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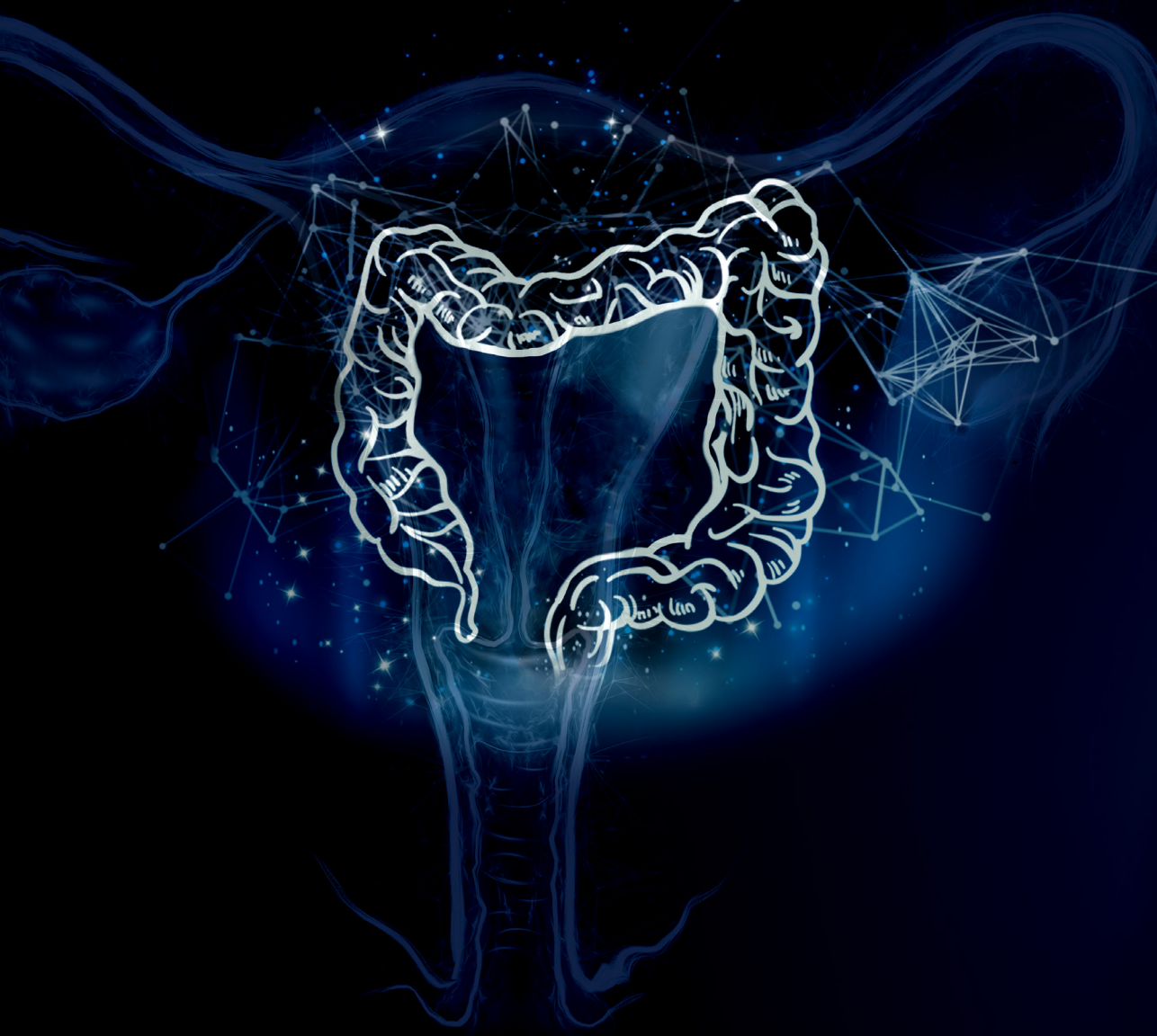
STUDIES ON THE ROLE OF OVARIAN METASTASES IN COLORECTAL CANCER

Richard van der Meer



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Richard van der Meer

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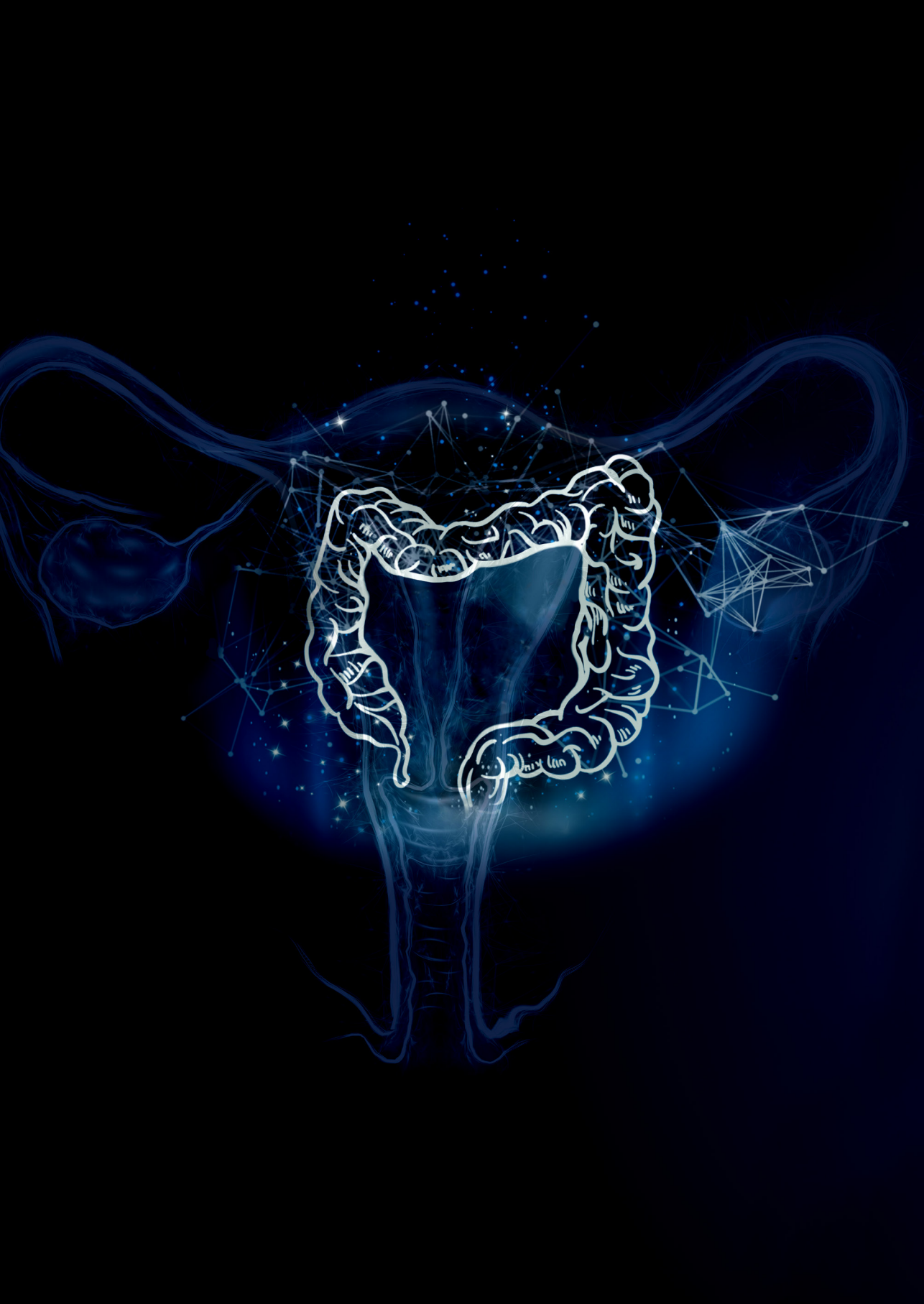

CHAPTER 1

General introduction

This introduction is partly based on a publication in the 'Nederlands Tijdschrift voor Heelkunde' (NTvH)[1]

1. van der Meer, R., Bakkers, C., de Hingh, I. H. J. T., Geomini, P. M. A. J., and Roumen, R. M. H. (2021) Ovariële metastasen bij dikkedarmkanker. Wat te doen? *Nederlands Tijdschrift voor Heelkunde.* **30**;5, 20-23

General introduction

Colorectal cancer (CRC) is the seventh leading cause of death in high-income countries, according to the World Health Organization (WHO). Increasing incidence rates of CRC among young adults (≤ 50 years) have been reported in most European countries, the US, and Canada.[1,2] The lifetime risk of CRC is similar in men and women: 4.4% and 4.1%, respectively.[3] By 2030, the worldwide burden of CRC is estimated to increase by 60% to more than 2.2 million new cases and 1.1 million cancer deaths.[4]

Several risk factors for the development of CRC are known, and many are lifestyle related and thus modifiable, including obesity, physical inactivity, large intake of red or processed meat, modest intake of foods containing whole grains or dietary fiber, a diet lacking dairy products, smoking, and alcohol consumption.[5,6] Additionally, unmodifiable risk factors for CRC have been identified, such as tall stature, older age, personal history of 1. colorectal polyps or CRC or 2. inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease), family history of CRC or adenomatous polyps, inherited syndromes (most commonly associated with CRC are Lynch syndrome and familial adenomatous polyposis, FAP), and a type 2 diabetes diagnosis.[5,6]

According to the Surveillance, Epidemiology, and End Results (SEER) database (between 2009–2018), 38% of all CRCs were staged as localized disease at diagnosis, 34% as regional disease, and 21% as distant metastases (stage IV CRC disease).[7] The five-year relative survival rates for localized, regional, and metastasized disease are 91%, 72%, and 15%, respectively.[8]

Individuals with distant CRC disease can be divided into patients who present with synchronous metastases (stage IV disease, defined as metastases occurring within six months of primary diagnosis of CRC) or those with metachronous metastases (metastases occurring beyond six months of CRC diagnosis).[9] In 2014 and 2015, two population-based studies, published by van Gestel et al.[10] and Elferink et al.[11], revealed that approximately 20% of all patients without distant metastases at diagnosis later developed metachronous metastases, resulting in a five-year overall survival of 9%. The most common sites for CRC metastases are the liver, lungs, peritoneum, and non-regional lymph nodes.[10,12,13]

The ovaries are generally considered an uncommon metastatic site for CRC. A large population-based study published by Segelman et al.[14] found a prevalence of synchronous and metachronous ovarian metastases (OMs) of 1.1% and 0.6%, respectively. However, these numbers might be misleading since micrometastatic OMs can be missed.[15–20,21] Indeed, OMs are more frequently found in post-mortem studies, with an incidence

ranging from 5% to 9.7%.[22] According to several studies, a five-year survival of 12–27% was found for all patients with OMs (including those who are operated on with curative intent).[22–26] Furthermore, OMs are primarily found in premenopausal CRC patients,[22,27] and, according to Segelman et al.[14], patients with metachronous OMs were generally younger but showed equally poor survival rates compared to older patients with other recurrences. This potentially suggests that the presence of ovarian metastasis (OM) is a sign of a more aggressive disease. Since OMs not seldomly co-occur with peritoneal dissemination,[28] or are misinterpreted as advanced ovarian cancer,[29] CRC patients with OMs are generally referred to tertiary hospitals. The general physician or original surgeon is bypassed in this situation. This, therefore, can impact the general or primary treating physician's view on the prevalence of this form of dissemination.

Of all OMs, 33% originate from the large intestine, followed by the endometrium (17%) and breast (14%).[30] Increased awareness of the presence of OMs is especially justified since OMs are less sensitive to systemic therapy compared to other metastatic sites of CRC, such as hepatic or pulmonary metastases.[25,31-36] The ovaries are therefore generally considered a 'sanctuary site'.[31-35] Unfortunately, most studies that found resistance of OMs to systemic therapy did not research its impact on overall survival compared to CRC patients with unaffected ovaries. This information may be useful for decisions on initiating, continuing, or changing systemic therapy.

Although several authors contend that the presence of OM suggests aggressive disease,[14,34,37,38] many contradictory studies still dispute its form of dissemination (varying from hematogenous, lymphatic, to transcoelomic dissemination) and – related to this – its concomitant treatment modality.[15,18,22,39-42] Terminology is often inappropriate and confusing because 'Krukenberg tumor' is frequently used to label OM.[38] The Krukenberg tumor was initially described by Friedrich Ernst Krukenberg (1896, Fig. 1), who defined strict histological features for its definitive diagnosis.[22,38,43] These traits are clearly reported by Serov et al.[44] in 1973 as follows: the presence of mucus-filled signet-ring cells that are accompanied by a 'sarcoma-like' proliferation of the ovarian stroma. Since it is impossible to confirm that all previous literature used the term 'Krukenberg tumor' appropriately – and to avoid further confusion – this thesis only uses the term OM, which consequentially encompasses all patients with real Krukenberg tumors.

To date, no consensus has been reached concerning an optimal management strategy for OMs.[45–47] Approaches vary from surgical resection (alone), systemic therapy with or without surgical debulking, to cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC).[22,26,48] Surgery for primary CRC is also combined with prophylactic (salpingo-)oophorectomy to prevent the outgrowth of micrometastatic OM or to block the development of OM. Young-Fadok et al.[21] presented preliminary

results of a prospective randomized trial analyzing 146 patients, of whom 74 had a prophylactic oophorectomy. The survival analysis reported in this publication, however, did not find a significant difference in disease-free or overall survival at five years.[21] Unfortunately, this underpowered study was not continued for unspecified reasons.[21] As such, it remains unknown whether a higher number of patients or a longer follow-up period would have yielded different results.

Fig. 1 Friedrich Ernst Krukenberg

Furthermore, prophylactic resection of the ovaries in CRC patients has mainly been studied in small non-randomized studies and is generally recommended only in patients with increased risk for ovarian cancer (patients that carry BRCA 1/2, MSH6, and PMC2 mutations).[15,17-20,22,49-53] Other disciplines, such as gynecology and urology, offer or routinely perform prophylactic resection of the ovaries during abdominal surgery (for endometrial and muscle-invasive bladder cancers, respectively).[54–56] In addition, in CRC patients, the potential prevention of ovarian malignancies, which impact disease-free and overall survival, stresses the need for 'shared decision making' regarding prophylactic surgery to improve patient satisfaction.[57] Although the meta-analysis from Thompson et al.[58] did not observe a superior oncologic outcome for prophylactic oophorectomy in CRC patients, no additional risk for post-operative complications or death was found. Thus, if a patient would like to opt for prophylactic oophorectomy, a balanced discussion (or informed consent) is needed.

Aims of this thesis

The overall aim of this thesis is to provide additional insight into CRC patients that develop OMs and to describe the impact of OMs. Additionally, the potential benefit of prophylactic salpingo-oophorectomy (PSO) in this context is further explored.

Specific aims

1. Reporting on the proportion of OMs and its clinical consequences in the Dutch CRC population
2. Reviewing the literature regarding OMs in young CRC patients
3. Exploring the origin and impact of systemic treatment-resistant OMs
4. Evaluating the presence of primary ovarian malignancies in CRC patients
5. Describing the clinical implications of PSO in CRC patients

Outline of this thesis

Since the presence and impact of OMs in Dutch CRC patients are currently unknown, we first conducted a population-based study in which the incidence, risk factors, treatment, and survival of OMs are studied (**Chapter 2**). Next, the clinical relevance of OMs in younger (premenopausal) patients is described in a cohort study and systematic review (**Chapters 3 and 4**). The impact of OMs on overall survival in stage IV CRC patients that received systemic therapy is investigated in **Chapter 5**. **Chapter 6** describes the biomarker concordance between CRCs and OMs. A subsequent study addressed the occurrence of primary ovarian cancer following CRC (**Chapter 7**). Finally, all previous findings are translated into clinical practice, whereby its (potential) clinical use is summarized in **Chapters 8 and 9**.

