63)	2.62	1.74-3.96	**<0.001**
Mixed/indeterminate	20 (4)	1.25	0.71-2.21	0.437	11 (7)	2.31	1.16-4.60	**0.018**
Unknown	103 (21)	1.19	0.85-1.66	0.316	13 (8)	1.19	0.63-2.25	0.600
Clinical T stage								
T1-T2	154 (31)	Ref.	Ref.	Ref.	77 (49)	Ref.	Ref.	Ref.
T3	88 (18)	1.20	0.87-1.64	0.272	47 (30)	1.31	0.91-1.89	0.153
T4	111 (22)	2.18	1.59-2.98	**<0.001**	11 (7)	1.32	0.65-2.66	0.444
Tx	145 (29)	1.02	0.77-1.35	0.896	23 (15)	0.62	0.38-0.99	**0.044**
Clinical N stage								
N0	178 (36)	Ref.	Ref.	Ref.	92 (58)	N.A.	N.A.	N.A.
N1	103 (21)	1.05	0.78-1.42	0.739	37 (23)	N.A.	N.A.	N.A.
N2/N3	125 (25)	1.44	1.06-1.94	**0.019**	18 (11)	N.A.	N.A.	N.A.
Nx	92 (18)	1.63	1.18-2.25	**0.003**	11 (7)	N.A.	N.A.	N.A.

Table 2. Multivariable logistic regression analyses for the presence of synchronous peritoneal metastases and multivariable cox regression analyses for the development of metachronous peritoneal metastases after potentially curative treatment. (continued)

	Synchronous PM	**Multivariable logistic regression analysis**			**Metachronous PM**	**Multivariable cox regression analysis**		
	n (%)	OR	95% CI	*P value*	n(%)	OR	95% CI	*P value*
Perioperative therapy								
Resection only	N.A.	N.A.	N.A.	N.A.	64 (41)	Ref.	Ref.	Ref.
Neoadjuvant therapy	N.A.	N.A.	N.A.	N.A.	36 (23)	1.23	0.77-1.94	0.385
Perioperative therapy	N.A.	N.A.	N.A.	N.A.	58 (37)	0.99	0.66-1.49	0.978
Distant metastases at primary diagnosis								
Yes	175 (35)	Ref.	Ref.	Ref.	N.A.	N.A.	N.A.	N.A.
No	323 (65)	0.75	0.59-0.96	**0.025**	N.A.	N.A.	N.A.	N.A.

PM peritoneal metastases; *OR* odds ratio; *HR* hazard ratio; *CI* confidence interval; *NOS* no other specified primary tumor location. Variables with a p-value < 0.1 in univariable analyses were combined in the multivariable regression models. N.A.: not applicable, variable not applicable in either synchronous or metachronous setting or variable not included due to non-significance in univariable analysis.

Treatment strategies of patients with peritoneal metastases

The different treatment strategies administered to patients with synchronous peritoneal metastases and patients with metachronous peritoneal metastases are depicted in *Figure 3*. Patients with synchronous peritoneal metastases received more systemic treatment in comparison with metachronous peritoneal metastases patients (35% vs. 18%, respectively, $p < 0.001$).

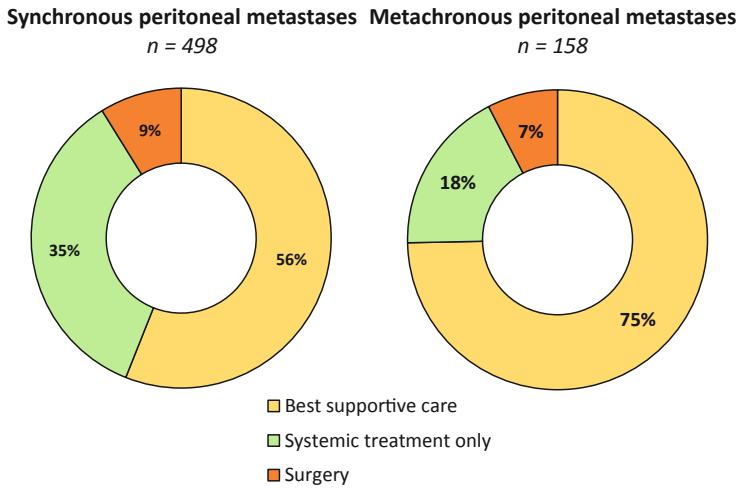


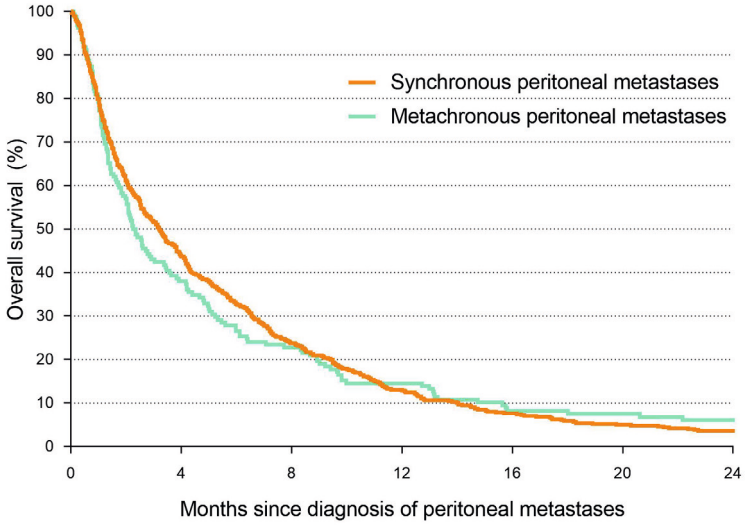
Figure 3. Treatment strategies for patients with synchronous peritoneal metastases or metachronous peritoneal metastases.
Surgery comprising: surgery only or a combination of surgery, radiotherapy or systemic treatment.

Survival of patients with peritoneal metastases

Median OS of all patients with peritoneal metastases was 2.9 months (IQR 1.2-7.4). Median OS was similar for patients with synchronous peritoneal metastases (3.2 months [IQR 1.2-7.6]) and metachronous peritoneal metastases (2.3 months [IQR 1.1-6.4]) (p = 0.731) (*Figure 4a*). Multivariable cox regression analysis showed no difference in survival between synchronous versus metachronous detection of peritoneal metastases (HR 0.88; 95% CI, 0.72-1.08) *(Supplementary Table 8.2*).

Patients with early metachronous peritoneal metastases (1.4 months [IQR 0.8-3.4]) had a worse OS compared to patients with late metachronous peritoneal metastases (2.6 months [IQR 1.2-8.9]) and patients with synchronous peritoneal metastases (3.2 months [IQR 1.2-7.6]) ($p < 0.001$) *(Supplementary Figure 8.1).*

In the group of patients who received tumor-directed treatment (i.e. systemic treatment or surgery), median OS was similar between synchronous peritoneal metastases (7.3 months [IQR 4.0-12.5]) and metachronous peritoneal metastases (7.8 months [IQR 3.0-18.0]) (p = 0.157) (*Figure 4b*). Also, in the group of patients who received BSC or no treatment, median OS was similar between synchronous peritoneal metastases (1.5 months [IQR 0.7-3.3]) and metachronous peritoneal metastases (1.9 months [IQR 0.6-4.3]) (p = 0.051) (*Figure 4c*).



Number at risk (number censored)

Synchronous PM	498 (0)	218 (0)	118 (0)	65 (0)	38 (0)	25 (0)	15 (6)
Metachronous PM	158 (0)	60 (0)	36 (0)	23 (0)	12 (2)	10 (2)	7 (4)

Figure 4a. Overall survival of all patients with synchronous (n=498) or metachronous (n=158) peritoneal metastases from gastric cancer (Log-rank: p = 0.731).
PM peritoneal metastases

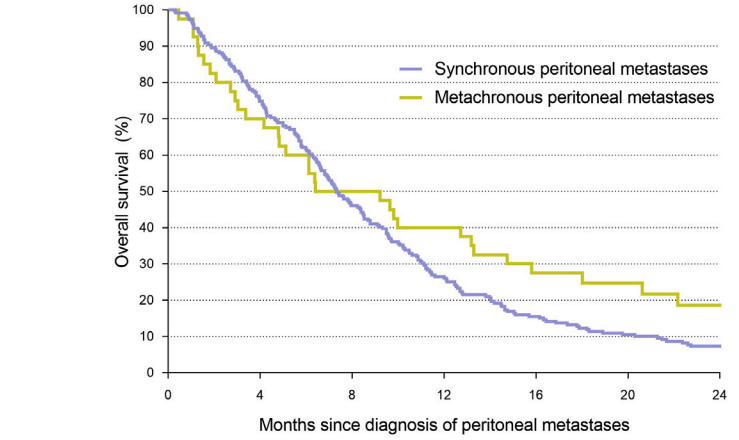


Figure 4b. Overall survival of all patients who received tumor-directed treatment with synchronous (n=219) or metachronous (n=40) peritoneal metastases from gastric cancer (Log-rank: p = 0.157).
PM peritoneal metastases

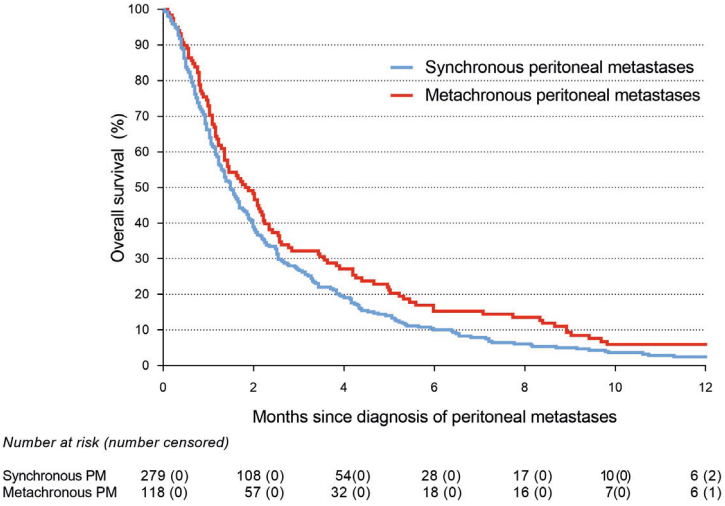


Figure 4c. Overall survival of all patients who received only best supportive care or no treatment with synchronous (n=279) or metachronous (n=118) peritoneal metastases from gastric cancer (Log-rank: *p* = 0.051).
PM peritoneal metastases

Discussion

The present study showed that approximately one third of all patients with gastric cancer are diagnosed with peritoneal metastases. Synchronous peritoneal metastases were diagnosed in 23% of all gastric cancer patients. After potentially curative treatment for non-metastatic gastric cancer, another 24% of patients developed metachronous peritoneal metastases during the first three years of follow-up. The presence of synchronous peritoneal metastases was associated with diffuse type histology, younger age, overlapping tumor location in the stomach, T4 stage, N2/N3 stage and no other distant metastases at primary diagnosis. The development of metachronous peritoneal metastases was associated with a diffuse or mixed/indeterminate type histology and a poorly differentiated tumor. Patients with synchronous peritoneal metastases more frequently received systemic treatment than patients with metachronous peritoneal metastases. In spite of this, survival was equally poor for both synchronous and metachronous peritoneal metastases from gastric cancer. Moreover, survival remained comparable between both groups when analyzed within different treatment groups.

To our knowledge, this is the first population-based study providing data on the incidence of metachronous peritoneal metastases in gastric cancer patients. As we recently described in a systematic review on the incidence of peritoneal metastases from gastric cancer, limited data is available from Western countries on metachronous peritoneal disease.[10] A few observational studies reported on recurrence rates of peritoneal metastases after curative surgery in gastric cancer, but these were mostly performed in Asian countries.[19-21] In these studies, the peritoneum was pointed out as recurrence site in 11-17% of all patients with gastric cancer after potentially curative surgery.[19-22] Our study reported metachronous peritoneal metastases in 24% of all patients who underwent potentially curative treatment for non-metastatic gastric cancer. The higher incidence in our study could be due to the fact that diffuse type gastric cancer is more prevalent in Western countries than it is in Asian countries or so called high risk areas.[23] The present study confirms previous data describing the association between diffuse type histology and a higher rate of peritoneal metastases as compared to intestinal type histology.[24] Also, as these previous published studies include a follow-up analysis of an RCT cohort and two single-center cohort studies, a certain selection bias cannot be refuted and may cause the lower peritoneal recurrence rate.[19-22] Since the data registration by the NCR in our study covers the complete Dutch population, this cohort represents unselected patients as they are seen in everyday practice.[25] It is important to note that

the reported incidence of metachronous peritoneal metastases might still be an underestimation of the actual number of peritoneal metastases because patients with non-metastatic gastric cancer who did not undergo potentially curative treatment and patients with distant metastases without peritoneal metastases at primary diagnosis may also develop peritoneal metastases at a later stage of disease. However, the survival of these patients is expected to be very poor.

Over the past decades, the proportion of diffuse type gastric cancer has increased compared to the intestinal type and the diffuse type histology is known to have a poorer prognosis.[26,27] Besides the fact that diffuse type carcinomas more often present with synchronous peritoneal metastases[24], our study showed that the diffuse type histology was strongly associated with the development of metachronous peritoneal metastases. This is in line with a previously published study that used follow-up data from an RCT.[22] This finding implies that a more intensive follow-up, primarily focused on the peritoneal cavity, should be further investigated in clinical trials for patients with diffuse type carcinomas who underwent potentially curative surgery. Besides the strong association of diffuse type histology gastric cancer and the development of metachronous peritoneal metastases, the proportion of patients developing metachronous peritoneal metastases is two times higher than the proportion of patients developing other distant metastases after potentially curative treatment for primary gastric cancer. Currently, routinely performing imaging such as f-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) is not recommended by the Dutch guidelines during follow-up after potentially curative treatment.[28] When patients experience symptoms suspected for recurrence of disease, guidelines recommend that patients receive radiologic examinations and/or a gastrointestinal endoscopic procedure.[28] If peritoneal metastases causes symptoms, which depends on their extent, size, and location, they usually manifest in an advanced stage of disease.[29] It is important to note that a recently published retrospective study found that an intensified follow-up and thus early diagnosis of disease recurrence did not affect the OS of gastric cancer patients. This implies that thorough surveillance strategies still require further investigation.[30] Besides a more intensive follow-up, adjusted treatment strategies could be suggested in this specific patient category. Nowadays, several studies are exploring the value of a prophylactic HIPEC combined to curative surgery in gastric cancer patients.[31-33] The recently published systematic review on this subject included 10 RCTs and 13 nonrandomized controlled trials and stated that the combination of gastric cancer resection and HIPEC could prolong survival.[31] However, they also report that the number of high-quality RCTs was low and patient selection bias probably played

a role in the outcomes of the nonrandomized controlled trials. Therefore, these results should be interpreted with caution. Nonetheless, the phase III GASTRICHIP trial currently investigates the effect of prophylactic HIPEC combined to curative surgery on OS but these results are still being awaited.[34]

This study found that patients with distant metastases at primary diagnosis were less likely to have synchronous peritoneal metastases. At first, this may seem contradictory, but this may be due to the fact that patients with distant metastases at primary diagnosis probably have not undergone extensively diagnostic procedures such as a staging laparoscopy since they are already considered to have unresectable disease. Therefore, peritoneal metastases may have been missed in these patients as detection of peritoneal metastases by radiological imaging alone is usually difficult. Moreover, it has also been reported by Riihimaki et al. that gastric cancer metastasizes either within the peritoneum or hematogenically, and seldom by both routes.[13]

In the present study, gastric cancer patients with metachronous peritoneal metastases were less often treated with systemic treatment than patients with synchronous peritoneal metastases. This may be explained by the rapid disease recurrence after prior given perioperative chemotherapy in patients with metachronous peritoneal metastases. It can be hypothesized that this rapid recurrence can lead to a certain despair against systemic treatment amongst clinicians during the decision-making process regarding the most suitable palliative treatment. In spite of the small number of patients receiving adjuvant therapy (n=66) in this study, patients with a shorter time interval between the last date of adjuvant chemotherapy and date of metachronous peritoneal metastases diagnosis were less often treated with palliative systemic treatment (data not shown) which could support the previous stated hypothesis. Moreover, the extent of peritoneal disease may have caused a difference in administering treatment to synchronous and metachronous peritoneal metastases patients. Unfortunately, no data on the extent of peritoneal metastases were available for patients included in this study.

As shown in this study, patients with peritoneal metastases from gastric origin have a very poor survival and there was no difference in OS between the synchronous and metachronous detection of peritoneal metastases. Interestingly, OS was significantly shorter in patients with early metachronous peritoneal metastases compared to patients with late metachronous or synchronous peritoneal metastases. This difference in survival was also observed in a previously published study on esophagogastric cancer and metastatic disease in general.[4] The more dismal prognosis in early metastatic

disease recurrence in the aforementioned study and our present study may be explained by a more aggressive tumor biology in these patients.

This is the first population-based study on both synchronous and metachronous peritoneal metastases from gastric cancer, providing data which represents unselected patients as seen in daily clinical practice. However, this study also has some limitations. The extent of peritoneal metastases was not available and is known to impact survival.[35-36] Moreover, it should be noted that it was not possible to undergo a primary tumor resection for patients with metachronous peritoneal metastases since the primary tumor was already removed during curative treatment. However, the difference in received treatments was mainly observed for systemic treatment (synchronous peritoneal metastases 35% vs. metachronous peritoneal metastases 18%). Finally, this study showed that there was no association between receiving perioperative treatment or not and the development of metachronous peritoneal metastases, but the NCR does not register the reason why a certain treatment was chosen or not. Moreover, the type of perioperative treatment (FLOT; fluorouracil plus leucovorin, oxaliplatin and docetaxel) that nowadays is being administered in gastric cancer patients is different than the type of perioperative treatment that was used in the present study (ECF/ECX; epirubicine, cisplatine and fluorouracil or capecitabine).[37,38] Therefore, these results should be interpreted with care.

In this study, 31% of all patients with gastric cancer in a Western European country were diagnosed with peritoneal metastases. Almost one quarter of patients with gastric cancer were diagnosed with peritoneal metastases at time of diagnosis. Another 24% of patients who underwent potentially curative treatment, developed metachronous peritoneal metastases from gastric cancer during the first three years of follow-up. Patients with metachronous peritoneal metastases were less often treated with systemic treatment than patients with synchronous peritoneal metastases but survival was comparable between both groups. Future studies are warranted to detect gastric cancer at an earlier stage and to examine strategies that lower the risk of peritoneal dissemination. Also, specific treatment options for patients with gastric peritoneal metastases should be further investigated.

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Chapter

9

Insights into synchronous peritoneal metastases from hepatobiliary origin: incidence, risk factors, treatment, and survival from a nationwide database

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Abstract

Introduction
This population-based study aimed to investigate incidence, risk factors, treatment, and survival of synchronous peritoneal metastases of hepatobiliary origin.

Methods
All Dutch patients diagnosed with hepatobiliary cancer between 2009 and 2018 were selected. Factors associated with peritoneal metastases were identified with logistic regression analyses. Treatments for patients with peritoneal metastases were categorized into local therapy, systemic therapy, and best supportive care (BSC). Overall survival (OS) was investigated using Log-rank test.

Results
In total, 12.649 patients were diagnosed with hepatobiliary cancer of whom 8% (n=1066) were diagnosed with synchronous peritoneal metastases (12% [n=882/6519] in biliary tract cancer [BTC] vs. 4% [n=184/5248] in hepatocellular carcinoma [HCC]). Factors that were positively associated with peritoneal metastases were the female sex (OR 1.18; 95% CI, 1.03-1.35), BTC (OR 2.93; 95% CI, 2.46-3.50), diagnosis in more recent years (2013-2015: OR 1.42; 95% CI, 1.20-1.68; 2016-2018: OR 1.48; 95% CI, 1.26-1.75), T3/T4 stage (OR 1.84; 95% CI, 1.55-2.18), N1/N2 stage (OR 1.31; 95% CI, 1.12-1.53) and other synchronous systemic metastases (OR 1.85; 95% CI, 1.62-2.12). Of all peritoneal metastases patients, 723 (68%) received BSC only. Median OS was 2.7 months (IQR 0.9-8.2) in peritoneal metastases patients.

Conclusions
Synchronous peritoneal metastases were found in 8% of all hepatobiliary cancer patients and occurred more often in BTC than in HCC. Most patients with peritoneal metastases received BSC only. Given the high incidence and dismal prognosis of peritoneal metastases patients, extended research in hepatobiliary peritoneal metastases is needed to achieve better outcome in these patients.

Introduction

Hepatobiliary cancers are a heterogeneous group of cancers originating from the liver (i.e., hepatocellular carcinoma [HCC]) and biliary tract cancer (BTC) (i.e., intrahepatic cholangiocarcinoma [CCA], gallbladder cancer and cystic duct cancer, perihilar CCA and distal CCA). Hepatobiliary cancer is the sixth most common diagnosed cancer worldwide, which can partly be explained by the high incidence of chronic infections with hepatitis B virus or hepatitis C virus in developing countries in Asia and Africa and the upcoming non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) which are the main risk factors for HCC and also common risk factors in biliary tract cancer (BTC).[1,3] The prognosis of HCC and BTC is generally poor with 5-year survival rates of 21% and 7%, respectively.[4-6] However, over the past few decades, treatment options for HCC and BTC patients have rapidly evolved which evidently improved survival outcomes in these patients.[7,8]

It is known that the peritoneum is one of the metastatic sites in advanced hepatobiliary cancer.[2,9-11] However, accurate data on the true incidence, treatment strategies and survival of synchronous peritoneal metastases from hepatobiliary origin is currently lacking. The few available studies focus on the primary hepatobiliary tumor in general and do not provide information on peritoneal metastases specifically. Therefore, the overall burden of peritoneal metastases from hepatobiliary origin is currently unknown.[2,9-11]

In the past decade, various treatment options became available in patients with peritoneal metastases. Radical surgery to remove peritoneal metastases with or without additional intra-peritoneal chemotherapy has shown promising results in colorectal, ovarian and gastric cancer.[12-14] However, no specific treatment strategies for patients with peritoneal metastases from hepatobiliary cancer are given in the current guidelines.[15-16] Therefore, to guide future research, details on the incidence, factors associated with the presence of peritoneal metastases, current treatment strategies and survival outcomes are designated.

The aim of the present study was to investigate incidence and factors associated with the presence of synchronous peritoneal metastases and to determine treatment strategies and survival of patients with hepatobiliary cancer and synchronous peritoneal metastases.

Methods

Data source

Data from the Netherlands Cancer Registry (NCR) were used. The NCR registers all patients with newly diagnosed malignancies in the Netherlands. Data on patient, tumor and treatment characteristics are routinely extracted from the medical records by trained data-managers. For the specification of the anatomical sites of the primary tumors, metastases and morphology of the primary tumor, the International Classification of Diseases for Oncology (ICD-O) valid at time of diagnosis is used. After 2009, separate codes for perihilar CCA and distal CCA were used by the NCR. Primary tumor stage is classified according to the Tumor Node Metastasis (TNM) classification valid at time of diagnosis. In case of unknown pathological T or N stage, clinical T or N stage was used. Due to the use of a different classification staging system before 2012, missing data was present in tumor and nodal stage. Follow-up of vital status was assessed on January 31, 2020 and was obtained by linking the NCR data to the municipal administrative database, in which all deaths and emigrated inhabitants of the Netherlands are registered. The study is approved by the privacy review board of the NCR as well as the scientific committee of the Dutch Hepatocellular & Cholangiocarcinoma Group (DHCG).

Study population

All Dutch patients diagnosed with hepatobiliary cancer between 2009 and 2018 were selected (ICD-O C22, C23, C24). The following patients were excluded: patients with a tumor in the Ampulla of Vater (C24.1) or patients with an unclear primary tumor location in the biliary tract (C24.0-NOS, C24.8, C24.9). Also, patients with neuroendocrine tumors, hepatoblastoma, trabecular carcinoma or mixed type cholangiocellular tumors were excluded based on the following morphology codes from ICD-O: 8013, 8041, 8153, 8180, 8190, 8240, 8244, 8246, 8249, 8574 and 8970. In patients with multiple primary hepatobiliary tumors, the tumor with the highest TNM stage was included. Patient characteristics included in this study were sex, age and year of diagnosis. Tumor characteristics included in this study were tumor stage, nodal stage and location of the primary tumor. The different primary tumors were categorized as HCC (C22.0) or BTC, comprising of intrahepatic CCA (C22.1), gallbladder carcinoma (C23.9; including cystic duct), perihilar CCA (C24.0-perihilar) and distal CCA (C24.0-distal). The following ICD-O codes were included in the definition of peritoneal metastases: C16.0-C16.9, C17.0-C17.9, C18.0-C18.9, C19.9, C20.9, C21.8, C23.9, C26.9, C48.0-C48.8, C49.4-C49.5, C52.9, C54.3-C54.9, C55.9, C56.9, C57.0-C57.8, C66.9, C67.0-C67.9, C76.2. Only metastases at primary diagnosis were included, i.e., synchronous disease. Patients were subcategorized into three groups according to the presence

and site of metastases: 1) synchronous peritoneal metastases, which includes all patients with peritoneal metastases; further subcategorized as 1a) peritoneal metastases without concurrent systemic metastases and 1b) peritoneal metastases with concurrent systemic metastases, 2) synchronous systemic metastases, which includes all patients with metastases other than peritoneal metastases and 3) no metastases, which includes all patients without distant metastases (i.e., M0 stage).

Treatment
Treatments given in patients with hepatobiliary peritoneal metastases in this cohort were categorized into the following groups.

1) Local therapy, defined as tumor-directed treatment that may include palliative resection of the primary hepatobiliary tumor and/or metastasectomy. Additionally, for HCC patients, radiofrequency ablation and transarterial chemo- or radioembolization were also included.
2) Systemic therapy, defined as tumor-directed treatment that may include chemotherapy, immunotherapy and/or targeted therapy.
3) Best supportive care (BSC) defined as no tumor-directed treatment that may include palliative interventions for symptom control (e.g., radiotherapy (on metastases), biliary or duodenum stent or biliary drainage) or receiving no treatment at all.

Statistical analyses
Baseline characteristics were compared between patients with synchronous peritoneal metastases (with or without concurrent systemic metastases), patients with synchronous systemic metastases other than peritoneal metastases and patients without synchronous distant metastases, using the chi-squared test for categorical variables or the Kruskal-Wallis test for continuous variables. Proportion and frequencies of hepatobiliary peritoneal metastases were calculated. Incidence rates of synchronous peritoneal metastases were calculated as the number of new patients per 100.000 inhabitants per year and were age standardized using the Revised European Standardized Rate (RESR).[17] RESR was presented as 3-year moving averages. Trends in incidence were calculated with the Estimated Annual Percent Change (EAPC).

The possible independent influence of sex, age, tumor stage, nodal stage, location of primary tumor, synchronous systemic metastases, and period of diagnosis on the presence of synchronous peritoneal metastases was tested by using uni- and multivariable logistic regression analyses.

The different treatments were compared in patients with hepatobiliary peritoneal metastases. For survival analyses, the Log-rank test was used to compare overall survival (OS) between the groups of patients with or without synchronous peritoneal metastases. In patients with synchronous peritoneal metastases, further comparisons on OS according to different treatments were performed, as well as comparisons according to different locations of primary tumors (HCC, intrahepatic CCA, gallbladder carcinoma and cystic duct carcinoma, perihilar CCA and distal CCA). Survival was defined as the time from diagnosis of the primary tumor until death or last follow-up date (January 31, 2020). Univariable cox regression analyses were performed in all patients with synchronous peritoneal metastases to identify characteristics associated with a poorer OS. Variables significant in univariable analyses ($p < 0.20$) were used in a multivariable cox regression model. SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC, United States) was used for all analyses. A p-value < 0.05 was considered statistically significant.

Results

Study population

Between 2009 and 2018, 12.786 patients were diagnosed with hepatobiliary cancer. Of these, 137 patients were excluded as they did not meet the included primary tumor morphology codes in this study. The final study population comprised 12.649 patients (HCC [n=5248, 41%] vs. BTC [n=7401, 59%]). Among them, 1066 (8%) patients had synchronous peritoneal metastases, 2630 (21%) patients had synchronous systemic metastases other than peritoneal metastases and 8953 (71%; HCC, 4287 [58%] vs. BTC, 4666 [52%]) patients had no systemic metastases at time of diagnosis. Within the patients with peritoneal metastases, 604 (57%) patients presented with peritoneal metastases and no concurrent systemic metastases, while462 (43%) patients presented with concurrent systemic metastases. Baseline characteristics are depicted in *Table 1*.

In 313 (29%) patients, peritoneal metastases were pathologically confirmed and in 356 (33%) patients, peritoneal metastases were radiologically confirmed. In 397 (37%) patients, the basis of diagnosis (radiological or pathological examination) was unknown.

Table 1. Patient- and tumor characteristics of patients with hepatobiliary cancer.

