The burden of peritoneal metastases

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]