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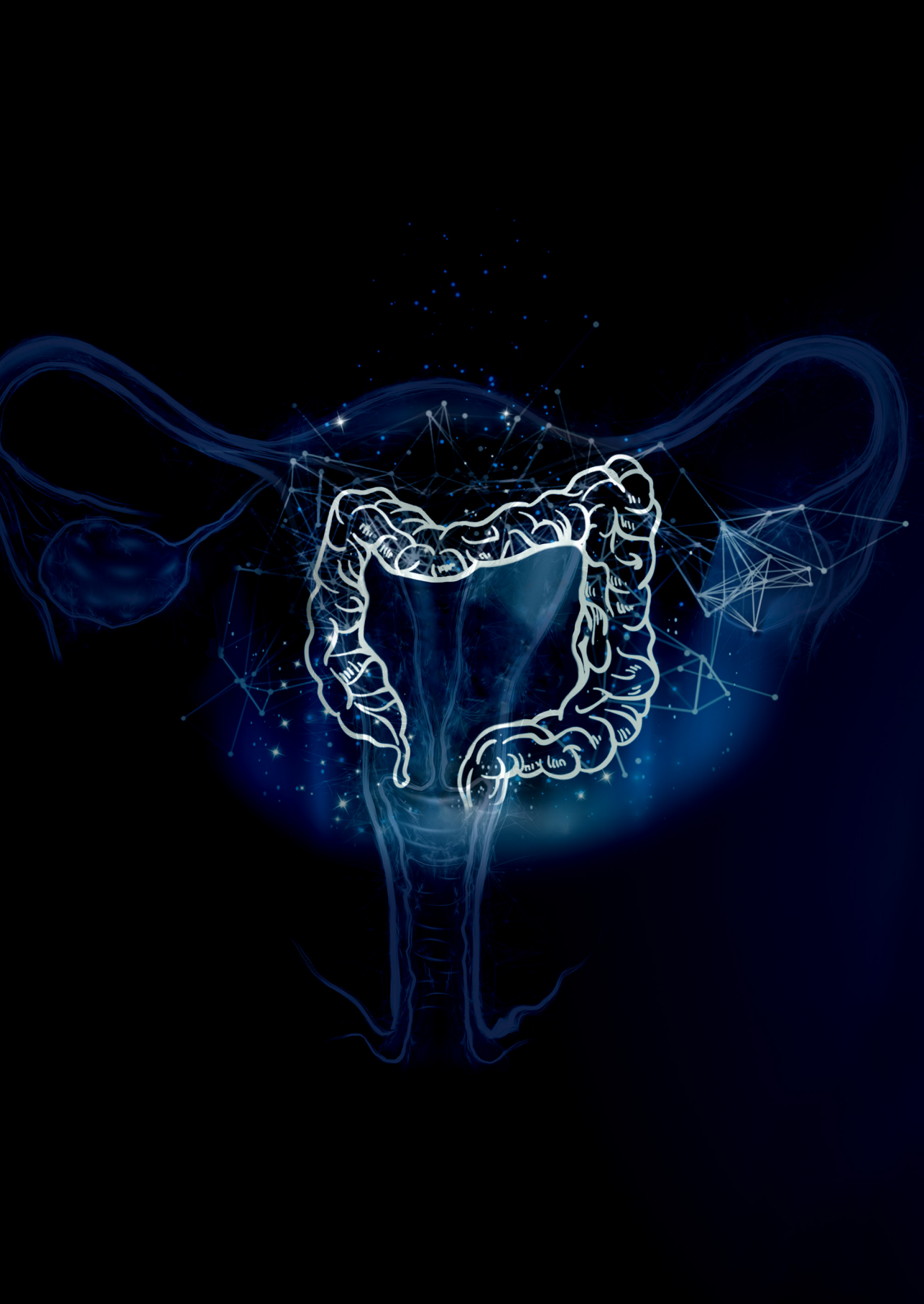

CHAPTER 2

Incidence, risk factors, treatment, and survival of ovarian metastases of colorectal origin: a Dutch population-based study

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Abstract

Objective

The aim of this nationwide study was to provide insight in the incidence, risk factors, treatment, and survival of patients with ovarian metastases from colorectal cancer (CRC).

Methods

Data from the Netherlands Cancer Registry were used. All newly diagnosed female CRC patients between 2008 and 2016 were included. Treatment was categorized as follows: cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (CRS-HIPEC); resection of the primary tumor; palliative treatment; and no treatment. Overall survival (OS) was investigated using Kaplan-Meier and multivariable Cox regression analyses.

Results

Of 53.883 female patients with CRC, 11.343 (21.1%) had metastases at time of diagnosis. Among them, 471 (4.2%) had ovarian metastases. Within latter group, 27.2% received CRS-HIPEC; 38.4% underwent resection of the primary tumor; 25.3% received palliative treatment; and 9.1% received no treatment. Median OS of all patients with ovarian metastases was 17.5 months. In patients receiving CRS-HIPEC, OS was significantly longer than in patients undergoing resection only (median OS 34.1 vs. 17.5 months, adjusted HR 0.44 [0.33 – 0.66]). Five-year OS was 28.5% for patients having underwent CRS-HIPEC, 11.0% for patients having underwent resection of the primary tumor, 1.2% for patients having underwent palliative treatment and 0.0% for patients without treatment.

Conclusions

Synchronous ovarian metastases are diagnosed in 4.2% of female colorectal patients presenting with metastatic disease. Risk factors are young age, T4/N+ tumor and histology of signet ring cell carcinoma. Median OS of the entire cohort was 17.5 months, ranging from 3.1 months in patients without treatment to 34.1 months in patients undergoing CRS-HIPEC.

Introduction

The ovaries are a common site for metastases from a variety of primary tumors, of which the colon and stomach are the most prevalent.[1] Rapid and extensive tumor growth may result in obstruction of the gastrointestinal tract. Occasionally, the large ovarian metastases are the presenting symptom of colorectal cancer (CRC) and may then be mistakenly diagnosed as primary ovarian cancer. Final diagnosis is often made using histopathological examination. Ovarian metastases of colorectal origin are rare and hence, accurate data on incidence, treatment, and prognosis of this metastatic form of CRC is lacking, and there are no population-based studies that look into these features. The treatment options for advanced CRC have expanded over the last decades, mostly by the additional value of adjuvant systemic therapy for T4/N+ tumors.[2] However, in case of ovarian metastases from primary CRC, the additional role of systemic therapy is controversial, as progression under chemotherapy is not uncommon, and – in case of neoadjuvant treatment – response at ovarian sites is usually not seen.[3,4] To date, the best treatment for these ovarian metastases is unclear. There is an ongoing discussion about how ovarian metastases develop from primary colorectal cancer. Some experts advocate ovarian metastases to be the result of lymphatic tumor spread, while others believe they occur resulting from hematogenous spread.[5–7] Furthermore, a growing group of experts consider ovarian metastases to be the result of peritoneal metastatic spread and advocate treatment by radical resection of the primary tumor and the metastases (cytoreductive surgery) followed by the administration of heated intraperitoneal chemotherapy (HIPEC).[8-10]

The purpose of this study was to determine the incidence, risk factors, treatment strategies, and survival for female CRC patients with ovarian metastases.

Methods

Data Source

Data were extracted from a population-based database: the Netherlands Cancer Registry (NCR). This registry covers all newly diagnosed cancer patients in the Netherlands. Information on patient, tumor, and treatment characteristics is consistently extracted from patients' files by trained data-managers of the NCR. Anatomical site of the primary tumor and metastases is registered according to the International Classification of Disease – Oncology (ICD-O). The tumor-node-metastasis (TNM) classification is used for stage notification of the primary tumor, according to the edition valid at time of cancer diagnosis. Comorbidities are registered for one region in the Netherlands, according to a slightly modified version of the Charlson comorbidity index.[11] Information about vital

status is obtained by conjoining NCR data with the Municipal Records Database, which documents all deaths in the Netherlands. All data in the NCR are anonymized; therefore, no ethics approval was acquired for this study.

Study population

For this study, all female patients diagnosed with CRC between 2008 and 2016 were evaluated. Patients with neuro-endocrine or appendix tumors were excluded. For patients with multiple primary colorectal tumors, the tumor with the highest stage was included. Patient characteristics included in this study are age, number of comorbidities, and year of diagnosis. Tumor characteristics included in this study are primary tumor location, tumor stage, differentiation grade, histology, and presence and location of any metastases. Primary tumor location was divided into anatomical subsites: proximal colon (caecum, ascending colon, hepatic flexure, transverse colon and splenic flexure; C18.0, C18.2-C18.5), distal colon (descending colon and sigmoid, C18.6-C18.7), colon not otherwise specified (C18.8-C18.9) and rectum (rectosigmoid and rectum, C19.9-C20.9). In case of unknown pathological T or N stage, clinical T or N stage was used.

Patients were subcategorized into four groups as follows: (1) ovarian Metastases (± peritoneal metastases), which comprises all patients with isolated ovarian metastases (C56.9), as well as patients with ovarian metastases and peritoneal metastases (C48.0-C48.2, C48.8), where ovarian metastases were either unilateral or bilateral, (2) ovarian and other Metastases, which comprises all patients with ovarian metastases and distant systemic metastases (e.g., lung, liver), (3) other metastases, which comprises all patients with any metastases other than ovarian metastases, and (4) no metastases, which comprises all non-metastasized patients.

Treatments

Treatments were categorized into the following groups: (1) tumor resection, being resection of the primary colorectal tumor (with or without metastasectomy or systemic therapy), (2) CRS-HIPEC, (3) palliative treatment, including palliative systemic therapy and/or palliative metastasectomy, without resection of the primary tumor, and (4) no treatment, when no surgical or systemic treatment was given, except for a possible ileostomy/colostomy in case of near obstruction in a palliative setting.

Statistical methods

Incidence rates were calculated as the number of new patients per 100,000 inhabitants per year and were age standardized using the European Standardized Rate (ESR), and trends were calculated through the Annual Percent Chance (APC). Patient and tumor characteristics were compared between the four groups and analyzed using chi-squared tests. The possible independent influence of age, T stage, N stage, differentiation grade,

histology, tumor location, and time of diagnosis on the presence of ovarian metastases was tested using multivariable logistic regression analyses. Treatment was compared between patients with ovarian metastases only and patients with ovarian and other metastases and tested using the chi-square test. Survival analyses were performed for all patients. Crude median OS was determined by use of the Kaplan-Meier method. For patients with ovarian metastases, the independent influence of age, T stage, N stage, differentiation grade, histology, tumor location, time of diagnosis, treatment, and presence of other metastases on survival was analyzed by means of a multivariable Cox regression analysis. OS was defined as the time from diagnosis to death. Patients still alive on January 31, 2018 were censored. All analyses were performed using SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC, United States). All tests were two-sided and conducted at the 5% level of significance.

Results

The final study population consisted of 53,883 female patients with CRC, diagnosed between 2008 and 2016 in the Netherlands. Among them, 11,343 (21.1%) presented with metastatic disease. Synchronous ovarian metastases were diagnosed in 471 (4.2%) patients, of whom 204 (43.3%) had isolated ovarian metastases and 267 (56.7%) had both ovarian and other distant metastases. (Fig. 1).

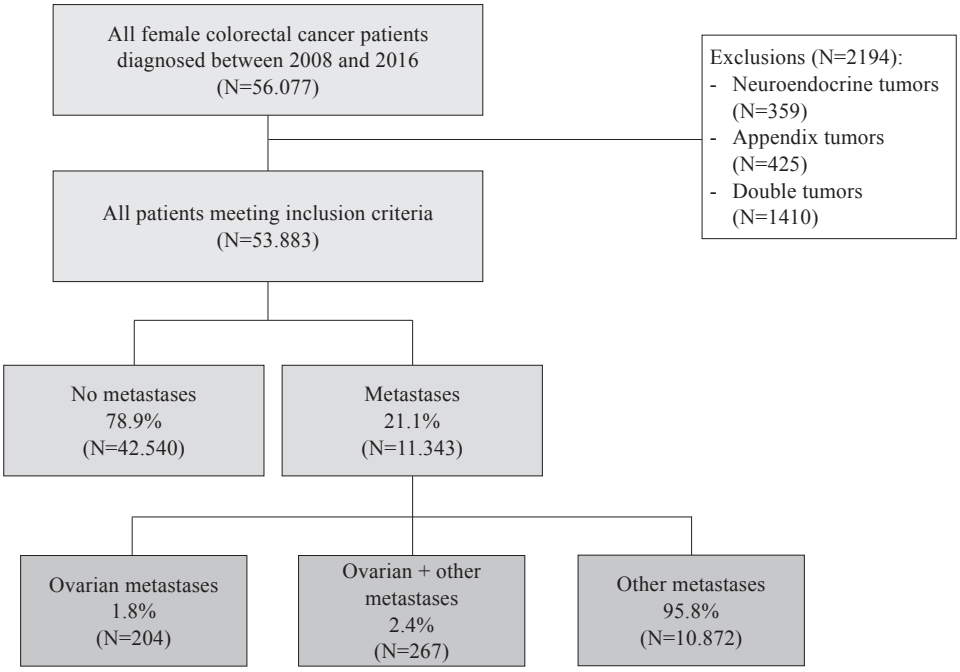

Fig. 1 Flowchart of the study population.

Incidence of ovarian metastases

The absolute number of newly diagnosed patients with concurrent ovarian metastases from CRC increased over time (Table 1). The European Standardized Incidence Rate also increased over time from 0.33 per 100,000 individuals in 2008 to 0.67 per 100,000 individuals in 2016) (Fig. 2). The Annual Percent Chance (APC) is 6.1% which is a significant yearly increase (p=0.02).

Table 1 Patient and tumor characteristics of the study population.

Site(s) of metastases	Ovarian (N= 204)	Ovarian + other (N= 267)	Systemic (N= 10.872)	No (N= 42.540)	Significance (*p*)
Age					
<50	45 (22%)	49 (7%)	727 7%)	1916 (5%)	<0.001
50-69	109 (53%)	145 (54%)	4552 (42%)	16268 (38%)	
≥70	50 (25%)	73 (27%)	5593 (51%)	24356 (57%)	
Number of comorbidities*					
0	33 (46%)	46 (52%)	1179 (34%)	3905 (30%)	<0.001
1	19 (27%)	24 (27%)	1155 (33%)	4003 (31%)	
≥2	19 (27%)	19 (21%)	1171 (33%)	5171 (40%)	
T-stage					
0-3	60 (29%)	69 (26%)	4753 (44%)	34792 (82%)	<0.001
4	113 (55%)	119 (45%)	3030 (28%)	5457 (13%)	
Unknown	31 (15%)	79 (30%)	3089 (28%)	2291 (5%)	
N-stage					
0	41 (20%)	44 (16%)	2274 (21%)	25729 (60%)	<0.001
1	58 (28%)	66 25%)	3478 (32%)	9398 (22%)	
2	75 (37%)	101 (38%)	3224 (30%)	4480 (11%)	
Unknown	30 (15%)	56 (21%)	1896 (17%)	2933 (7%)	
Differentiation grade					
Well/moderate	110 (54%)	122 (46%)	4440 (41%)	27979 (66%)	<0.001
Poor/undifferentiated	35 (17%)	45 (17%)	1713 (16%)	5275 (12%)	
unknown	59 (29%)	100 (37%)	4719 (43%)	9286 (22%)	
Histology					
Adenocarcinoma	137 (67%)	208 (78%)	9137 (84%)	36126 (85%)	<0.001
Mucinous adenocarcinoma	40 (20%)	44 (16%)	901 (8%)	4575 (11%)	
Signet cell carcinoma	24 (12%)	11(4%)	220 (2%)	411 (1%)	
Other/NOS	3 (1%)	4 (2%)	614 (6%)	1428 (3%)	
Tumor location					
Ascending colon	99 (49%)	116 (43%)	4602 (42%)	18132 (43%)	<0.001
Descending colon	64 (31%)	109 (41%)	3046 (28%)	11946 (28%)	
Sigmoid	12 (6%)	16 (6%)	458 (4%)	743 (2%)	
Rectum	29 (14%)	26 (10%)	2766 (25%)	11719 (28%)	
Time of diagnosis					
2008 – 2010	62 (30%)	69 (26%)	3373 (31%)	13251 (31%)	<0.001
2011 – 2013	62 (30%)	79 (30%)	3706 (34%)	13606 (32%)	
2014 – 2016	80 (39%)	119 (45%)	3793 (35%)	15683 (37%)	

NOS: Not otherwise specified; *Data on comorbidities were only available for a subgroup of patients. Percentages might not add up due to rounding.