	Total group n=12 649	**PM without concurrent systemic metastases** n=604	**PM with concurrent systemic metastases** n=462	**Systemic metastases and not PM** n=2630	**No metastases** n=8953	*P value*[a]
Sex, No. (%)						
Male	7513	297 (49)	220 (48)	1434 (55)	5562 (62)	**<0.001**
Female	5136	307 (51)	242 (52)	1196 (45)	3391 (38)	
Age at diagnosis, median (IQR)		70 (61-77)	68 (60-76)	69 (61-77)	70 (62-78)	**<0.001**
Period of diagnosis, No. (%)						
2009-2011	4191	187 (31)	120 (26)	847 (32)	2527 (34)	**0.002**
2012-2014	3923	199 (33)	150 (32)	769 (29)	2248 (31)	
2015-2018	4535	218 (36)	192 (42)	1014 (39)	2594 (35)	
Primary tumor location, No. (%)						
HCC	5248	112 (19)	72 (16)	777 (30)	4287 (58)	**<0.001**
BTC	7401	492 (81)	390 (84)	1853 (70)	4666 (52)	
Tumor stage, No. (%)						
T1/T2	4875	136 (23)	92 (20)	636 (24)	4011 (45)	**<0.001**
T3/T4	4275	244 (40)	180 (39)	951 (36)	2900 (32)	
Missing data	3499	224 (37)	190 (41)	1043 (40)	2042 (23)	

Table 1. Patient- and tumor characteristics of patients with hepatobiliary cancer. (continued)

	Total group n=12 649	**PM without concurrent systemic metastases** n=604	**PM with concurrent systemic metastases** n=462	**Systemic metastases and not PM** n=2630	**No metastases** n=8953	*P value*[a]
Nodal stage, No. (%)						
N0	6361	239 (40)	119 (26)	839 (32)	5164 (58)	**<0.001**
N1/N2	3457	188 (31)	224 (48)	1157 (44)	1888 (21)	
Missing data	2831	177 (29)	119 (26)	634 (24)	1901 (21)	

[a]Missing data were not included in the comparative analyses; Percentages might not add up to 100% due to rounding; *PM* peritoneal metastases, *IQR* interquartile range; *HCC* Hepatocellular carcinoma; *BTC* biliary tract cancer.

Incidence of peritoneal metastases

Synchronous peritoneal metastases were found in 12% (n=882/6519) of patients with BTC (17% [n=273/1378] in gallbladder cancer and cystic duct cancer, 14% [n=245/1750] in intrahepatic CCA, 12% [n=266/1907] in perihilar CCA and 5% [n=98/1729] in distal CCA) and in 4% (n=184/5248) of patients with HCC (*Figure 1*). The proportion of hepatobiliary synchronous peritoneal metastases increased slightly but significantly over time (7.0% in 2009 vs. 8.5% in 2018, p = 0.005) (*Figure 2A*). The 3-year moving average of RESR was 0.48 per 100.000 individuals in 2010 and increased to 0.81 per 100.000 individuals in 2017 (*Figure 2B*). The corresponding EAPC for peritoneal metastases from hepatobiliary cancer showed a significant annual increase of 7.3% (p < 0.001).

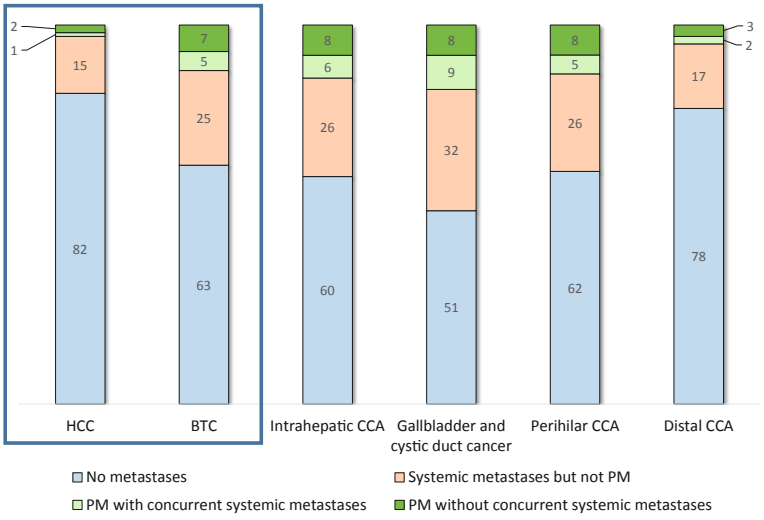


Figure 1. Presence of (type of) metastases for the different hepatobiliary cancers. *HCC* hepatocellular carcinoma; *BTC* biliary tract cancer; *CCA* cholangiocarcinoma.

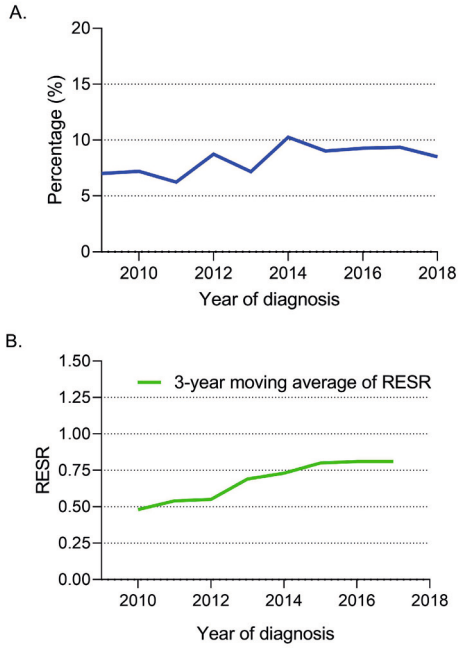


Figure 2. A) Proportion of hepatobiliary cancer patients presenting with synchronous peritoneal metastases in all hepatobiliary cancer patients, diagnosed between 2009 and 2018 (p = 0.005). **B)** 3-year moving average trends in incidence of patients with hepatobiliary cancer with synchronous peritoneal metastases between 2009 and 2018 in the Netherlands.
RESR revised European standardized rate.

Factors associated with synchronous hepatobiliary peritoneal metastases

In multivariable logistic regression analyses, the following factors were positively associated with the presence of synchronous peritoneal metastases (*Table 2*): the female sex, diagnosis in 2013-2015 or 2016-2018, BTC, T3/T4 stage tumor, N+ stage and synchronous systemic metastases at other sites. In patients aged >65 years, a significantly lower incidence of synchronous peritoneal metastases was found compared to patients aged <65 years.

Table 2. Uni- and multivariable logistic regression analyses for the likelihood of peritoneal metastases among hepatobiliary cancer patients diagnosed between 2009 and 2018 in the Netherlands.

	Total group n=12 649	**Univariable logistic regression analyses**			**Multivariable logistic regression analysis**		
		OR	95% CI	*P value*	OR	95% CI	*P value*
Sex				**<0.001**			
Male	7513 (59)	Ref.	Ref.		Ref.	Ref.	Ref.
Female	5136 (41)	1.62	1.43-1.84		1.18	1.03-1.35	**0.014**
Age at diagnosis				**<0.001**			
<65 years	4028 (32)	Ref.	Ref.		Ref.	Ref.	Ref.
65-75 years	4233 (33)	0.88	0.76-1.03		0.83	0.71-0.97	**0.021**
>75 years	4388 (35)	0.74	0.63-0.86		0.62	0.53-0.73	**<0.001**
Period of diagnosis				**<0.001**			
2009-2012	4191 (33)	Ref.	Ref.		Ref.	Ref.	Ref.
2013-2015	3923 (31)	1.24	1.05-1.45		1.42	1.20-1.68	**<0.001**
2016-2018	4535 (36)	1.26	1.08-1.47		1.48	1.26-1.75	**<0.001**
Primary tumor location				**<0.001**			
HCC	5248 (41)	Ref.	Ref.		Ref.	Ref.	Ref.
BTC	7401 (59)	3.72	3.16-4.38		2.93	2.46-3.50	**<0.001**

Table 2. Uni- and multivariable logistic regression analyses for the likelihood of peritoneal metastases among hepatobiliary cancer patients diagnosed between 2009 and 2018 in the Netherlands. (continued)

	Total group n=12 649	**Univariable logistic regression analyses**			**Multivariable logistic regression analysis**		
		OR	95% CI	*P value*	OR	95% CI	*P value*
Tumor stage				**<0.001**			
T1/T2	4875 (39)	Ref.	Ref.		Ref.	Ref.	Ref.
T3/T4	4275 (34)	2.24	1.90-2.65		1.84	1.55-2.18	**<0.001**
Missing data	3499 (28)	2.74	2.31-3.24		1.79	1.48-2.16	**<0.001**
Nodal stage				**<0.001**			
N0	6361 (50)	Ref.	Ref.		Ref.	Ref.	Ref.
N1/N2	3457 (27)	2.27	1.96-2.63		1.31	1.12-1.53	**<0.001**
Missing data	2831 (22)	1.96	1.67-2.30		1.70	1.42-2.03	**<0.001**
Synchronous distant metastases				**<0.001**			
No	9557 (76)	Ref.	Ref.		Ref.	Ref.	Ref.
Yes	3092 (24)	2.60	2.29-2.96		1.85	1.62-2.12	**<0.001**

HCC hepatocellular carcinoma; *BTC* biliary tract cancer; *OR* Odds Ratio; *CI* Confidence Interval.

Treatment of hepatobiliary peritoneal metastases

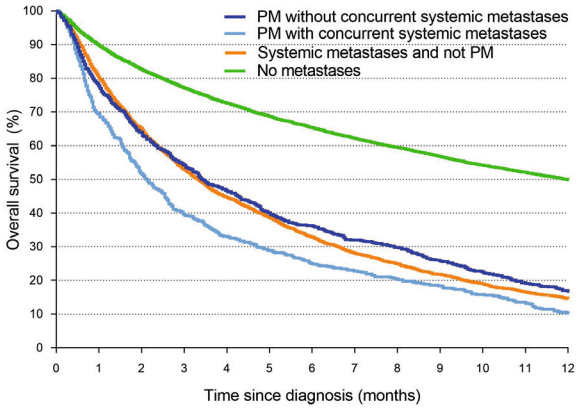
Among all patients with synchronous peritoneal metastases (n=1066), 343 (32%) patients received tumor-directed treatment while 723 (68%) patients did not receive any tumor directed treatment. Among the patients who received tumor-directed treatment, 77 (22%) patients underwent local therapy from whom 25 patients also received systemic therapy. Systemic therapy as only treatment was given in 266 (78%) patients. No patients underwent resection of the peritoneal metastases and no patients received pressurized intraperitoneal aerosol chemotherapy (PIPAC).

In patients who received systemic therapy, details regarding the prescribed regimens were registered in 142 (53%) patients. Sorafenib was the mostly used agent in patients with HCC (n=30) and the combination of gemcitabine and cisplatin was the mostly used combination in biliary tract cancer (n=98).

Survival

Median OS of all patients with synchronous peritoneal metastases was 2.7 months (interquartile range [IQR] 0.9-8.2); 3.4 months (IQR 1.1-9.3) for patients with peritoneal metastases and no concurrent systemic metastases and 2.1 months (IQR 0.8-6.0) for patients with peritoneal metastases and concurrent systemic metastases. Median OS was 3.3 months (IQR 1.3-8.0) for patients with systemic metastases other than peritoneal metastases and 11.9 months (IQR 3.5-36.5) for patients without distant metastases (i.e., M0 stage) (*Figure 3a*, $p < 0.001$). Among patients with synchronous peritoneal metastases, median OS was 8.6 months (IQR 3.5-14.2) for patients who underwent tumor-directed treatment (i.e., local therapy; 10.5 months [IQR 5.2-17.8]) or systemic therapy; 7.8 months [IQR 3.4-13.2]) and 1.7 months (IQR 0.7-4.0) in patients who received BSC only (*Figure 3b*, $p < 0.001$).

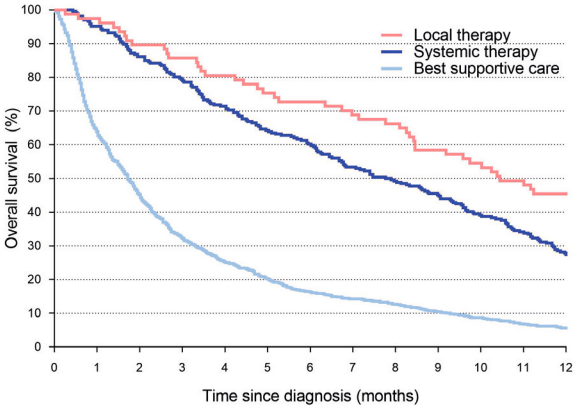
Median OS was 1.9 months (IQR 0.7-5.7), 2.7 months (IQR 0.8-9.1), 2.8 months (IQR 1.1-7.5), 3.0 months (IQR 1.0-9.3) and 3.9 months (IQR 1.5-7.8) in patients with peritoneal metastases from HCC, intrahepatic CCA, gallbladder and cystic duct cancer, perihilar CCA and distal CCA, respectively (*Figure 3c*, $p = 0.460$).



Number at risk (censored)

No metastases	8953 (0)	6902 (3)	5834 (4)	5068 (4)	3474 (4)
Systemic metastases but not PM	2630 (0)	1388 (3)	861 (0)	570 (1)	358 (0)
PM with concurrent systemic metastases	462 (0)	181 (1)	114 (0)	84 (0)	44 (0)
PM without concurrent systemic metastases	604 (0)	328 (0)	219 (0)	156 (0)	92 (0)

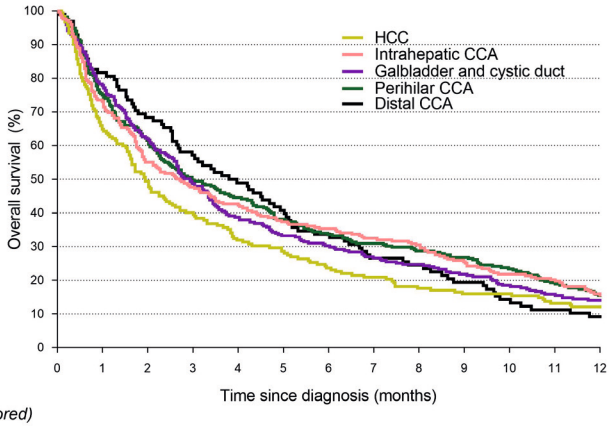
Figure 3a. Overall survival of all patients with hepatobiliary cancer according to presence and localization of metastases (Log-rank: $p < 0.001$).
PM peritoneal metastases.



Number at risk (number censored)

Local therapy	77 (0)	66 (0)	56 (0)	45 (0)	32 (0)
Systemic therapy	266 (0)	211 (0)	160 (0)	120 (0)	69 (0)
Best supportive care	723 (1)	232 (0)	117 (0)	75 (0)	35 (0)

Figure 3b. Overall survival of all patients with peritoneal metastases of hepatobiliary origin according to treatment strategy (Log-rank: $p < 0.001$).



Number at risk (number censored)

HCC	184 (0)	73 (0)	43 (0)	29 (0)	18 (9)
Intrahepatic CCA	245 (1)	116 (0)	86 (0)	62 (0)	36 (6)
Galbladder and cystic duct	273 (0)	132 (0)	82 (0)	59 (0)	35 (7)
Perihilar CCA	266 (0)	132 (0)	89 (0)	71 (0)	39 (5)
Distal CCA	98 (0)	56 (0)	33 (0)	19 (0)	9 (0)

Figure 3c. Overall survival of all patients with peritoneal metastases according to location of the primary tumor (Log-rank: p = 0.460).
CCA cholangiocarcinoma.

In multivariable analyses, age >75 years (hazard ratio [HR] 1.66; 95% confidence interval [CI], 1.42-1.95), N+ stage (HR 1.25; 95% CI, 1.07-1.45) and the presence of systemic metastases (HR 1.49; 95% CI, 1.31-1.70) were associated with worse OS in patients with peritoneal metastases. Undergoing local therapy (HR 0.38; 95% CI, 0.29-0.48) and receiving systemic therapy (HR 0.43; 95% CI, 0.37-0.51) were associated with improved OS (*Table 3*).

Table 3. Uni- and multivariable cox regression analyses for survival of all patients with peritoneal metastases from hepatobiliary origin.

	Total group n=1066	**Median OS** (months)	**Univariable cox regression analyses**			**Multivariable cox regression analysis**		
			HR	95% CI	*P value*	HR	95% CI	*P value*
Sex					0.272			
Male	517 (49)	2.3	Ref.	Ref.		-	-	
Female	549 (52)	2.8	0.93	0.83-1.06		-	-	
Age at diagnosis					**<0.001**			
<65 years	386 (36)	4.8	Ref.	Ref.		Ref.	Ref.	Ref.
65-75 years	362 (34)	2.9	1.22	1.06-1.41		1.10	0.95-1.27	0.225
>75 years	318 (30)	1.6	2.07	1.78-2.42		1.66	1.42-1.95	**<0.001**
Period of diagnosis					0.766			
2009-2012	307 (29)	2.6	Ref.	Ref.		-	-	
2013-2015	349 (33)	3.3	0.98	0.84-1.14		-	-	
2016-2018	410 (38)	2.4	1.03	0.89-1.20		-	-	
Primary tumor location					0.094			
HCC	184 (17)	1.9	Ref.	Ref.		-	-	
BTC	882 (83)	3.0	0.87	0.74-1.02		-	-	

Table 3. Uni- and multivariable cox regression analyses for survival of all patients with peritoneal metastases from hepatobiliary origin. (continued)

	Total group n=1066	**Median OS** (months)	**Univariable cox regression analyses**			**Multivariable cox regression analysis**		
			HR	95% CI	*P value*	HR	95% CI	*P value*
Tumor stage					**<0.001**			
T1/T2	228 (21)	3.8	Ref.	Ref.		Ref.	Ref.	Ref.
T3/T4	424 (40)	3.2	1.15	0.98-1.36		1.01	0.85-1.19	0.939
Missing data	414 (39)	2.2	1.49	1.27-1.76		1.10	0.93-1.31	0.279
Nodal stage					**<0.001**			
N0	358 (34)	3.8	Ref.	Ref.		Ref.	Ref.	Ref.
N1/N2	412 (39)	2.7	1.29	1.11-1.49		1.25	1.07-1.45	**0.004**
Missing data	296 (28)	1.9	1.65	1.41-1.93		1.53	1.30-1.79	**<0.001**
Treatment					**<0.001**			
Best supportive care	723 (68)	1.7	Ref.	Ref.		Ref.	Ref.	Ref.
Local therapy	77 (7)	10.5	0.32	0.25-0.41		0.38	0.29-0.48	**<0.001**
Systemic treatment	266 (25)	7.8	0.41	0.36-0.48		0.43	0.37-0.51	**<0.001**

Table 3. Uni- and multivariable cox regression analyses for survival of all patients with peritoneal metastases from hepatobiliary origin. (continued)

	Total group n=1066	**Median OS** (months)	**Univariable cox regression analyses**			**Multivariable cox regression analysis**		
			HR	95% CI	*P value*	HR	95% CI	*P value*
Synchronous distant metastases					**<0.001**			
No	604 (57)	3.4	Ref.	Ref.		Ref.	Ref.	Ref.
Yes	462 (43)	2.1	1.32	1.17-1.50		1.49	1.31-1.70	**<0.001**

HCC hepatocellular carcinoma; *BTC* biliary tract cancer; *OS* overall survival; *HR* Hazard Ratio; *CI* Confidence Interval.

Discussion

This first population-based study investigating hepatobiliary peritoneal metastases shows that synchronous peritoneal metastases were found in 8% of patients diagnosed with hepatobiliary cancer. Peritoneal metastases occurred more often in patients with biliary tract cancers as compared to patients with HCC. Only a minority of the patients with hepatobiliary cancer and synchronous peritoneal metastases received tumor-directed treatment and the prognosis of these patients is very poor.

The incidence of synchronous peritoneal metastases in BTC patients is notably higher than in HCC patients. In this study, synchronous peritoneal metastases are frequently present in BTC and were found in 12% of these patients, which is similar to previously reported incidences.[2,10,18] A small German cohort study identified a higher incidence of peritoneal metastases in patients with intrahepatic CCA (22%, vs. 14% in this study). This can be explained by the fact that the German study also included metachronous metastases.[6] However, this study contained only single-center data of 370 patients with intrahepatic CCA. Therefore, the reported incidence of peritoneal metastases from BTC in this study with comprehensive population-based data is likely to give a more accurate estimation of the true incidence of synchronous peritoneal metastases from BTC.

In the current study, the incidence of synchronous peritoneal metastases was low in patients with HCC (4%). Available literature showed that incidences of peritoneal metastases in HCC patients ranged from 3% up to 12%.[19-22] The highest incidence of peritoneal metastases (12%) was reported in a previously published study of 135 patients with HCC in which all patients had a rupture of the hepatocellular tumor. Although the mechanism of peritoneal dissemination in HCC patients has not been completely elucidated, it is logical to assume that rupture of the primary tumor provokes peritoneal seeding due to direct spillage and thereby spread of cancer cells into the peritoneal cavity.[21-23] Few previous studies also reported on peritoneal dissemination after radiofrequency ablations (RFA), which is one of the curative treatment options for HCC.[24,25] Llovet et al. described that peritoneal dissemination was found in 13% of 32 patients with HCC after performing RFA.[25]

A T4 stage tumor, N+ stage and synchronous systemic metastases were associated with the presence of synchronous peritoneal metastases. These risk factors were previously identified for peritoneal metastases from other primary malignancies, such as colorectal cancer and gastric cancer and underscores the more advanced tumor stage in which peritoneal

metastases occur.[26,27] Diagnosis of the primary hepatobiliary tumor in the most recent years of this study was also positively associated with the presence of peritoneal metastases. The improved use and precision of imaging techniques, such as positron emission tomography (PET) - computed tomography (CT) and diffusion-weighted magnetic resonance imaging, together with increased awareness for peritoneal metastases, could have contributed to higher detection rates and incidence of peritoneal metastases.[28,29] Also, BTC in comparison with HCC was associated with the presence of peritoneal metastases. This implies that these different tumor types should probably be regarded as different disease entities resulting in different metastatic patterns. In contrast, older age (>75 years) was associated with a lower incidence of synchronous peritoneal metastases. Older patients often have a poor condition in comparison with younger patients and thus probably receive a less thorough diagnostic work-up which reduces the chance of discovering peritoneal metastases.

Almost 70% of all patients with synchronous peritoneal metastases did not receive any tumor-directed treatment, probably due to the late discovery of the disease which results in extensive disease at time of diagnosis. As a result, curative intent therapy is often not possible in this advanced tumor stage. In this study, median OS was five times higher in patients with synchronous peritoneal metastases who received tumor-directed treatment compared to patients who received BSC only. This large difference in median OS is probably largely the result of treatment selection bias as patients with a good performance status and less extensive disease are generally more likely to receive tumor-directed treatment. Moreover, it is important to note that median OS might not be the most suitable endpoint to validate therapeutic strategies in peritoneal metastases patients. Instead of using OS, quality of life or patient reported outcomes (PROs) might provide a more valuable insight in the effect of given therapies since it often concerns very fragile patients. Unfortunately, our study did not contain any data on quality of life but this should be investigated in future studies on PROs.

In the past decade, more systemic treatment options became available for advanced BTC and HCC patients.[7,8] However, data on systemic treatment strategies specifically in hepatobiliary peritoneal metastases are still scarce. In this study details on specific systemic treatments are lacking in a large proportion of patients. Hence, future studies on systemic treatment options are warranted for patients with hepatobiliary peritoneal metastases. Curative intent treatment options like cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) in patients with peritoneal metastases are previously described in colorectal, ovarian, and

gastric cancer.[12-14] In contrast, only few cohort studies investigated CRS-HIPEC in patients with hepatobiliary peritoneal metastases.[30-32] In a retrospective cohort study, Mehta et al. reported a prolonged 5-year survival in HCC patients after CRS-HIPEC of 49.4%.[30] However, they believe that selection bias may have played a significant role and they stress the importance of the extent of peritoneal disease regarding the favorable outcomes in this study. Another retrospective cohort study explored the role of CRS-HIPEC in biliary cancer patients and they found an improved OS in these patients in comparison to systemic therapy alone.[31] However, this study included only a limited study population and it was not possible to exclude selection bias. Still, these encouraging results suggests that future prospective research on intraperitoneal treatment strategies may be helpful to provide more insight into potential effective treatment options for these patients. For patients with more extensive disease, experimental treatment options like PIPAC are being studied in patients with a variety of gastrointestinal tumors.[33,34] As PIPAC is currently not standard of care in the Netherlands, our study did not contain patients who received PIPAC as palliative treatment. With the high incidence of peritoneal metastases in hepatobiliary cancer and promising results regarding PIPAC in other primary malignancies, this treatment option should be further investigated for this specific patient category.

However, it is important to keep in mind that there are some difficulties when considering local treatment for hepatobiliary peritoneal metastases. HCC has high recurrence rates of 70% at 5 years after curative intent primary tumor resection.[35] Therefore, recurrence after CRS-HIPEC is very likely in HCC patients. Also, infectious complications, like cholangitis, are common in BTC patients after curative resection.[36] Thus, to perform local treatment of peritoneal metastases at a later point in time could be challenging due to the resulting adhesions.

In the present cohort, the prognosis of patients with synchronous peritoneal metastases of hepatobiliary origin is poor with a median OS of 2.7 months. As shown in this study, there is no difference in survival between patients with peritoneal metastases from HCC and peritoneal metastases from BTC. In contrast, previous studies have shown that in patients with HCC with other distant metastases than peritoneal metastases (i.e., lung-, lymph node- and bone metastases), OS was considerably higher (8 months) than the reported OS of HCC patients with peritoneal metastases in this study (3 months).[2,37] This indicates that survival is worse when peritoneal metastases are present in HCC.

Although this is the first nationwide study on synchronous peritoneal metastases from hepatobiliary origin, it has several limitations. Firstly, there is no data available on metachronous hepatobiliary peritoneal metastases because the NCR only comprises metastases diagnosed simultaneously with the primary hepatobiliary tumor. Population-based studies with adequate follow-up information on metachronous peritoneal metastases are warranted to provide a more complete overview of the total burden of hepatobiliary peritoneal metastases. Furthermore, data on extent of peritoneal disease, possible influence of performance status, differentiation grade and morphology of the primary tumor on incidence of peritoneal metastases, treatment and OS could not be investigated since these data were missing in a substantial number of patients. Moreover, no pathological confirmation of peritoneal metastases diagnosis was available in a part of the patients in this study and radiological examination used as diagnostic tool for the diagnosis of peritoneal metastases is more sensitive to fault diagnosis as compared to a histological examination. However, as limited data is currently available on peritoneal metastases in hepatobiliary cancer this study provides unique and valuable information from a large nationwide cohort which may be used as basis for future diagnostic or therapeutic research on this relevant patient category.

In this nationwide cohort, synchronous peritoneal metastases were diagnosed in 8% of all patients with hepatobiliary cancer. A higher proportion of peritoneal metastases was found in BTC than in HCC (12% vs. 3%). Survival of patients with peritoneal metastases was poor in all primary hepatobiliary tumors. Also, the vast majority of all patients with peritoneal metastases did not receive tumor-directed treatment and survival in patients who received BSC only was 1.7 months. Given the high incidence and poor prognosis, development of treatment strategies for patients with hepatobiliary peritoneal metastases is warranted.

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Chapter 10

Incidence, treatment, and survival of synchronous peritoneal metastases in pancreatic cancer: update of a nationwide cohort

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Abstract

Introduction
The aim of the study was to gain insight in the incidence, treatment, and survival of patients with synchronous pancreatic peritoneal metastases.

Methods
All patients diagnosed with pancreatic cancer between 2008 and 2018 in the Netherlands Cancer Registry were evaluated. The patients were subcategorized as (1) synchronous peritoneal metastases, (2) synchronous systemic metastases, and (3) no metastases.

Results
In total, 25.334 patients with pancreatic cancer were included. Among them, 3524 (14%) presented with synchronous peritoneal metastases, 10.659 (42%) with systemic metastases, and 11.151 (44%) without metastases at the time of diagnosis. The proportion of the patients diagnosed with peritoneal metastases increased over time (11%, 2008; 16%, 2018; $p < 0.001$). Of these patients, 964 (27%) received cancer treatment and 2560 (73%) received best supportive care (BSC) only. The median overall survival (OS) in patients with peritoneal metastases, systemic metastases, and without metastases was 1.9, 2.4, and 8.0 months, respectively ($p < 0.001$). In the patients with peritoneal metastases, the median OS was 5.0 months when undergoing cancer treatment and 1.3 months with BSC ($p < 0.001$).

Conclusions
Patients with pancreatic cancer are increasingly diagnosed with synchronous peritoneal metastases. Given the current dismal prognosis, research to improve treatment is designated for this patient category.