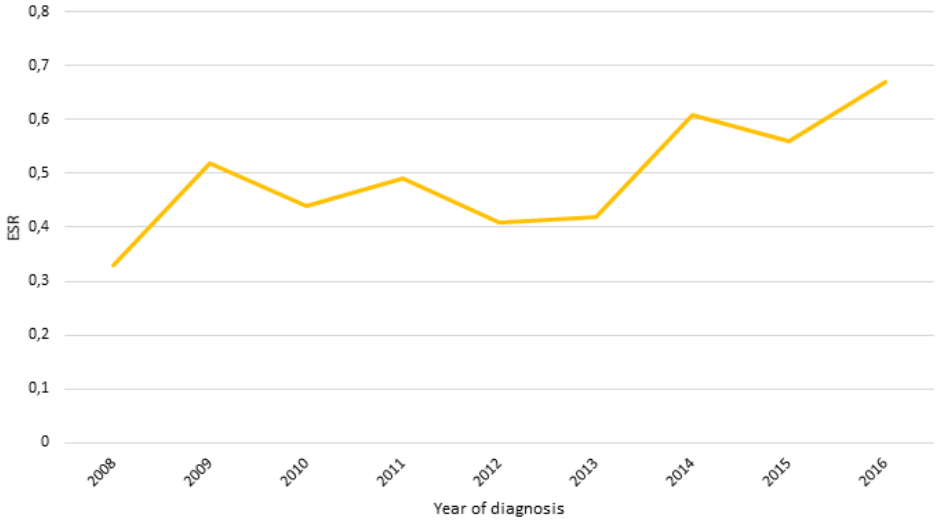

Fig. 2 Trends in incidence of female patients with newly diagnosed colorectal cancer with synchronous ovarian metastases (N=471) between 2008 and 2016 in The Netherlands (European Standardized Rate).

Patient characteristics of the study population

There were considerable differences in patient and tumor characteristics between the four groups (Table 1). Median age of patients having ovarian metastases was 60.8 years and 61.4 years for patients having both ovarian and other metastases. These patients having ovarian metastases were significantly younger compared with patients having other, non-ovarian metastases (median 69.1 years) and patients having no metastases (median 71.0 years, $p<0.001$). Furthermore, patients with metastases more often had T4 tumors, with the highest proportion of T4 tumors in the group of patients having only ovarian metastases ($p<0.001$). Signet ring cell carcinoma and mucinous adenocarcinoma occurred more frequently in the groups with ovarian metastases compared with the groups with other or no metastases ($p<0.001$).

Risk factors for ovarian metastases

As shown in Table 2, women over 50 years were less likely to develop ovarian metastases compared to women under 50 (proportion ovarian metastases 1.2% in women aged 50-69 and 0.4% in women aged over 70 vs. 3.4% in women aged under 50, adjusted OR 0.36 [0.28 – 0.47] and adjusted OR 0.11 [0.09 – 0.15], respectively). Furthermore, T4 tumors were more likely to metastasize to the ovaries than T0-3 tumors (2.7% vs. 0.3%, adjusted OR 5.76, [4.58 – 7.25]), and tumors with lymph node involvement compared to tumors without lymph node involvement (1.0% vs. 0.3%, adjusted OR 2.23 [1.68 – 2.96] and 2.2% versus 0.3%, adjusted OR 3.98 [3.02 – 5.25] for N1 and N2 stage, respectively). A poor differentiation grade, however, lowered the risk of developing

ovarian metastases in this cohort (adjusted OR 0.75 [0.57 – 1.00]), compared with well/moderately differentiated tumors (1.1% vs. 0.8%). The sigmoid was the most likely location of the primary tumor to metastasize to the ovaries (2.3%).

Table 2 Multivariable logistic regression analyses for the likelihood of ovarian metastases among female colorectal cancer patients diagnosed between 2008 and 2016 in the Netherlands.

	Patients with ovarian metastases (N=471)	Adjusted OR	95% CI
Age			
<50	94 (3.4%)	Ref.	Ref.
50-69	254 (1.2%)	0.36	0.28 – 0.47
≥70	123 (0.4%)	0.11	0.09 – 0.15
T-stage			
0-3	129 (0.3%)	Ref.	Ref.
4	232 (2.7%)	5.76	4.58 – 7.25
Unknown	110 (2.0%)	5.96	4.34 – 8.15
N-stage			
0	85 (0.3%)	Ref.	Ref.
1	124 (1.0%)	2.23	1.68 – 2.96
2	176 (2.2%)	3.98	3.02 – 5.25
Unknown	86 (1.8%)	2.27	2.27 – 4.60
Differentiation grade			
Well/moderate	232 (0.7%)	Ref.	Ref.
Poor/undifferentiated	80 (1.1%)	0.75	0.57 – 1.00
Unknown	159 (1.1%)	0.97	0.76 – 1.23
Histology			
Adenocarcinoma	345 (0.8%)	Ref.	Ref.
Mucinous adenocarcinoma	84 (1.5%)	2.08	1.61 – 2.70
Signet cell carcinoma	35 (5.3%)	3.59	2.41 – 5.45
Other/NOS	7 (0.3%)	0.26	0.12 – 0.55
Tumor location			
Ascending colon	215 (0.9%)	Ref.	Ref.
Descending colon	173 (1.1%)	1.19	0.97 – 1.48
Sigmoid	28 (2.3%)	1.69	1.11 – 2.58
Rectum	55 (0.4%)	0.48	0.35 – 0.65
Time of diagnosis			
2008 – 2010	131 (0.8%)	Ref.	Ref.
2011 – 2013	141 (0.8%)	1.15	0.90 – 1.47
2014 – 2016	199 (1.0%)	1.50	1.19 – 1.89

OR: Odds Radio; *CI*: Confidence Interval ; *NOS*: Not otherwise specified

Treatments in patients with ovarian metastases

Of all patients with synchronous ovarian metastases (with or without other metastases, n=471), 128 (27.2%) patients received CRS-HIPEC, 181 (38.4%) patients underwent resection of the primary tumor, 119 (25.3%) received palliative treatment and 43 patients (9.1%) received no treatment (Fig. 3). Among the patients who received CRS-HIPEC, 84 (65.6%) also received adjuvant chemotherapy. Among the patients who underwent resection of the primary tumor, 58 patients (32.0%) also underwent metastasectomy (i.e., ovarian, liver or lung metastases), 24 patients (13.3%) also received adjuvant systemic therapy, and 82 patients (45.3%) also underwent both metastasectomy and adjuvant systemic therapy. Among the patients who received palliative treatment, 10 (8.4%) patients underwent metastasectomy (without resection of the primary tumor), 82 (68.9%) received systemic therapy, and 27 (22.7%) received both. Treatments differed between patients with or without other metastases besides ovarian metastases ($p<0.0001$).

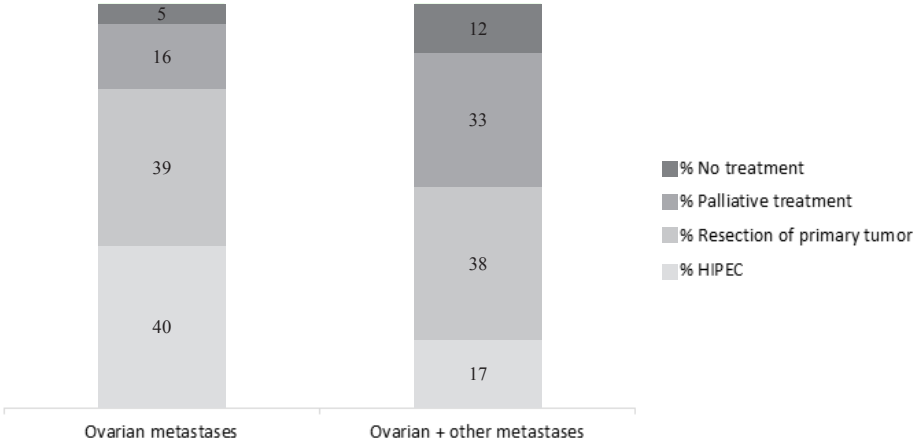

Fig. 3 Observed percentages of different treatment strategies in female colorectal cancer patients with ovarian metastases (with or without other metastases), diagnosed between 2008 and 2016 in the Netherlands.

Survival of the study population

Median OS for all patients with ovarian metastases was 17.5 months, 14.2 months for patients with ovarian and other metastases, and 25.5 months for patients with ovarian metastases without other distant metastases. The crude 5-year OS was 12.3%, 4.5% for patients with ovarian and other metastases, and 21.8% for patients with ovarian metastases without other distant metastases (Fig. 4a). Patients with other metastases (without ovarian metastases) showed a median survival of 10.7 months and a 5-year crude OS of 9.9% *(*Table 3*)*.

Table 3 Survival of female colorectal cancer patients, categorized by the presence and site of metastases.

	Median overall survival (months)	5-year crude survival (%)
No metastases (N=42.540)	117	67.2
Ovarian metastases (N=204)	25.5	21.8
Ovarian and other metastases (N=267)	14.2	4.5
Other metastases (N=10.872)	10.7	9.9

Factors influencing survival in patients with ovarian metastases

Independent effects of patient, tumor, and treatment characteristics on survival in all patients with ovarian metastases are shown in Table 4. Patients over the age of 70 years had the worst prognosis compared to patients of younger age (12.0 months vs. 24.5 months, adjusted HR 1.61 [1.17 – 2.23]). T stage, lymph node involvement, and tumor histology had no significant effect on OS. Poorly/undifferentiated tumors showed worse OS than well/moderately differentiated tumors (13.5 months vs. 24.6 months, adjusted HR 1.43 [1.70 – 1.92]). Patients diagnosed between 2011 and 2013 showed better OS compared to patients diagnosed between 2008 and 2010 (18.0 vs. 17.1 months, adjusted HR 1.34 [1.03-1.74]), however patients diagnosed after these aforementioned periods (2014-2016) did not show significant better OS compared to patients diagnosed between 2008 and 2010 (18.2 vs. 17.1 months, adjusted HR 1.28 [0.97-1.67]). The presence of other metastases besides ovarian metastases led to worse OS compared to ovarian metastases only (14.2 months vs. 25.5 months, adjusted HR 1.31 [1.03 – 1.65]).

OS was the best in patients that underwent CRS-HIPEC compared with resection of the primary tumor (34.1 months vs. 17.5 months, adjusted HR 0.44 [0.33 – 0.60]). Although crude median OS in patients undergoing palliative treatment was lower than for patients undergoing resection of the primary tumor, it did not differ significantly in multivariable analysis (12.6 months vs. 17.5 months, adjusted HR 0.96 [0.66 – 1.40]) (Fig. 4b).

Table 4 Multivariable cox regression survival analyses for all patients with ovarian metastases (N=471).

	Crude median overall survival (months)	Adjusted HR	95% CI
Age			
<50	24.5	Ref.	Ref.
50-69	20.0	1.19	0.89 – 1.58
≥70	12.0	1.61	1.17 – 2.23
T-stage			
0-3	23.2	Ref.	Ref.
4	23.1	1.27	0.98 – 1.65
Unknown	9.9	1.89	1.27 – 2.81
N-stage			
0	17.5	Ref.	Ref.
1	22.6	1.23	0.89 – 1.72
2	21.5	1.15	0.84 – 1.59
Unknown	8.6	1.25	0.85 – 1.84
Differentiation grade			
Well/moderate	24.6	Ref.	Ref.
Poor/undifferentiated	13.5	1.43	1.07 – 1.92
Unknown	11.8	1.51	1.16 – 1.96
Histology			
Adenocarcinoma	17.9	Ref.	Ref.
Mucinous adenocarcinoma	20.7	1.18	0.89 – 1.56
Signet cell carcinoma	12.9	1.25	0.85 – 1.84
Other/NOS*	-	1.21	0.51 – 2.85
Tumor location			
Ascending colon	14.4	Ref.	Ref.
Descending colon	20.7	0.78	0.62 – 0.98
Sigmoid	11.0	1.09	0.70 – 1.71
Rectum	23.6	0.76	0.53 – 1.08
Time of diagnosis			
2008 – 2010	17.1	Ref.	Ref.
2011 – 2013	18.0	1.34	1.03 – 1.74
2014 – 2016	18.2	1.28	0.97 – 1.67
Treatment			
Primary tumor resection	17.5	Ref.	Ref.
HIPEC	34.1	0.44	0.33 – 0.60
Palliative	12.6	0.96	0.66 – 1.40
None	3.1	2.96	1.92 – 4.58
Other metastases			
-	25.5	Ref.	Ref.
+	14.2	1.31	1.03 – 1.65

HR: Hazard Ratio; *CI*: Confidence Interval; *NOS*: Not otherwise specified; *HIPEC*: Hyperthermic Intraperitoneal Chemotherapy

*Number too small to report adequate survival rates.

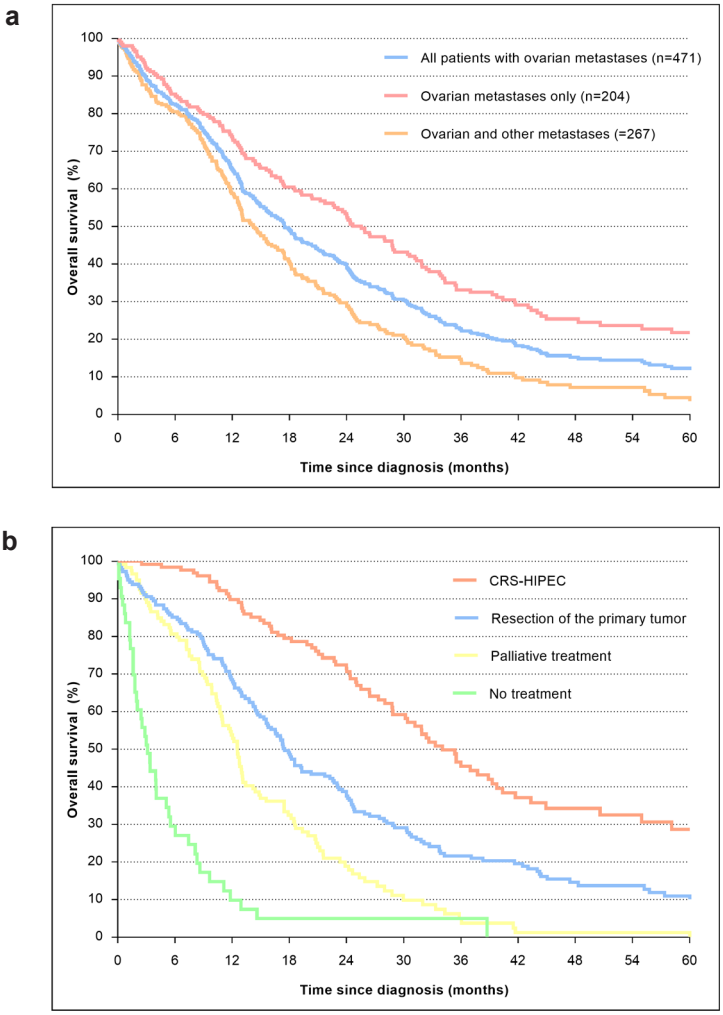

Fig. 4 ***a*** Overall survival of patients with ovarian (±other) metastases. ***b*** Overall survival of patients with ovarian metastases in accordance with different treatment strategies.