Introduction

Pancreatic cancer is known for its poor prognosis, with a reported median overall survival (OS) of 3.5 months and a 5-year median OS of 7%.[1,2] A phenomenon underlying this poor prognosis is late discovery of the disease, resulting in locally advanced or metastatic disease at time of diagnosis in approximately 80% of the patients.[3–7] In recent years, systemic treatment options for advanced pancreatic cancer have rapidly evolved. The use of combination chemotherapy with fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) as well as nab-paclitaxel and gemcitabine as the first-line treatment in patients with metastatic pancreatic cancer demonstrated a significantly better median OS (11.1 and 8.5 months, respectively) compared with gemcitabine (6.8 months), being the standard regimen in these patients.[8–10]

The peritoneal cavity is one of the most common metastatic sites in pancreatic cancer.[11] However, as peritoneal metastases are very difficult to detect by traditional imaging, only limited data regarding the incidence, treatment, and prognosis of this metastatic form of pancreatic cancer are available. As response measurement to evaluate systemic treatment is not possible in patients with peritoneal metastases, these patients are usually excluded from clinical trials. Therefore, very little is known about systemic treatment of patients with peritoneal metastases from pancreatic origin.

The aim of the current study was to investigate the trend in the incidence of synchronous pancreatic peritoneal metastases and to gain insight in the treatment strategies and survival of these patients.

Methods

Data source

All patients with newly diagnosed malignancies in the Netherlands are registered by the Netherlands Cancer Registry (NCR). Data on patient, tumor, and treatment characteristics were extracted from medical records by trained data managers of the NCR. The International Classification of Diseases for Oncology (ICD-O), valid at time of diagnosis, was used for the specification of the anatomical sites of the primary tumor and metastases. Localization of the primary tumor was categorized as pancreatic head (C25.0), pancreatic body (C25.1), pancreatic tail (C25.2), and other (comprising pancreatic duct, pancreatic neck, and pancreas not otherwise specified: C25.3, C25.7–C25.9). All ICD-O codes included in the definition of peritoneal metastases are presented in *Supplementary Table 10.1*. The TNM classification valid at time

of diagnosis was used for stage notification of the primary tumor. In case of unknown pathological tumor or nodal stage, clinical tumor or nodal stage were used. Vital status of all patients was obtained by linking NCR data to the Municipal Records Database. This database contains all deaths and emigrated inhabitants of the Netherlands. Follow-up was complete until January 31, 2020. Data collected by the NCR are anonymized and deidentified. According to the Central Committee on Research involving Human Subjects (CCMO, the Hague, the Netherlands), no ethics approval is obligated for this study design. The Privacy Review Board of the Netherland Cancer Registry approved this study.

Study population

All patients diagnosed with pancreatic cancer between 2008 and 2018 were selected from the NCR. Patients with neuroendocrine tumors were excluded. In patients who presented with multiple primary pancreatic tumors, the tumor with the first incidence date was included. Patient characteristics included in this study are sex, age, and year of diagnosis. Tumor characteristics included in this study are localization of the primary tumor, tumor stage, and nodal stage. All metastases were diagnosed at time of diagnosis of the primary tumor (synchronous metastases). Patients were subcategorized according to sites of metastases as follows: (1) peritoneal metastases, which include all patients with peritoneal metastases with and without concurrent systemic metastases; (2) systemic metastases, which include all patients with systemic metastases at 1 or more locations; and (3) no metastases, which include all patients without metastases at time of diagnosis.

Treatments

Treatments given in this cohort were divided into 2 groups:

1. Cancer treatment, including systemic therapy (chemotherapy or targeted therapy), resection of the primary tumor, metastasectomy, radiotherapy to primary tumor or metastases.
2. Best supportive care (BSC), being no surgical or systemic treatment, except for palliative interventions (eg, gastroenterostomy and/or hepatojejunostomy, duodenal stent, or biliary drainage).

Statistical Analysis

Differences in baseline characteristics were analyzed by means of the chi-squared test for categorical variables or one-way ANOVA test for continuous variables. The Revised European Standardized Rate (RESR) was used for incidence rates, calculated as the number of newly diagnosed patients per 100.000 inhabitants per year, standardized by age. Although the RESR is the most up-to-date tool to calculate incidence rates, also the ESR was

calculated, as this currently is the most commonly used rate in available literature.[12] Trends in incidence were calculated through the estimated annual percent of change. Treatments for patients diagnosed in different periods (2008–2010, 2011–2013, 2014–2016, and 2017–2018) were compared to explore any changes in treatment strategies over time. Differences in treatment strategies were analyzed by means of the chi-squared test. Survival was compared, between the different groups according to presence and localization of metastases, between the different treatment groups and between the different chemotherapy regimens, using the Log-rank test. Survival was defined from time of diagnosis until death. All patients alive on January 31, 2020, were censored. Univariable cox regression analyses were performed to investigate the influence of sex, age, period of diagnosis, tumor location, tumor stage, nodal stage, presence of peritoneal metastases, and treatment on survival. Thereafter, variables significant in univariable cox regression analyses were used in a multivariable cox regression model. SAS/STAT statistical software (SAS System 9.4; SAS Institute, Cary, NC) was used for all analyses. All tests were 2-sided and conducted at the 5% level of significance.

Results

Study population

Between 2008 and 2018, 25.334 patients were registered in the NCR with pancreatic cancer. Among them, 3524 (14%) had peritoneal metastases, 10.659 (42%) had systemic metastases, and 11.151 (44%) had no metastases. In patients with peritoneal metastases, 1326 (38% of the total peritoneal metastases) presented with solitary peritoneal metastases, whereas 2198 (62% of the total peritoneal metastases) presented with peritoneal metastases and other systemic metastases (*Figure 1*).

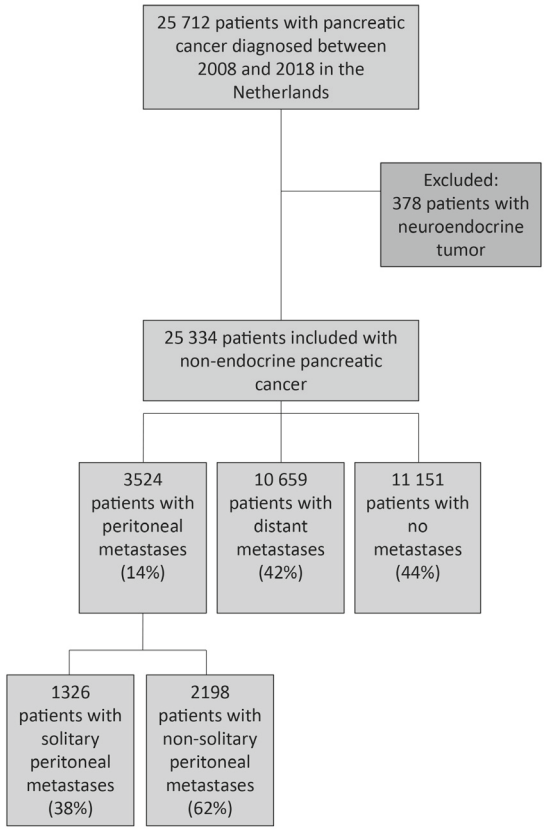

Figure 1. Flowchart of the study population.

Of all the patients with pancreatic cancer (n=25.334), the liver (n=10.710, 42%) was the most prevalent metastatic site, the peritoneum (n=3524, 14%) was the second most prevalent, the lungs (n=2607, 10%) were the third most prevalent site, and distant lymph nodes (n=2152, 8%) were the fourth most prevalent site of metastases. Baseline characteristics of the study population according to the groups by presence and sites of metastases are presented in *Table 1*.

In the patients with peritoneal metastases, 1152 (33%) had a primary pancreas tumor located in the tail, 1011 (29%) had a primary tumor located in the head, 629 (18%) had a primary tumor located in the body, and 732 (21%) patients had a location of the tumor that was not specified.

Table 1. Patient- and tumor characteristics

	Peritoneal metastases without systemic metastases n=1326	**Peritoneal metastases with systemic metastases** n=2198	**Systemic metastases** n=10 659	**No metastases** n=11 151	*P value*
Sex, No. (%)					**<0.001**
Male	692 (52)	1110 (51)	5564 (52)	5387 (48)	
Female	634 (48)	1088 (50)	5095 (48)	5764 (52)	
Age at diagnosis, No. (%)					**<0.001**
<65 years	392 (30)	717 (32)	3338 (31)	2883 (26)	
65-75 years	490 (37)	807 (37)	3745 (35)	3595 (32)	
>75 years	444 (33)	674 (31)	3576 (34)	4673 (42)	
Median age (interquartile range)	70 (63-77)	69 (62-76)	70 (62-77)	72 (64-80)	**<0.001**
Period of diagnosis, No. (%)					**<0.001**
2008-2010	294 (22)	433 (20)	2675 (25)	2845 (26)	
2011-2013	335 (25)	510 (23)	2770 (26)	2950 (26)	
2014-2016	401 (30)	701 (32)	3023 (28)	3124 (28)	
2017-2018	296 (22)	554 (25)	2191 (21)	2232 (20)	

Table 1. Patient- and tumor characteristics (continued)

	Peritoneal metastases without systemic metastases n=1326	**Peritoneal metastases with systemic metastases** n=2198	**Systemic metastases** n=10 659	**No metastases** n=11 151	*P value*
Localization primary tumor, No. (%)					**<0.001**
Head	472 (36)	539 (25)	5323 (50)	8434 (76)	
Body	234 (18)	395 (18)	1522 (14)	946 (9)	
Tail	352 (27)	800 (36)	2157 (20)	662 (6)	
Other	268 (20)	464 (21)	1657 (16)	1109 (10)	
Tumor stage, No. (%)					**<0.001**
T0-T3	609 (46)	1141 (52)	5663 (53)	6368 (57)	
T4	384 (29)	517 (24)	2245 (21)	2705 (24)	
Unknown	333 (25)	540 (25)	2751 (26)	2078 (19)	
Nodal stage, No. (%)					**<0.001**
N0	507 (38)	647 (29)	3567 (33)	4582 (41)	
N1/N2	330 (25)	768 (35)	3806 (36)	4080 (37)	
Unknown	489 (37)	783 (36)	3286 (31)	2489 (22)	

Incidence of peritoneal metastases

The number of patients diagnosed with peritoneal metastases from pancreatic cancer increased over time (11% in 2008, 16% in 2018, $p < 0.001$; *Figure 2A*). The RESR was 1.61 per 100,000 individuals in 2008 and increased to 2.46 per 100,000 individuals in 2018. The ESR increased over time from 1.09 per 100,000 individuals in 2008 to 1.55 per 100,000 individuals in 2018 (*Figure 2B*). The corresponding estimated annual percent of change for peritoneal metastases from pancreatic cancer showed a significant overall annual increase of 5.0% (RESR, $p < 0.001$) and 4.5% (ESR, $p < 0.001$).

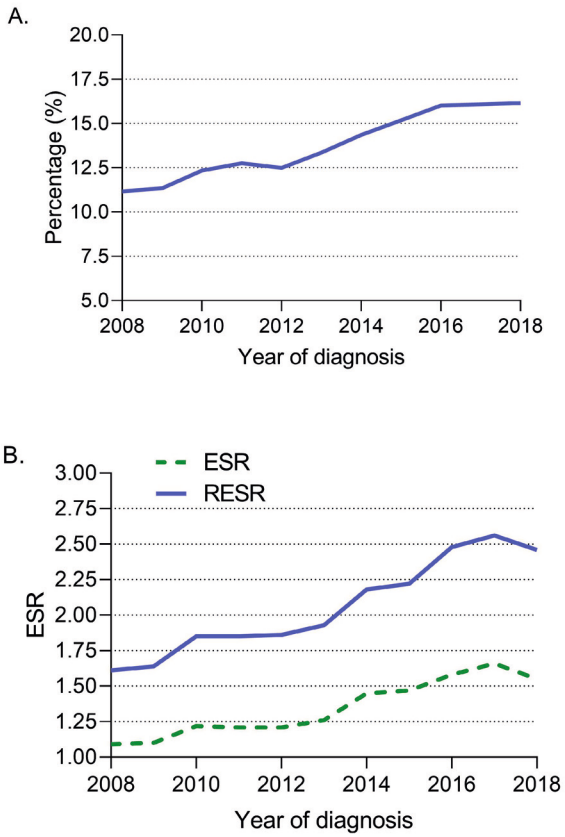

Figure 2. A) Proportion of pancreatic cancer patients presenting with synchronous peritoneal metastases in all pancreatic cancer patients, diagnosed between 2008 and 2018 (n=25.334). **B)** Trends in the incidence of patients with pancreatic cancer with synchronous peritoneal metastases (n=3524) between 2008 and 2018 in the Netherlands.
RESR Revised European Standardized Rate; *ESR* European Standardized Rate.

Treatment of peritoneal metastases from pancreatic cancer

Of all the patients with peritoneal metastases from pancreatic cancer (n=3524), 964 (27%) received cancer treatment and 2560 (73%) received BSC (*Table 2*). Over time, no significant change in proportion of the patients receiving cancer treatment was found (p = 0.515).Within the patients who underwent cancer treatment, the following treatments were applied: chemotherapy (n=902); radiotherapy targeting either the primary tumor, metastases, or both (n=42); metastasectomy (n=37); resection of the primary tumor (n=22); and targeted therapy (n=19). Among these patients, 55 received more than 1 treatment (*Supplementary Table 10.2*).

Details regarding chemotherapeutic regimens were registered for 478 patients (2015–2018), being FOLFIRINOX (n=240/964, 25%), gemcitabine (n=119/964, 12%), nab-paclitaxel–gemcitabine (n=29/964, 3%), and other (n=94/964, 10%).

Table 2. Trends in treatment over four time periods in patients with peritoneal metastases of pancreatic origin (n=3524)

Year of diagnosis	2008-2010	2011-2013	2014-2016	2017-2018	Total	*P value*
Best supportive care, No. (%)	520 (72)	612 (72)	794 (72)	634 (75)	2560	0.515
Cancer treatment*, No. (%)	207 (29)	233 (28)	308 (28)	216 (25)	964	

* Systemic therapy or resection of primary tumor or radiotherapy.

Survival of the study population

The median OS for the patients with peritoneal metastases was 1.9 months (2.6 months for patients without other metastases and 1.6 months for patients also with systemic metastases otherwise). In the patients with systemic metastases, the median OS was 2.4 months and in the patients without metastases, the median OS was 8.0 months (p < 0.001; *Figure 3*). In the patients with peritoneal metastases undergoing cancer treatment, OS was significantly better (median 5.0 months) as compared with the patients receiving BSC (median 1.3 months, p < 0.001; *Figure 4*). The patients who received FOLFIRINOX had a significantly better median OS (6.8 months) than the patients who received gemcitabine (4.8 months, p = 0.003; *Figure 5*). As only 29 patients received combination of nab-paclitaxel and gemcitabine, those patients could not be included in survival analyses. Over time, no differences in survival in patients with peritoneal metastases were seen. The

median OS was 1.9 months (2008–2010), 1.8 months (2011–2013), 1.9 months (2014–2016), and 1.8 months (2017–2018, p = 0.242).

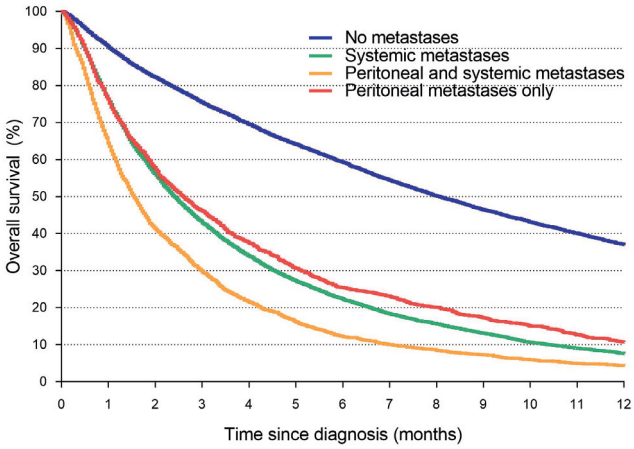

Figure 3. Overall survival of all patients with pancreatic cancer according to presence and location of metastases (Log-rank: $p < 0.001$).

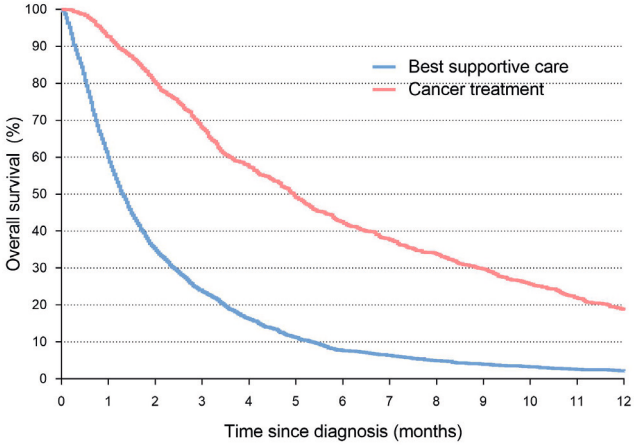

Figure 4. Overall survival of all patients with peritoneal metastases of pancreatic origin according to different treatment strategies (Log-rank: $p < 0.001$).

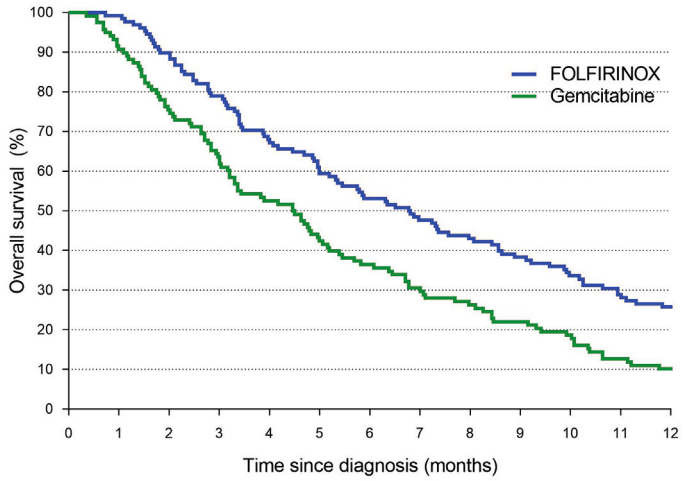

Figure 5. Overall survival of patients with peritoneal metastases of pancreatic origin according to different systemic therapies (Log-rank: *p = 0.003*) (n=359).

Factors influencing survival in patients with peritoneal metastases

In univariable analyses, peritoneal metastases (i.e., with or without systemic metastases), sex, age, localization of primary tumor, tumor stage, nodal stage, and treatment were significantly associated with OS and included in the multivariable analyses. In multivariable analyses, the patients with peritoneal metastases with the primary tumor located in the tail (1.7 months, adjusted hazard ratio [HR], 1.23; 95% confidence interval [CI], 1.13–1.34) or in the body (1.8 months, HR 1.14; 95% CI, 1.03–1.26) had a statistically significant worse survival compared with the patients with a primary tumor located in the head (2.5 months). The median OS was better in the patients with peritoneal metastases who received cancer treatment compared with the patients who received BSC (5.0 vs. 1.3 months, HR 0.37; 95% CI, 0.34–0.40, *Table 3*).

Table 3. Multivariable cox regression survival analysis for all patients with peritoneal metastases from pancreatic origin (n=3524)

	Median OS (months)	Adjusted HR (95% CI)
Peritoneal metastases		
Peritoneal metastases without systemic metastases	2.61	Ref.
Peritoneal metastases with systemic metastases	1.55	1.49 (1.39-1.60)

Table 3. Multivariable cox regression survival analysis for all patients with peritoneal metastases from pancreatic origin (n=3524) (continued)

	Median OS (months)	Adjusted HR (95% CI)
Sex		
Male	1.62	Ref.
Female	2.10	0.81 (0.76-0.86)
Age at diagnosis		
<65 years	2.78	Ref.
65-75 years	1.79	1.18 (1.09-1.28)
>75 years	1.32	1.23 (1.12-1.34)
Localization primary tumor		
Head	2.51	Ref.
Body	1.82	1.14 (1.03-1.26)
Tail	1.67	1.23 (1.13-1.34)
Other	1.54	1.20 (1.09-1.32)
Tumor stage		
T0-T3	1.88	Ref.
T4	2.28	0.91 (0.84-1.00)
Unknown	1.42	1.09 (1.00-1.20)
Nodal stage		
N0	2.21	Ref.
N1/N2	1.98	1.10 (1.01-1.20)
Unknown	1.51	1.28 (1.18-1.39)
Treatment of peritoneal metastases		
Best supportive care	1.29	Ref.
Cancer treatment	5.00	0.37 (0.34-0.40)

OS overall survival; *HR* Hazard Ratio; *CI* Confidence Interval.

Discussion

The present study shows that synchronous peritoneal metastases are increasingly diagnosed in pancreatic cancer with up to 16% of the patients presenting with peritoneal metastases in the most recent year (2018) of the study. This is remarkably higher than a previous reported study, which reported the incidence of pancreatic peritoneal metastases (9%, 1995–2009; 11%, 2009–2013).[13] Given this finding, the peritoneal cavity is increasingly recognized as a route of metastatic dissemination in pancreatic cancer.

The high incidence of peritoneal metastases in the current study could be explained by better registration or by increased awareness. More effective treatments are becoming available for peritoneal metastases from appendiceal, colorectal, and ovarian cancer in the recent years. Furthermore, with the increased use of diagnostic laparoscopy in pancreatic cancer, the detection of peritoneal metastases has improved.[14–16] Improved in imaging techniques, such as computed tomography scanning and diffusion-weighted magnetic resonance imaging, may also have attributed to the increased detection rate of peritoneal disease, particularly in centers specialized in the treatment for peritoneal metastases.[17]

In the patients with peritoneal metastases receiving cancer treatment, OS was 4 times as long as compared with patients receiving BSC. This could be explained by treatment selection bias, because the patients with a good performance status are more likely to receive cancer directed treatment. This may have led to better survival based on a better condition rather than on an effectiveness of systemic treatment. Nevertheless, survival of the patients who received cancer treatment was still very poor. Furthermore, the patients with primary pancreatic tumors located in the tail showed a significant lower OS compared with tumors in the head or the body, which is in line with a previously published study.[11] This may be due to the absence or late presentation of alarming symptoms, such as jaundice.[18,19] Besides, tumors located in the body and tail are associated with more aggressive disease biology than tumors in the pancreatic head.[20]

There is currently a lack of curative treatment options for patients with metastatic pancreatic cancer. Some have advocated aggressive debulking combined with heated intraperitoneal chemotherapy; however, experience with this treatment is very limited.[21,22] Given the morbidity and prolonged postoperative recovery of this treatment and the generally short life expectancy of patients with pancreatic peritoneal metastases, such treatment will currently not be applicable for most patients. However, this may change

once more effective chemotherapeutic drugs suitable for intraperitoneal delivery may become available.

With the introduction of FOLFIRINOX in 2011 and the combination of nab-paclitaxel and gemcitabine in 2013, palliative treatment options have expanded for patients with advanced and/or metastatic pancreatic cancer.[8–10] The randomized controlled trial of Conroy et al[9] showed a median OS of 11.1 months in patients with metastatic pancreatic cancer (performance status of 0 or 1) when treated with FOLFIRINOX. Another randomized controlled trial by VonHoff et al[10] showed a median OS of 8.5 months in patients treated with nab-paclitaxel–gemcitabine compared with 6.7 months in patients treated with gemcitabine (Karnofsky performance status of 70 or more). Ever since, FOLFIRINOX and nab-paclitaxel–gemcitabine are considered standard therapies in selected patients (performance status of 0 or 1, Karnofsky >70) with advanced pancreatic cancer.[23] Because these studies do not specify the OS for different metastatic sites, comparisons with the current study are difficult. Moreover, patients in these studies had a high performance status, and information about this score was not available in the current study.

Although the number of patients who received the combination nab-paclitaxel with gemcitabine is small in this cohort, there is a significantly better median OS in patients with peritoneal metastases receiving FOLFIRINOX compared with patients receiving gemcitabine (6.8 vs. 4.8 months). In a previously published study, the median OS for peritoneal metastases of pancreatic origin was 7.1 months with FOLFIRINOX and 2.3 months with gemcitabine, which is comparable with the current cohort.[24] Moreover, the study of Kang et al[25] suggested that the combination of gemcitabine and nab-paclitaxel might result in a longer progression free survival in patients with peritoneal metastases. Future research investigating nab-paclitaxel–gemcitabine and FOLFIRINOX in patients with peritoneal metastases of pancreatic origin is designated.

This study has several limitations. First, this is a retrospective study with the inherent limitations associated with this methodology. Data on comorbidities, differentiation grade, and morphology of the primary tumor were missing in a substantial number of patients (no pathological confirmation), and therefore, possible influences of these factors on the incidence of peritoneal metastases and OS could not be investigated. Second, the NCR only registers metastases diagnosed simultaneously with diagnosis of the primary tumor. Therefore, data on metachronous peritoneal metastases of pancreatic origin are lacking. It is suggested that approximately half of the peritoneal metastases from pancreatic cancer are metachronous.[24] Because of the aggressive behavior

of pancreatic cancer, limited research is available about metachronous metastases in pancreatic cancer.

To conclude, the incidence of peritoneal metastases from pancreatic cancer increased from 11% in 2008 to 16% in 2018 in the NCR. The peritoneum is now recognized as the second most prevalent metastatic site in pancreatic cancer. Unfortunately, only a small proportion of these patients received cancer treatment and survival is very poor. Future research to improve the best type of systemic treatment is designated to improve prognosis for this relevant patient category.

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Chapter 11

Synchronous peritoneal metastases from lung cancer: incidence, associated factors, treatment, and survival: a Dutch population-based study

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Abstract

Introduction
Peritoneal metastases from lung cancer are rare and it is unknown how they affect the prognosis of patients with lung cancer. This population-based study aimed to assess the incidence, associated factors, treatment and prognosis of peritoneal metastases from lung cancer.

Methods
Data from the Netherlands Cancer Registry were used. All patients diagnosed with lung cancer between 2008 and 2018 were included. Logistic regression analyses were performed to identify factors associated with the presence of peritoneal metastases. Cox regression analysis was performed to identify factors associated with the overall survival (OS) of patients with peritoneal metastases.

Results
Between 2008 and 2018, 129.651 patients were diagnosed with lung cancer, of whom 2533 (2%) patients were diagnosed with peritoneal metastases. The European Standardized Rate of peritoneal metastases increased significantly from 0.6 in 2008 to 1.4 in 2018 ($p < 0.001$). Age between 50 and 74 years, T3-4 tumor stage, N2-3 nodal stage, tumor morphology of a small cell lung cancer or adenocarcinoma, and the presence of systemic metastases were associated with the presence of peritoneal metastases. The median OS of patients with peritoneal metastases was 2.5 months. Older age, male sex, T3-4 tumor stage, N2-3 nodal stage, not receiving systemic treatment, and the presence of systemic metastases were associated with a worse OS.

Conclusions
Synchronous peritoneal metastases were diagnosed in 2% of patients with lung cancer and resulted in a very poor survival.

Introduction

Lung cancer is the most common type of cancer worldwide, annually affecting more than 400.000 people in Europe alone.[1] Since half of the patients with lung cancer are simultaneously diagnosed with metastatic disease, the prognosis is generally poor, making lung cancer the leading cause of cancer-related death in Europe.[1-4]

Despite the frequent encounter of systemic metastases, peritoneal metastases are rare and little is known about their incidence and how they affect survival. Available literature is limited to case reports and one population-based study focusing on peritoneal metastases from multiple extra-abdominal primary tumors.[5-8] The latter used the National Cancer Registry Ireland to identify 139 patients with peritoneal metastases from lung cancer.

Abdominal cancers have a higher tendency for peritoneal spread, affecting approximately 10% of these patients.[9-12] Although cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy is a treatment option for selected patients with peritoneal metastases from several abdominal cancers, it is not available for patients with peritoneal metastases from extra-abdominal cancers, such as lung cancer.[9,13] As a first step to guide future therapeutic research, the incidence of and associated factors for peritoneal metastases, as well as current treatment options and survival outcomes, should be explored.

Therefore, the aim of this study was to investigate the incidence of synchronous peritoneal metastases from lung cancer in a Dutch population-based cohort and to describe the characteristics, associated factors, treatment strategies and survival outcomes of these patients.

Methods

Data from the Netherlands Cancer Registry (NCR) were used.[14] The NCR registers all newly diagnosed cancers, and specifically trained data managers of the NCR obtain patient-, tumor- and treatment characteristics from the medical records. The topography and morphology of primary tumors and synchronous metastatic sites were recorded according to the International Classification of Disease for Oncology (ICD-O).[15,16] After the initial registration, the follow-up consist of a yearly evaluation of the vital status. All data are anonymized. No ethics approval was required for this study according to the

Central Committee on Research involving Human Subjects in The Hague, the Netherlands. The privacy review board of the NCR approved the study.

All patients diagnosed with lung cancer between 1 January 2008 and 31 December 2018 were included in this study. Primary tumor morphologies according to the ICD-O were divided in small cell lung cancer (SCLC; 8041-8045) and non-small cell lung cancer (NSCLC). NSCLC was subdivided into (1) squamous cell carcinoma (8070-8076, 8078, 8083, 8084, 8094), (2) adenocarcinoma (8140, 8144, 8250-8255, 8480, 8481, 8490, 8570, 8572, 8573), and (3) other (8001, 8002, 8010, 8012-8014, 8020, 8021, 8046, 8244, 8246, 8560, 8574). Other tumor morphologies, such as mesotheliomas and carcinoid tumors, were excluded. In case of multiple primary lung tumors in one patient, only the firstly diagnosed tumor was included. If multiple tumors were simultaneously diagnosed, the tumor with the highest stage was included.

The following metastatic sites were considered as peritoneal metastases: C16.0-C16.3, C16.5, C16.6, C16.8, C16.9, C17.0-C17.3, C17.8, C17.9, C18.0-C18.4, C18.6-C18.9, C19.9, C20.9, C21.8, C23.9, C26.9, C48.0-C48.2, C48.8, C49.4, C49.5, C52.9, C53.9, C54.0-C54.3, C54.8, C54.9, C55.9, C56.9, C57.0-C57.4, C57.8, C66.9, C67.0, C67.1, C67.4, C67.8, C67.9, C76.2, C76.3. All other metastatic sites were considered as systemic metastases. The Tumor Node Metastasis (TNM) system was used, valid at time of diagnosis, to classify tumor characteristics.

Patients were subcategorized into four groups: (1) patients with lung cancer without synchronous metastases, (2) patients with lung cancer and synchronous metastases, (3) patients with lung cancer and synchronous peritoneal metastases, and (4) patients with lung cancer and both synchronous systemic metastases and peritoneal metastases.

Treatment regimens were categorized as follows: (1) best supportive care (BSC) only; (2) local treatment (comprising surgery and/or radiotherapy); and (3) systemic treatment (comprising chemotherapy and/or immunotherapy and/or targeted therapy).

The vital status was assessed on 31 January 2020 by linking the NCR to the Municipal Administrative Database, which comprises the vital status and date of death of all inhabitants of the Netherlands.

Statistical analysis

Incidence rates of peritoneal metastases were calculated as the number of new patients per 100.000 inhabitants per year and were age standardized using both the European Standardized Rate (ESR) and the revised ESR (RESR).[17] The latter is the most up-to-date method for calculating incidence rates, but the former has frequently been used in previous studies, facilitating comparison to available literature. Trends over time were assessed through the Estimated Annual Percent Change (EAPC). Categorical variables were represented as n (%) and compared between the four groups with the chi-square test. Continuous variables were represented as mean (± standard deviation) and compared between the four groups with the one-way ANOVA test. Univariable logistic regression analyses were performed to identify characteristics associated with the presence of synchronous peritoneal metastases ($p < 0.10$) which were subsequently combined in a multivariable logistic regression model. Overall survival (OS) of patients with peritoneal metastases was estimated with the Kaplan-Meier method and compared with the Log-rank test (solitary peritoneal metastases vs. peritoneal metastases and systemic metastases). OS was defined as the time from diagnosis of the primary tumor until death or last follow-up date (31 January 2020). Univariable cox regression analyses were performed in all patients with peritoneal metastases to identify characteristics associated with a worse OS ($p < 0.10$) and were subsequently combined in a multivariable cox regression model. All statistical analyses were performed with SAS 9.4 (SAS Institute, North Caroline, United Stated). A p-value <0.05 was considered statistically significant.

Results

The final study population comprised 129.651 patients with lung cancer. Within this group, 62.890 (48.5%) patients did not have synchronous metastatic disease, 64.228 (49.5%) patients had synchronous systemic metastases only, 326 (0.3%) patients had synchronous peritoneal metastases only, and 2207 (1.7%) patients had both synchronous systemic metastases and peritoneal metastases. Thus, a total of 2533 (2.0%) patients with lung cancer were diagnosed with synchronous peritoneal metastases.

Table 1. Patient- and tumor characteristics

	Synchronous peritoneal metastases without systemic metastases n=326	**Synchronous peritoneal metastases with systemic metastases** n=2207	**Synchronous systemic metastases** n=64 228	**No metastases** n=62 890	*P value*[a]
Sex, No. (%)					**<0.001**
Male	181 (55)	1302 (59)	37 269 (58)	37 466 (60)	
Female	145 (45)	905 (41)	26 959 (42)	25 424 (40)	
Age at diagnosis, mean (SD)	67 (11)	67 (10)	68 (11)	69 (10)	**<0.001**
Tumor histology, No. (%)					**<0.001**
SCLC	42 (13)	458 (21)	12 261 (19)	6026 (10)	
NSCLC					
Adenocarcinoma	159 (49)	963 (44)	27 872 (43)	20 183 (32)	
Squamous cell carcinoma	47 (14)	211 (9)	8 173 (13)	19 532 (31)	
Other	78 (24)	575 (26)	15 922 (25)	17 149 (27)	
Tumor stage, No. (%)					**<0.001**
T0-2	99 (30)	674 (31)	21 760 (34)	36 549 (58)	
T3-4	180 (55)	1288 (58)	34 887 (54)	22 680 (36)	
Missing data	47 (14)	245 (11)	7581 (12)	3661 (6)	

Table 1. Patient- and tumor characteristics (continued)

	Synchronous peritoneal metastases without systemic metastases n=326	**Synchronous peritoneal metastases with systemic metastases** n=2207	**Synchronous systemic metastases** n=64 228	**No metastases** n=62 890	*P value*[a]
Nodal stage, No. (%)					**<0.001**
N0-1	92 (28)	344 (16)	12 055 (19)	34 374 (55)	
N2	115 (35)	827 (37)	23 977 (37)	16 829 (27)	
N3	81 (25)	892 (40)	22 889 (36)	8131 (13)	
Missing data	38 (12)	144 (7)	5307 (8)	3556 (6)	
WHO performance					**<0.001**
WHO 0-1	68 (21)	370 (17)	10 151 (16)	12 609 (20)	
WHO 2-4	26 (8)	272 (12)	5223 (8)	3189 (5)	
Missing data	232 (72)	1565 (71)	48 854 (76)	47 092 (75)	

[a]Missing data were excluded from comparative analyses; *SD* standard deviation; *NSCLC* Non-Small Cell Lung Cancer; *SCLC* Small Cell Lung Cancer; *WHO* World Health Organization.

Table 1 contains the baseline characteristics of (1) patients with lung cancer without synchronous metastases, (2) patients with lung cancer and synchronous systemic metastases, (3) patients with lung cancer and solitary synchronous peritoneal metastases, and (4) patients with lung cancer and both synchronous systemic metastases and peritoneal metastases. Patients with metastatic disease more often had a SCLC tumor histology than patients without metastatic disease (13-21% vs. 10%, respectively). This difference was more pronounced for patients with systemic metastases (19%) and patients with systemic metastases and peritoneal metastases (21%) than for patients with solitary peritoneal metastases (13%). A similar trend was observed for tumor stage, nodal stage, and World Health Organization (WHO) performance status: patients with systemic metastatic disease were more likely to have a T3-4 tumor stage or N2-3 nodal stage or WHO performance status 2-4 than patients without systemic metastatic disease (T3-4 tumor stage: 54-58% vs. 36%, respectively [$p < 0.001$]; N2-3 nodal stage: 60-77% vs. 40%, respectively [$p < 0.001$]; WHO performance status 2-4: 23-43% vs. 20%, respectively [$p < 0.001$]).

Figure 1 presents the ESR and the RESR of lung cancer with peritoneal metastases (with or without systemic metastases) from 2008 to 2018. The ESR significantly increased from 0.6 in 2008 to 1.3 in 2018 (EAPC of 7.3%, $p < 0.001$), as well as the RESR, which increased from 0.8 in 2008 to 1.8 in 2018 (EAPC of 7.4%, $p < 0.001$).

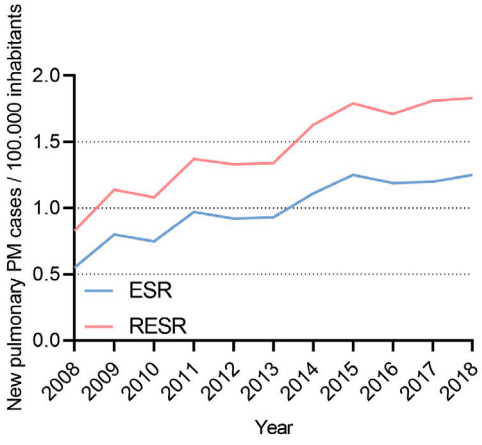


Figure 1. European standardized rate of pulmonary peritoneal metastases over time.
PM peritoneal metastases; *ESR* European standardized rate; *RESR* revised European standardized rate.

Figure 2 shows an overview of pattern of synchronous systemic metastases, stratified for patients with lung cancer and synchronous systemic metastases and for patients with lung cancer and both synchronous systemic metastases and peritoneal metastases. Remarkably, patients with both synchronous systemic metastases and peritoneal metastases more often had systemic metastases located in the liver, bones, and adrenal glands, whereas patients with synchronous systemic metastases only more often had systemic metastases located in the lungs and pleura. Brain metastases were equally diagnosed in both groups.

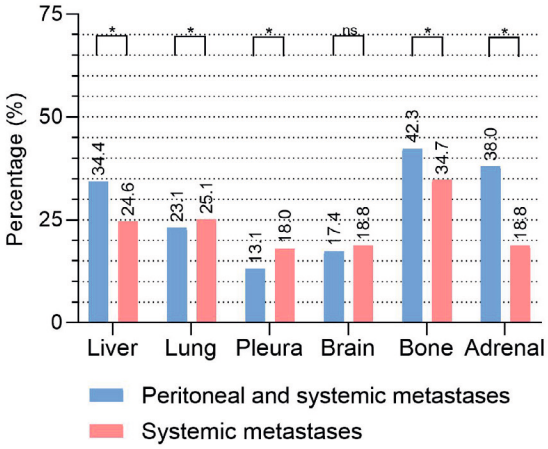


Figure 2. Patterns of synchronous systemic metastases.
NS not statistically significant; * statistically significant.

Factors associated with peritoneal metastases

Table 2 presents the results of uni- and multivariable logistic regression analyses. These showed that patients aged 50-74 had a higher odds (odds ratio [OR] 1.1; 95% confidence interval [CI], 1.08-1.27) of having synchronous peritoneal metastases compared to patients aged ≥ 75 years. Furthermore, tumor histology of a SCLC (OR 1.54; 95% CI, 1.32-1.80) or adenocarcinoma (OR 1.58; 95% CI, 1.37-1.82), a T3-4 tumor stage (OR 1.30; 95% CI, 1.19-1.43), an N2-3 nodal (N2: OR 1.40; 95% CI, 1.24-1.57, N3: OR 1.53; 95% CI, 1.35-1.72), a WHO performance status of 2-4 (OR 1.45; 95% CI 1.25-1.69), and the presence of synchronous systemic metastases (OR 5.02; 95% CI, 4.44-5.69), were significantly associated with the presence of synchronous peritoneal metastases.

Table 2. Logistic regression analyses for the presence of synchronous peritoneal metastases in patients with lung cancer.

	Peritoneal metastases	**Univariable logistic regression analyses**			**Multivariable logistic regression analysis**		
	n (%)	OR	95% CI	*P value*	OR	95% CI	*P value*
Age at diagnosis				**<0.001**			
<50 year	107 (2)	1.18	0.97-1.45		1.00	0.81-1.22	0.977
50-74 year	1348 (2)	1.26	1.16-1.37		**1.17**	**1.08-1.27**	**<0.001**
≥75 year	1078 (2)	Ref.	Ref.		Ref.	Ref.	Ref.
Sex				0.804			
Male	1483 (2)	Ref	Ref		-	-	-
Female	1050 (2)	1.01	0.93-1.09		-	-	-
Tumor histology				**<0.001**			
SCLC	500 (3)	2.94	2.52-3.42		**1.54**	**1.32-1.80**	**<0.001**
NSCLC							
- Adenocarcinoma	1122 (2)	2.51	2.19-2.87		**1.58**	**1.37-1.82**	**<0.001**
- Squamous cell carcinoma	258 (1)	Ref.	Ref.		Ref.	Ref.	Ref.
- Other	653 (2)	2.12	1.83-2.45		**1.56**	**1.35-1.81**	**<0.001**
Tumor stage				**<0.001**			
T0-2	773 (1)	Ref.	Ref.		Ref.	Ref.	Ref.
T3-4	1468 (3)	1.92	1.76-2.10		**1.30**	**1.19-1.43**	**<0.001**
Missing data	292 (3)	1.96	1.71-2.25		1.28	1.10-1.48	0.001

Table 2. Logistic regression analyses for the presence of synchronous peritoneal metastases in patients with lung cancer. (continued)

	Peritoneal metastases	**Univariable logistic regression analyses**			**Multivariable logistic regression analysis**		
	n (%)	OR	95% CI	*P value*	OR	95% CI	*P value*
Nodal stage				**<0.001**			
N0-1	436 (1)	Ref.	Ref.		Ref.	Ref.	Ref.
N2	942 (2)	2.46	2.19-2.76		**1.40**	**1.24-1.57**	**<0.001**
N3	973 (3)	3.34	2.98-3.74		**1.53**	**1.35-1.72**	**<0.001**
Missing data	182 (2)	2.19	1.84-2.60		1.22	1.02-1.48	0.034
WHO performance				**<0.001**			
WHO 0-1	438 (2)	Ref.	Ref.		Ref.	Ref.	Ref.
WHO 2-4	298 (3)	1.84	1.59-2.14		**1.45**	**1.25-1.69**	**<0.001**
Missing data	1797 (2)	0.97	0.88-1.08		0.90	0.81-1.01	0.058
Synchronous systemic metastases				**<0.001**			
No	326 (1)	Ref.	Ref.		Ref.	Ref.	Ref.
Yes	2207 (3)	6.63	5.90-7.45		**5.02**	**4.44-5.69**	**<0.001**

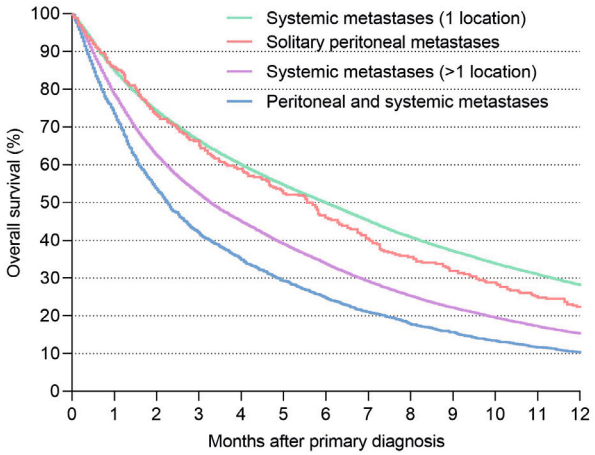
CI Confidence Interval; *OR* Odds Ratio; *NSCLC* Non-Small Cell Lung Cancer; *SCLC* Small Cell Lung Cancer; *WHO* World Health Organization.

Treatment of peritoneal metastases

The majority of patients with synchronous peritoneal metastases only received BSC (n=1754, 69%). The remaining patients received systemic treatment (n=354, 14%), local treatment (surgery and/or radiotherapy; n=189, 7%), or both (n=236, 9%). Patients with solitary synchronous peritoneal metastases more often only received BSC than patients with both systemic metastases and peritoneal metastases (78% vs. 68%, respectively, $p < 0.001$). Systemic treatment was administered to 19% of patients with solitary synchronous peritoneal metastases and to 24% of patients with both synchronous systemic metastases and peritoneal metastases ($p = 0.051$). Patients with solitary synchronous peritoneal metastases less often received local treatment than patients with both synchronous systemic metastases and peritoneal metastases (8% vs. 18%, $p < 0.001$).

Survival of patients with metastatic lung cancer

The median OS of all patients with synchronous peritoneal metastases was 2.5 months (interquartile range [IQR] 1.0-6.6), and the 1- and 2- year survival rates were 12.0% and 4.0%, respectively. Patients with solitary peritoneal metastases had a median OS of 5.6 months (IQR 1.9-11.0) and a 1- and 2-year survival rate of 22.1% and 10.5%, respectively. Patients with systemic metastases in one location had a median OS of 6.0 months (IQR 1.9-13.5) and a 1- and 2-year survival rate of 28.2% and 12.5%, respectively. The survival of patients with solitary peritoneal metastases was not significantly different from patients with systemic metastases in one location ($p = 0.199$). Patients with both systemic metastases and peritoneal metastases had a median OS of 2.3 months (IQR 1.0-6.0) and a 1- and 2- year survival rate of 10.4% and 3.0%, respectively. Patients with systemic metastases in more than one location (but not including peritoneum) had a median OS of 3.3 months (IQR 1.2-8.1) and a 1- and 2-year survival rate of 15.3% and 5.6%, respectively. The survival rate of patients with both systemic metastases and peritoneal metastases was significantly worse than patients with systemic metastases in more than one location ($p < 0.001$) (*Figure 3*).



Number at risk (number censored)		
Systemic metastases (1 location)	34 559 (0)	8718 (3004)
Solitary peritoneal metastases	326 (0)	64 (17)
Systemic metastases (>1 location)	29 677 (0)	4080 (981)
Peritoneal and systemic metastases	2207 (0)	209 (43)

Figure 3. Overall survival of patients with metastatic lung cancer.

Among patients with synchronous peritoneal metastases, multivariable cox regression analysis showed that younger age (<50 years: hazard ratio [HR] 0.77; 95% CI, 0.63-0.95; 50-74 years: HR 0.85; 95% CI, 0.78-0.93), female sex (HR 0.89; 95% CI, 0.82-0.97), and systemic treatment (HR 0.54; 95% CI, 0.49-0.60) were associated with a better OS. A T3-4 tumor stage (HR 1.19; 95% CI, 1.09-1.31), an N2-3 nodal stage (N2: HR 1.29; 95% CI, 1.14-1.45; N3: HR 1.31; 95% CI, 1.17-1.48), a WHO performance status 2-4 (HR 2.33; 95% CI, 1.99-2.71), and the presence of synchronous systemic metastases (HR 1.72; 95% CI, 1.52-1.95) were associated with a worse OS (*Table 3*).

Table 3. Cox regression analyses for the survival of patients with lung cancer with synchronous peritoneal metastases.

	Median OS (months)	Univariable cox regression analyses			Multivariable cox regression analysis		
		HR	95% CI	*P value*	HR	95% CI	*P value*
Age at diagnosis				**<0.001**			
<50 years	3.7	0.68	0.55-0.83		**0.77**	**0.63-0.95**	**0.015**
50-74 years	3.0	0.77	0.71-0.83		**0.85**	**0.78-0.93**	**<0.001**
≥75 years	2.0	Ref.	Ref.		Ref.	Ref.	Ref.
Sex				**<0.001**			
Male	2.3	Ref.	Ref.		Ref.	Ref.	Ref.
Female	2.8	0.56	0.79-0.93		**0.89**	**0.82-0.97**	**0.006**
Tumor histology				**<0.001**			
SCLC	3.5	0.94	0.81-1.09		0.96	0.82-1.12	0.566
NSCLC							
- Adenocarcinoma	2.7	0.92	0.81-1.06		0.99	0.86-1.14	0.898
- Squamous cell carcinoma	2.7	Ref.	Ref.		Ref.	Ref.	Ref.
- Other	1.9	1.25	1.08-1.44		**1.21**	**1.05-1.40**	**0.011**
Tumor stage				**<0.001**			
T0-2	3.2	Ref.	Ref.		Ref.	Ref.	Ref.
T3-4	2.4	1.20	1.10-1.31		**1.19**	**1.09-1.31**	**<0.001**
Missing data	1.7	1.47	1.28-1.68		1.28	1.11-1.48	**<0.001**

Table 3. Cox regression analyses for the survival of patients with lung cancer with synchronous peritoneal metastases. (continued)

	Median OS (months)	**Univariable cox regression analyses**			**Multivariable cox regression analysis**		
		HR	95% CI	*P value*	HR	95% CI	*P value*
Nodal stage				**<0.001**			
N0-1	3.7	Ref.	Ref.		Ref.	Ref.	Ref.
N2	2.4	1.32	1.17-1.48		**1.29**	**1.14-1.45**	**<0.001**
N3	2.4	1.36	1.21-1.52		**1.31**	**1.17-1.48**	**<0.001**
Missing data	1.4	1.92	1.61-2.29		1.77	1.47-2.12	**<0.001**
WHO performance				**<0.001**			
WHO 0-1	5.2	Ref.	Ref.		Ref.	Ref.	Ref.
WHO 2-4	1.5	2.45	2.10-2.85		**2.33**	**1.99-2.71**	**<0.001**
Missing data	2.3	1.66	1.49-1.85		**1.72**	**1.54-1.92**	**<0.001**
Systemic treatment				**<0.001**			
No	1.9	Ref.	Ref.		Ref.	Ref.	Ref.
Yes	5.6	0.58	0.53-0.64		**0.54**	**0.49-0.60**	**<0.001**
Local treatment				**<0.001**			
No	2.3	Ref.	Ref.		Ref.	Ref.	Ref.
Yes	3.7	0.83	0.75-0.92		1.02	0.91-1.14	0.748

Table 3. Cox regression analyses for the survival of patients with lung cancer with synchronous peritoneal metastases. (continued)

	Median OS (months)	**Univariable cox regression analyses**			**Multivariable cox regression analysis**		
		HR	95% CI	*P value*	HR	95% CI	*P value*
Synchronous systemic metastases				**<0.001**			
No	5.6	Ref.	Ref.		Ref.	Ref.	Ref.
Yes	2.3	1.66	1.47-1.87		**1.72**	**1.52-1.95**	**<0.001**

CI Confidence Interval; *HR* Hazard Ratio; *NSCLC* Non-Small Cell Lung Cancer; *SCLC* Small Cell Lung Cancer

Discussion

This study aimed to provide an overview of the incidence, associated factors, treatment, and survival of patients with lung cancer with synchronous peritoneal metastases. Synchronous peritoneal metastases were found in 2.0% of patients with lung cancer. Most patients with synchronous peritoneal metastases also had synchronous systemic metastases. The incidence of synchronous peritoneal metastases in patients with lung cancer increased over time. Younger age, a poorer WHO performance status, SCLC or adenocarcinoma tumor histology, and advanced disease (T, N and M stage) were associated with the presence of synchronous peritoneal metastases. The median OS of all patients with synchronous peritoneal metastases was 2.5 months, and an older age, male sex, a poorer WHO performance status, advanced disease (T, N and M stage), and not receiving systemic treatment were associated with a worse OS.

An Irish population-based cohort identified that 0.4% of patients with lung cancer were diagnosed with synchronous or metachronous peritoneal metastases.[7] They reported a much lower incidence of peritoneal metastases than the current study. This is most likely related to the improvement and increased use of diagnostic modalities, such as (FDG-PET) computed tomography (CT), and the increasing knowledge and awareness of peritoneal metastases over time.[18] The analysis from Flanagan et al. was performed with patients diagnosed between 1999 and 2012, whereas the current study was performed with patients diagnosed between 2008 and 2018. Three other studies also described small cohorts of patients with lung cancer with peritoneal metastases, which summed up to a total of 66 patients with peritoneal metastases. In these studies, the incidence of peritoneal metastases ranged from 0.8 to 1.2%.[6,19,20] These studies reported on patients diagnosed with lung cancer and peritoneal metastases, between 1990 and 2012.

Even so, the reported incidence of peritoneal metastases in the current study is likely to be an underestimation of the true incidence: the current cohort did not include metachronous peritoneal metastases, whereas Flanagan et al. reported that a third of the patients with lung cancer with peritoneal metastases had a metachronous onset of peritoneal metastases. Furthermore, peritoneal metastases are not easily detected on abdominal CT-scans, nor is a diagnostic laparoscopy or laparotomy routinely performed in patients with lung cancer, which has probably resulted in missed diagnoses of synchronous peritoneal metastases. Therefore, the currently reported incidence of peritoneal metastases from lung cancer is likely an underestimation. This

is reflected by the much higher incidence rates of peritoneal metastases from autopsy studies, where peritoneal metastases are found in 2.7-16.0% of patients with lung cancer.[21-23]

The current study showed that patients with lung cancer with peritoneal metastases have a poor prognosis. This is comparable to the median OS of 2.0-2.8 months reported in other cohorts.[6,7,19,20] However, in contrast to these studies, the current study showed that patients with solitary peritoneal metastases have a more favorable OS than patients with both systemic metastases and peritoneal metastases. Hypothetically, this might be related to differences in the chosen treatment. However, this study found that systemic therapy was equally offered to both patients with solitary peritoneal metastases and to patients with both systemic metastases and peritoneal metastases.

In the current study, 69% of patients with peritoneal metastases did not receive either systemic or local treatment. This remarkably high number could partially be explained given that a quarter of the patients had already died during the first month after diagnosis, possibly withholding them from starting with any treatment. Nevertheless, the Irish cohort also reported on a high percentage of patients (48%) who did not receive tumor-directed treatment. This possibly reflects the extremely poor condition of patients with peritoneal metastases from lung cancer, given that 34-50% of patients with lung cancer are considered to have an Eastern Cooperative Oncology Group performance scale ≥ 2, severely limiting their treatment options.[24-26] Since these analyses were performed on general lung cancer populations, it is likely that the performance status of patients with metastatic lung cancer is even worse.

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Chapter 12

Updated incidence, treatment and survival of a nationwide cohort of patients with peritoneal metastases of unknown origin

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Abstract

Introduction
The aim of this study was to investigate the incidence, treatment and survival of patients with peritoneal metastases of unknown origin.

Methods
All Dutch patients diagnosed in 2017 and 2018 with peritoneal metastases of unknown origin were evaluated. Data were extracted from the Netherlands Cancer Registry (NCR). Patients with peritoneal metastases of unknown origin were categorized into the following histological subtypes: 1) adenocarcinoma, 2) mucinous adenocarcinoma, 3) carcinoid, 4) unspecified carcinoma and 5) other. Treatments were compared between the different histological subtypes in patients with peritoneal metastases of unknown origin. Overall survival (OS) was calculated using the Kaplan–Meier method for all patients with cancer of unknown origin and between histological subtypes in patients with peritoneal metastases of unknown origin. Significant differences in OS were assessed by using the Log-rank test.

Results
In total, 3026 patients were diagnosed with cancer of unknown origin, 513 (17%) among them were diagnosed with peritoneal metastases of unknown origin. Most patients with peritoneal metastases of unknown origin patients received best supportive care only (76%), whereas 22% received systemic treatment and 4% underwent metastasectomy. Median OS was 1.1 months for all patients with peritoneal metastases of unknown origin but varied from 0.6 months to 30.5 months depending on the underlying histology.

Conclusions
In this study, peritoneal metastases of unknown origin were diagnosed in 17% of all patients with cancer of unknown primary and the reported survival in this cohort was extremely poor. Since survival differed among histological subtypes and recently more treatment options became available for a selected group of patients with peritoneal malignancies, it is of great importance to identify the histology of the metastases and whenever possible the primary tumor.

Introduction

Peritoneal metastases are thought to be caused mainly by dissemination of tumor cells trough the abdominal cavity. As a result, relatively high incidences of peritoneal metastases are described from multiple primary intra-abdominal tumors such as colorectal, ovarian and gastric cancer.[1–4] However, peritoneal metastases may also be diagnosed in patients in whom the primary tumor site is unknown and remains unknown after initial workup.[5, 6] In approximately 3–5% of all patients diagnosed with metastatic cancer, the primary tumor location remains unknown.[5–7] In patients with metastases from an unknown origin, survival is generally poor.[7, 8]

For long, peritoneal metastases were generally considered as incurable with only very few treatment options available. However, the amount of new treatment strategies for peritoneal metastases from a variety of primary tumors is currently expanding. Multimodal treatments such as cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) in a selected group of patients with peritoneal metastases from colorectal, ovarian or gastric cancer, have revealed promising results on survival in several studies.[9–11] In case of more extensive intraperitoneal disease not amendable for complete cytoreduction, alternative treatment options such as systemic therapy or chemotherapy applied intraperitoneally by pressurized intraperitoneal aerosol chemotherapy (PIPAC) or intraperitoneally administered chemotherapy (INTERACT) are currently being investigated.[12–16] This evolution in treatment options emphasizes the value of determining the primary tumor location in patients with peritoneal metastases whenever possible.

In peritoneal metastases from an unknown origin, the underlying tumor histology differs among patients.[5, 7] This is important as peritoneal metastases from different tumor histologies may result in a different biological behavior and therefore require other diagnostic tools and treatment strategies. Thus, a better understanding of different histological subtypes in patients with an unknown primary tumor is warranted and may contribute to a more suitable approach in these patients.

Therefore, the aim of this study is to determine the incidence, treatment and survival of patients with peritoneal metastases from an unknown origin and to gain more insight into the different histological subtypes of these patients.

Methods

Data source

For this nationwide cohort study, data were extracted from the Netherlands Cancer Registry (NCR). Specially trained data managers of the NCR routinely collect data on patient, tumor and treatment characteristics from medical records. For the specification of primary tumor location, location of metastases and histologic characteristics, the International Classification of Disease for Oncology (ICD-O) was used. The NCR provided follow-up information on vital status, which was obtained by linking NCR data to the municipal administrative database in which all deaths and emigrated inhabitants of the Netherlands are registered. The latest linkage with the municipal administrative database for the present study was January 31, 2020. Since all data were anonymized, no ethics approval was obligated for this study.