Discussion

To the best of our knowledge, this is the first nationwide study that investigated the incidence, risk factors, treatment, and survival of synchronous ovarian metastases of primary CRC. Previously reported incidence numbers are quite divergent: 3% is reported in a study published in 1981, while 14% is reported in another study.[12,13] In the current study, synchronous ovarian metastases were present in about 4% of all metastatic CRC patients. The aforementioned studies were based on hospital cohorts unlike the

nationwide cohort in the present study, which may partly explain the differences in incidences reported. Moreover, in up to 45% of the cases, ovarian tumors may mistakenly be assumed to be primary ovarian tumors or metastases from other primary tumors.[14] Besides, inconsequent usage of terminology is an issue in the literature concerning ovarian metastases. Both "Krukenberg tumor" and "metastases of gastrointestinal origin" are frequently used but are very indiscriminate: actual Krukenberg tumors ought to have specific features, and ovarian metastases from CRC are biologically dissimilar relative to ovarian metastases from primary gastric cancer, but are regularly assembled in studies.[15,16]

In the present cohort, women at younger age were more likely to present with synchronous ovarian metastases compared with older women. This is in line with previously published results and reinforces the hypothesis that premenopausal CRC patients are more likely to develop ovarian metastases.[13,17–20]

It is remarkable that patients with ovarian-only metastases have a considerably longer median OS compared to patients with other distant metastases, even though treatments for liver- and lung metastases from CRC have improved over the past years. This is opposite to formerly described comparisons of survival rates from ovarian metastases and other metastases.[21–23] In our cohort, median OS for all patients with ovarian metastases (with or without other metastases) was similar to earlier reported survival rates in smaller cohorts.[24,25]

Regardless of treatment, we believe that the reported outcome in this study demonstrate that the presence of ovarian metastases may not be as adverse as it is commonly thought, especially when adequate treatment can be performed. Surprisingly, patients that underwent resection of the primary tumor did not show better survival compared with patients undergoing palliative therapy (palliative metastasectomy and/or palliative systemic therapy, leaving the primary tumor in situ). Patients who received CRS-HIPEC showed significantly better survival rates compared with patients who received any other treatment. This is in line with previously reported results.[18,26]

The rationale to perform CRS-HIPEC in patients with colorectal ovarian metastases is that they are thought to be the result of peritoneal metastatic spread themselves and often are accompanied by peritoneal metastases. During the study period, about a quarter of the patients with ovarian metastases were treated with CRS-HIPEC. Survival of these patients was longer as compared with patients having undergone resection of the primary tumor alone. Despite this significant difference, a selection bias should certainly be kept in mind. Patients having distant metastases besides ovarian metastases are usually not considered candidates to receive CRS-HIPEC and will have a worse prognosis. Also,

patients with extensive intraperitoneal disease (Peritoneal Cancer Index; PCI > 20) are perceived inoperable for CRS, as it is known that CRS- HIPEC is not beneficial in these cases.[27-29] Unfortunately, no correction for PCI was achievable since data on PCI was not available. The role of HIPEC as an adjunct to CRS for peritoneal metastases of colorectal cancer was recently questioned by the French PRODIGE-7 study and likewise will need further research for the treatment of colorectal ovarian metastases as well.[30]

Although this is the first nationwide study on ovarian metastases from colorectal origin, it has several limitations. The NCR only comprises patients with synchronous ovarian metastases from CRC. Consequently, there is no data available on a number of patients with metachronous ovarian metastases from CRC, as metachronous ovarian metastases are reported in about 1–7% of metastatic CRC patients.[31-33] Furthermore, there is no data available on follow-up except for patients' vital status. Therefore, no information about disease-free survival is available in the present study. Another limitation in this study is the fact that data on comorbidities was only available for a subgroup of patients. Hence, a good overview of the possible risks of the different treatment regimens was not obtained, which might be of great value in (shared) decision-making when it comes to different treatment modalities for patients with ovarian metastases from CRC.

The data reported in this study suggest that young female CRC patients are at greater risk to develop ovarian metastases. Currently, there is an ongoing discussion about the implementation of prophylactic salpingo-oophorectomy in female patients undergoing surgery for CRC.[32,34-36] Further research, by means of a randomized controlled trial, could provide more insights in the value of prophylactic salpingo-oophorectomy in female CRC patients. Such a trial is currently in preparation in the Netherlands.

Conclusion

In this population-based study, the incidence of synchronous ovarian metastases in metastatic CRC patients is 4.2%. These metastases tend to occur in younger patients with signet ring cell tumors. Median OS of these patients is 17.5 months, ranging from 3.1 months in untreated patients to almost 3 years after CRS-HIPEC. In general, patients with ovarian metastases show better survival compared to patients with metastases to other distant organs. These findings are valuable when consulting patients diagnosed with colorectal ovarian metastases.

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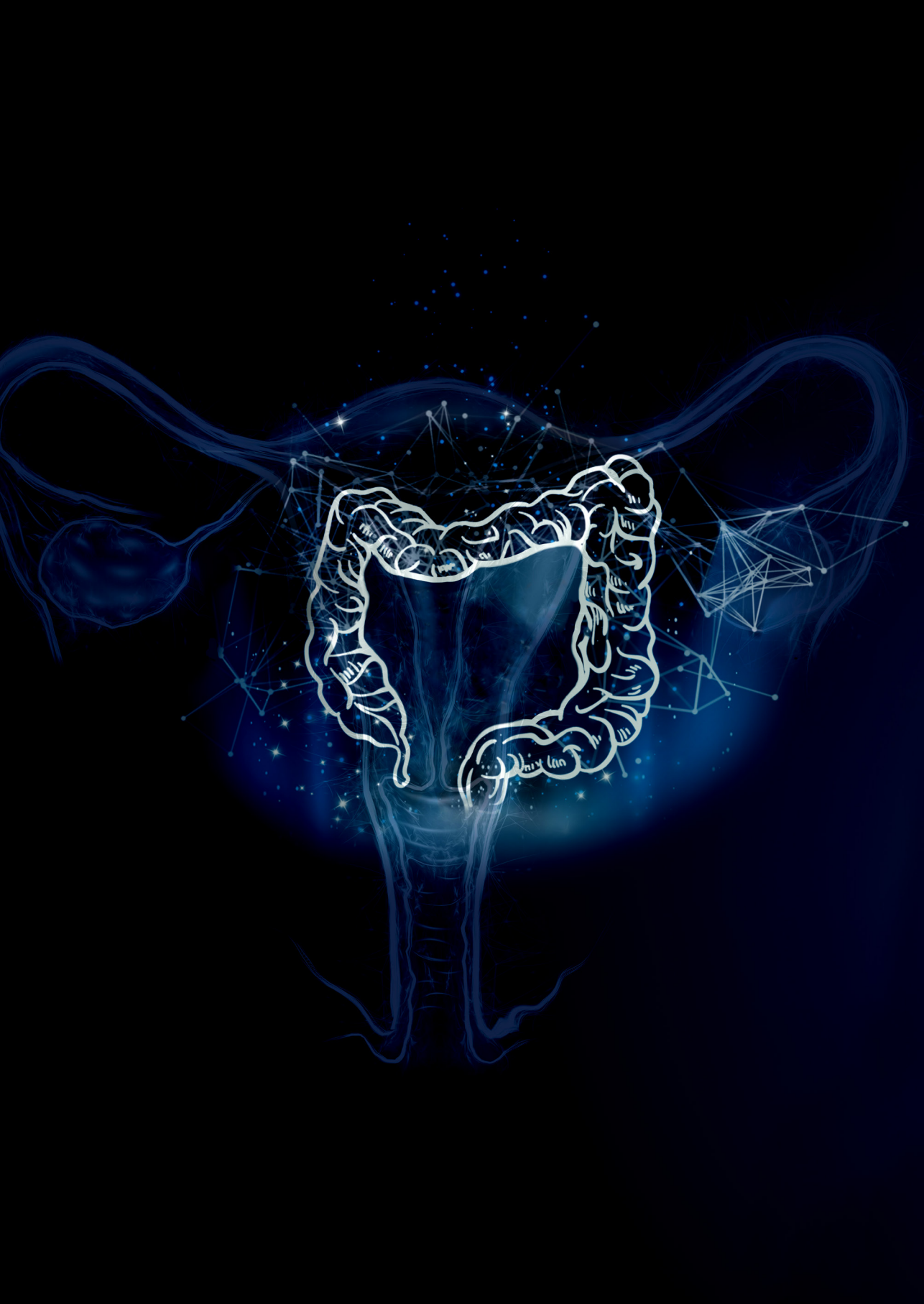

CHAPTER 3

Ovarian metastases in young women with colorectal cancer: a retrospective multicenter cohort study

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Abstract

Background and purpose

Previous studies indicated that approximately 3.4% of female colorectal cancer (CRC) patients are at increased risk of developing ovarian metastases (OM). It has been suggested that young women more frequently develop this form of metastatic disease.

Methods

This study evaluated, in 6 Dutch hospitals, the proportion of young women with CRC who developed OM.

Results

In a cohort of 200 young (age ≤55) women with CRC, the proportion of patients diagnosed with synchronous or metachronous OM was calculated. This study revealed that 5% (n=10) of young female CRC patients developed ovarian metastases resulting in a 5-year overall survival rate of approximately 40%. Furthermore, six patients had concurrent peritoneal metastases, five patients had bilateral ovarian metastases, and five patients had synchronous metastases, while the median time of the occurrence of metachronous metastases (n=5) was 19 months.

Conclusion

This retrospective multicenter cohort study indicates that 5% of young women with CRC either present with or develop OM. This result appears to be clinically relevant and demonstrates the need for improved surveillance for young women diagnosed with CRC.

Introduction

Background

In the Netherlands, colorectal cancer (CRC) is one of the most commonly diagnosed cancers with around 11,700 new cases in 2020.[1] Increased incidence of CRC among young adults (50 years of age and younger) has recently been reported.[2,3] In women, the lifetime risk of developing CRC (4.1%) is slightly lower than for men (4.4%).[4] For men and women combined, distant metastases generally develop in approximately 22% of patients diagnosed with primary CRC,[5] and in women, CRC metastases may also develop in the ovaries. A recently published population-based study reported a proportion of synchronous ovarian metastases (OM) in a total female population of 1%, while other literature reported a mean proportion of synchronous and/or metachronous OM of 3.4% (range 1-10%).[6–12] Once diagnosed with OM, the prognosis of the individual patient is poor, with a reported 5-year survival varying between 12 and 27%.[7,12–14]

In 2019, the Dutch guideline for CRC management was updated and discussed the role of prophylactic salpingo-oophorectomy to reduce the risk of developing OM and primary ovarian cancer. Although it is mentioned that prophylactic salpingo-oophorectomy could be offered to postmenopausal women, no guidance is provided for premenopausal women. The latter point is especially relevant since premenopausal CRC patients appear to be more frequently diagnosed with OM (4.6%) compared to postmenopausal women (0.8%), according to various studies.[12,15–28] However, the number of diagnosed metastases described in these studies were mainly either synchronous or metachronous,[15] resulting in a potential underestimation of the real burden.

Aim of the present study

The aim of the present study was to investigate the occurrence of either synchronous or metachronous OM in young (≤55 years of age), female CRC patients. To this end, we conducted a retrospective cohort study, using data from 6 Dutch hospitals, and calculated the proportion of synchronous and metachronous OM arising in these patients.

Material and Methods

Design, setting and participants

For this retrospective cohort study, data was obtained for all patients who had undergone CRC surgery from 2011-2015 in 6 Dutch hospitals in the Southeast Netherlands (Máxima Medical Center, Veldhoven; Catharina Cancer Institute, Eindhoven; Elkerliek Hospital, Helmond; Sint Jans Gasthuis, Weert; Zuyderland Hospital, Geleen-Sittard-Heerlen; VieCuri Medical Center, Venlo). This time period was chosen to obtain follow-up data

for at least 5 years.

All young women, defined as ≤55 years of age, were selected and included for evaluation. All of these women underwent resection of a primary colorectal malignancy. Pathology reports according to the TNM-classification were retrieved and patients were excluded from analyses when no residual disease or malignancy was found in the final pathology workup. Patients with neuro-endocrine tumors or appendiceal carcinomas were also excluded from this study as these are different tumor types. Operative records, hospital charts, and pathologic reports were reviewed for patients either who underwent oophorectomy at the time of primary resection of the colon or rectum or who underwent this procedure at a later time. Follow-up was obtained from available clinical records and these data were assimilated to determine the total proportion of patients diagnosed with OM.

To find and add potentially missing data, all pathology records of the selected patients were checked with the Dutch national pathology archive (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief, PALGA). Data was checked by matching the pathology number of the pathology report of the specific hospital to all known pathology specimens within PALGA for each patient. Since the Catharina Cancer Institute in Eindhoven is a nation-wide referral center for cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC), a correction was made to prevent selection bias. To do so, patients referred from hospitals other than the six included in the listed cohort of hospitals were censored from the study.

Synchronous metastases were defined as metastases diagnosed during, or within 3 months after, colorectal surgery, while metachronous metastases were defined as those occurring after 3 months. Finally, to compare the overall patient survival, the cohort was divided into 3 groups: women with no metastases, those with metastases including OM, and those with extra-ovarian metastases only. Survival curves were estimated using the Kaplan–Meier method and differences in the survival curves were compared using a log-rank test. These analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, Illinois, USA).

Ethics approval and consent to participate

The regional Medical Research Ethics Committee of Máxima MC approved the study and confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study and therefore an official approval of this study was not required under the WMO (Máxima MC METC protocol number 19.016-N19.011). Because of the retrospective nature of the study, informed consent was waived. Additionally, this study was also approved by the institutional review boards of the other participating centers.

Results

Patient characteristics

The initial study population consisted of 7173 patients and 6973 patients were excluded for various reasons (Fig. 1). No patients with previous gynecological surgery combined with oophorectomy were found. The final study population that met the inclusion criteria consisted of 200 young female CRC patients. Of these, 10 (5%) had OM (see Table 1 for patient characteristics and follow-up data). Of the two hundred patients selected for study, three were lost to follow-up and twelve had a recorded follow-up period of less than 4 years. At the time of primary surgery, 5 patients had synchronous OM and 5 other patients developed metachronous metastases to the ovary. The median time of the occurrence of metachronous metastases was 19 months (range 11-62 months).

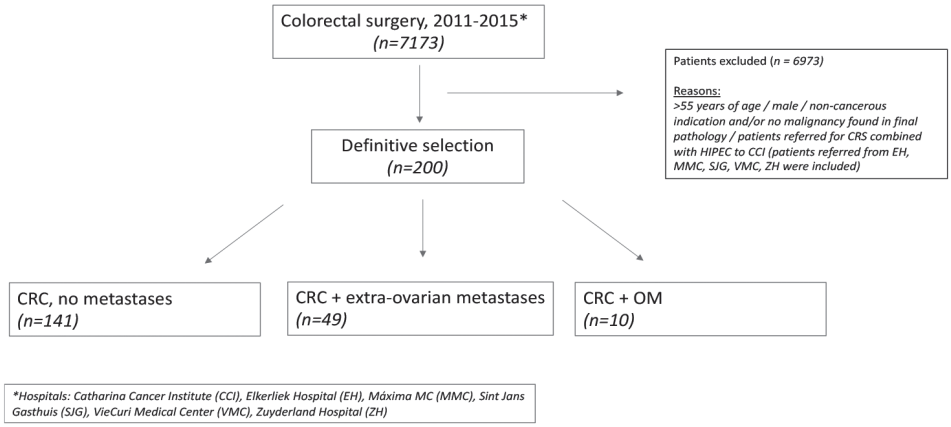

Fig. 1 Flowchart of patient selection

Median Age and TNM Staging

Median age at diagnosis of CRC patients with OM was 46 years (range 29-55 years). Resection of the primary tumor was categorized as curative (no residual disease) in 9 patients and palliative in 1 patient. Tumor status was T3 and T4 in 3 and 7 patients, respectively. Nodal status was N0, N1 and N2 in 1, 5 and 4 patients, respectively. Nine patients presented with, or developed during follow-up, systemic metastases besides OM. Six of these patients were diagnosed with additional peritoneal metastases either with hepatic metastasis (n=1), pulmonary metastasis (n=1), or both (n=1). Three other patients had hepatic metastasis, and only one had no evidence of further metastatic spread.