Study population

All patients diagnosed in 2017 and 2018 with cancer of unknown primary (C80.9) were screened for eligibility. Patients with peritoneal metastases from an unknown origin were included for analyses. Peritoneal metastases were defined according to the ICD-O (C48.0 – C48.2, C48.8). Patients with peritoneal metastases were subcategorized as follows: 1) isolated peritoneal metastases from an unknown origin, which included all patients with only peritoneal metastases from an unknown origin and 2) peritoneal metastases from an unknown origin and concurrent systemic metastases, which included all patients with peritoneal metastases from an unknown origin and concurrent other metastases. Patient and tumor characteristics included in this study are sex, age and histological subtype. The histology of the primary tumor was categorized into 1) adenocarcinoma (8140, 8144, 8310, 8380, 8441), 2) mucinous carcinoma (8480, 8481), 3) carcinoid (8240, 8249), 4) unspecified carcinoma (8000, 8001, 8010, 8020, 8012, 8032, 8041, 8046, 8070) and 5) other (8490, 8680, 8801, 8803, 8936, 8980, 8246, 8244, 8013, 8120, 8315, 8720). The treatments for patients with peritoneal metastases from an unknown origin were defined as: 1) metastasectomy, 2) systemic treatment or 3) only best supportive care (BSC) and no tumor directed treatment. Within patients who underwent resection of metastases, resection of other metastases than the peritoneum was also included.

Statistical analysis

Proportion of frequencies was presented for patients with peritoneal metastases from an unknown origin. Baseline characteristics of patients with isolated peritoneal metastases from an unknown origin were compared to

patients with peritoneal metastases from an unknown origin and concurrent systemic metastases of unknown origin by means of the chi-squared test for categorical variables or unpaired *t*-test for continuous variables. All tests were two-sided and a p-value of < 0.05 was considered statistically significant. Treatments were compared between the different histological subtypes in patients with peritoneal metastases from an unknown origin by means of the chi-squared test. Median overall survival (OS) was calculated using the Kaplan–Meier method for all patients with cancer of unknown origin and for patients with peritoneal metastases from an unknown origin between the different histological subtypes. Significant differences in OS were assessed by using the Log-rank test. OS was calculated from time of diagnosis until death or loss to follow-up. All patients alive on January 31, 2020, were censored. All analyses were performed with SAS statistical software (SAS system 9.4, SAS Institute, Cary, NC, USA).

Results

Study population

In 2017 and 2018, 3026 patients were diagnosed with cancer from an unknown primary origin. Among them, 513 (17%) patients had peritoneal metastases from an unknown origin of which 160 (31%) presented with isolated peritoneal metastases from an unknown origin and 353 (69%) presented with peritoneal metastases from an unknown origin and concurrent systemic metastases of unknown origin (*Figure 1*). In patients where the primary tumor location is unknown, the peritoneum ranks 5th as metastatic site after the liver (n=1316, 43%), lymph nodes (n=1178, 39%), lung (n=870, 29%) and bone (n=743, 25%). In patients with peritoneal metastases from an unknown origin and concurrent systemic metastases of unknown origin (n=353), in 156 patients (44%) 2 organs were involved (peritoneum and one other site), in 101 patients (29%) 3 organs were involved, in 67 patients (19%) 4 organs were involved, in 29 patients (8%) > 5 organs were involved. Baseline characteristics of patients with peritoneal metastases from an unknown origin are presented in *Table 1*. Patients with isolated peritoneal metastases from an unknown origin were older and had more often a (mucinous) adenocarcinoma compared to patients with peritoneal metastases from an unknown origin and concurrent systemic metastases of unknown origin.

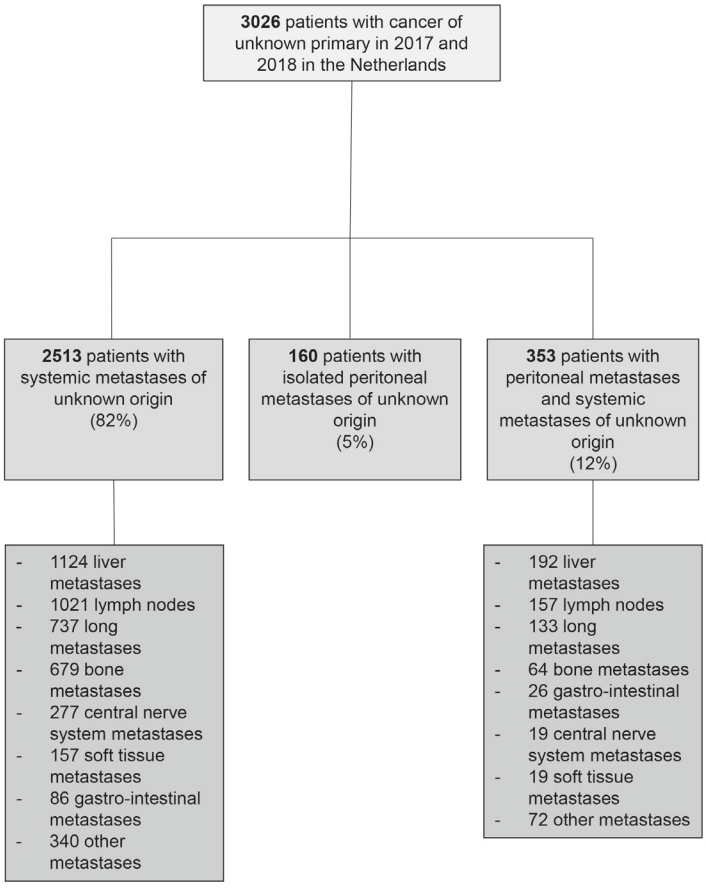


Figure 1. Flowchart of the study population.

Table 1. Characteristics of patients with peritoneal metastases of unknown origin.

	Total PM-CUP	**Isolated PM-CUP**	**PM-CUP and systemic metastases**	
	n=513	n=160	n=353	*P value*
Sex, No. (%)				
Male	227 (44)	70 (44)	157 (44)	
Female	286 (56)	90 (56)	196 (56)	0.878
Age, median (IQR)	74 (66-82)	78 (71-85)	72 (64-80)	**<0.001**
Tumor histology, No. (%)				
Adenocarcinoma	233 (45)	93 (58)	140 (40)	
Mucinous adenocarcinoma	22 (4)	14 (9)	8 (2)	
Carcinoid	16 (3)	1 (1)	15 (4)	
Unspecified carcinoma	185 (36)	42 (26)	143 (41)	
Other	57 (11)	10 (6)	47 (13)	**<0.001**

Percentages might not add up to 100% due to rounding; *PM-CUP* peritoneal metastases of unknown origin; *IQR* interquartile range.

Treatments in peritoneal metastases from unknown origin

Of all patients with peritoneal metastases from an unknown origin, 22 (4%) underwent resection of metastases, 102 (20%) received systemic treatment and 389 (76%) received only BSC. In patients with isolated peritoneal metastases from an unknown origin, 5 (3%) patients underwent resection of metastases, 25 (16%) patients received systemic treatment and 130 (81%) received only BSC and in patients with peritoneal metastases from an unknown origin and concurrent systemic metastases of unknown origin, 17 (5%) patients underwent resection of metastases, 77 (22%) received systemic treatment and 259 (73%) patients received only BSC ($p = 0.153$). *Figure 2* provides an overview of the applied treatments between the different histological subtypes within patients with peritoneal metastases from an unknown origin. Treatments differed significantly between the histological subtypes ($p < 0.001$). Patients with mucinous adenocarcinoma more often underwent metastasectomy (14%) whereas patients with a carcinoid more often received systemic treatment (69%).

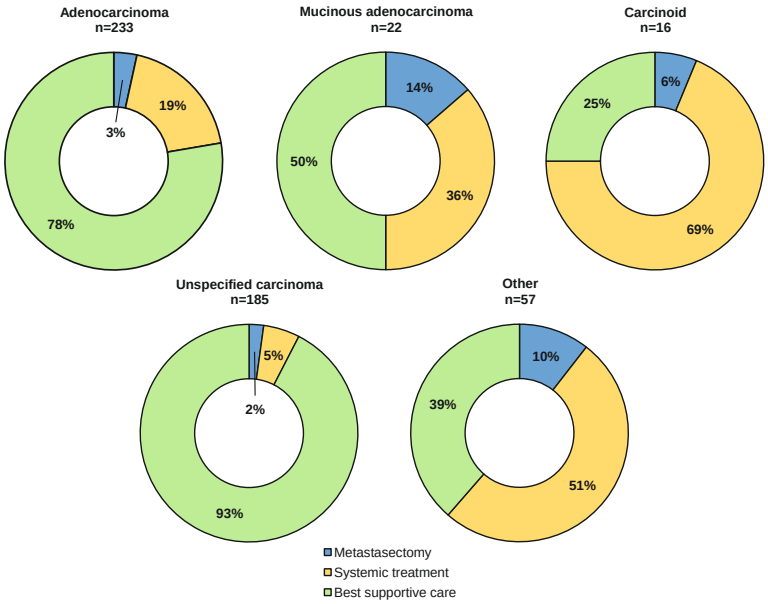
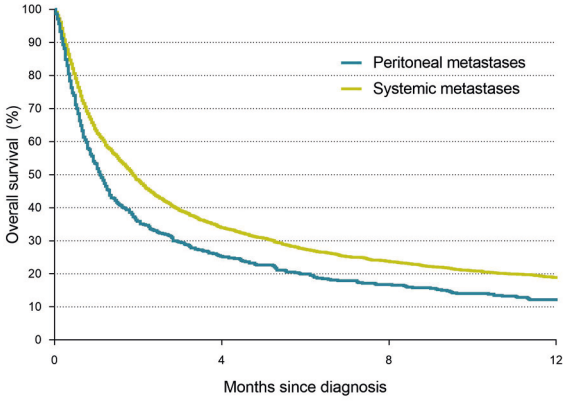


Figure 2. Treatments of patients with peritoneal metastases of unknown origin between the different histological subtypes.

Survival of peritoneal metastases from an unknown origin

Median follow-up time in patients with peritoneal metastases from an unknown origin was 4.2 months. Patients with peritoneal metastases from an unknown origin had a significantly shorter OS (1.1 months, interquartile range [IQR] 0.4–4.0) as compared to patients with cancer of unknown origin without peritoneal involvement (1.9 months, IQR 0.6–7.1) ($p < 0.001$) (*Figure 3*). Median OS did not differ significantly between the patients with isolated peritoneal metastases from an unknown origin (1.1 months, IQR 0.5–3.8) as compared to patients with peritoneal metastases from an unknown origin and concurrent systemic metastases of unknown origin (1.1 months, IQR 0.4–4.2) ($p = 0.712$). Median OS was significantly better in patients with peritoneal metastases from an unknown origin who underwent metastasectomy (8.2 months, IQR 3.9-not reached) or receiving systemic treatment (8.7 months, IQR 3.6–19.0) as compared to patients with peritoneal metastases from an unknown origin who received only BSC (0.7 months, IQR 0.3–1.5) ($p < 0.001$). Median OS was 1.1 months (IQR 0.5–2.8) for patients with peritoneal metastases from an unknown origin with an adenocarcinoma, 7.7 months (IQR 2.8-not reached) for patients with peritoneal metastases from an unknown origin with a mucinous adenocarcinoma, 30.5 months (IQR 22.4-not reached) for patients with peritoneal metastases from an unknown origin with a carcinoid and 0.6

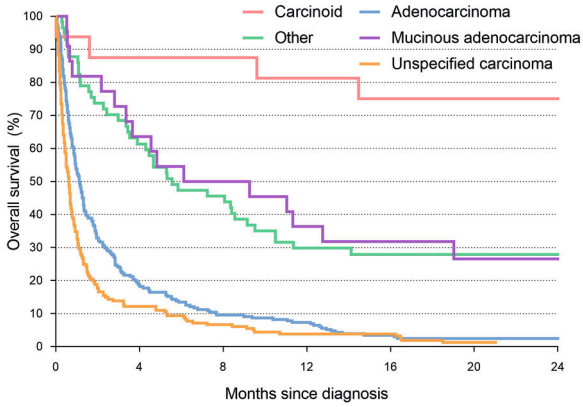
months (IQR 0.3–1.3) for patients with peritoneal metastases from an unknown origin with an unspecified carcinoma ($p < 0.001$) (*Figure 4*).



Number at risk (number censored)

Peritoneal metastases	513 (1)	128 (0)	85 (0)	60 (5)
No peritoneal metastases	2513 (2)	851 (0)	595 (0)	444 (57)

Figure 3. Overall survival of patients with cancer of unknown primary (Log-rank: $p < 0.001$).



Number at risk (number censored)

Adenocarcinoma	233 (0)	43 (0)	22 (0)	17 (1)	7 (0)	4 (3)	1 (2)
Mucinous adenocarcinoma	22 (0)	14 (0)	11 (0)	8 (0)	7 (1)	5 (1)	2 (4)
Carcinoid	16 (0)	14 (0)	14 (0)	13 (1)	10 (3)	7 (2)	4 (4)
Unspecified carcinoma	185 (0)	22 (0)	12 (0)	7 (0)	6 (0)	1 (2)	0 (0)
Other	57 (0)	35 (0)	26 (0)	16 (2)	12 (4)	10 (1)	5 (9)

Figure 4. Overall survival of patients with peritoneal metastases of unknown origin between the different histological subtypes (Log-rank: $p < 0.001$).

Discussion

The present study showed that peritoneal metastases from an unknown origin were diagnosed in 17% of all patients with an unknown primary tumor. Among these patients, 31% patients presented with isolated peritoneal metastases from an unknown origin. To date, this is the highest reported incidence of peritoneal metastases from an unknown origin in population-based studies.[5, 6, 17]

We have previously shown that peritoneal metastases from an unknown origin were diagnosed in 11% of all patients with an unknown primary tumor in a cohort diagnosed from 1984 and upwards. Previously published population-based studies reported an incidence of peritoneal metastases from an unknown origin ranging from 9 to 13%, with 2012 as the most recent reported year.[5, 6, 17] Interestingly, these reported incidence rates of peritoneal metastases from an unknown origin were lower than in the incidence of 17% in the present study. Meanwhile, recent literature showed that the incidence of cancer from an unknown primary in general decreases due to the improvement and increased use of diagnostic tools such as positron emission tomography (PET) – computed tomography (CT) or more extensive morphological examination and therefore more effective detection of the primary tumor.[5, 18] The increasing incidence of peritoneal metastases from an unknown origin in this study could be a relative increase due to an overall decrease of patients with cancer of unknown primary. This could be caused by a lack of further diagnostic testing for a primary tumor due to the dismal prognosis of patients in whom peritoneal metastases from an unknown origin are present, in contrast to patients with metastases where the suspected prognosis warrants further investigation.

Patients with peritoneal metastases from an unknown origin have a dismal prognosis with a median OS of 1.1 months as shown in this study. This is comparable to the median OS of 42 days in peritoneal metastases from an unknown origin patients reported in our previously published cohort.[5] This implies that limited progress, on improving the prognosis of these patients, has been made in the past decade.

A finding with clinical importance is that patients with peritoneal metastases from an unknown origin with a carcinoid histology had a remarkably higher survival than patients with other histological subtypes. Previous studies also reported that neuroendocrine carcinomas (e.g., carcinoid) of unknown primary in general have a more prognostic favorable clinicopathological entity as compared to other metastases of unknown primary.[19] This is partly explained

by the inherently less aggressive behavior of neuroendocrine tumors as well as the availability of an effective systemic treatment.[20] Indeed, in the current cohort the proportion of patients receiving systemic treatment is relatively high in peritoneal metastases from an unknown origin with a carcinoid histology as compared to the other histological types. Not surprisingly, the treatment in these patients consisted predominantly of hormone therapy, such as octreotide. One has to realize however that according to a population-based study on neuroendocrine carcinomas, the survival of neuroendocrine carcinomas of unknown primary was worse than those with an identified primary tumor.[21] This is probably because metastases of unknown primary in general are often characterized by a more aggressive tumor behavior.[22]

In the present study, almost 80% of the patients with peritoneal metastases from an unknown origin did not receive any treatment. An explanation for this remarkably high number could be that half of the patients already died within the first month after the diagnosis. Consequently, these patients did not have the opportunity to start with any form of treatment. In a previous report, we showed that 87% of the patients did not receive any treatment. In this cohort, upward from 1984, the usage of systemic therapy was increased from 8% in the earliest period to 16% in most recent years (2010).[5] In our present cohort, 20% of all patients received systemic treatment, which empowers this previous reported increasing trend in systemic treatment application for patients with peritoneal metastases from an unknown origin. Nevertheless, survival did not improve in this period of time despite this increasing trend in systemic treatment application.

Patients who received tumor-directed treatment in the current study had a significantly better OS compared to patients who did not receive any treatment. However, these reported outcomes should be interpreted with care because it is conceivable that treatment selection bias might play an important role, as patients with a good condition are more likely to receive tumor-directed treatment.[23] Furthermore, especially in patients with cancer of unknown primary, performance status appeared to be an important prognostic factor for survival. Therefore, according to the Dutch guidelines, it is recommended to make a distinction between patients with a low performance status and a good performance whether to receive tumor-directed treatment or not. Unfortunately, in the present study, data on performance status was missing in a substantial number of patients and therefore, possible influence on the given treatments could not be investigated.

As previously stated, new multimodal treatment strategies for peritoneal malignancies have changed the prognosis of patients with peritoneal

metastases from a variety of origins. In patient with isolated and limited colorectal peritoneal metastases, survival was significantly better in patients undergoing CRS-HIPEC, and therefore this treatment strategy is now recommended by most (inter)national guidelines.[10, 24, 25] Furthermore, promising results have been published in studies on CRS-HIPEC for strictly selected patients with peritoneal metastases from ovarian cancer and currently a randomized controlled trial (PERISCOPE II, NCT03348150) investigates the role of this treatment modality in patients with isolated limited gastric peritoneal metastases.[9, 11] Besides new treatment options with curative intent, different variants of intraperitoneal chemotherapy are currently being explored for patients with more extensive disease.[12, 13, 15, 16] Hence, as effective treatment options are becoming more available for patients with peritoneal malignancies, it is crucial that the primary tumor will be identified. However, despite the recommendation in the Dutch guidelines for a high dose CT or PET/CT scan in patients with an unknown primary tumor, a recent study demonstrated that only 25% of these patients received this extensive diagnostic workup.[23] This clearly needs more attention in daily clinical practice.

This study has some limitations. First, data on performance status were missing in a substantial amount of patients and therefore possible influence of this factor could not be investigated. Second, there was no data available about the use of diagnostic tools in patients with peritoneal metastases from an unknown origin. However, this study used nationwide data from the NCR which provides highly accurate data on tumor and patients characteristics, strengthening the generalizability.

This study provides an up-to-date overview of the incidence of patients with peritoneal metastases from an unknown origin. Peritoneal metastases were diagnosed in 17% of all patients with cancer of unknown primary and the survival of all patients with peritoneal metastases from an unknown origin was extremely poor. Moreover, in comparison with our previous reported cohort, a continuous increasing trend in the application of systemic treatment has been shown. Nevertheless, this increasing trend did not result in better survival outcomes for patients with peritoneal metastases from an unknown origin. Despite this, survival differed among each histological subtype and recently more treatment options became available for a selected group of patients with peritoneal malignancies. Therefore, it is of great importance to identify the histology of the peritoneal metastases and the primary tumor whenever possible.

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Chapter 13

Summary and discussion

Summary and discussion

Since reliable and up-to-date epidemiological information on peritoneal metastases is currently lacking, the aim of this thesis was to provide insight into the burden of peritoneal metastases by exploring epidemiological and clinical aspects from a variety of primary malignancies. This thesis comprised population-based data derived from the Netherlands Cancer Registry (NCR).

Previously, peritoneal metastases were considered as a terminal condition without effective treatment options. Nowadays, a more proactive attitude towards peritoneal metastases is practiced due to the evolution of locoregional and systemic therapies for these patients depending on their primary origin.[1] This renewed interest in peritoneal metastases points out the need for up-to-date epidemiological data regarding the origin of peritoneal metastases as described in **chapter 2**. The cohort in this study included all patients with a cancer diagnosis in 2019 or 2020 in the Netherlands. Among these patients, 4% were diagnosed with peritoneal metastases at time of primary tumor diagnosis, being 17% of all patients with metastatic cancer. Thus, these numbers reveal that synchronous peritoneal metastases affect a relevant part of all cancer patients. The total impact of peritoneal metastases is expected to be even higher, as metachronous peritoneal metastases frequently occur after curative resection of malignancies of the alimentary and hepatobiliary tract, which is also described by studies on colon- and gastric cancer from this thesis.

Chapter 2 reveals that ovarian cancer was the most common origin of peritoneal metastases in females. Colon cancer was the most common origin in male patients. Besides the most studied primary tumors such as ovarian-, colon-, gastric- and appendiceal cancer[2-5], 40% of all peritoneal metastases in this study arise from less-known primaries being pancreatic-, lung-, endometrial-, biliary tract- and esophageal cancer. Thereby, this high proportion should encourage future epidemiological and clinical research regarding these understudied malignancies.

Peritoneal metastases of colorectal origin

The first chapters of this thesis aimed to gain more insight into peritoneal metastases of colorectal origin, whereby **chapter 3** reported the results of a population-based study in which patients with synchronous peritoneal metastases and metachronous peritoneal metastases from colorectal cancer (CRC) were compared. This study included patients with a CRC diagnosis in the first 6 months of 2015, with follow-up until 2019. Among all patients with CRC, 5.7% of the patients were diagnosed with synchronous peritoneal

metastases. After potentially curative surgery for primary CRC, another 5.5% of patients developed metachronous peritoneal metastases during the first three years of follow-up. This is the highest incidence of both synchronous and metachronous colorectal peritoneal metastases ever reported in previous published population-based studies.[4,6-8] This increase in incidence is probably the result of more awareness for this metastatic entity during diagnostic work-up or follow-up after primary CRC surgery as well as further improvement of diagnostic imaging techniques.

A strong association was found in CRC patients between the presence of synchronous distant metastases and synchronous peritoneal metastases. Interestingly, **chapter 8** describes that patients with gastric cancer and synchronous distant metastases were less likely to be diagnosed with synchronous peritoneal metastases. In gastric cancer patients, it can be assumed that patients with distant metastases at primary diagnosis probably will not undergo extensive diagnostic procedures since they are considered to have unresectable disease with no curative treatment options available.[1,9] In contrast, fit patients with CRC and limited isolated peritoneal metastases may undergo curative intent treatment such as cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (CRS-HIPEC).[1,10] Hence, they will probably receive a more thorough diagnostic work-up, thereby increasing the likelihood of discovering distant metastases and undergoing a curative intent treatment if they are considered as eligible.

The presence of systemic distant metastases during the initial diagnosis of primary CRC was found to be a risk factor for the development of metachronous peritoneal metastases as well. Nowadays, CRC patients with synchronous distant metastases (i.e., liver and lung) are increasingly being treated with curative intent.[11] Therewith, it will become more relevant that patients with synchronous distant metastases receive a more intensified follow-up of the peritoneal cavity after undergoing curative treatment. Among patients with high-risk tumors (i.e. T4 tumor stage with or without lymph node involvement or perforated colon cancer), the COLOPEC trial revealed that metachronous peritoneal metastases were found during early second look diagnostic laparoscopy (within 2 months after primary resection) in 10% of patients.[12] Currently, a second and third look laparoscopy is being investigated for patients with high-risk colon tumors in the COLOPEC 2 trial, aiming for detection of peritoneal metastases at an early stage.[13] Detection of colorectal peritoneal metastases at an early stage could improve patient survival since it will likely increase the number of patients eligible for curative intent treatment.

Given the inadequacy of currently available radiological imaging techniques (i.e. computed tomography [CT]) in detecting peritoneal metastases, it is of great importance to seek for innovative, more sensitive imaging modalities.[14,15] The value of magnetic resonance imaging (MRI) with diffusion weighted imaging (DWI) in determining the peritoneal tumor load in CRC patients is currently being investigated by the randomized DISCO multicenter trial (NCT04231175) and might also be valuable in improving detection of peritoneal metastases.[16] Moreover, a fibroblast activation protein inhibitor (FAPI) with positron emission tomography (PET) imaging attains more scientific attention in CRC patients as it appears to detect peritoneal metastases that were previously undetectable through conventional imaging.[17] Although these diagnostic modalities may offer improved accuracy in detecting peritoneal metastases, they are associated with higher costs compared to conventional imaging.[18,19]

Furthermore, **chapter 4** investigated the type of surgical approach during primary tumor resection as a potential risk factor for the development of metachronous peritoneal metastases in CRC patients. This study included all CRC patients who underwent open or laparoscopic resection of the primary tumor in the Netherlands in the first 6 months of 2015. The 3-year cumulative incidence of patients who developed metachronous colorectal peritoneal metastases after a laparoscopic primary tumor resection was 3.7% and 7.3% after an open primary tumor resection. Previously, we also reported a lower rate of synchronous colorectal peritoneal metastases during initial primary laparoscopic resection than during open resection and therefore it was hypothesized that peritoneal metastases might have been overlooked during laparoscopic primary resection.[20] Subsequently, this would lead to an increased number of patients diagnosed with metachronous colorectal peritoneal metastases after a laparoscopic approach. Interestingly, the results of the present study indicate a contrasting outcome, revealing that patients who underwent laparoscopic resection of primary CRC were less frequently diagnosed with metachronous colorectal peritoneal metastases than patients who underwent open resection for primary CRC. One possible explanation could be that open surgery triggers a more pronounced inflammatory response than laparoscopic surgery, potentially facilitating the proliferation of malignant cells.[21,22] Although multivariable regression analysis aimed to correct for relevant confounders such as T4 tumor stage, positive lymph nodes and colon perforation, residual bias probably still should be taken into account since no data were available on mutational status, vascular invasion or factors that complicate laparoscopic surgery (i.e., colonic obstruction, abdominal wall involvement).

Altogether, the findings described in **chapter 3** and **chapter 4** may contribute to a more tailored follow-up approach after primary surgery for CRC. Moreover, by identifying patients being at risk for peritoneal metastases, it may guide future clinical trials investigating strategies that lower the risk of peritoneal dissemination or for detection of colorectal peritoneal metastases at an earlier stage.

Over the past two decades, CRS-HIPEC has been increasingly applied as curative intent treatment in highly selected patients with isolated limited colorectal peritoneal metastases but whether the onset of peritoneal metastases (i.e., synchronous or metachronous) has impact on outcome was not yet investigated.[1] Therefore, **chapter 5** included all patients with synchronous or metachronous peritoneal metastases and a primary CRC diagnosis within the first 6 months of 2015. This study found that, after correction for covariables, overall survival (OS) was similar between patients with synchronous and patients with metachronous colorectal peritoneal metastases, as measured from the diagnosis date of the peritoneal metastases. Patients with metachronous peritoneal metastases were more often treated with CRS-HIPEC than patients with synchronous peritoneal metastases (16% vs. 8%). This may be due to the fact that patients with non-metastatic CRC undergo standardized follow-up after primary tumor resection which may have resulted in detection of metachronous peritoneal metastases at an earlier and thus less advanced stage.[23] In contrast, since it is known that clinical symptoms of peritoneal metastases only occur in a part of the patients and usually manifest in an advanced stage of disease, synchronous peritoneal metastases are frequently discovered in an advanced stage.[24] Furthermore, there was no difference in disease-free survival (DFS) and OS between synchronous and metachronous peritoneal metastases within the subgroup of patients treated with CRS-HIPEC. This indicates that the onset of peritoneal metastases is not relevant in determining the suitable treatment strategy and that a similar prognosis may be expected for patients selected to undergo treatment regardless of the onset of colorectal peritoneal metastases.

As reported in **chapter 5**, curative intent treatment modalities such as CRS-HIPEC are available for a minority of patients with colorectal peritoneal metastases. Patients who are not eligible for curative treatment, due to too extensive disease, often only receive best supportive care (BSC), or one of various palliative treatment options.[1] Whether to resect an asymptomatic primary colorectal tumor in patients with unresectable isolated synchronous peritoneal metastases was not previously reported and thus **chapter 6** describes the outcome of a palliative primary tumor resection in these

patients. This study included all patients diagnosed with isolated synchronous colorectal peritoneal metastases between 2009 and 2020. Patients who underwent curative intent therapy (i.e., CRS-HIPEC, debulking surgery or metastasectomy) or a primary tumor resection in an emergency setting were excluded. A primary tumor resection was performed in 35% of all included patients and within this group of patients we found an improved OS compared to patients who only received palliative systemic treatment (median 13.7 months vs. 10.3 months). However, a higher sixty-day mortality was reported for patients in the primary tumor resection group as compared to patients who received systemic therapy only. This finding is in line with the recently published CAIRO4 randomized controlled trial for patients with CRC and distant metastases.[25] After performing multivariable cox regression analysis, aiming to correct for relevant confounders, a primary tumor resection remained associated with an improved median OS. Unfortunately, no data on the peritoneal cancer index (PCI) score was available, which is relevant in this respect since it may be that patients with less extensive peritoneal disease were more prone to undergo a primary tumor resection. Therefore, residual confounding probably still plays an important role. In spite of this, it is not likely that a randomized controlled trial will address this issue for peritoneal metastases patients in the near future. While keeping this in mind, this study provides valuable information to guide the decision-making process by clinicians and their patients. Based on the results of this study, it is not advised to perform a primary tumor resection in all patients with peritoneal metastases of colorectal origin, but a primary tumor resection could be considered in patients with symptoms or patients who prefer treatment.