Table 1 Patient characteristics of included patients with ovarian metastases

Pt no. (hospital)	Age at diagnosis	Type of operation (location of tumor)	pTNM, tumor type, curative surgery (yes/no)	OM syn/ meta (after X months), side	Other recurrence(s) (yes/no)	Alive at the end[a] of follow-up (yes/no)
1. (CCI)	48	Right hemicolectomy, bilat oophorectomy (ascending colon)	T4N1M1 (liver, ovary), adeno (no)	Synchronous, bilateral	No	No, deceased after 26 months[b]
2. (CCI)	50	Left hemicolectomy (splenic flexure)	T4N1M0, adeno (yes)	Metachronous (62), bilateral	Yes, lung, Peritoneal	Yes, palliative situation (>5 years of follow-up)[b]
3. (CCI)	40	Right hemicolectomy (ascending colon)	T4N1M0, adeno (yes)	Metachronous (11), bilateral	Yes, Peritoneal	No, deceased after 30 months[b]
4. (CCI)	45	LAR (rectum)	T3N2M1 (liver), adeno (yes)	Metachronous (19), left	Yes, lung, peritoneal	Yes, palliative situation (>5 years of follow-up)[b]
5. (ZH)	46	Anterior resection (rectosigmoid)	T3N1M1 (liver), adeno (yes)	Metachronous (24), left	No	No, deceased after 59 months
6. (ZH)	35	CRS and HIPEC. Right Ext Hemi and bilat oophorectomy (transverse colon)	T4N2M1 (ovary, peritoneal), adeno (yes)	Synchronous, bilateral	Yes, peritoneal	No, deceased after 36 months[b]
7. (MMC)	46	LAR and hysterectomy and bilat oophorectomy (rectum)	T3N1M1(ovary), mucinous (yes)	Synchronous, left	No	Yes (>5 years of follow-up)
8. (MMC)	55	Sigmoid colectomy (sigmoid)	T3N0M0, adeno (yes)	Metachronous (13), left	Yes, liver	No, deceased after 47 months[b]
9. (MMC)	29	CRS and HIPEC, anterior resection and bilat oophorectomy (rectosigmoid)	T4N2M1 (ovary, peritoneal), SRCC (yes)	Synchronous, right	Yes, Peritoneal	No, deceased after 15 months
10. (VMC)	41	CRS and HIPEC, sigmoid colectomy and bilat oophorectomy (sigmoid)	T3N2M1 (ovary, liver), adeno (yes)	Synchronous, bilateral	Yes, Peritoneal	Yes, palliative situation (>5 years of follow-up)[b]

No, number; CCI, Catharina Cancer Institute; ZH, Zuyderland Hospital; MMC, Máxima Medical Center; VMC, VieCuri Medical Center; LAR, Low Anterior Resection; Ext, extended; Bilat, bilateral; CRS, Cytoreductive surgery; HIPEC; hyperthermic intraperitoneal chemotherapy; pTNM, Pathological Tumor-Node-Metastasis; Adeno, adenocarcinoma; Mucinous; mucinous carcinoma; SRCC, signet ring cell carcinoma; OM, ovarian metastases; Syn, Synchronous; Meta, Metachronous.

[a] 5-years after surgery for colorectal cancer

[b] This patient received adjuvant chemotherapy

Survival Analysis

Median survival of patients with OM was 46.9 months (95% CI, 9.5 to 84.3 months). The crude 5-year survival for patients with OM was 40%; for extra-ovarian metastases, only a crude 5-year survival of 55% was measured. In CRC patients without distant metastases, survival was measured 98% (Fig. 2). Of note, survival of patients diagnosed with OM versus those diagnosed with extra-ovarian metastases and synchronous OM versus metachronous OM were not statistically significant different (*p*-values of 0.701 and 0.665, respectively).

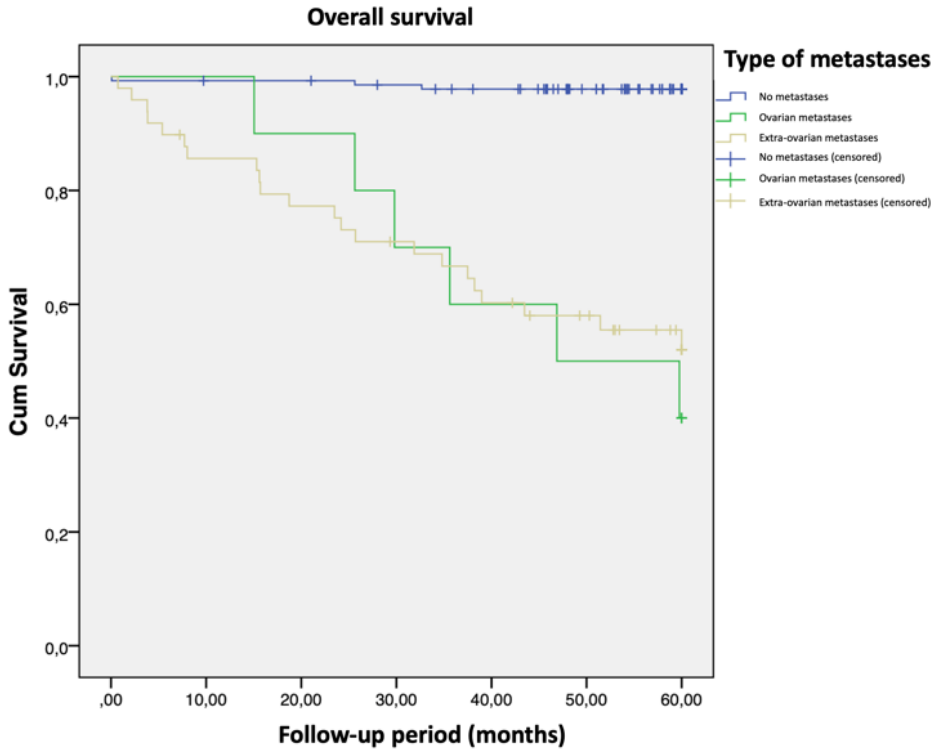

Fig. 2 Kaplan-Meier overall survival

Additional Findings

Of all CRC patients with OM, five had bilateral OM, and of the patients who had unilateral OM, four were left-sided and one was right-sided. Additionally, beyond the 10 patients with OM, one other patient had ovarian involvement because of direct disease spread and one other patient had a synchronous (primary) ovarian carcinoma.

Discussion

The present cohort study demonstrates that young CRC women have a 5% risk of developing OM at some point during the course of their cancer disease. This finding indicates that the development of OM is not a rare phenomenon in young women with CRC. A Dutch population-based study reported a proportion of 3.6% for synchronously present OM in young (<50 years of age) women compared with 0.7% in older (≥50 years of age) women.[12] The result of the present study shows an even higher proportion which is most likely due to the inclusion of patients who also developed metachronous OM. Moreover, compared with other cohort studies in which the proportion of OM in young patients could be calculated,[15–19,21–28] this study is of additional value due to the combination of a relatively large cohort, a thorough review of clinical records, the use of modern imaging modalities (both pre and postoperatively), and long-term follow-up.

OM are generally considered uncommon because large population-based studies largely focus on the entire population of female CRC patients.[12,29] Nevertheless, in our opinion, treating physicians need increased awareness of the possible occurrence of OM in young women. Furthermore, a discussion of prophylactic salpingo-oophorectomy with these women should be considered to mitigate the likelihood of developing stage IV cancer or primary ovarian cancer. Although we are unaware of any studies that have focused on prophylactic salpingo-oophorectomy as an elective procedure during CRC surgery to prevent primary ovarian cancer, prophylactic salpingo-oophorectomy could also be considered in this population given the fact that this procedure during hysterectomies results in a decreased incidence of primary ovarian cancer.[30–32]

In the present study, 6 out of 10 patients with OM also initially presented with, or later developed, peritoneal metastases. The exact mechanism of dissemination from colon to ovary is unknown; however, several metastatic pathways have been suggested. For example, direct spread from the primary tumor, passage of malignant cells through the peritoneal fluid, lymphatic system, or blood vessels have all been considered as potential mechanisms for disease spread.[33] Miller et al.[34] suggested that one of the reasons for higher rates of OM in premenopausal women is because of hematogenous spread to the well-vascularized stromal tissue of the ovary. The present study showed, in concordance with previous studies, that bilateral OM occur with high frequency (32% to 77%),[7–10,34–37] and that this observation seemingly supports the hematogenous model for disease spread.[39] This finding also supports (considering) the removal of the contralateral ovary in case an abnormal ovary is found during surgery for colorectal cancer.[9] Fujiwara et al.[35] found in 16 out of 20 patients with OM that metastatic lesions were located centrally in the ovary and did not invade the capsule, suggesting lymphatic or hematogenous spread.[16] Similarly, various studies described patients with OM who did not display

either lymphatic (N0) or peritoneal involvement.[40–42] Taken together, these observations suggest that disease dissemination is hematogenous in nature; however, it bears noting that, in the patient cohort outlined in this study, nodal involvement (i.e., N1, N2) was observed in nine out of ten patients. Increased angiogenesis, the presence of growth factors in ovarian stromal tissue (including epidermal growth factor (EGF), hepatocyte growth factor (HGF) and transforming growth factor–α (TFGa), as well as increased expression of cyclooxygenases and prostaglandins that favor tumor cell growth, all potentially influence tumor dissemination to the preferred tissue environment of the ovaries.[43] The combination of all these factors might explain why OM are less sensitive to systemic chemotherapy and therefore are considered 'sanctuary sites'.[44,45] Our results could, however, indicate that peritoneal dissemination is highly plausible, and prompts the question whether there is an added value for systemic therapy in this patient population.

The median survival of patients with OM was 46.9 months, and almost all women (9 out of 10) were deceased or reached a palliative situation after final follow-up even when (curative) cytoreductive surgery was performed combined with administration of hyperthermic intraperitoneal chemotherapy (HIPEC). The crude 5-year overall survival rate of 40% observed in this OM cohort is slightly higher than earlier reports that showed 5-year survival rates up to 27%.[7,12–14,20,46–48] This finding might be explained, at least in part, by the fact that the patient cohort in the present study was selected for a younger patient population. Furthermore, no difference in overall survival between patients suffering from OM and those with extra-ovarian metastases was observed (albeit that the number of patients in this category was small). Other reports have shown that OM results in shortened survival compared with patients with only extra-ovarian metastases, and that resection of OM could result in improved overall survival.[8,44,49–51] The reduced chemotherapeutic sensitivity, as well as factors mentioned above, could therefore be seen as arguments in favor of prophylactic salpingo-oophorectomy, or a metastasectomy, when OM occurs.

The limitation of this cohort study is its retrospective nature, so, for example, exact menopausal status could not be determined. It is therefore difficult to conclude that a patient's menopausal status impacts the occurrence of OM, albeit that a premenopausal status is quite likely in the majority of those patients in our selected cohort since the average age for menopause in Dutch women is 50-51.[52] Additionally, all women with CRC or ovarian recurrences who did not undergo surgery or had only micro-metastatic disease within the ovary during follow-up, could be overlooked in our analyses. Therefore, the actual risk of OM in this population is likely higher than the calculated risk obtained in this study.

As stated earlier, given the relatively high incidence of OM in younger CRC patients, discussing the possibility of prophylactic salpingo-oophorectomy might be considered because this procedure would almost certainly result in a reduction in the development of OM. When offering "shared decision making" the treating physician / surgeon should display balance in the conversation and explain both the benefits and side effects of prophylactic salpingo-oophorectomy. One clear benefit is the reduction of primary ovarian carcinoma as the lifetime risk of developing invasive primary ovarian carcinoma within the general population is approximately 1.3%.[53] Within our retrospective patient cohort, beyond the 10 patients with OM, one additional patient developed a primary ovarian carcinoma.

The removal of the ovaries in premenopausal women has more negative consequences than in postmenopausal women, making this procedure controversial. While postmenopausal women primarily only might suffer from the effects of decreased concentrations of testosterone and androstenedione, which affects general wellbeing and sexual desire, premenopausal women are exposed to an early, induced menopause.[54,55] In addition to decreased sexual function, development of osteoporosis, increased risk of cardiac events, and dementia may occur.[56–58] Furthermore, it has been reported that ovary removal in women below the age of 45 appears to have an increased mortality risk compared to those above this age.[57] Many negative consequences can, however, largely be prevented by the use of hormone replacement therapy (HRT), which is advised in these specific situations.[58–60]

Although prophylactic salpingo-oophorectomy could prevent the development or further proliferation of OM, it is questionable whether this procedure could also result in improved patient survival. Prophylactic salpingo-oophorectomy could prevent future surgery for removal of OM, whether or not surgery is combined with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy. Prophylactic salpingo-oophorectomy could also be useful to prevent ovarian cancer. The estimated cost of a quality-adjusted life-year (QALY) for performing this procedure is nevertheless expected to be very low, especially when it is compared with other oncological procedures. We calculated that the cost of one quality-adjusted life-year, depending on the factors included (e.g., costs of additional operating time (10-15 minutes), histopathology, consultation of gynecologists, and possible HRT in younger women), is expected to be around €2.500.[61] This is much lower than the €80.000 which in the Netherlands is considered to be the maximum amount for one QALY.[62]

In conclusion, this cohort study determined that 5% of young women with CRC either initially present with, or later develop, OM. This result is clinically relevant and demonstrates the need for improved attention towards young women with CRC.

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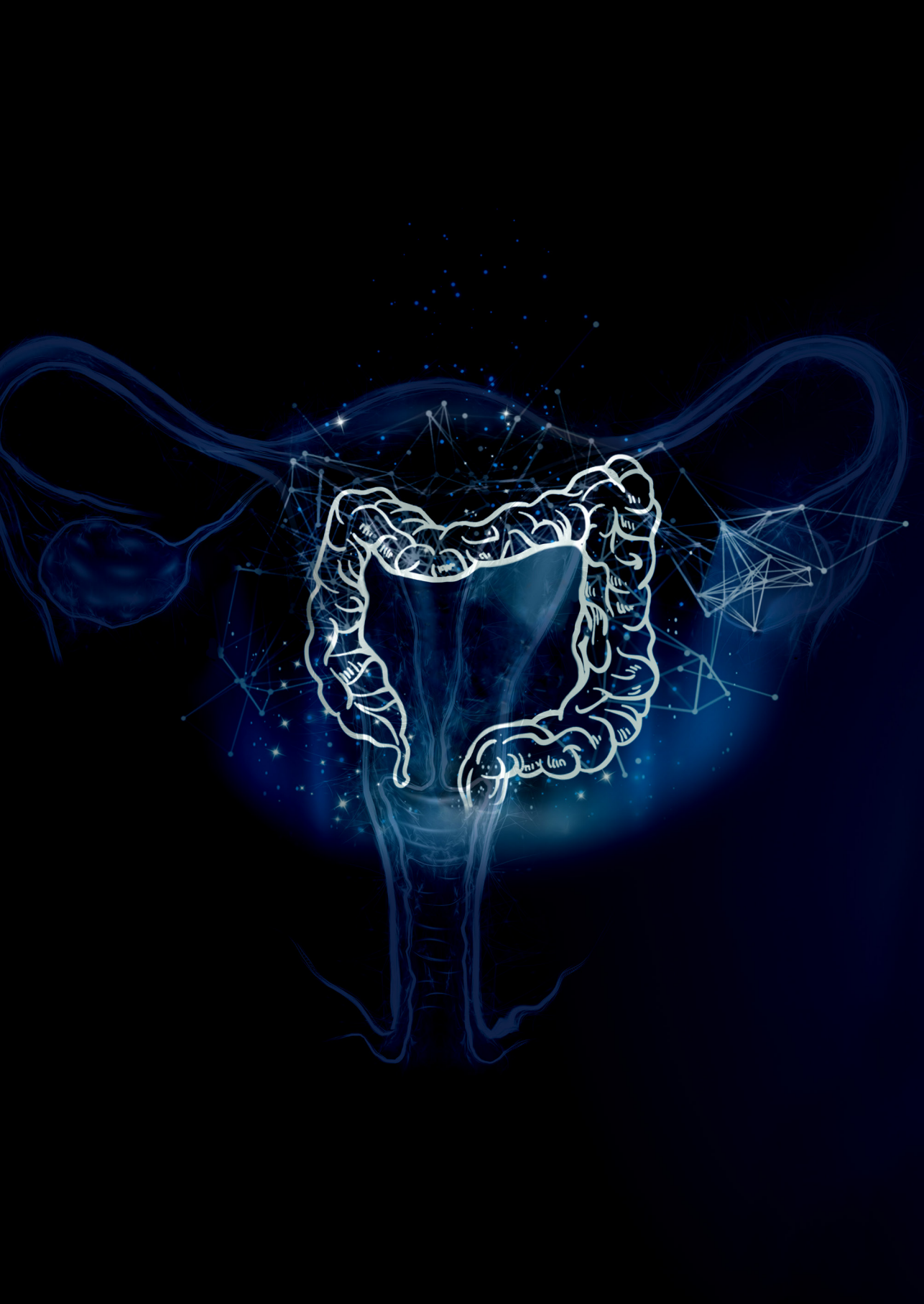

CHAPTER 4

Ovarian metastases from colorectal cancer in young women: a systematic review of the literature

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Abstract

Background and purpose

In female colorectal cancer patients, a mean proportion of synchronous and/or metachronous ovarian metastases of 3.4% was described. Previous literature showed that young or premenopausal women (≤55 years of age) may be more frequently affected. Once ovarian metastases are diagnosed, the prognosis of the patient is generally dismal, with 5-year survival varying from 12 to 27%.

The present study is aimed at determining the proportion of young or premenopausal women diagnosed with colorectal cancer who presented with or developed ovarian metastases by reviewing the current literature on this topic.

Methods

This review was performed by querying MEDLINE and EMBASE databases using a combination of terms: "colorectal neoplasms, colorectal cancer, ovarian neoplasms, Krukenberg tumor, young adult, young age, premenopause". Studies that indicated ovarian metastases, either synchronous or metachronous (or a combination of the two) in young women was retrieved and analyzed.

Results

The review identified 14 studies encompassing 3379 young or premenopausal female colorectal cancer patients. In this selected group of patients, a mean proportion of ovarian metastases of 4.6% [95% CI: 4.0;5.4] was found.

Conclusions

This review showed that approximately one in twenty young female colorectal cancer patients will present with or develop ovarian metastases. Since outcome of this specific oncological pathology is often dismal, this finding is clinically relevant. It demonstrates the need to develop strategies to lower the incidence of ovarian metastases with adequate treatment and counseling of these patients.

Introduction

Globally, colorectal cancer (CRC) is the second most commonly diagnosed form of cancer within the female population, with about 800,000 new cases diagnosed worldwide in 2018.[1] The majority of European countries, US, and Canada have reported increasing incidence rates of colorectal cancer among young adults (≤50 years of age).[2,3] Women have a cumulative lifetime risk for colon and rectal cancer of 1.12% and 0.65%, respectively.[1] Recently, a large population-based study (over fifty thousand female patients) was published showing an incidence of synchronous CRC ovarian metastases (OM) of 0.8%.[4] Other studies reported proportions of synchronous and/or metachronous OM in female CRC populations varying from 1 to 10%,[5–9] with a mean proportion of 3.4%.[10] This proportion seems to significantly increase in the young female group.[6,11–15] Once OM is diagnosed, the prognosis of the individual patient is usually dismal, with a 5-year survival varying from 12 to 27%.[4,6,16,17]

For each patient presenting with OM stemming from primary CRC, it is unclear what the best tailored surgical and/or systemic therapy for these patients should include.[8,18,19] Prophylactic salpingo-oophorectomy (PSO) of macroscopically normal ovaries/ fallopian tubes during primary surgery for CRC to prevent OM might be a valuable option, but this is controversial and remains a subject of ongoing debate.[20–22]

Since 2019, the American guideline (American Society of Colon and Rectal Surgeons) mentions that prophylactic oophorectomy may be considered in all postmenopausal patients and prophylactic oophorectomy should be considered in selected premenopausal women to remove microscopic synchronous OM and to eliminate the risk of metachronous ovarian metastatic disease and primary ovarian cancer.[23]

Of course, the removal of the ovaries in premenopausal women has more consequences than in postmenopausal women and no survival benefit for prophylactic surgery has been found.[24] The risk of immediate complications from the procedure itself are, however, minimal and comparable in both groups. While postmenopausal women potentially suffer from the effects of decreased concentrations of androstenedione and testosterone, which influence sexual desire and general wellbeing, premenopausal women have to face the effect of a prematurely induced menopause.[21,25] The long-term effect of oophorectomy in premenopausal women can result in a decreased sexual function, development of osteoporosis, and an increased risk of cardiac events and dementia.[26–28] According to Rocca and colleagues, patients who underwent bilateral oophorectomy for a non-cancerous indication below the age of 45 showed an increased mortality rate when compared to older patients.[27] However, many negative consequences may be overcome by the use of exogenous hormone replacement therapy (HRT) which is strongly advised

in these patients.[13,28,29] Moreover, although it has been suggested that PSO might be considered in premenopausal women, the exact proportion of OM is unknown and the latest review on this topic was published in 1986.[30]

The aim of the present study was to investigate the occurrence of OM arising in young and premenopausal women (≤55 years of age) diagnosed with CRC. To accomplish this, we performed a comprehensive review of the literature on this topic.

Materials and methods

Regarding the search and study selection, this review was conducted according to the guidelines of PRISMA.[31]

Scope and research question

The research question of the review was as follows: what proportion of the premenopausal (or women of at least ≤ 55 years of age) colorectal cancer population suffers at some time from colorectal ovarian metastases?

It should be noted that in this review, young women are defined as ≤55 years of age. The cut-off value of 55 years of age was set because the average age of the menopause is 51 years and menopause at >55 years of age is considered a "late" menopause.[32–35]

Search strategy

The MEDLINE and EMBASE databases were searched for evidence related to the aforementioned question with the use of the following text, MeSH, and EMBASE subject headings: "colorectal neoplasms," "colorectal cancer." These results were combined with "ovarian neoplasms," or "Krukenberg tumor," and "young adult", "young age" or "premenopause" (supplementary file).

The results were limited to studies published from 1950 to December 31st, 2020. Articles were selected for inclusion in the literature review if they were fully published English language reports. Inclusion required reports on quantity of OM arising in young (or premenopausal) female CRC patients. Excluded were studies on primary ovarian carcinoma, solitary metastases to organs other than the ovaries, or studies in which a proportion of OM arising in CRC patients could not be calculated (for example: case studies and case series that described 3 or more cases). In addition, 1 author (R.M.) hand-searched the reference lists of the included articles, and all review articles were discussed with the senior authors (I.H and R.R.).

Results

Literature search

We found 4301 studies in the MEDLINE database and the addition of EMBASE database searches uncovered another 875 unique studies. After removing 45 duplicates, a total of 5131 titles and abstracts were retrieved and screened for eligibility (Fig. 1).

In summary, 12 retrospective cohort studies and 2 prospective cohort studies were analyzed for this manuscript. Table 1 indicates the study characteristics and outcomes of OM occurrence in female CRC patients.

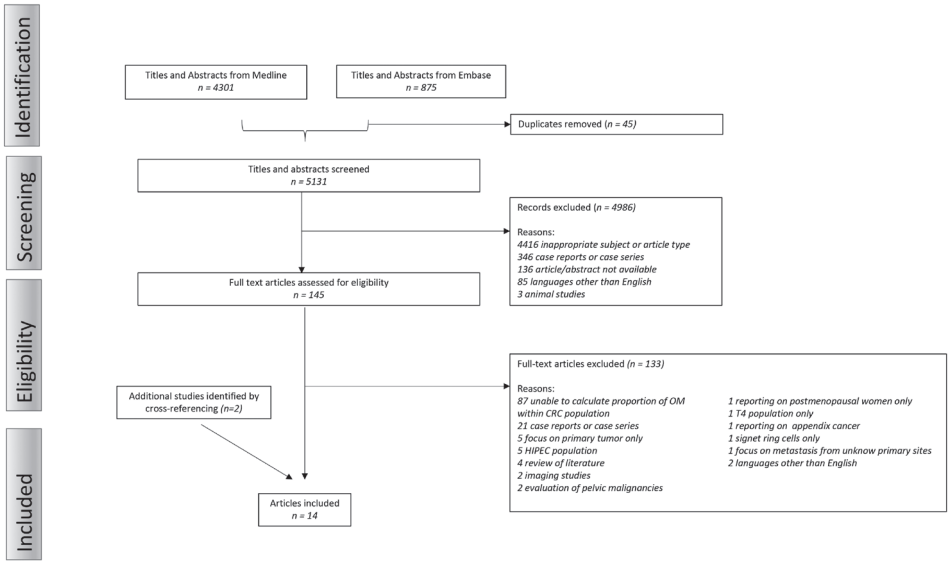

Fig. 1 PRISMA study selection

Population-based- or retrospective cohort studies

The majority of studies (12 out of 14) were retrospective nationwide population-based or cohort studies. Bakkers et al.[4], the most recently published article, investigated a Dutch population using data from the Netherlands Cancer Registry. They found 53,883 female patients diagnosed with CRC between 2008 and 2016, however, only data from synchronous metastases were available. Among these patients, 2737 patients were below the age of 50 and 94 (3.4%) were diagnosed with OM In the "elderly group" (≥50 years of age), 377 (0.7%) of 51,146 had OM. It was unknown whether OM were diagnosed by pre- or postoperative imaging, by definitive pathology or otherwise. Haleshappa et al.[36] investigated a CRC population below the age of 40. All patients (n=39) underwent surgery between 2010 and 2014, and 9 (23.1%) patients presented

with OM at the time of surgery. It was unknown whether OM were diagnosed by pre- or postoperative imaging, by definitive pathology or otherwise. In 2008, Yamaguchi et al.[37], noted 3 (50.0%) women with OM out of a total of 6 premenopausal women diagnosed with CRC, and this premenopausal cohort is the smallest cohort of all retrieved studies. Two patients were diagnosed by definitive pathology and one patient by post-operative imaging. The postmenopausal group consisted of 103 CRC patients, in which only 1 (1.0%) patient presented with OM; this OM was diagnosed by post-operative imaging. All patients underwent surgery between 2000 and 2005 on primary metastases (synchronous disease) or developed metastases (metachronous disease). Sakakura et al.[38] found a total of 9 cases of synchronous or metachronous OM within a cohort of 452 patients with colorectal cancer between 1990 and 2000, 70 (15.5%) of whom were premenopausal, and 3 (4.3%) patients in this group presented with or developed OM. Furthermore, 6 (1.6%) of the 382 postmenopausal patients presented with or developed OM. One patient had macroscopic OM during primary surgery; OM in the remaining eight patients were found, in an undescribed way, during follow-up (the authors also specified that most of these OM were detected within one year after initial operation). McGill et al.[39] reviewed charts of all female patients admitted between 1985 and 1996 with gastric or colorectal cancer. A total of 788 patients with colorectal cancer were included: 19 (2.4%) had oophorectomy performed at the time of primary surgery, and none developed metachronous OM. Out of 788 patients, 41 (5.2%) were premenopausal of which 3 (7.3%) had OM, while only 2 (0.3%) out of 747 postmenopausal women did have OM. All patients were diagnosed by definitive pathology. Domergue et al.[40] analyzed 78 patients younger than 40 years of age treated for CRC between 1966 and 1983. Among these 78 patients, 38 (48.7%) were women and there was no comparative older (i.e., post-menopausal) group. A total of 3 (7.9%) patients were diagnosed with metachronous OM within the 3-year follow-up period. It was unknown whether OM were diagnosed by pre- or postoperative imaging, by definitive pathology or otherwise. In 1983, Pitluk et al.[41] presented data on 31 CRC patients below the age of 40 who underwent surgery between 1968 and 1978. Among them, 17 were female, of which 4 (23.5%) presented with synchronous OM. No data on metachronous OM were available in this study. It was unknown whether OM were diagnosed by pre- or postoperative imaging, by definitive pathology or otherwise. O'Brien et al.[42] studied a total of 255 patients between 1969 and 1979 who were diagnosed with CRC, of whom pathologic specimens were obtained. The menopausal state of these women was available, however, the exact number within each specific group was not presented. Within the premenopausal group, 28% suffered from synchronous or metachronous OM, compared to 3.6% of the postmenopausal group. It was unknown whether OM were diagnosed by pre- or postoperative imaging, by definitive pathology or otherwise. In 1981, Blamey and co-workers performed two different analyses within a female CRC population.

Table 1 Summary of the eligible studies

Study	Type (retrospective/ prospective)	Metastasis (synchronous/ metachronous/ both)	Type of diagnosis (imaging, definitive pathology, otherwise)	Follow-up period	Menopausal state or age	
					% Premenopausal or ≤55y (N / total)	% Postmenopausal or >55y (N / total)
Bakkers et al. [2020] *N=53,883*	Retrospective	Synchronous	NA	5-year	3.4% (94/2,737)[a]	0.7% (377/51,146)[b]
Haleshappa et al. [2017] *N=39*	Retrospective	Synchronous	NA	5-year	23.1% (9/39)[c]	NA
Yamaguchi et al. [2008] *N=109*	Retrospective	Both	Definitive pathology/imaging	NA	50% (3/6)	1.0% (1/103)
Sakakura et al. [2004] *N=452*	Retrospective	Both	Otherwise	5-year	4.3% (3/70)[a]	1.6% (6/382)[d]
McGill et al. [1999] *N=788*	Retrospective	Synchronous	Definitive pathology	NA	7.3% (3/41)[a]	0.3% (2/747)[b]
Domergue et al. [1988] *N=38*	Retrospective	Metachronous	NA	3-year	7.9% (3/38)[c]	NA
Pitluk et al. [1983] *N=17*	Retrospective	Synchronous	NA	5-year[e]	23.5% (4/17)[c]	NA
Cutait et al. [1983] *N=350*	Prospective	Synchronous[f]	Definitive pathology	>5-year	5.7% (2/35)[g]	0.6% (2/315)
O'brien et al. [1981] *N=255*	Retrospective	Both	NA	NA	28% (NA)	3.6% (NA)
Blamey et al. [1981] *N=882*	Retrospective	Synchronous	NA	5-year[e]	3.8% (12/316)	4.2% (24/566)
Blamey et al. [1981] *N=882*	Retrospective	Metachronous	Otherwise	NA	2.8% (9/316)	0.7% (4/566)
MacKeigan et al. [1979] *N=162*	Prospective	Both	Definitive pathology (n=4), NA (n=8)	NA	25.0% (6/24)	4.3% (6/138)
Walton et al. [1976] *N=38*	Retrospective	Synchronous	NA	2-year	13.2% (5/38)[c]	NA
Recalde et al. [1974] *N=18*	Retrospective	Metachronous	NA	5-year	22.2% (4/18)[h]	NA

NA = not applicable (relevant or specific outcome not reported)

[a] <50y

[b] ≥50y

[c] ≤40y

[d] >50y

[e] Only mentioned for overall survival, not for recurrent disease nor for disease free survival

[f] This study did not find any patient with metachronic disease

[g] including 1 perimenopausal woman (age unknown)

[h] ≤35y

The first study described a cohort of patients with synchronous OM consisting of 882 patients who underwent resection of CRC between 1950 and 1978.[43] At the time of primary tumor resection, 12 (3.8%) out of 316 patients below 55 years of age, and 24 (4.2%) out of 566 patients above 55 years of age were diagnosed with ovarian involvement. It was unknown whether OM were diagnosed by pre- or postoperative imaging, by definitive pathology or otherwise. It was, however, reported that thirty patients had an oophorectomy or bilateral oophorectomies and six patients with advanced disease did not have any oophorectomy. The second study of Blamey et al.[44] investigated ovarian recurrence after resection of CRC in the same cohort of 882 patients. A total of 9 (2.8%) patients out of 316 younger than 55 years of age were diagnosed with ovarian recurrence, compared to 4 (0.7%) in the elderly group. It was unknown whether OM were diagnosed by pre- or postoperative imaging or by definitive. The authors anyhow reported that all patients were seen with signs of an abdominal or pelvic mass which was indicative for ovarian recurrence. Walton et al.[45] is the fourth study that investigated patients diagnosed with CRC under the age of 40 within a 10-year interval. In this study, of the 38 women analyzed, 5 (13.2%) were diagnosed with synchronous OM. In this study, no data on metachronous OM was available. It was unknown whether OM were diagnosed by pre- or postoperative imaging, by definitive pathology or otherwise. The final retrospective cohort study is from Recalde et al.[46] in which patients below the age of 35 were included. This cohort consisted of 21 males and 19 females with CRC operated between 1949 and 1968. Of the 19 females, one was excluded from the analyses without any explanation and among the remaining 18 patients, 4 (22.2%) developed OM. It was unknown whether OM were diagnosed by postoperative imaging, by definitive pathology or otherwise.