The findings of **chapter 5** and **chapter 6** demonstrate the present-day outcomes of unselected patients with peritoneal metastases from CRC in everyday clinical practice. These studies highlight variations in given treatments and outcomes across different patient groups. Consequently, the results can provide valuable guidance in the decision-making process between clinician and their patients.

Peritoneal metastases of gastric origin

The systematic review described in **chapter 7** aimed to provide an overview of the incidence, risk factors and survival of patients with peritoneal metastases of gastric origin. The review identified 17 studies that reported on incidence numbers, risk factors or survival of patients with synchronous peritoneal metastases from gastric cancer. Five population-based studies reported on incidence of synchronous gastric peritoneal metastases, ranging from 10% to 21%. The reported incidence in surgical cohort studies (i.e., studies which included patients who underwent a staging laparoscopy) ranged from

13% to 40%. Factors associated with an increased risk for the presence of synchronous peritoneal metastases were younger age, non-cardia cancer, female sex, signet ring cell carcinoma, diffuse type histology or linitis plastica, T4 tumor stage, Hispanic ethnicity and more than one location of metastases. Few studies reported on survival in patients with synchronous peritoneal metastases from gastric cancer and the median OS ranged from 2 to 9 months.

Based on the studies included in this review, the peritoneum is pointed out as one of the most common synchronous metastatic sites in patients with gastric cancer. Due to the high occurrence of peritoneal metastases in gastric cancer and the difficult clinical diagnosis of these metastases, a diagnostic laparoscopy became part of the standard diagnostic work-up towards curative intent surgery in the Netherlands in 2016.[26]

Only studies focusing on synchronous peritoneal metastases were available during the inclusion period of this review. Therewith, it exposed the lack of comprehensive epidemiologic data on peritoneal recurrence after potentially curative treatment. **Chapter 8** aimed to investigate incidence, risk factors, treatment and survival of synchronous or metachronous peritoneal metastases in patients with gastric cancer and to describe possible differences between synchronous and metachronous peritoneal metastases. All patients diagnosed with gastric cancer in 2015 and 2016 were included. This study found that after a follow-up period of three years, approximately one third of all patients with gastric cancer are diagnosed with peritoneal metastases. At primary gastric cancer diagnosis, already 23% of all patients had synchronous peritoneal metastases. The 3-year cumulative incidence of metachronous peritoneal metastases in patients who underwent potentially curative treatment was 22.8%. A strong association was found between having a diffuse type histology and the presence of synchronous peritoneal metastases as well as the development of metachronous peritoneal metastases. These high incidence numbers may suggest that a more intensified follow-up, focusing on the peritoneum, should be further explored. Moreover, several studies have investigated a prophylactic HIPEC combined to curative primary tumor surgery as potential treatment strategy in gastric cancer patients without peritoneal metastases. Unfortunately, the effectiveness of a prophylactic HIPEC is still questionable due to the overall low quality of current available randomized controlled trials.[27] The phase III GASTROCHIP trial is currently investigating the effectiveness of a prophylactic HIPEC combined with curative surgery and might be of great value in clarifying this issue.[28] **Chapter 8** also found that metachronous peritoneal metastases patients were less often treated with systemic

therapy in comparison with synchronous peritoneal metastases, which may be explained by the rapid disease recurrence after prior given perioperative chemotherapy in these patients. Conceivably, clinicians might feel more pessimistic against systemic therapy during the decision-making process due to the rapid disease recurrence.

Summarizing these findings, these two chapters provide a more comprehensive perspective on the incidence of peritoneal metastases in gastric cancer patients. They reveal that peritoneal metastases frequently occur in gastric cancer patients and that patients with peritoneal metastases have a dismal prognosis. These results underscore the importance of clinical trials investigating specific treatment options for this particular metastatic manifestation.

Peritoneal metastases of hepatopancreatobiliary origin

As described in **chapter 2**, peritoneal metastases often arise from hepatopancreatobiliary cancers. **Chapter 9** aimed to investigate the incidence and risk factors of synchronous peritoneal metastases and to determine treatment strategies and survival of patients with hepatobiliary cancer and synchronous peritoneal metastases. All patients diagnosed with hepatobiliary cancer between 2009 and 2018 were included in this study and peritoneal metastases were found in 8% of all patients. Peritoneal metastases were more often present in patients with biliary tract cancer than in patients with hepatocellular cancer (12% vs. 3%). Overall, almost 70% of all patients with synchronous peritoneal metastases from hepatobiliary cancer did not receive any treatment. Survival in patients who received BSC only was 1.7 months. **Chapter 10** comprises a population-based study on the increasing trend in incidence of peritoneal metastases in pancreatic cancer and it aimed to provide insight into treatment strategies and survival of patients with pancreatic peritoneal metastases. This study included all patients diagnosed with pancreatic cancer between 2008 and 2018. It was noted that synchronous peritoneal metastases were increasingly diagnosed in patients with pancreatic cancer, with 11% of patients presenting with peritoneal metastases in 2008 compared to 16% in 2018. Moreover, a previously published population-based study reported an incidence of 9% of peritoneal metastases in pancreatic cancer between the years 1995 and 2009.[29] The constant improvement of imaging modalities over the years and more awareness regarding peritoneal spread in general probably have played an important role in this increasing incidence.

The incidence of peritoneal metastases in pancreatic cancer is similar to the incidence in biliary tract cancer, whereas hepatocellular cancer patients

have a notable lower risk to be diagnosed with synchronous peritoneal metastases. In general, hepatocellular carcinoma (HCC) is less frequently diagnosed with distant metastases (18%), whereas biliary tract cancer and pancreatic cancer tend to exhibit a higher rate of metastasis to distant organs at primary diagnosis (+/- 50%).[30-34] The anatomical characteristics (surrounded by extensive lymph nodes and blood vessels), lack of early symptoms and aggressive biological tumor behavior of biliary tract cancer and pancreatic cancer make them more prone to distant metastasis compared to HCC.[35] Only a small proportion of patients with pancreatic cancer and peritoneal metastases received tumor-directed therapy (27%). The amount of patients with pancreatic peritoneal metastases who did not receive any treatment is comparable to patients with hepatobiliary peritoneal metastases described in **chapter 9**.

Unfortunately, late discovery of disease is common in patients with hepatopancreatobiliary cancer resulting in extensive disease at time of diagnosis. This probably has led to the large proportion of hepatopancreatobiliary patients with peritoneal metastases who did not receive any treatment at all. Only a limited number of cohort studies have examined the use of CRS-HIPEC in patients with hepatobiliary peritoneal metastases and showed improved results in comparison with systemic therapy alone.[36-38] Nevertheless, it is important the note that they were unable to fully exclude the presence of selection bias. Currently, two small clinical trials enroll patients with peritoneal metastases from biliary tract cancer (NCT05285358) or pancreatic cancer (NCT05371223) to investigate whether pressurized intraperitoneal aerosolized chemotherapy (PIPAC) in combination with systemic therapy provides a survival benefit in these patients. However, it is important to bear in mind that certain challenges arise when considering local treatment options for this patient group as HCC has high recurrence rates after primary tumor resection and resection in patients with biliary tract cancer is often associated with infectious complications.[39,40]

In spite of its frequently encounter, very little has been reported on peritoneal metastases from hepatopancreatobiliary cancer. Although the incidence rate of synchronous peritoneal metastases in hepatopancreatobiliary cancer patients is significantly higher than for instance in CRC patients, very little scientific interest has been generated in terms of clinical trials regarding specific treatment options for this patient category.[1] This might be related to the relatively low absolute number of patients in Western countries. Based on **chapter 3**, the absolute number of patients with synchronous colorectal peritoneal metastases was two times higher than the absolute number of

patients with synchronous peritoneal metastases of hepatopancreatobiliary origin described in **chapter 9** and **chapter 10**.

Peritoneal metastases from lung cancer and of unknown origin
While lung cancer is a major global health problem with increasing incidence rates, little is known on the incidence of peritoneal metastases from lung cancer and how they affect survival.[41] **Chapter 11** included all patients diagnosed with lung cancer between 2008 and 2018. Among these patients, 2% were diagnosed with synchronous peritoneal metastases. Younger age, a T3 or T4 tumor stage, positive lymph nodes, a poorer WHO performance status and having other synchronous distant metastases were associated with the presence of synchronous peritoneal metastases. These risk factors were previously identified for peritoneal metastases in for instance CRC, ovarian cancer and gastric cancer and underline the advanced stage of disease in which peritoneal metastases occur.[5,42,43]

Chapters 3-11 in this thesis aimed to gain more insight into peritoneal metastases from particular primary origins. Remarkably, **chapter 2** describes that an unknown primary tumor location was the fifth most common origin in all patients diagnosed with synchronous peritoneal metastases. **Chapter 12** aimed to address the incidence of peritoneal metastases of unknown origin and to investigate the treatment and survival of patients with peritoneal metastases of unknown origin. The study included all patients diagnosed with synchronous peritoneal metastases of unknown origin in 2017 and 2018. This study showed that peritoneal metastases were found in 17% of all patients with an unknown primary tumor. While this is the highest reported incidence of peritoneal metastases of unknown origin ever described in population-based cohorts, recent literature stated that the incidence of cancer from an unknown primary in general is decreasing.[44-46] An explanation for this finding could be that patients with peritoneal metastases receive less thorough diagnostic testing in comparison to patients with other metastases where the suspected prognosis and possible treatment options warrants further investigation.

This study showed that the distribution of given palliative treatments, being metastasectomy, systemic treatment or BSC only, as well as the survival of patients with peritoneal metastases differed among each histological subtype. For example, patients with a carcinoid histology more often received systemic treatment as compared to the other histological types included in the study. Hence, it is becoming more important to identify the histology of the peritoneal metastases but also the primary tumor, especially since more curative intent treatment options became available for a selected group of

patients with limited peritoneal metastases of appendiceal-, colorectal- and ovarian origin.[1]

Future perspectives

Real-world data
Real-world data and randomized controlled trials are both valuable tools in the scientific world. While randomized controlled trials remain essential for establishing causal relationships and assessing treatment efficacy, real-world data plays an increasingly important role in complementing randomized controlled trial findings, providing insights into real-world effectiveness, safety, and outcomes in diverse patient populations.[47] As personalized medicine gains prominence, there is an increasing recognition of the limitations of randomized controlled trials in capturing the full spectrum of patient characteristics and treatment responses due to the small number of eligible patients. The emergence of precision medicine has led to an increasing interest in real-world data and it is becoming more important because of the ability to capture a broader patient population and evaluate the impact of interventions in diverse clinical settings.[48]

As peritoneal metastases have been regarded as a less common pattern of cancer metastasis for which large randomized controlled trials are not often being conducted, population-based studies can offer important insights into this manifestation of disease. For patients with peritoneal metastases from a less-known or understudied primary origin, population-based studies should be used to identify evidence gaps in health care and to guide and complement future clinical trials. Nowadays, treatment modalities have expanded for a selected group of patients with peritoneal metastases and real-world data could provide valuable insights into the patterns of utilization, sequencing, and combinations of treatment that are used in peritoneal metastases. Future research in the treatment of peritoneal metastases should include both clinical trials for an objective assessment of treatment outcomes as well as population-based studies for real-time monitoring of treatment effectiveness. However, it is important to note that population-based studies may be subject to selection bias due to non-random treatment allocation and incomplete or missing data, potentially influencing treatment comparisons and outcomes.[47]

Nationwide cancer registry
Essential for high quality population-based studies is of course the availability of a nationwide cancer registry. Preserving quality of nationwide cancer registries is vital for ensuring the reliability, validity, and usefulness of the

collected data. As stated by different chapters in this thesis, the extent of peritoneal disease, also referred to as the PCI score, is currently not registered by the NCR. The PCI score is known to be an important factor to determine a patients' eligibility for curative intent treatment such as CRS-HIPEC and for the prognosis of patients.[49,50] Therefore, the PCI score could be of great value in understanding certain treatment allocations and differences in long-term survival in patients with peritoneal metastases. Currently, the registration of the PCI score is being implemented in gastric cancer patients within the NCR. Also, since 2019 the HIPEC registry was created to collect data for patients who underwent a CRS-HIPEC for pseudomyxoma peritonei, colorectal- and appendiceal cancer. Within this registry, which is part of the NCR, more specific surgical and postoperative outcomes are being obtained including the PCI score. Moreover, the HIPEC registry also includes patients with metachronous peritoneal metastases and in the near future, 3-year follow-up data on recurrence or progression of disease will be collected for patients who underwent a CRS-HIPEC in 2019. These promising developments could lead to a more accurate representation of patients with peritoneal metastases of colorectal- or gastric origin and better insight in treatment effectiveness.

To comprehensively assess the impact of cancer and evaluate treatment effectiveness, it is essential to include follow-up data, especially regarding recurrence of disease. Moreover, by tracking these events, registries can identify patterns and trends related to metastatic disease, providing insights into the aggressiveness of cancer, potential risk factors, and the effectiveness of treatment strategies. The reported results in this thesis on colorectal- and gastric cancer, demonstrate that metachronous peritoneal metastases have a substantial impact on patient outcome. Whilst no follow-up data is being collected by the NCR on a large-scale, there is a possibility to collect this data on special request.

In the future, it is expected that the burden of registration will further expand as the prevalence and complexity of cancer cases continue to rise.[51] To alleviate the registration load and sustain high-quality registration, several strategies can be implemented. First, optimizing data collection processes through the integration of electronic health records and automatic data extraction can streamline data capture and reduce manual entry errors. Second, exploring innovative approaches such as utilizing artificial intelligence to assist with data processing and analysis can help reduce workload on registrars. Lastly, promoting international collaboration and harmonization of cancer registry practices can facilitate the exchange of knowledge, best practices, and resources, ultimately enhancing the efficiency and quality of cancer registration across different regions.

Conclusion

Based on the articles included in this thesis, it is evident that peritoneal metastases represent a significant burden in various cancer types. The incidence of peritoneal metastases varies across primary tumors and it is a common type of metastatic spread in gastro-intestinal primary tumors but also arises from extraperitoneal primary tumors, affecting a relevant part of cancer patients. In spite of progress that has been made with regards to the treatment of peritoneal metastases, prognosis of these patients remains generally poor. The findings in this thesis may contribute to the development of evidence-based approaches for managing peritoneal metastases and improving patient outcomes. Further research and continued efforts in registering and analyzing data on peritoneal metastases will enhance our understanding of this disease and help guide future treatment strategies.

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Chapter

14

Impact

Impact

This thesis focused on epidemiological and clinical aspects of peritoneal metastases. Although peritoneal metastases are traditionally considered a less common mode of cancer spread, its impact on a significant number of patients each year appears to be substantial across various types of primary tumors. The results described in this thesis underscore the frequent occurrence of peritoneal metastases in gastric cancer and colorectal cancer (CRC). Additionally, it shed light on less-known origins of peritoneal metastases, being liver cancer, biliary tract cancer, lung cancer or cancer of unknown primary.

While brain, liver, bone and lung metastases have received considerable attention in terms of treatment strategies, peritoneal metastases have historically been less explored. Studies have shown that peritoneal metastases are not as rare as previously believed. In fact, the occurrence of peritoneal metastases may be equal or even surpass the proportion of metastases to the brain, liver, bone, or lung in certain cancer types. Ever since the developments in surgical techniques, a more proactive attitude has been adopted towards peritoneal metastases. These developments entail cytoreductive surgery (surgical procedure in which all visible tumor is removed; CRS) and hyperthermic intraperitoneal chemotherapy (deliver localized, heated chemotherapy in the abdomen; HIPEC), as well as intraperitoneal chemotherapy. Furthermore, modern systemic therapy has shown promising results in patients with peritoneal metastases from a selected group of primary tumors.

Relevance
In concomitance with the renewed interest in peritoneal metastases, more reliable, up-to-date epidemiological information was warranted. Therefore, this thesis provides insight into the occurrence and risk factors of peritoneal metastases from a variety of primary tumors by using nationwide data from the Netherlands Cancer Registry (NCR). Additionally, it presents information on specific treatment strategies, and it reveals the severity of this disease entity. Since this thesis utilizes nationwide data, it enables the evaluation of peritoneal metastases as it is presented in a real-life setting. For instance, this thesis describes that the number of patients with peritoneal metastases from CRC in the Netherlands has increased over the last years. It also depicts on the high number of patients with peritoneal metastases of gastric origin, which was the highest number of peritoneal metastases ever described in literature. Moreover, this thesis reported a very high proportion of peritoneal

metastases in patients with liver cancer, pancreatic cancer and biliary tract cancer.

Altogether, these high numbers of patients diagnosed with peritoneal metastases underscore that peritoneal metastases affect a relevant part of cancer patients. Variations in given treatments were observed among different patient's groups in gastric cancer and CRC, such as between patients with peritoneal metastases that were diagnosed simultaneously with the primary tumor (synchronous) and patients that developed peritoneal metastases later during follow-up after curative intent treatment (metachronous). These distinctions can be helpful in guiding the decision-making process for treatment and follow-up between clinicians and their patients. Furthermore, this thesis exposes the extremely poor prognosis of patients with peritoneal metastases and thereby identifies an important knowledge gap which should encourage future studies to investigate specific treatment options for this patient category.

Substantial effort has been made to improve the management of patients with peritoneal metastases, both globally as well as in the Netherlands. These endeavors comprise a range of trials, including the prevention and early detection of colorectal peritoneal metastases (COLOPEC 1 & 2), the optimization of treatment of colorectal peritoneal metastases by adding perioperative systemic therapy to CRS-HIPEC (CAIRO6), palliative approaches regarding the management of extensive peritoneal metastases in CRC patients (PIPAC I & II and INTERACT I & II), the treatment of peritoneal metastases in gastric cancer with CRS-HIPEC (PERISCOPE-II), as well as the application of CRS-HIPEC for peritoneal metastases in ovarian carcinomas (OVHIPEC 1 & 2). While these trials may not stem directly from this particular thesis, they do underscore this research domain as active, where real-life data hold significant relevance in evaluating treatment strategies and exploring areas with yet limited knowledge.

Target population

In the Netherlands, yearly 3730 patients were diagnosed with peritoneal metastases simultaneously with the primary tumor (years 2019 and 2020). The total amount of patients with synchronous peritoneal metastases is expected to be even higher as small peritoneal metastases are often not diagnosed with current radiological techniques. As such, it is thought that a relevant proportion of patients remains undetected. Moreover, peritoneal metastases also frequently occur at a later moment during follow-up after treatment for their primary tumor.

The findings of this thesis hold relevance for both patients diagnosed with peritoneal metastases and the medical professionals involved in their treatment. The results from this thesis might offer directions for a personalized approach in treating these patients. Besides patients with peritoneal metastases, the results of this thesis are also relevant for patients with colorectal- and gastric cancer without (peritoneal) metastases, as several studies in this thesis provided information on risk factors for the development of peritoneal metastases in nonmetastatic colorectal- and gastric cancer. The risk factors that were identified could improve the clinical decision-making regarding follow-up care in these patients.

Finally, the spread of cancer to the peritoneum is a significant health concern that often is unnoticed or underreported in a broader audience. By raising awareness among policymakers through the findings of this thesis, we can bring attention to this critical issue and advocate for improved healthcare policies, increased funding for research and treatment options, and enhanced support for patients and their families.

Activity

This thesis comprises studies with real-world data (data as presented in a real-life setting) which reflect the actual Dutch population encountered in every day clinical practice. Thereby, the results are informative for a wide range of health care providers and patients worldwide. For example, the number of patients with gastric cancer is a lot higher in Asian countries, thus the epidemiological and clinical information from this thesis on gastric peritoneal metastases is even more relevant in those regions. However, the generalizability of our findings to the population in Asia might be difficult due to the influence of different epidemiological and clinical aspects in those countries as compared to Western countries. The findings of this thesis impose the significant burden of peritoneal metastases as metastatic manifestation on individuals and healthcare systems. Translation of results from these population-based studies into clinical practice ensures that healthcare professionals are provided with up-to-date information to enable the best possible care for patients with peritoneal metastases.

Chapter

15

Nederlandse samenvatting

Nederlandse samenvatting

Het doel van dit proefschrift was om meer inzicht te krijgen in epidemiologische en klinische aspecten van buikvliesuitzaaiingen, oftewel peritoneale metastasen, bij verschillende primaire kankersoorten in de dagelijkse klinische praktijk.

Tot ongeveer 20 jaar geleden werden peritoneale metastasen beschouwd als een terminale ziekte zonder effectieve behandelingsopties. Tegenwoordig wordt er, afhankelijk van de primaire kankersoort, een meer proactieve houding aangenomen ten opzichte van peritoneale metastasen als gevolg van de ontwikkeling van lokale en systemische therapieën voor deze patiënten.

In navolging van deze proactieve houding is er ook meer behoefte aan actuele epidemiologische gegevens met betrekking tot peritoneale metastasen en de mogelijke primaire kankersoorten van waaruit deze metastasen kunnen ontstaan. In **hoofdstuk 2** worden epidemiologische gegevens over de primaire kankersoorten bij peritoneale metastasen beschreven. Het cohort in deze studie omvatte alle patiënten in Nederland met een kankerdiagnose in 2019 of 2020. Bij 4% van alle patiënten met kanker waren deze peritoneale metastasen al aanwezig ten tijde van de primaire kanker diagnose (zogenaamde synchrone peritoneale metastasen). Dit komt overeen met 17% van alle patiënten die een kankerdiagnose mét metastasen hadden. Absoluut gaat het om 3730 patiënten per jaar. Deze cijfers laten zien dat een relevant deel van alle kankerpatiënten te maken krijgt met synchrone peritoneale metastasen. De totale hoeveelheid peritoneale metastasen is naar verwachting nog groter, aangezien een deel van de patiënten met kanker in eerste instantie behandeld worden met een operatie en op een later moment peritoneale metastasen zullen ontwikkelen (zogenaamde metachrone peritoneale metastasen). Dit wordt nader onderzocht in dit proefschrift in de studies over darm- en maagkanker.

Hoofdstuk 2 laat zien dat eierstokkanker de meest voorkomende primaire kankersoort van peritoneale metastasen is bij vrouwen. Bij mannelijke patiënten is darmkanker de meest voorkomende primaire kankersoort waaruit peritoneale metastasen ontstaan. Naast de meest bekende primaire kankersoorten van waaruit peritoneale metastasen zich manifesteren, zoals eierstok-, dikke darm-, maag- en blinde darmkanker, zagen we dat 40% van alle peritoneale metastasen in deze studie voorkomen bij minder bekende primaire kankersoorten, namelijk alvleesklier-, long-, baarmoeder-, galweg- en slokdarmkanker. Dit hoge percentage zou toekomstig epidemiologisch

of klinisch onderzoek naar peritoneale metastasen bij deze onderbelichte kankersoorten moeten stimuleren.

Peritoneale metastasen bij darmkanker

De eerste hoofdstukken van dit proefschrift hebben als doel meer inzicht te krijgen in peritoneale metastasen bij darmkanker. **Hoofdstuk 3** beschrijft de resultaten van een studie waarin patiënten met synchrone peritoneale metastasen en metachrone peritoneale metastasen bij darmkanker werden vergeleken. Van alle patiënten met darmkanker werden bij 5.7% van de patiënten peritoneale metastasen vastgesteld bij primaire diagnose (synchroon). Bij 5.5% van de patiënten werden metachrone peritoneale metastasen vastgesteld na een eerdere, in opzet curatieve, behandeling voor darmkanker. Dit zijn de hoogst beschreven proporties van patiënten met peritoneale metastasen bij darmkanker in de literatuur. Deze stijging in het vóórkomen van peritoneale metastasen kan komen doordat men tegenwoordig meer bedacht is op de eventuele aanwezigheid van peritoneale metastasen tijdens diagnostisch onderzoek of tijdens de follow-up na een operatie voor primaire darmkanker. Een andere verklaring voor de stijging in het vóórkomen van peritoneale metastasen is de verbetering van diagnostische middelen zoals beeldvorming.

In **hoofdstuk 3** werd een sterke correlatie gevonden tussen de aanwezigheid van synchrone afstandsmetastasen en synchrone peritoneale metastasen bij patiënten met darmkanker. Interessant genoeg beschrijft **hoofdstuk 8** dat patiënten met maagkanker en synchrone afstandsmetastasen juist minder vaak gediagnosticeerd werden met synchrone peritoneale metastasen. Bij patiënten met maagkanker kan verondersteld worden dat ze waarschijnlijk geen uitgebreide diagnostiek meer zullen ondergaan wanneer er afstandsmetastasen zijn vastgesteld bij primaire diagnose. Er zijn op dat moment namelijk geen curatieve behandelopties meer beschikbaar. Daarentegen komen fitte patiënten met darmkanker en beperkte peritoneale metastasen wél in aanmerking voor een curatieve behandeling zoals cytoreductieve chirurgie met intraperitoneale, verwarmde chemotherapie (CRS-HIPEC). Wanneer deze patiënten uitgebreidere diagnostiek ondergaan, zal de kans groter worden dat er afstandsmetastasen worden ontdekt.

De aanwezigheid van systemische afstandsmetastasen tijdens de initiële diagnose van darmkanker was ook gecorreleerd met de ontwikkeling van metachrone peritoneale metastasen op een later moment. Tegenwoordig worden steeds meer patiënten met darmkanker en synchrone afstandsmetastasen (bijv. in de lever en longen) behandeld met curatieve intentie. Hierdoor wordt het steeds belangrijker dat deze patiënten

nauwlettender opgevolgd worden voor het optreden van eventuele peritoneale metastasen op een later moment. Wanneer peritoneale metastasen bij darmkanker vroegtijdig gedetecteerd worden zou dit wellicht de overleving van de patiënt kunnen verbeteren doordat patiënten bij diagnose minder uitgebreide ziekte blijken te hebben.

In **hoofdstuk 4** wordt beschreven of het type chirurgische benadering (laparoscopische resectie versus open resectie) tijdens de primaire tumorresectie een potentiële risicofactor is voor de ontwikkeling van metachrone peritoneale metastasen bij patiënten met darmkanker. Na een laparoscopische resectie van de primaire darmtumor bleek de 3-jaars cumulatieve incidentie van metachrone peritoneale metastasen 3.7% te zijn, terwijl dit na een open resectie van de primaire tumor 7.3% was. In een eerdere studie vonden we een lager percentage synchrone peritoneale metastasen tijdens een laparoscopische resectie in vergelijking met een open resectie. Vervolgens werd verondersteld dat peritoneale metastasen mogelijk over het hoofd waren gezien tijdens de laparoscopische resectie van de primaire tumor. De verwachting was dan ook dat het aantal patiënten dat metachrone peritoneale metastasen na een laparoscopische benadering hoger zou zijn. De huidige studie geeft echter het tegenovergestelde resultaat en laat dus zien dat patiënten juist meer peritoneale metastasen hebben na een eerdere open resectie. Hoewel geprobeerd is om te corrigeren voor relevante verstorende factoren zoals een hoger tumorstadium, positieve lymfeklieren en perforatie van de darmwand, zal resterende selectiebias een rol hebben gespeeld omdat er geen gegevens beschikbaar waren over mutatiestatus, vasculaire invasie of factoren die een laparoscopische ingreep moeilijker maken (bijvoorbeeld obstructie van de dikke darm of betrokkenheid van de buikwand).

De bevindingen beschreven in **hoofdstuk 3** en **hoofdstuk 4** kunnen bijdragen aan een meer op maat gemaakte follow-up na primaire chirurgie voor darmkanker. Bovendien zou het identificeren van patiënten die een hoger risico hebben op peritoneale metastasen, toekomstige klinische studies kunnen bijsturen die onderzoek doen naar nieuwe technieken voor het voorkomen of vroeger diagnosticeren van peritoneale metastasen.