Prospective cohort studies

Two prospective cohort studies were also included in this report. Cutait et al.[12] analyzed a total study population of 350 CRC patients who underwent surgery between 1968 and 1975. Among them, 201 (57.4%) patients underwent unilateral or bilateral oophorectomy at the time of CRC surgery (performing an oophorectomy was based upon the individual surgeon's preference and judgement) while 134 patients were not subjected to oophorectomy at the time of surgery. Thirty patients were excluded from this prospective study because the patient was diagnosed with: (1) a previous bilateral oophorectomy; (2) previous ovarian cancer; (3) polyposis coli; or (4) death within the immediate postoperative period. Of these 350 patients, 35 (10.0%) were pre- or perimenopausal, of whom 2 (5.7%) suffered from synchronous OM, compared to 2 (0.6%) patients of the postmenopausal group. This study did not find patients with metachronous OM. All patients were diagnosed by definitive pathology. MacKeigan et al.[15] studied a total of 24 (14.8%) premenopausal patients out of a total patient population of 162 who underwent oophorectomy at the time of colon surgery or subsequently underwent surgery between

1960 and 1976. Six (25.0%) of the 24 patients were diagnosed with synchronous or metachronous OM, compared to 6 (4.3%) in the post-menopausal group. Four patients had micro-metastatic disease and thus were diagnosed by definitive pathology. Of the remaining eight patients it was unknown whether OM were diagnosed by postoperative imaging, by definitive pathology or otherwise.

A calculation of all these studies together encompasses a total of 3379 young patients of whom 157 (4.6%) were diagnosed with OM at some point in time after CRC diagnosis. A boxplot of the selected studies in the present review (Fig. 2) indicates that this mean proportion is 4.6%, with a 95% confidence interval of 4.0% - 5.4%.

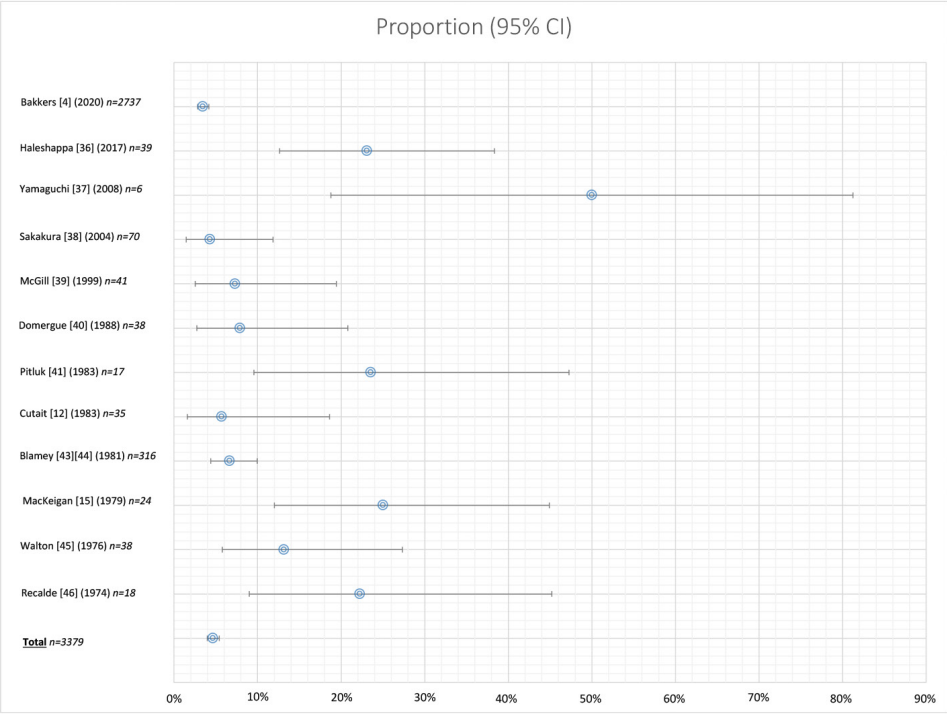

Fig. 2 Boxplot of OM in CRC patients

Discussion

The present review of the literature demonstrates that a varying proportion of young women diagnosed with CRC display synchronous and/or metachronous OM ranging from 3% to 50%, with a mean proportion of 4.6%. The risk for developing OM should thus be regarded as substantial and clinically relevant in young female CRC patients. Generally, it seems to be that the prognosis of these patients is negatively affected by the presence of OM, we therefore suggest to consider offering the possibility of PSO to younger women during surgery for primary CRC in a shared decision making process. When offering "shared decision making", the professional has to keep in mind the positive effects of PSO and of course the negative side effects as already mentioned previously. One additional positive side-effect is the reduction of occurrence of primary ovarian carcinoma. The lifetime risk of developing invasive primary ovarian carcinoma within the general female population is 1 out of 78.[47] This may be even more relevant given the increased risk of developing primary ovarian carcinoma after the occurrence of CRC when compared to the general population. According to Chang et al.[48] and Shin et al.[49], the hazard ratio varies between 3-7. This effect could be seen in patients with hereditary non-polyposis colorectal cancer (HNPCC) syndrome, but it also appears to be independent from this syndrome as well.[48–50] Alternatively, when oophorectomy is not eligible, PSO could be waived and after adequate counseling prophylactic salpingectomy could be done safely during elective surgery to prevent ovarian cancer.[51–53]

Several other disciplines already perform surgery to prevent OM. Gynecologists generally perform oophorectomies in patients operated for endometrial cancer to reduce the risk of OM which is approximately 6% in these patients.[54] However, this risk is reduced to 0.5% should patients also show <50% myometrial invasion, endometrioid histology, well-differentiated cancer, and negative lymph and vascular space invasion.[54] Therefore, it is currently advised to preserve the ovaries in this specific group of premenopausal women. Moreover, urologists routinely remove all female reproductive organs, ovaries included, in case of radical cystectomy due to urothelial bladder cancer. Ovarian involvement in these patients is estimated to be <1%.[55,56]

The high proportion of OM within the young population stresses the need for increased awareness in the interpretation of a newly found ovarian mass on diagnostic imaging tests, especially in case of a previous history of colorectal cancer.[57] It is possible that an OM is initially misdiagnosed and surgery for a presumed primary ovarian malignancy is performed.[58–62] Therefore, a thorough patient evaluation before surgery for suspected primary ovarian neoplasms is important.[63] Pre-operatively, the CA125/CEA ratio, the ADNEX model, or a coloscopy could be helpful to predict the likelihood of an OM.[57,64–69] When the suspicion of OM is low and surgery is performed, the possibility

of OM stemming from primary CRC should still be considered for ovarian tumors having mucinous and/or endometrioid-like differentiation, even when characteristic clinicopathologic features of metastases are lacking.[57] Immunostaining for cytokeratin 20 (CK20) and cytokeratin 7 (CK7) could, for that reason, be supportive in differentiating between OM and primary ovarian neoplasms. Predominantly, primary ovarian cancer cells are positive for CK7 and negative for CK20, whereas colorectal tumors are negative for CK7 and positive for CK20.[70–72]

This literature review has several limitations. Firstly, based on all studies presented in this review, it is difficult to state whether younger females are more frequently affected with OM due to the presence of more advanced tumor stages compared to older females. The study from Bakkers et al.[4], however, showed that the odds for developing OM was significantly increased in young women with CRC, even when corrected for possible confounders such as T- and N-stage by multivariable logistic regression analysis. Secondly, the included studies contain a large heterogeneity in patients' age cut-offs and thereby (probably) underestimates the true proportion of OM within the whole premenopausal group over time. Thirdly, another important issue is the difference in focus on synchronous versus metachronous OM. In 6 of 14 studies, including the largest one, only data on synchronous OM was available, with a mean proportion of 4.0% (127 out of 3188 women).[4,35,38,40,42,44] And finally, 3 out of 14 studies only included data on metachronous OM, resulting in a mean proportion of 4.3% (16 out of 372 patients).[40,44,46] As a result, the majority of the included studies in this review only present outcomes on either synchronous or metachronous metastases. Given the knowledge that according to one large population-based study (n=4566) from Segelman et al.[73] who found a prevalence of 0.9% for synchronous OM and a cumulative incidence of 0.8% for metachronous OM in patients diagnosed with CRC, an assumption could be made that the mean proportion of 4.6% in this review could actually be doubled to express an approximation of the real disease burden. Consequently, this could result in a proportion varying from 5 to 10% for younger colorectal cancer patients. To the best of our knowledge, almost all patients with OM, especially those included in the retrospective cohort studies, underwent surgery because of OM detected using pre-operative imaging or during surgery. Therefore, microscopic metastases to the ovaries could have been missed.[74,75] Such underestimation of OM could be even more prevalent in patients that did not undergo surgery in the palliative setting as these lesions are usually not detected on radiological imaging or mistaken for primary ovarian neoplasms. Due to aforementioned reasons and combined with a lack of prospective randomized controlled studies, no meta-analysis of the data could be performed. Furthermore, because of different follow-up periods in all studies, no calculations could be done on specific incidence or prevalence rates. However, the strength of the review is the comprehensive nature of this overview of OM in the young CRC population in the English literature.

Conclusion

This review of the literature showed that about one in twenty young female CRC patients will present with or develop ovarian metastases. Since outcome of this specific oncological entity is often dismal, this finding is clinically relevant. It demonstrates the need to develop strategies to lower the incidence of ovarian metastases with adequate treatment and counseling of these patients.

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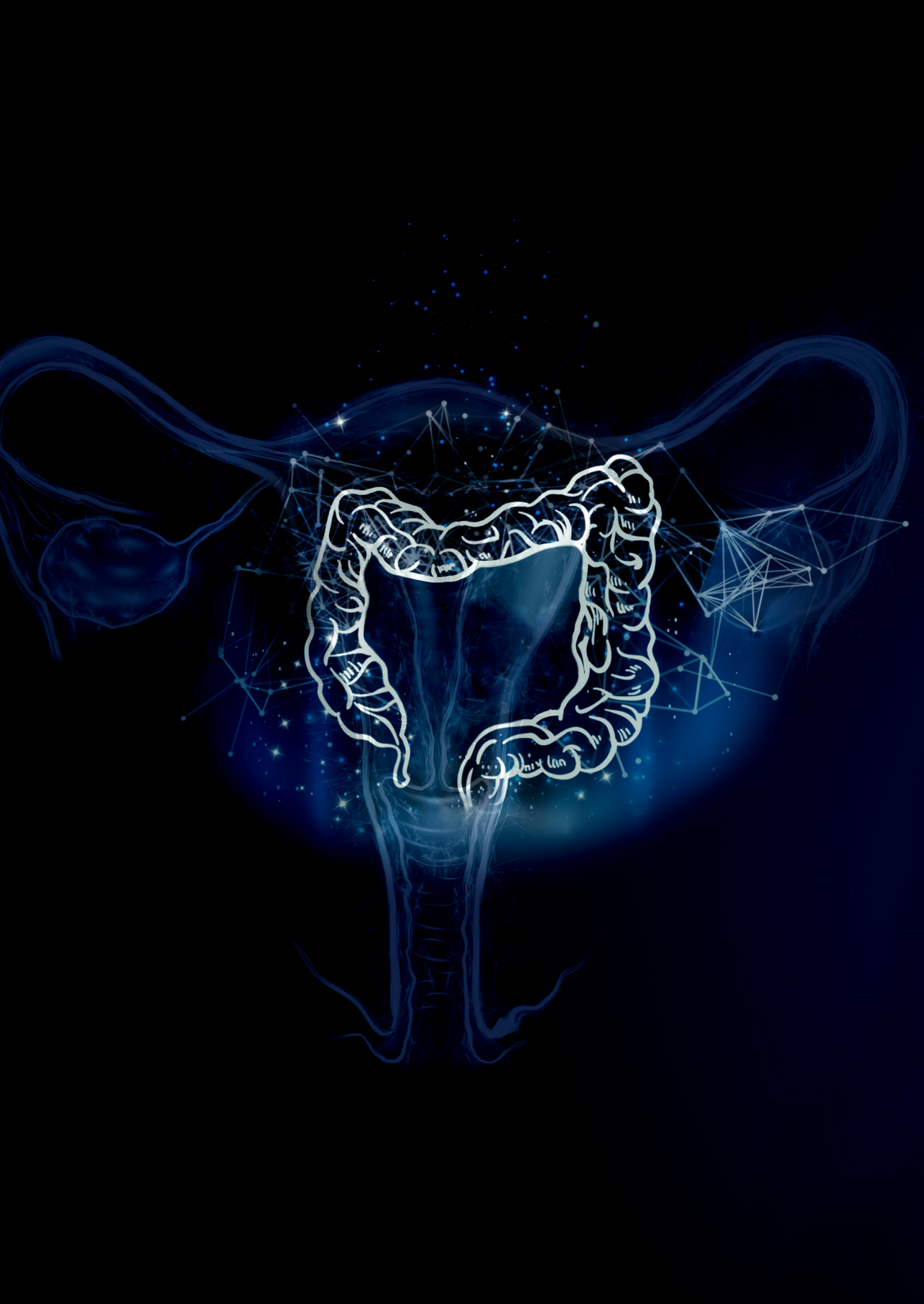
Supplementary

Supplementary file search strategy for all used databases

((((((colorectal*[tw] OR colon[tw] OR rectal*[tw]))) AND (((“Colorectal Neoplasms”[Mesh]) OR (“Neoplasms”[Mesh]) OR carcinoma*[tw] OR neoplas*[tw] OR tumour*[tw] OR sarcoma*[tw] OR adenoma*[tw] OR tumor*[tw] OR cancer*[tw] OR cancer[sb] OR oncolog*[tw] OR malignan*[tw] OR metasta*[tw] OR carcinogen*[tw] OR oncogen*[tw] OR precancerous[tw] OR paraneoplastic[tw])))) AND ((((ovarian*[tw] OR ovar*[tw] OR ovarian recurrence*[tw]))) AND ((“Ovarian Neoplasms”[Mesh] OR “Krukenberg Tumor”[Mesh] OR “Neoplasms”[Mesh] OR carcinoma*[tw] OR neoplas*[tw] OR tumour*[tw] OR sarcoma*[tw] OR adenoma*[tw] OR tumor*[tw] OR cancer*[tw] OR cancer[sb] OR oncolog*[tw] OR malignan*[tw] OR metasta*[tw] OR carcinogen*[tw] OR oncogen*[tw] OR anticarcinogen*[tw] OR precancerous[tw] OR paraneoplastic[tw] OR carcinosarcoma*[tw] OR krukenberg*[tw])))) AND (((“Premenopause”[Mesh] OR premenopaus*[tiab] OR pre menopaus*[tiab] OR premenopausal period[tiab] OR pre menopausal period[tiab] OR “Adult”[MESH] OR “Middle aged”[Mesh] OR “Young Adult”[MESH] OR young adul*[tiab] OR young age[tiab])))



CHAPTER 5

A propensity score-matched analysis of oncological outcome after systemic therapy for stage IV colorectal cancer: Impact of synchronous ovarian metastases

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Abstract

The reported incidence of synchronous and metachronous ovarian metastases (OM) from colorectal cancer (CRC) is approximately 3.4%. OM from CRC are often considered sanctuary sites due to their lower sensitivity to systemic treatment. It has thus been hypothesized that the presence of OM decreases overall survival. Therefore, the purpose of this study was to evaluate the impact of synchronous OM on overall survival in female patients with stage IV CRC treated with systemic therapy alone with palliative intent. The present study used data from the Netherlands Cancer Registry and included female CRC patients with synchronous systemic metastases who were treated with systemic therapy between 2008 and 2018. A subsample was created using propensity score matching to create comparable groups. Propensity scores were determined using a logistic regression model in which the dependent variable was the presence of OM and the independent variables were the variables that differed significantly between both groups. This study included 5,253 patients with stage IV CRC that received systemic therapy. Among these patients, 161 (3%) had OM while 5,092 (97%) had extra-ovarian metastases only. Three-year overall survival rates did not show a significant difference between patients with OM compared to patients without ovarian metastases. Moreover, the propensity score matched analysis showed that the presence of OM in patients treated with systemic therapy for stage IV CRC disease was not associated with decreased three-year overall survival. However, the results of the present study should be interpreted with caution, due to its observational character and used selection criteria.