CRS-HIPEC wordt in de laatste twee decennia steeds vaker toegepast als curatieve behandeling bij fitte patiënten met beperkte peritoneale metastasen bij darmkanker. Echter, er is nog niet eerder onderzocht of de timing van het ontwikkelen van peritoneale metastasen (synchroon of metachroon) invloed heeft op de uitkomsten van deze patiëntengroep. In **hoofdstuk 5** wordt beschreven dat, na correctie voor covariabelen, de

algehele overleving vergelijkbaar was tussen patiënten met synchrone en metachrone peritoneale metastasen. Patiënten met metachrone peritoneale metastasen werden vaker behandeld met CRS-HIPEC dan patiënten met synchrone peritoneale metastasen (16% vs. 8%). Een verklaring hiervoor kan zijn dat patiënten met darmkanker maar zonder metastasen na primaire chirurgie gestandaardiseerde follow-up krijgen waardoor de peritoneale metastasen in verhouding vroegtijdiger gedetecteerd worden. Synchrone peritoneale metastasen worden in het algemeen vaak ontdekt in een verder gevorderd stadium omdat klinische symptomen slechts bij een deel van de patiënten voorkomen en deze symptomen meestal pas op een laat moment aan het licht komen. Echter, er was geen verschil in ziektevrije overleving en algehele overleving tussen synchrone en metachrone peritoneale metastasen binnen de subgroep van patiënten die behandeld werden met CRS-HIPEC. De resultaten uit deze studie impliceren dat de timing van het ontwikkelen van peritoneale metastasen niet in acht hoeft worden genomen bij het bepalen van de meest geschikte behandelstrategie en dat een vergelijkbare prognose mag worden verwacht voor patiënten met zowel synchrone als metachrone peritoneale metastasen.

Helaas kan de meerderheid van de patiënten met peritoneale metastasen bij darmkanker niet behandeld worden middels een CRS-HIPEC. Patiënten die niet in aanmerking komen voor curatieve behandeling vanwege te uitgebreide ziekte, krijgen vaak enkel symptoombestrijding of een van de verschillende palliatieve behandelingen die beschikbaar zijn. Het effect van het verwijderen van een asymptomatische primaire darmtumor bij patiënten met niet-operabele synchrone peritoneale metastasen werd nog niet eerder onderzocht. Dit vraagstuk wordt beschreven in **hoofdstuk 6**. Patiënten met afstandsmetastasen, patiënten die een curatieve behandeling ondergingen (bijv. CRS-HIPEC, debulkingchirurgie of metastasectomie) of patiënten die een spoedresectie van de primaire tumor ondergingen werden uitgesloten van deze studie. In 35% van alle geïncludeerde patiënten werd de primaire tumor verwijderd en binnen deze groep patiënten vonden we een betere algehele overleving in vergelijking met patiënten die alleen palliatieve systemische therapie kregen (mediaan 13.7 maanden versus 10.3 maanden). Na 60 dagen werd er echter een hoger sterftecijfer gezien bij patiënten die een primaire tumor resectie ondergingen in vergelijking met patiënten die alleen systemische therapie ontvingen. Deze laatste bevinding komt overeen met de recent gepubliceerde CAIRO4-trial waarin patiënten met darmkanker en afstandsmetastasen werden onderzocht.

Een resectie van de primaire tumor was gecorreleerd met een verbeterde algehele overleving in de huidige studie nadat we corrigeerde voor

mogelijk andere relevante factoren die van invloed konden zijn op de algehele overleving (bijv. leeftijd, geslacht). Er waren helaas geen gegevens beschikbaar over de uitgebreidheid van de peritoneale metastasen (de zogeheten peritoneal cancer index [PCI] score). Deze score is van belang omdat er wellicht eerder geneigd werd naar een primaire tumor resectie bij patiënten met minder uitgebreide peritoneale ziekte binnen ons cohort waardoor selectiebias niet geheel kan worden uitgesloten. Desondanks zal deze kwestie in de nabije toekomst niet beantwoord gaan worden door klinische trials en daarom biedt deze studie waardevolle informatie om het gesprek tussen clinici en hun patiënten te begeleiden. Op basis van de resultaten van deze studie adviseren we niet om een primaire tumor resectie uit te voeren bij alle patiënten met peritoneale metastases bij darmkanker, maar een primaire tumor resectie kan wel overwogen worden bij patiënten met symptomen of patiënten die een behandeling prefereren.

De resultaten beschreven in **hoofdstuk 5** en **hoofdstuk 6** laten de uitkomsten van patiënten met peritoneale metastasen bij darmkanker zien in de dagelijkse klinische praktijk. Deze bevindingen kunnen waardevol zijn gedurende de gesprekken tussen de arts en zijn patiënten om het meest geschikte behandelplan te kiezen.

Peritoneale metastasen bij maagkanker

Hoofdstuk 7 beschrijft middels een review de incidentie, risicofactoren en overleving van patiënten met peritoneale metastasen bij maagkanker. De systematische review identificeerde 17 studies. Vijf population-based studies rapporteerden over de incidentie van synchrone peritoneale metastasen, variërend van 10% tot 21%. De incidentie in studies waar alle patiënten een stadiëringslaparoscopie ondergingen varieerde van 13% tot 40%. Een jongere leeftijd, distale tumor locatie, vrouwelijk geslacht, zegelringcel carcinoom, diffuus histologie type of linitis plastica, T4 tumor stadium, Spaanse etniciteit en meer dan één metastaselocaties waren gecorreleerd met de aanwezigheid van synchrone peritoneale metastasen. Een algehele overleving van 2 tot 9 maanden werd gerapporteerd bij patiënten met synchrone peritoneale metastasen in een aantal studies.

Hoofdstuk 8 had als doel de incidentie, risicofactoren, behandeling en overleving van synchrone én metachrone peritoneale metastasen bij patiënten met maagkanker te beschrijven. Uit **hoofdstuk 7** bleek namelijk dat er nog geen eerdere population-based studie was uitgevoerd naar metachrone peritoneale metastasen bij maagkanker. Bij de primaire diagnose maagkanker had 23% van alle patiënten ook synchrone peritoneale metastasen. Patiënten die eerder een curatieve behandeling hebben ondergaan hadden een 3-jaars

cumulatieve incidentie van metachrone peritoneale metastasen van 22.8%. Er werd een correlatie gevonden tussen het hebben van een diffuse histologie type en de aanwezigheid van synchrone peritoneale metastasen, evenals de ontwikkeling van metachrone peritoneale metastasen op een later moment. Mogelijk zou een intensievere follow-up, gericht op het peritoneum, verder onderzocht moet worden voor deze patiëntengroep. Verschillende studies hebben de waarde van een profylactische HIPEC in combinatie met curatieve primaire tumor resectie onderzocht als eventuele behandeling strategie bij patiënten met maagkanker zonder peritoneale metastasen. De effectiviteit hiervan is nog twijfelachtig vanwege de lage kwaliteit van de beschikbare studies hierover. De GASTROCHIP-fase III studie onderzoekt momenteel de effectiviteit van een profylactische HIPEC in combinatie met curatieve chirurgie. Deze studie zou verduidelijking kunnen geven met betrekking tot dit vraagstuk. De studie in **hoofdstuk 8** beschreef ook dat patiënten met metachrone peritoneale metastasen minder vaak behandeld werden met systemische therapie in vergelijking met patiënten met synchrone peritoneale metastasen. Dit kan mogelijk verklaard worden doordat deze patiënten kortgeleden nog perioperatieve chemotherapie hebben ontvangen en vervolgens er weer zeer snel recidief van ziekte is opgetreden bij deze patiënten waardoor clinici zich mogelijk terughoudender opstellen tegenover het opnieuw starten van systemische therapie.

De voorgaande twee hoofdstukken met betrekking tot peritoneale metastasen bij maagkanker laten zien dat deze vorm van metastasering vaak voorkomt en dat de patiënten een sombere prognose hebben. De resultaten benadrukken dat klinische trials naar specifieke behandelingen voor patiënten met peritoneale metastasen van belang zijn.

Peritoneale metastasen bij hepatopancreatobiliaire kanker

Hoofstuk 2 liet eerder al zien dat peritoneale metastasen vaak ontstaan vanuit hepatopancreatobiliaire tumoren (HPB-tumoren). **Hoofdstuk 9** had als doel de incidentie en risicofactoren van synchrone peritoneale metastasen te onderzoeken bij patiënten met lever- en galwegkanker en om behandelingsstrategieën en overleving van deze patiënten te bepalen. Bij 8% van alle patiënten met lever- en galwegkanker werden peritoneale metastasen gevonden. Peritoneale metastasen kwamen vaker voor bij patiënten met galwegkanker dan bij patiënten met leverkanker (hepatocellulair carcinoom [12% versus 3%]). Bijna 70% van alle patiënten met synchrone peritoneale metastasen bij lever- en galwegkanker kregen geen palliatieve behandeling maar ontvingen enkel symptoombestrijding. De overleving van deze patiëntengroep die enkel symptoombestrijding kreeg was 1.7 maanden.

Hoofdstuk 10 onderzocht de trend in incidentie van peritoneale metastasen bij alvleesklierkanker. Deze studie had tevens als doel inzicht te geven in behandelingsstrategieën en overleving van patiënten met peritoneale metastasen bij alvleesklierkanker. Synchrone peritoneale metastasen bleken steeds vaker te worden vastgesteld bij patiënten met alvleesklierkanker, met een incidentie van 11% in 2008 en 16% in 2018. Bovendien beschreef een eerder gepubliceerde studie een incidentie van 9% peritoneale metastasen bij alvleesklierkanker tussen de jaren 1995 en 2009. De voortdurende verbetering van beeldvormende technieken in de loop der jaren evenals de toegenomen alertheid met betrekking tot peritoneale metastasen bij alvleesklierkanker zullen waarschijnlijk een belangrijke rol gespeeld hebben in de toename van incidentie. Slechts een klein deel van de patiënten met peritoneale metastasen bij alvleesklierkanker kreeg een tumor gerichte behandeling (27%) zoals systemische therapie. Het aandeel patiënten dat enkel symptoombestrijding kreeg in deze studie is vergelijkbaar met het aandeel patiënten met peritoneale metastasen bij lever- en galwegkanker zoals beschreven in **hoofdstuk 9**. Patiënten met HPB-tumoren krijgen deze diagnose vaak in een vergevorderd stadium doordat de ziekte pas laat wordt ontdekt. Hierdoor komt een groot aandeel van de patiënten, door slechte conditie en te uitgebreide ziekte, niet meer toe aan een behandeling.

Er is zeer weinig bekend over peritoneale metastasen bij HPB-tumoren ondanks het feit dat het frequent voorkomt. Terwijl de proportie van synchrone peritoneale metastasen bij patiënten met HPB-tumoren aanzienlijk hoger is dan bijvoorbeeld bij patiënten met darmkanker, zijn er weinig klinische onderzoeken naar specifieke behandelopties voor deze patiëntengroep. Dit komt waarschijnlijk door het relatief lage absolute aantal patiënten. Op basis van **hoofdstuk 3** was het absolute aantal patiënten met synchrone peritoneale metastasen bij darmkanker twee keer zo hoog in vergelijking met het absolute aantal patiënten met synchrone peritoneale metastasen bij HPB-tumoren zoals beschreven in **hoofdstuk 9** en **hoofdstuk 10**.

Peritoneale metastasen bij longkanker en van een onbekende origine
Longkanker is een wereldwijd gezondheidsprobleem met toenemende incidentiecijfers. Desondanks is er weinig bekend over het optreden van peritoneale metastasen bij longkanker en hoe deze de overleving bij patiënten met longkanker kunnen beïnvloeden. In **hoofdstuk 11** hebben we alle patiënten met de diagnose longkanker (2008 tot en met 2018) geïncludeerd. Bij 2% van deze patiënten werden synchrone peritoneale metastasen vastgesteld. Jongere leeftijd, een T3 of T4 tumorstadium, positieve lymfeklieren, een slechtere WHO-performance status en het hebben van synchrone afstandsmetastasen waren gecorreleerd met het diagnosticeren

van synchrone peritoneale metastasen. Deze risicofactoren werden eerder ook al geïdentificeerd voor peritoneale metastasen bij bijvoorbeeld dikke darm-, eierstok- en maagkanker. Een aantal van de bovengenoemde factoren laat zien dat peritoneale metastasen bij longkanker in een ver gevorderd stadium optreden.

De **hoofdstukken 3-11** hadden als doel om meer inzicht te geven in peritoneale metastasen bij specifieke primaire kankersoorten. **Hoofdstuk 2** beschrijft echter dat een onbekende primaire tumor, de op vier na meest voorkomende origine is, van alle patiënten die gediagnosticeerd zijn met synchrone peritoneale metastasen. **Hoofdstuk 12** van dit proefschrift beschrijft daarom de incidentie, behandeling en de overleving van patiënten met synchrone peritoneale metastasen vanuit een onbekende origine. Deze landelijke cohortstudie toonde aan dat synchrone peritoneale metastasen werden gevonden bij 17% van alle patiënten met een onbekende primaire tumor. Dit is de hoogste gerapporteerde proportie van peritoneale metastasen van onbekende origine die ooit is beschreven in cohorten gebaseerd op bevolkingsonderzoek. Recente literatuur gaf echter aan dat het aantal patiënten met metastasen met een onbekende primaire origine in het algemeen aan het afnemen is. Een verklaring voor onze bevinding zou kunnen zijn dat wanneer patiënten de diagnose peritoneale metastasen krijgen, er vervolgens minder uitgebreide diagnostiek wordt uitgevoerd in vergelijking met patiënten met andere metastasen locaties. Wellicht is de neiging voor verder diagnostisch onderzoek groter bij de andere metastase locaties vanwege het feit dat de te verwachte prognose beter is en er meer behandelingsopties mogelijk zijn in vergelijking met peritoneale metastasen. Deze studie toonde tevens aan dat het aantal patiënten dat een palliatieve behandeling (metastasectomie of systemische behandeling) kreeg verschilde tussen bepaalde histologische subtypes evenals dat de overleving van patiënten met peritoneale metastasen verschilden per histologisch subtype. Bijvoorbeeld, patiënten met een carcinoid histologie ontvingen vaker systemische behandeling in vergelijking met de andere histologische typen die in de studie populatie voorkwamen.

Tegenwoordig zijn er steeds meer curatieve behandelingsopties beschikbaar voor een selecte groep patiënten met beperkte peritoneale metastasen bij blinde darm-, eierstok- en dikke darmkanker. Het wordt daarom nog meer van belang dat we bij patiënten met peritoneale metastasen met een onbekende origine, de histologie én de primaire tumor zullen gaan identificeren.

Conclusie

Op basis van de artikelen die zijn beschreven in dit proefschrift, blijkt dat peritoneale metastasen een relevant deel van de kankerpatiënten treft. De incidentie van peritoneale metastasen varieert per primaire kankersoort en metastasen naar het peritoneum komen veel voor bij gastro-intestinale primaire kankersoorten, maar kunnen ook bij primaire kankersoorten buiten de buikholte optreden. Ondanks dat er vooruitgang is geboekt ten aanzien van de behandeling van peritoneale metastasen, blijft de prognose van deze patiënten over het algemeen slecht. De bevindingen in dit proefschrift kunnen bijdragen aan de ontwikkeling van nieuwe behandelingen voor patiënten met peritoneale metastasen en het verbeteren van de uitkomsten voor deze patiënten. Verder onderzoek en inspanningen met betrekking tot het registreren en analyseren van data over peritoneale metastasen zijn nodig en zullen ons meer inzicht in deze ziekte geven.

Chapter 16

Appendices

Supplementary data
List of publications
Curriculum Vitae
Dankwoord

Appendix 1: Supplementary data

Chapter 1 – no supplementary data

Chapter 2 – no supplementary data

Chapter 3

Supplementary Table 3.1. Univariable logistic regression analyses for the presence of synchronous peritoneal metastases.

	Univariable logistic regression analyses		
	OR	95% CI	*P value*
Age at diagnosis			**0.009**
<50 years	1.88	1.25-2.86	
50-74 years	Ref.	Ref.	
≥75 years	1.20	0.97-1.49	
Sex			0.218
Male	Ref.	Ref.	
Female	1.14	0.93-1.39	
ASA score			**<0.001**
ASA 1	0.65	0.44-0.98	
ASA 2	Ref.	Ref.	
ASA ≥3	1.55	1.16-2.06	
Missing data	2.62	2.07-3.31	
Primary tumor location			**<0.001**
Right colon	1.34	1.08-1.67	
Left colon	Ref.	Ref.	
Rectum	0.33	0.24-0.45	
Primary tumor differentiation			**<0.001**
Good/moderate	Ref.	Ref.	
Poor/none	3.77	2.81-5.08	
Missing data	5.40	4.33-6.75	

Supplementary Table 3.1. Univariable logistic regression analyses for the presence of synchronous peritoneal metastases. (continued)

	Univariable logistic regression analyses		
	OR	95% CI	*P value*
Tumor histology			**<0.001**
Adenocarcinoma	Ref.	Ref.	
Mucinous adenocarcinoma	2.72	2.05-3.60	
Signet ring cell carcinoma	12.22	7.71-19.37	
Tumor stage			**<0.001**
T0-3	Ref.	Ref.	
T4	11.13	8.75-14.15	
Missing data	17.70	13.20-23.74	
Nodal stage			**<0.001**
N0	Ref.	Ref.	
N1	3.08	2.29-4.13	
N2	8.17	6.22-10.73	
Missing data	8.68	6.08-12.40	
Synchronous systemic metastases			**<0.001**
No	Ref.	Ref.	
Yes	7.42	6.03-9.14	
Tumor perforation			**<0.001**
No	Ref.	Ref.	
Yes	3.15	2.02-4.92	
Missing data	5.48	4.44-6.78	

ASA American society of anesthesiologists score; *OR* odds ratio; *CI* confidence interval.

Supplementary Table 3.2. Univariable cox regression analyses for the development of metachronous peritoneal metastases.

	Univariable cox regression analyses		
	OR	95% CI	*P value*
Age at diagnosis			**0.002**
<50 years	2.10	1.38-3.20	
50-74 years	Ref.	Ref.	
≥75 years	0.99	0.77-1.28	
Sex			0.182
Male	Ref.	Ref.	
Female	1.16	0.93-1.44	
ASA score			0.602
ASA 1	1.22	0.91-1.63	
ASA 2	Ref.	Ref.	
ASA ≥3	1.04	0.77-1.41	
Missing data	1.02	0.74-1.42	
Primary tumor location			**0.001**
Right colon	1.23	0.96-1.57	
Left colon	Ref.	Ref.	
Rectum	0.72	0.54-0.95	
Primary tumor differentiation			**<0.001**
Good/moderate	Ref.	Ref.	
Poor/none	2.29	1.69-3.11	
Missing data	1.12	0.78-1.61	
Tumor histology			**<0.001**
Adenocarcinoma	Ref.	Ref.	
Mucinous adenocarcinoma	1.60	1.12-2.28	
Signet ring cell carcinoma	4.42	2.25-8.71	
Tumor stage			**<0.001**
T0-3	Ref.	Ref.	
T4	5.09	4.06-6.39	

Supplementary Table 3.2. Univariable cox regression analyses for the development of metachronous peritoneal metastases. (continued)

	Univariable cox regression analyses		
	OR	95% CI	*P value*
Nodal stage			**<0.001**
N0	Ref.	Ref.	
N1	3.84	2.93-5.02	
N2	5.95	4.49-7.86	
Missing data	0.48	0.12-1.96	
Primary tumor resection margins			**<0.001**
Clear resection margins	Ref.	Ref.	
No clear resection margins	3.33	2.24-4.97	
Missing data	0.37	0.21-0.64	
Synchronous systemic metastases			**<0.001**
No	Ref.	Ref.	
Yes	3.83	2.97-4.93	
Tumor perforation			**0.040**
No	Ref.	Ref.	
Yes	1.81	1.14-2.87	
Missing data	1.04	0.64-1.67	

ASA American society of anesthesiologists score; *OR* odds ratio; *CI* confidence interval.

Supplementary Table 3.3. Univariable cox regression analysis in high-risk primary tumors for the development of metachronous peritoneal metastases after primary tumor resection.

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Age at diagnosis			**0.044**
<50 years	1.72	1.12-2.64	
50-74 years	Ref.	Ref.	
≥75 years	1.05	0.79-1.40	

Supplementary Table 3.3. Univariable cox regression analysis in high-risk primary tumors for the development of metachronous peritoneal metastases after primary tumor resection. (continued)

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Sex			0.205
Male	Ref.	Ref.	
Female	1.17	0.92-1.50	
ASA score			0.569
ASA 1	1.07	0.77-1.50	
ASA 2	Ref.	Ref.	
ASA ≥3	0.93	0.65-1.32	
Missing data	1.25	0.87-1.79	
Primary tumor location			**0.014**
Right colon	1.21	0.92-1.58	
Left colon	Ref.	Ref.	
Rectum	0.72	0.51-1.02	
Primary tumor differentiation			**0.016**
Good/moderate	Ref.	Ref.	
Poor/none	1.59	1.15-2.21	
Missing data	1.25	0.85-1.85	
Tumor histology			**<0.001**
Adenocarcinoma	Ref.	Ref.	
Mucinous adenocarcinoma	1.51	1.03-2.21	
Signet ring cell carcinoma	3.25	1.64-6.41	
Primary tumor resection margins			**0.006**
Clear resection margins	Ref.	Ref.	
No clear resection margins	1.96	1.28-3.00	
Missing data	0.78	0.34-1.78	
Synchronous systemic metastases			**<0.001**
No	Ref.	Ref.	
Yes	1.78	1.35-2.37	

Supplementary Table 3.3. Univariable cox regression analysis in high-risk primary tumors for the development of metachronous peritoneal metastases after primary tumor resection. (continued)

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Tumor perforation			0.933
No	Ref.	Ref.	
Yes	1.09	0.66-1.80	
Missing data	1.05	0.62-1.77	
Adjuvant treatment			**0.028**
No	Ref.	Ref.	
Yes	0.76	0.59-0.97	

ASA American society of anesthesiologists score; *HR* hazard ratio; *CI* confidence interval.

Chapter 4

Supplementary Table 4.1. Univariable cox competing risk regression analyses for the development of metachronous peritoneal metastases.

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Primary surgery type			**<0.001**
Laparoscopic	Ref.	Ref.	
Open	2.0	1.6-2.6	
Sex			0.197
Male	Ref.	Ref.	
Female	1.2	0.9-1.5	
Age at diagnosis			0.159
<50	1.6	0.9-2.7	
50-74	Ref.	Ref.	
≥75	1.1	0.9-1.50	

Supplementary Table 4.1. Univariable cox competing risk regression analyses for the development of metachronous peritoneal metastases. (continued)

	Univariable cox regression analyses		
	HR	95% CI	*P value*
ASA score			0.820
ASA 1	1.0	0.7-1.4	
ASA 2	Ref.	Ref.	
ASA ≥3	1.1	0.8-1.5	
Missing data	1.2	0.8-1.8	
Primary tumor location			**<0.001**
Right colon	1.4	1.1-1.9	
Left colon	Ref.	Ref.	
Rectum	0.7	0.5-1.0	
Tumor histology			**<0.001**
Adenocarcinoma	Ref.	Ref.	
Mucinous adenocarcinoma	1.7	1.2-2.5	
Signet ring cell carcinoma	5.3	2.7-10.5	
Primary tumor differentiation			**<0.001**
Good/moderate	Ref.	Ref.	
Poor/none	2.3	1.7-3.3	
Missing data	1.3	0.9-2.0	
Tumor stage			**<0.001**
T0-3	Ref.	Ref.	
T4	5.9	4.5-7.6	
Nodal stage			**<0.001**
N0	Ref.	Ref.	
N1	3.5	2.6-4.8	
N2	6.8	4.9-9.3	
Tumor perforation			**0.008**
No	Ref.	Ref.	
Yes	2.2	1.3-3.6	
Missing data	1.3	0.7-2.2	

Supplementary Table 4.1. Univariable cox competing risk regression analyses for the development of metachronous peritoneal metastases. (continued)

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Resection margins			**<0.001**
Clear	Ref.	Ref.	
Not clear	3.6	2.2-5.9	
Missing data	2.2	0.7-7.0	

ASA American society of anesthesiologists score; *HR* Hazard Ratio; *CI* confidence interval.

Chapter 5

Supplementary Table 5.1. Univariable cox regression analyses for overall survival of the study cohort.

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Age at diagnosis			**<0.001**
<50 years	0.80	0.59-1.09	
50-74 years	Ref.	Ref.	
≥75 years	1.74	1.47-2.07	
Sex			0.156
Male	Ref.	Ref.	
Female	1.12	0.96-1.31	
ASA score			**<0.001**
ASA 1	0.72	0.55-0.94	
ASA 2	Ref.	Ref.	
ASA ≥3	1.44	1.16-1.79	
Missing data	1.80	1.50-2.17	
Primary tumor location			**0.019**
Right colon	Ref.	Ref.	
Left colon	0.79	0.66-0.93	
Rectum	0.87	0.69-1.08	

Supplementary Table 5.1. Univariable cox regression analyses for overall survival of the study cohort. (continued)

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Primary tumor differentiation			**<0.001**
Good/moderate	Ref.	Ref.	
Poor/undifferentiated	2.52	2.03-3.13	
Missing data	1.66	1.39-1.98	
Tumor histology			**0.003**
Adenocarcinoma	Ref.	Ref.	
Mucinous adenocarcinoma	0.97	0.77-1.22	
Signet ring cell carcinoma	1.83	1.32-2.53	
Tumor stage			**<0.001**
T0-3	Ref.	Ref.	
T4	1.02	0.86-1.21	
Missing data	2.21	1.75-2.79	
Nodal stage			**<0.001**
N0	0.74	0.60-0.91	
N1	0.91	0.75-1.10	
N2	Ref.	Ref.	
Missing data	2.28	1.71-3.04	
Synchronous systemic metastases			**<0.001**
No	Ref.	Ref.	
Yes	1.36	1.17-1.59	
Tumor perforation			**<0.001**
No	Ref.	Ref.	
Yes	0.98	0.70-1.38	
Missing data	1.85	1.55-2.19	
Presentation of peritoneal metastases			**0.003**
Synchronous	Ref.	Ref.	
Metachronous	0.79	0.67-0.92	

Supplementary Table 5.1. Univariable cox regression analyses for overall survival of the study cohort. (continued)

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Treatment of peritoneal metastases			**<0.001**
Best supportive care	4.56	3.77-5.51	
Palliative treatment	Ref.	Ref.	
CRS-HIPEC	0.31	0.23-0.43	

ASA American association of anesthesiologists score; *HR* hazard ratio; *CI* confidence interval; *CRS* cytoreductive surgery; *HIPEC* hyperthermic intraperitoneal chemotherapy.

Supplementary Table 5.2. Univariable cox regression analyses for overall survival in synchronous peritoneal metastases.

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Age at diagnosis			**<0.001**
<50 years	0.74	0.48-1.14	
50-74 years	Ref.	Ref.	
≥75 years	1.57	1.27-1.95	
Sex			0.728
Male	Ref.	Ref.	
Female	1.04	0.85-1.27	
ASA score			**<0.001**
ASA 1	0.76	0.49-1.17	
ASA 2	Ref.	Ref.	
ASA ≥3	1.42	1.06-1.91	
Missing data	2.04	1.60-2.59	
Primary tumor location			**0.040**
Right-sided colon	Ref.	Ref.	
Left-sided colon	0.79	0.64-0.98	
Rectum	1.11	0.81-1.53	

Supplementary Table 5.2. Univariable cox regression analyses for overall survival in synchronous peritoneal metastases. (continued)

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Primary tumor differentiation			**<0.001**
Good/moderate	Ref.	Ref.	
Poor/none	2.67	1.98-3.61	
Missing data	1.82	1.45-2.28	
Tumor histology			**0.064**
Adenocarcinoma	Ref.	Ref.	
Mucinous adenocarcinoma	0.83	0.63-1.10	
Signet ring cell carcinoma	1.43	0.98-2.07	
Tumor stage			**<0.001**
T0-3	Ref.	Ref.	
T4	0.92	0.72-1.17	
Missing data	1.98	1.49-2.63	
Nodal stage			**<0.001**
N0	0.91	0.69-1.20	
N1	1.03	0.80-1.33	
N2	Ref.	Ref.	
Missing data	2.38	1.75-3.26	
Synchronous systemic metastases			**0.005**
No	Ref.	Ref.	
Yes	1.34	1.09-1.65	
Tumor perforation			**<0.001**
No	Ref.	Ref.	
Yes	0.93	0.59-1.48	
Missing data	2.19	1.77-2.72	

Supplementary Table 5.2. Univariable cox regression analyses for overall survival in synchronous peritoneal metastases. (continued)

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Treatment of peritoneal metastases			**<0.001**
Best supportive care	4.76	3.66-6.20	
Palliative treatment	Ref.	Ref.	
CRS-HIPEC	0.27	0.17-0.42	

ASA American association of anesthesiologists score; *HR* hazard ratio; *CI* confidence interval; *CRS* cytoreductive surgery; *HIPEC* hyperthermic intraperitoneal chemotherapy.

Supplementary Table 5.3. Univariable cox regression analyses for overall survival in metachronous peritoneal metastases.

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Age at diagnosis			**<0.001**
<50 years	0.86	0.54-1.36	
50-74 years	Ref.	Ref.	
≥75 years	1.95	1.48-2.56	
Sex			**0.081**
Male	Ref.	Ref.	
Female	1.24	0.97-1.58	
ASA score			**0.002**
ASA 1	0.70	0.49-0.99	
ASA 2	Ref.	Ref.	
ASA ≥3	1.48	1.07-2.04	
Missing data	1.26	0.89-1.80	
Primary tumor location			0.162
Right-sided colon	Ref.	Ref.	
Left-sided colon	0.78	0.59-1.03	
Rectum	0.79	0.57-1.09	
Primary tumor differentiation			**<0.001**
Good/moderate	Ref.	Ref.	
Poor/none	2.34	1.70-3.24	
Missing data	1.09	0.73-1.65	
Tumor histology			**0.006**
Adenocarcinoma	Ref.	Ref.	
Mucinous adenocarcinoma	1.18	0.80-1.75	
Signet ring cell carcinoma	3.62	1.84-7.11	
Tumor stage			0.552
T0-3	Ref.	Ref.	
T4	1.08	0.84-1.38	

Supplementary Table 5.3. Univariable cox regression analyses for overall survival in metachronous peritoneal metastases. (continued)

	Univariable cox regression analyses		
	HR	95% CI	*P value*
Nodal stage			**0.014**
N0	0.60	0.44-0.82	
N1	0.79	0.60-1.05	
N2	Ref.	Ref.	
Missing data	1.24	0.31-5.05	
Synchronous systemic metastases			0.187
No	Ref.	Ref.	
Yes	1.21	0.92-1.59	
Tumor perforation			0.409
No	Ref.	Ref.	
Yes	1.06	0.64-1.76	
Missing data	0.69	0.39-1.24	
Adjuvant treatment after surgery for primary colorectal cancer			**0.042**
No	Ref.	Ref.	
Yes	0.77	0.59-0.99	
Treatment of peritoneal metastases			**<0.001**
Best supportive care	4.93	3.73-6.53	
Palliative treatment	Ref.	Ref.	
CRS-HIPEC	0.40	0.26-0.61	

ASA American association of anesthesiologists score; *HR* hazard ratio; *CI* confidence interval; *CRS* cytoreductive surgery; *HIPEC* hyperthermic intraperitoneal chemotherapy.

Chapter 6 – no supplementary data

Chapter 7

Supplementary results 7.1 Search strategies

Pubmed search strategy
Date of search: 15 August 2021
Search query: (((((Peritoneal Neoplasms[MeSH Terms]) OR (peritoneal metastases OR peritoneal metastasis OR peritoneal carcinomatosis OR peritoneal dissemination OR peritoneal spread OR peritoneal disease OR peritoneal tumour OR peritoneal tumor))) AND (((gastric neoplasms[MeSH Terms]) OR (gastric cancer OR gastric malignancy OR gastric neoplasm OR stomach cancer OR stomach malignancy OR stomach neoplasm OR gastric carcinoma)))) AND ((((incidence[MeSH Terms]) OR (incidence)) OR ((prevalence[MeSH Terms]) OR (prevalence))) OR ((risk factors[MeSH Terms]) OR (risk factors)))) NOT ((case report) OR (review))
Publication date restriction: 2000-2021
Items found: 1100

EMBASE search strategy
Date of search: 15 August 2021
Search query: ('incidence':ab,ti OR 'prevalence':ab,ti OR 'risk factors':ab,ti) AND ('peritoneum metastasis':ab,ti OR 'peritoneum tumor':ab,ti OR 'peritoneal disease':ab,ti OR 'carcinomatous peritonitis':ab,ti OR 'peritoneal disease'/exp/mj) AND ('stomach cancer':ab,ti OR 'stomach carci-noma':ab,ti OR 'stomach cancer'/exp/mj)
Publication date restriction: 2000-2021
Items found: 111

Cochrane search strategy
Date of search: 15 August 2021
Search query: Gastric peritoneal metastases
Publication date restriction: 2000-2021
Items found: 81

Supplementary results 7.2 Reasons for exclusion of potentially eligible studies after full text screening

Different study population (n=9)

1. Ji L, Selleck MJ, Morgan JW, Xu J, Babcock BD, Shavlik D, Wall NR, Langridge WH, Lum SS, Garberoglio CA, Reeves ME, Solomon N, Namm JP, Senthil M. Gastric Cancer Peritoneal Carcinomatosis Risk Score. Ann Surg Oncol. 2020 Jan;27(1):240-247.
2. Yook JH, Oh ST, Kim BS. Clinicopathological analysis of Borrmann type IV gastric cancer. Cancer Res Treat. 2005 Apr;37(2):87-91.
3. Fanotto V, Fornaro L, Bordonaro R, Rosati G, Rimassa L, Di Donato S, Santini D, Tomasello G, Leone F, Silvestris N, Stragliotto S, Scartozzi M, Giampieri R, Nichetti F, Antonuzzo L, Cinieri S, Avallone A, Pellegrino A, Melisi D, Vasile E, Gerratana L, Aprile G. Second-line treatment efficacy and toxicity in older vs. non-older patients with advanced gastric cancer: A multicentre real-world study. J Geriatr Oncol. 2019 Jul;10(4):591-597.
4. Solon JG, O'Neill M, Chang KH, Deady S, Cahill R, Moran B, Shields C, Mulsow J. An 18 year population-based study on site of origin and outcome of patients with peritoneal malignancy in Ireland. Eur J Surg Oncol. 2017 Oct;43(10):1924-1931.
5. Koo DH, Ryu MH, Ryoo BY, Seo J, Lee MY, Chang HM, Lee JL, Lee SS, Kim TW, Kang YK. Improving trends in survival of patients who receive chemotherapy for metastatic or recurrent gastric cancer: 12 years of experience at a single institution. Gastric Cancer. 2015 Apr;18(2):346-53.
6. Sarela AI, Yelluri S; Leeds Upper Gastrointestinal Cancer Multidisciplinary Team. Gastric adenocarcinoma with distant metastasis: is gastrectomy necessary? Arch Surg. 2007 Feb;142(2):143-9; discussion 149.
7. Dhobi MA, Wani KA, Parray FQ, Wani RA, Wani ML, Peer GQ, Abdullah S, Wani IA, Wani MA, Shah MA, Thakur N. Gastric cancer in young patients. Int J Surg Oncol. 2013;2013:981654.
8. Sarela AI, Miner TJ, Karpeh MS, Coit DG, Jaques DP, Brennan MF. Clinical outcomes with laparoscopic stage M1, unresected gastric adenocarcinoma. Ann Surg. 2006 Feb;243(2):189-95.
9. Ahmed A, Ukwenya AY, Makama JG, Mohammad I. Management and outcome of gastric carcinoma in Zaria, Nigeria. Afr Health Sci. 2011 Sep;11(3):353-61.

Metastatic disease (n=6)

1. Korivi BR, Faria S, Aly A, Sun J, Patnana M, Jensen CT, Wagner-Bartak N, Bhosale PR. Intestinal and diffuse gastric cancer: a retrospective study comparing primary sites. Clin Imaging. 2019 Jul-Aug;56:33-40. doi: 10.1016/j.clinimag.2019.03.002. Epub 2019 Mar 3. PMID: 30870726.

2. Tan HL, Chia CS, Tan GHC, Choo SP, Tai DW, Chua CWL, Ng MCH, Soo KC, Teo MCC. Metastatic gastric cancer: Does the site of metastasis make a difference? Asia Pac J Clin Oncol. 2019 Feb;15(1):10-17.
3. Carmona-Bayonas A, Jiménez-Fonseca P, Echavarria I, Sánchez Cánovas M, Aguado G, Gallego J, Custodio A, Hernández R, Viudez A, Cano JM, Martínez de Castro E, Macías I, Martín Carnicero A, Garrido M, Mangas M, Álvarez Manceñido F, Visa L, Azkarate A, Ramchandani A, Fernández Montes A, Longo F, Sánchez A, Pimentel P, Limón ML, Arias D, Cacho Lavin D, Sánchez Bayona R, Cerdá P, García Alfonso P; AGAMENON Study Group. Surgery for metastases for esophageal-gastric cancer in the real world: Data from the AGAMENON national registry. Eur J Surg Oncol. 2018 Aug;44(8):1191-1198.
4. Chen S, Li YF, Feng XY, Zhou ZW, Yuan XH, Chen YB. Significance of palliative gastrectomy for late-stage gastric cancer patients. J Surg Oncol. 2012 Dec;106(7):862-71.
5. Shridhar R, Almhanna K, Hoffe SE, Fulp W, Weber J, Chuong MD, Meredith KL. Increased survival associated with surgery and radiation therapy in metastatic gastric cancer: a Surveillance, Epidemiology, and End Results database analysis. Cancer. 2013 May 1;119(9):1636-42.
6. Kim DY, Kim HR, Kim YJ, Kim S. Clinicopathological features of patients with Borrmann type IV gastric carcinoma. ANZ J Surg. 2002 Oct;72(10):739-42.

Different outcome measure (n=4)

1. Rona KA, Schwameis K, Zehetner J, Samakar K, Green K, Samaan J, Sandhu K, Bildzukewicz N, Katkhouda N, Lipham JC. Gastric cancer in the young: An advanced disease with poor prognostic features. J Surg Oncol. 2017 Mar;115(4):371-375.
2. Kim SH, Choi YH, Kim JW, Oh S, Lee S, Kim BG, Lee KL. Clinical significance of computed tomography-detected ascites in gastric cancer patients with peritoneal metastases. Medicine (Baltimore). 2018 Feb;97(8):e9343.
3. Kim DY, Joo JK, Ryu SY, Park YK, Kim YJ, Kim SK. Clinicopathologic characteristics of gastric carcinoma in elderly patients: a comparison with young patients. World J Gastroenterol. 2005 Jan 7;11(1):22-6. doi: 10.3748/wjg.v11.i1.22. PMID: 15609390; PMCID: PMC4205377.
4. Nakamura R, Saikawa Y, Takahashi T, Takeuchi H, Asanuma H, Yamada Y, Kitagawa Y. Retrospective analysis of prognostic outcome of gastric cancer in young patients. Int J Clin Oncol. 2011 Aug;16(4):328-34.

Recurrent disease only (n=1)

1. Kong JH, Lee J, Yi CA, Park SH, Park JO, Park YS, Lim HY, Park KW, Kang WK. Lung metastases in metastatic gastric cancer: pattern of lung metastases and clinical outcome. Gastric Cancer. 2012 Jul;15(3):292-8.

Used same data registry (n=2)

1. Thomassen I, Bernards N, van Gestel YR, Creemers GJ, Jacobs EM, Lemmens VE, de Hingh IH. Chemotherapy as palliative treatment for peritoneal carcinomatosis of gastric origin. Acta Oncol. 2014 Mar;53(3):429-32.
2. Allen CJ, Newhook TE, Vreeland TJ, Das P, Minsky BD, Blum M, Song S, Ajani J, Ikoma N, Mansfield PF, Roy-Chowdhuri S, Badgwell BD. Yield of peritoneal cytology in staging patients with gastric and gastroesophageal cancer. J Surg Oncol. 2019 dec;120(8):1350-1357.

Supplementary table 7.1. Risk factors for peritoneal metastases reported in population-based studies.

First author Year	Risk factors for gastric peritoneal metastases	
	Reported	*Risk factors*
Koemans[12, a] 2021	No	
Koemans[15, a] 2020	Yes	- Non-cardia cancer - Age <45 years - Female sex - T2-T4 stage - >1 metastasis location - Diffuse type histology - Diagnosis in 2013-2017
Thomassen[16] 2013	Yes	- Signet ring cell carcinoma - Linitis plastica - Non-cardia cancer - Age <60 years - Female sex - T3/T4 stage - N1-N3 stage - Poor tumour differentiation
Riihimäki[17] 2016	Yes	- Signet ring cell carcinoma - Non-cardia cancer - Age <60 years - Female sex
Choi[18] 2020	Yes	- Hispanic ethnicity

Supplementary table 7.2. Inclusion criteria of studies on gastric cancer and staging laparoscopy.

First author Year	Inclusion criteria
Allen[25] 2020	- Gastric cancer - Pathological confirmation - Underwent SL
Hu[26] 2016	- Advanced gastric cancer - Underwent SL
Yang[27] 2020	- Gastric cancer - Potentially resectable - Pathological confirmation - Preoperative M0 - Underwent SL
Bhatti[28] 2014	- Gastric cancer - Potentially resectable - Preoperative M0 - Underwent SL
Convie[29] 2015	- Gastric cancer - Potentially resectable - Preoperative M0 - Underwent SL
Munasinghe[30] 2013	- Gastric cancer - Potentially resectable - Underwent SL

Chapter 8

Supplementary Table 8.1. Univariable logistic regression analyses for the presence of synchronous peritoneal metastases and univariable cox regression analyses for the development of metachronous peritoneal metastases after potentially curative treatment.

	Synchronous PM	**Univariable logistic regression analyses**			**Metachronous PM**	**Univariable cox regression analyses**		
	n (%)	OR	95% CI	*P value*	n (%)	HR	95% CI	*P value*
Sex				**0.052**				0.104
Male	276 (55)	Ref.	Ref.		86 (54)	Ref.	Ref.	
Female	222 (45)	1.24	1.01-1.51		72 (46)	1.30	0.95-1.77	
Age				**<0.001**				**0.013**
< 65 years	178 (36)	Ref.	Ref.		56 (35)	Ref.	Ref.	
65 - 75 years	161 (32)	0.64	0.49-0.82		58 (37)	0.84	0.58-1.21	
> 75 years	159 (32)	0.37	0.29-0.48		44 (28)	0.56	0.37-0.83	
Primary tumor location				**<0.001**				**0.013**
Proximal	135 (27)	Ref.	Ref.		51 (32)	Ref.	Ref.	
Distal	139 (28)	0.77	0.59-1.01		65 (41)	0.88	0.61-1.26	
Overlapping sites	183 (37)	2.02	1.55-2.62		37 (23)	1.60	1.04-2.45	
NOS	41 (8)	1.11	0.74-1.65		5 (3)	0.52	0.20-1.33	
WHO Performance status				0.202				0.688
0-1	198 (41)	Ref.	Ref.		98 (62)	Ref.	Ref.	
≥2	75 (15)	1.33	0.98-1.81		15 (9)	1.16	0.68-1.99	
Unknown	225 (45)	1.07	0.86-1.33		45 (28)	0.91	0.64-1.29	

Supplementary Table 8.1. Univariable logistic regression analyses for the presence of synchronous peritoneal metastases and univariable cox regression analyses for the development of metachronous peritoneal metastases after potentially curative treatment. (continued)

	Synchronous PM	**Univariable logistic regression analyses**			**Metachronous PM**	**Univariable cox regression analyses**		
	n (%)	OR	95% CI	*P value*	n (%)	HR	95% CI	*P value*
Tumor differentiation				**<0.001**				**<0.001**
Good/moderate	50 (10)	Ref.	Ref.		20 (13)	Ref.	Ref.	
Poor/undifferentiated	221 (44)	2.23	1.60-3.11		107 (68)	3.36	2.10-5.38	
Unknown	227 (46)	2.94	2.10-4.10		31 (20)	3.28	1.88-5.73	
Lauren classification				**<0.001**				**<0.001**
Intestinal	83 (17)	Ref.	Ref.		34 (22)	Ref.	Ref.	
Diffuse	292 (59)	3.15	2.41-4.13		100 (63)	3.67	2.50-5.40	
Mixed/indeterminate	20 (4)	1.59	0.93-2.73		11 (7)	2.87	1.44-5.70	
Unknown	103 (21)	1.51	1.10-2.07		13 (8)	1.35	0.71-2.56	
Clinical T stage				**<0.001**				**0.002**
T1-T2	154 (31)	Ref.	Ref.		77 (49)	Ref.	Ref.	
T3	88 (18)	1.28	0.95-1.72		47 (30)	1.42	0.99-2.04	
T4	111 (22)	2.52	1.88-3.38		11 (7)	1.77	0.94-3.34	
Tx	145 (29)	1.10	0.85-1.41		23 (15)	0.60	0.38-0.95	

Supplementary Table 8.1. Univariable logistic regression analyses for the presence of synchronous peritoneal metastases and univariable cox regression analyses for the development of metachronous peritoneal metastases after potentially curative treatment. (continued)

	Synchronous PM	**Univariable logistic regression analyses**			**Metachronous PM**	**Univariable cox regression analyses**		
	n (%)	OR	95% CI	*P value*	n (%)	HR	95% CI	*P value*
Clinical N stage				**<0.001**				0.279
N0	178 (36)	Ref.	Ref.		92 (58)	Ref.	Ref.	
N1	103 (21)	1.21	0.92-1.58		37 (23)	1.33	0.90-1.96	
N2/N3	125 (25)	1.85	1.42-2.41		18 (11)	1.44	0.87-2.39	
Nx	92 (18)	1.67	1.25-2.24		11 (7)	1.38	0.74-2.55	
Perioperative therapy								**0.022**
Resection only	N.A.	N.A.	N.A.		64 (41)	Ref.	Ref.	
Neoadjuvant therapy	N.A.	N.A.	N.A.		36 (23)	1.63	1.08-2.45	
Perioperative therapy	N.A.	N.A.	N.A.		58 (37)	1.52	1.07-2.16	
Distant metastases at primary diagnosis				**<0.001**				
Yes	175 (35)	Ref.	Ref.		N.A.	N.A.	N.A.	
No	323 (65)	0.66	0.53-0.81		N.A.	N.A.	N.A.	

PM peritoneal metastases; *OR* odds ratio; *CI* confidence interval; *Ref* reference; *NOS* no other specified primary tumor location. N.A.: not applicable, variable not applicable in either synchronous or metachronous setting.

Supplementary Table 8.2. Uni- and multivariable cox regression analyses for overall survival of patients with synchronous or metachronous peritoneal metastases (n=656).

	Median OS (months)	Univariable cox regression analyses			Multivariable cox regression analysis		
		HR	95% CI	*P value*	aHR	95% CI	*P value*
Presentation of PM				0.730			
Synchronous	3.2	Ref.	Ref.		Ref.	Ref.	Ref.
Metachronous	2.3	1.03	0.86-1.24		0.88	0.72-1.08	0.221
Sex				0.914			
Male	2.6	Ref.	Ref.		N.A.	N.A.	N.A.
Female	3.2	0.99	0.85-1.16		N.A.	N.A.	N.A.
Age				**<0.001**			
< 65 years	5.1	Ref.	Ref.		Ref.	Ref.	Ref.
65 - 75 years	2.6	1.41	1.17-1.70		1.20	0.99-1.46	0.064
> 75 years	2.0	1.76	1.45-2.13		1.17	0.94-1.45	0.167
Primary tumor location				**0.079**			
Proximal	3.0	Ref.	Ref.		Ref.	Ref.	Ref.
Distal	3.0	1.00	0.82-1.22		1.00	0.82-1.23	0.536
Overlapping sites	3.2	0.98	0.80-1.19		0.95	0.77-1.17	0.370
NOS	1.5	1.51	1.09-2.09		1.47	1.06-2.05	**0.022**

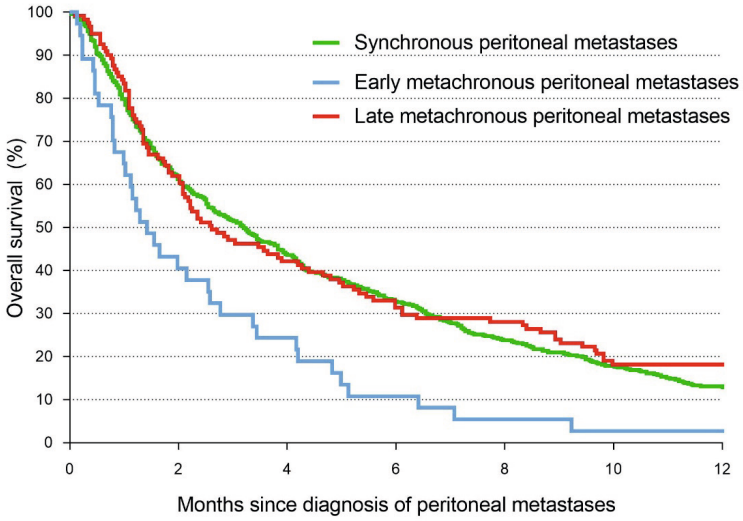
Supplementary Table 8.2. Uni- and multivariable cox regression analyses for overall survival of patients with synchronous or metachronous peritoneal metastases (n=656). (continued)

	Median OS (months)	Univariable cox regression analyses			Multivariable cox regression analysis		
		HR	95% CI	*P value*	aHR	95% CI	*P value*
WHO Performance status				**<0.001**			
0-1	4.3	Ref.	Ref.		Ref.	Ref.	Ref.
≥2	2.3	1.30	1.03-1.65		1.02	0.80-1.31	0.857
Unknown	2.1	1.40	1.18-1.65		1.12	0.94-1.34	0.191
Tumor differentiation				**0.014**			
Good/moderate	3.1	Ref.	Ref.		Ref.	Ref.	Ref.
Poor/undifferentiated	3.3	1.32	1.01-1.73		1.53	1.14-2.07	**0.005**
Unknown	2.6	1.49	1.12-1.94		1.76	1.30-2.38	**<0.001**
Lauren classification				**0.025**			
Intestinal	3.7	Ref.	Ref.		Ref.	Ref.	Ref.
Diffuse	3.1	1.20	0.98-1.49		1.22	0.95-1.55	0.114
Mixed/indeterminate	2.8	1.35	0.90-2.02		1.43	0.95-2.16	0.087
Unknown	1.6	1.49	1.15-1.93		1.29	0.98-1.69	0.069

Supplementary Table 8.2. Uni- and multivariable cox regression analyses for overall survival of patients with synchronous or metachronous peritoneal metastases (n=656). (continued)

	Median OS (months)	Univariable cox regression analyses			Multivariable cox regression analysis		
		HR	95% CI	*P value*	aHR	95% CI	*P value*
Clinical T stage				0.399			
T1-T2	3.1	Ref.	Ref.		N.A.	N.A.	N.A.
T3	3.4	1.00	0.81-1.24		N.A.	N.A.	N.A.
T4	3.5	1.07	0.85-1.33		N.A.	N.A.	N.A.
Tx	2.3	1.18	0.96-1.44		N.A.	N.A.	N.A.
Clinical N stage				**0.049**			
N0	3.0	Ref.	Ref.		Ref.	Ref.	Ref.
N1	3.3	1.03	0.84-1.27		1.18	0.95-1.46	0.128
N2/N3	2.7	1.04	0.85-1.28		1.18	0.94-1.47	0.150
Nx	2.0	1.39	1.11-1.75		1.24	0.98-1.57	0.077
Treatment of PM				**<0.001**			
Systemic treatment	7.4	Ref.	Ref.		Ref.	Ref.	Ref.
Surgery	6.7	0.91	0.67-1.23		0.99	0.72-1.36	0.946
Best supportive care	1.6	3.1	2.57-3.68		3.16	2.57-3.89	**<0.001**

PM peritoneal metastases; *aHR* adjusted hazard ratio; *CI* confidence interval; *Ref* reference; *NOS* no other specified primary tumor location. N.A.: not applicable, variable not included due to non-significance in univariable analysis.



Number at risk (number censored)

Synchronous PM	498 (0)	304 (0)	218 (0)	163 (0)	118 (0)	89 (0)	62 (0)
Early metachronous PM	37 (0)	15 (0)	9 (0)	4 (0)	2 (0)	1 (0)	1(0)
Late metachronous PM	120 (0)	75 (0)	51 (0)	38 (0)	34 (0)	22 (0)	20 (4)

Supplementary Figure 8.1. Overall survival of all patients with peritoneal metastases stratified according to synchronous, early metachronous, or late metachronous onset (n=656) (Log-rank: $p < 0.001$).
PM peritoneal metastases.

Chapter 9 – no supplementary data

Chapter 10

Supplementary Table 10.1. Metastases codes considered as peritoneal metastases

ICD-O Metastases codes considered as peritoneal metastases
C16.0-C16.3, C16.5, C16.6, C16.8-C17.3, C17.8-C18.4, C18.6-C18.9, C19.9, C20.9, C21.8, C23.9, C26.9, C48.0-C48.2, C48.4, C48.8, C49.4, C49.5, C52.9, C53.9-C54.3, C54.8, C54.9, C55.9, C56.9-C57.4, C57.8, C66.9-C67.1, C67.4, C67.8, C67.9, C76.2

Supplementary Table 10.2. Patients who received a combination of different cancer treatments

Combination therapies	Amount of patients
Resection of primary tumor and metastasectomy	7
Targeted therapy and chemotherapy	18
Radiotherapy* and chemotherapy	14
Resection of primary tumor and chemotherapy	4
Metastasectomy and chemotherapy	8
Radiotherapy and resection of primary tumor	3
Metastasectomy, radiotherapy and chemotherapy	1
Total	55

***Radiotherapy to primary tumor or metastases**

Chapter 11 – no supplementary data

Chapter 12 – no supplementary data

List of publications

1. **Rijken A**, Pape M, Simkens GA, de Hingh IHJT, Luyer MDP, van Sandick JW, van Laarhoven HWM, Verhoeven RHA, van Erning FN. Peritoneal metastases from gastric cancer in a nationwide cohort: incidence, treatment and survival. *Under review.*
2. **Rijken A**, Loef C, van de Wouw YAJ, van Erning FN, de Hingh IHJT. Updated Incidence, Treatment and Survival of a Nationwide Cohort of Patients with Peritoneal Metastases of Unknown Origin. *Indian J Surg Oncol* 2023;14(Suppl 1):S67-S73. doi: 10.1007/s13193-022-01567-x.
3. **Rijken A**, Galanos LJK, Burger JWA, Nienhuijs SW, van Erning FN. Peritoneal Metastases from Extraperitoneal Primary Tumors: Incidence, Treatment, and Survival from a Nationwide Database. *Indian J Surg Oncol* 2023;14(Suppl 1):S60-S66. doi: 10.1007/s13193-022-01592-w.
4. **Rijken A**, van de Vlasakker VCJ, Simkens GA, Rovers KP, van Erning FN, Koopman M, Verhoef C, de Wilt JHW, de Hingh IHJT. Primary tumor resection or systemic treatment as palliative treatment for patients with isolated synchronous colorectal cancer peritoneal metastases in a nationwide cohort study. *Clin Exp Metastasis*. 2023;40(4):289-298. doi: 10.1007/s10585-023-10212-y.
5. **Rijken A**, Bakkers C, Klümpen HJ, van der Geest LG, de Vos-Geelen J, van Erning FN, de Hingh IHJT. Insights into synchronous peritoneal metastases from hepatobiliary origin: Incidence, risk factors, treatment, and survival from a nationwide database. *Eur J Surg Oncol*. 2023;49(8):1436-1443. doi: 10.1016/j.ejso.2023.03.004.
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7. van de Vlasakker VCJ*, van den Heuvel TBM*, **Rijken A**, Nienhuijs SW, Ketelaers SHJ, Verrijssen AE, Rutten HJ, Nieuwenhuijzen GAP, Burger JWA, de Hingh IHJT. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy with Intra-Operative Radiotherapy for Patients with Locally Advanced or Locally Recurrent Rectal Cancer and Peritoneal Metastases. *Cancers (Basel).* 2023;15(3):858. doi: 10.3390/cancers15030858.
8. Bakkers C*, Rovers KP*, **Rijken A**, Simkens GAAM, Bonhof CS, Nienhuijs SW, Burger JWA, Creemers GJM, Brandt-Kerkhof ARM, Tuynman JB, Aalbers AGJ, Wiezer MJ, de Reuver PR, van Grevenstein WMU, Hemmer PHJ, Punt CJA, Tanis PJ, Mols F, de Hingh IHJT; Dutch Peritoneal Oncology Group and the Dutch Colorectal Cancer Group. Perioperative Systemic Therapy Versus Cytoreductive Surgery and HIPEC Alone for Resectable Colorectal Peritoneal Metastases: Patient-Reported Outcomes of a

Randomized Phase II Trial. *Ann Surg Oncol*. 2023 May;30(5):2678-2688. doi: 10.1245/s10434-023-13116-z.

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Curriculum vitae

Anouk Rijken was born on November 25th, 1995 in Veghel, the Netherlands. She lived in Erp with her parents, Marijke and Ben, and her younger sister, Lotte. After graduating from high school in 2014 (VWO at Zwijsen College, Veghel), she studied Health Sciences at Maastricht University. After one year, she switched to Medical School at Maastricht University. During her clinical rotations she attended an international internship at the tropical disease department in Samarinda, East-Kalimantan, Indonesia. She finished her scientifical internship at the surgical department of the Catharina Hospital, supervised by Prof. dr. Ignace de Hingh in 2020. While finishing her internships, she worked as a student-researcher at the same department.

After her final medical internship at the surgical department at the Catharina Hospital in Eindhoven, she received her Medical Degree in September 2021. Afterwards, Anouk started her PhD under supervision of Prof. dr. Ignace de Hingh and dr. Felice van Erning at the Netherlands Comprehensive Cancer Organisation in collaboration with the surgical department of the Catharina Hospital in Eindhoven, which has resulted in this thesis.

Some of the results described in this thesis have been presented at international meetings (Digestive Disease Week [Chicago, United Stated, 2023], European Society of Surgical Oncology [Bordeaux, France, 2022] and national meetings (Chirurgendagen [The Hague, 2022 and Veldhoven, 2023], Digestive Disease Days [Veldhoven, 2023], GROW Science Day [Maastricht, 2023]).

As of September 2023, Anouk started with clinical work (ANIOS) at the intensive care and emergency department at the Elkerliek Ziekenhuis in Helmond.

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