Introduction

Globally, colorectal cancer (CRC) is the second most commonly diagnosed form of cancer amongst the female patient population.[1] Approximately 20-25% of patients with CRC present with metastatic disease at initial diagnosis.[2] The reported incidence of synchronous and metachronous ovarian metastases (OM) is approximately 3.4%.[3]

OM from CRC are predominantly considered to be sanctuary sites due to their lower lesser sensitivity to systemic treatment and by their lack of measurable (or visible) response compared to other metastatic sites (small sample size studies found response rates of 0-24% for OM vs. 33-56% for extra-ovarian metastases).[4-10] Systemic treatment unresponsive OM are mainly found prior to the introduction of epidermal growth factor receptor (EGFR) antibody treatment, but also since this treatment has already been implemented.[5,8,10] Two main theories have been advocated to underly this phenomenon: 1. The presumed chemo-resistance of OM may be due to the favourable ovarian micro-environment for tumour growth;[6,11] 2. The presence of specific gene mutations within the metastases (for example Rat sarcoma virus (RAS) mutations, which are predictive biomarkers in EGFR directed treatment).[9,12-14] Furthermore, it is well known that the co-existence of peritoneal metastases can negatively affect patient prognosis.[15-19] Unfortunately, all studies that reported on relatively chemo-resistant OM were limited in sample size, and mostly no statements regarding its impact on overall survival compared to patients with unaffected ovaries were made.[4-10]

Based on the above observations and theories, we hypothesized that it is likely that systemic therapy resistant OM result in a shortened overall survival. Therefore, the aim of the current study was to test this hypothesis by evaluating the impact of the presence of synchronous OM on overall survival in female patients with stage IV CRC treated with systemic therapy alone with palliative intent.

Methods

Data collection

Data from the Netherlands Cancer Registry (NCR) were used. The NCR is a population-based registry covering all newly diagnosed malignancies in the Netherlands as notified by the automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnoses (the 'Landelijke Medische Registratie'; LMR). Within the NCR, trained administrators routinely extract information on patient and tumour characteristics, diagnosis, and treatment from the medical records. The anatomical site of the tumour is registered according to the International Classification of Disease –

Oncology (ICD-O). The Union for International Cancer Control tumour-node-metastasis (TNM) classification is used for stage notification of the primary tumour, according to the edition valid at the time of diagnosis. Comorbidity is registered according to the Charlson Comorbidity Index,[20] though for a subgroup only. Vital status is obtained by annual linkage of the NCR to the Municipal Personal Records Database. Follow-up on vital status was complete up to 31 January 2020.

Study population

The present study included Dutch female patients with synchronously metastasized colorectal cancer (stage IV) who were diagnosed between 2008 and 2018. Synchronous metastases are defined as: (clinically) diagnosed before start of the primary treatment or pathologically confirmed during primary treatment. Patients with a primary tumour located in the appendix or with a neuroendocrine tumour were excluded. All patients were treated with systemic therapy. Patients who underwent any local treatment of metastases, like metastasectomy, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) or radiotherapy, were also excluded.

Patients were categorized into two groups based on the presence of OM: patients with OM (one or more metastatic sites) or those without OM. Furthermore, the presence of (ovarian) metastasis could be based on the following clinical signs: metastatic disease found by medical imaging, intra-abdominal metastasis found during surgery or metastatic disease proven by needle biopsy.

Propensity score matched sample

Because data from the current study were population-based, comparing survival of patients with OM to patients without OM may be biased. To overcome this problem, a subsample was created using propensity score matching (PSM) to create comparable groups. Propensity scores were determined using a logistic regression model in which the dependent variable was the presence of OM and the independent variables were the variables that are clinically relevant to treatment and outcome and that differed significantly between both groups (patients with and those without OM) in the total study population. These factors were age (≤55, 56-75, ≥76 years), T stage (0-3, 4, unknown), N stage (0, 1, 2, unknown), location of the primary tumour (proximal colon, distal colon, colon other/not otherwise specified, rectum), morphology (adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, other/not otherwise specified), and the presence of metastases in the liver, peritoneum, lung, and distant lymph nodes. The number of metastatic sites was also included (1, 2, 3, ≥4), as was resection of the primary tumour. The propensity score represented the probability that a patient would have OM. On the basis of the propensity scores, patients with OM were matched 1:1 to patients without OM, optimizing the number of matches by matching the patients

with the fewest number of matches first. Individuals were matched on propensity scores using a calliper width equal to 0.2 of the standard deviation of the logit propensity score. Balance in covariates was evaluated using standardized differences. A standardized difference between -0.10 and 0.10 indicated an adequate balance.

Statistical analyses

Patient, tumour, and treatment characteristics were compared between the groups based on the presence of OM using Chi-squared test or Fisher's exact test as appropriate. Crude median- and three-year overall survival rates were calculated with the Kaplan-Meier method and tested with the Log-Rank test. Multivariable Cox regression analysis was used to determine the independent influence of the presence of OM on the risk of death. Overall survival was defined as the time from diagnosis to the date of death or last follow-up date.

All analyses were performed for both the total study population and the propensity score matched samples. Additionally, as a sensitivity analysis, multivariable Cox regression analysis was repeated for the total study population after the exclusion of the patients with solitary OM.

Analyses were performed using SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC, United States). All tests were two-sided and significance noted at the 5% level or lower.

Results

Total study population

Between 2008 and 2018, 14,223 female patients were diagnosed with synchronic metastases from CRC, of whom 5,253 (37%) were included in the study (Fig. 1). Among these 5,253 patients who were treated with systemic therapy, 161 (3%) had OM while 5,092 (97%) did not have OM. Table 1 lists the patient characteristics of the total study population by the presence of OM. Considerable differences in patient and tumour characteristics were found between the two groups. Patients with OM were significantly younger: 35% (56 out of 161) vs. 18% (939 out of 5,092) for ≤55 years of age ($p<0.0001$). Further, significant differences were found in Charlson Comorbidity Index (CCI), T-and N-stage, location of primary tumour, tumour morphology, liver-, peritoneal- and lung metastases and number of metastatic sites.

Overall survival for total study population

The crude median survival length of the study population was 13.1 months. The

three-year overall survival rate did not show a significant difference between patients with OM (6.8%) and patients without OM (8.0%) (p=0.607) (Fig. 2). However, after adjustment for other variables in multivariable analysis, the hazard ratio of death was lower for patients with OM compared with patients without OM (crude median OS 13.7 vs 13.1 months, adjusted HR 0.80, 95% CI 0.67-0.97, Table 2). Exclusion of patients with solitary OM gave a similar result: adjusted HR 0.81, 95% CI 0.67-0.98.

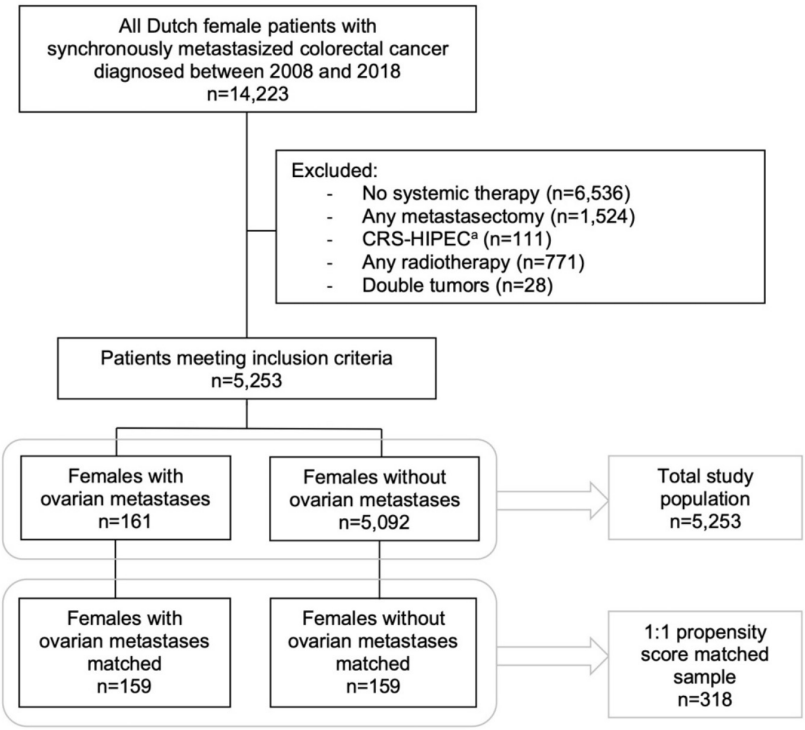

Fig. 1 Flowchart of the study population. [a] Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Table 1 Baseline characteristics of the total study population and the propensity score matched sample

	Total study population N=5,253			Propensity score matched sample N=318			Standardized differences	
	F + OM[a] N=161	F – OM[b] N=5,092	P-value	F + OM N=159	F – OM N=159	P-value	Unmatched	Matched
Age			**<0.0001**			0.580		
≤55	56 (35%)	939 (18%)		55 (35%)	48 (30%)		0.38	0.09
56-75	94 (58%)	3,196 (63%)		93 (58%)	102 (64%)		-0.09	-0.12
≥76	11 (7%)	957 (19%)		11 (7%)	9 (6%)		-0.36	0.05
Charlson Comorbidity Index[c]			**0.035**			0.312		
0								
1	35 (85%)	980 (66%)		35 (85%)	28 (72%)		0.06	0.11
≥2	5 (12%)	396 (27%)		5 (12%)	8 (20%)		-0.21	-0.10
	1 (3%)	108 (7%)		1 (3%)	3 (8%)		-0.13	-0.11
Period of diagnosis			0.171			0.294		
2008-2011	57 (35%)	1,979 (39%)		57 (36%)	44 (28%)		-0.07	0.18
2012-2015	56 (35%)	1,920 (38%)		55 (35%)	62 (39%)		-0.06	-0.09
2016-2018	48 (30%)	1,193 (23%)		47 (29%)	53 (33%)		0.14	-0.08
T stage			**0.002**			0.781		
0-3	43 (27%)	2,020 (40%)		43 (27%)	46 (29%)		-0.28	-0.04
4	56 (35%)	1,305 (25%)		56 (35%)	59 (37%)		0.20	-0.04
Unknown	62 (38%)	1,767 (35%)		60 (38%)	54 (34%)		0.08	0.08
N stage			**0.026**			0.777		
0	33 (21%)	964 (19%)		33 (20%)	30 (19%)		0.04	0.05
1	39 (24%)	1,686 (33%)		39 (25%)	39 (25%)		-0.20	0.00
2	48 (30%)	1,543 (30%)		48 (30%)	56 (35%)		-0.01	-0.11
Unknown	41 (25%)	899 (18%)		39 (25%)	34 (21%)		0.19	0.07
Location primary tumour			**0.012**			0.820		
Proximal colon								
Distal colon	83 (51%)	2,384 (47%)		81 (51%)	84 (53%)		0.09	-0.04
Colon other/NOS[d]	51 (32%)	1,589 (31%)		51 (32%)	45 (28%)		0.01	0.08
Rectum	16 (10%)	932 (18%)		11 (7%)	20 (13%)		0.14	0.03
	11 (7%)	187 (4%)		16 (10%)	10 (6%)		-0.24	-0.08

Table 1 Continued

	Total study population N=5,253			Propensity score matched sample N=318			Standardized differences	
	F + OM[a] N=161	F – OM[b] N=5,092	P-value	F + OM N=159	F – OM N=159	P-value	Unmatched	Matched
Morphology			**<0.0001**			0.917		
Adenocarcinoma	125 (78%)	4,499 (88%)		124 (78%)	127 (80%)		0.19	0.04
Mucinous adenocarcinoma	21 (13%)	367 (7%)		21 (13%)	19 (12%)		-0.29	-0.05
Signet ring cell carcinoma								
Other/NOS	15 (9%)	91 (2%)		14 (9%)	13 (8%)		0.33	0.02
	0 (0%)	135 (3%)		0 (0%)	0 (0%)		-0.23	0.00
Differentiation grade			0.375			0.117		
Well/moderate	77 (48%)	2,154 (42%)		76 (48%)	62 (39%)		0.11	0.18
Poor/undifferentiated	23 (14%)	787 (16%)		23 (14%)	36 (23%)		-0.03	-0.21
Unknown	61 (38%)	2,151 (42%)		60 (38%)	61 (38%)		-0.09	-0.01
Liver metastases			**<0.0001**			0.201		
Yes	95 (59%)	4,144 (81%)		95 (60%)	106 (67%)		-0.50	-0.14
No	66 (41%)	948 (19%)		64 (40%)	53 (33%)		0.50	0.14
Peritoneal metastases			**<0.0001**			0.567		
Yes	100 (62%)	1,143 (22%)		98 (62%)	93 (58%)		0.88	0.06
No	61 (38%)	3,949 (78%)		61 (38%)	66 (42%)		-0.88	-0.06
Lung metastasis			**0.029**			0.889		
Yes	33 (21%)	1,445 (28%)		33 (21%)	32 (20%)		-0.18	0.02
No	128 (79%)	3,647 (72%)		126 (79%)	127 (80%)		0.18	-0.02
Distant lymph node metastases			0.054			**<0.0001**		
Yes								
No	23 (14%)	1,043 (20%)		22 (14%)	95 (60%)		-0.16	-1.08
	138 (86%)	4,049 (80%)		137 (86%)	64 (40%)		0.16	1.08
Number of metastatic sites			**<0.0001**			0.913		
1	11 (7%)	2,704 (53%)		11 (7%)	11 (7%)		-1.17	0.00
2	54 (33%)	1,678 (33%)		54 (34%)	49 (31%)		0.01	0.07
3	66 (41%)	554 (11%)		65 (41%)	71 (45%)		0.73	-0.08
≥4	30 (19%)	156 (3%)		29 (18%)	28 (17%)		0.52	0.02

Table 1 Continued

	Total study population N=5,253			Propensity score matched sample N=318			Standardized differences	
	F + OM[a] N=161	F – OM[b] N=5,092	P-value	F + OM N=159	F – OM N=159	P-value	Unmatched	Matched
Resection of the primary tumour			0.396			0.115		
Yes								
No	56 (35%)	1,610 (32%)		56 (35%)	43 (27%)		0.07	0.18
	105 (65%)	3,482 (68%)		103 (65%)	116 (73%)		-0.07	-0.18

[a] *Patients with ovarian metastases*
[b] *Patients without ovarian metastases*
[c] *Only available for a part of the study population*
[d] *Not otherwise specified*
Bold characters represent statistically significant P-values.

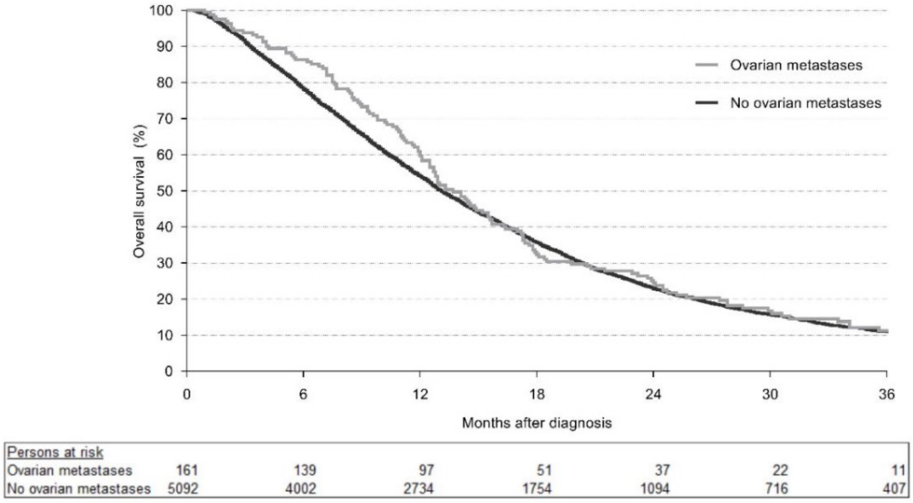

Fig. 2 Three-year overall survival total study population. *Log-Rank test:* p=0.607

Table 2 Crude median overall survival and multivariable adjusted hazard ratios for mortality for the presence of ovarian metastasis for the total study population and the propensity score matched sample

	Total study population N=5,253		**Propensity score matched sample** N=318	
	Median OS (months)	Adjusted^ HR (95% CI)	Median OS (months)	Adjusted HR (95% CI)
Ovarian metastasis				
Yes	13.7	**0.80 (0.67-0.97)**	13.7	0.81 (0.61-1.09)
No	13.1	1.00 (reference)	9.5	1.00 (reference)

^Adjusted for age, period of diagnosis, T stage, N stage, location primary tumour, morphology, differentiation grade, liver metastasis, peritoneal metastasis, lung metastasis, distant lymph node metastasis, number of metastatic sites, resection of the primary tumour
Bold characters represent statistically significant P-values.

Propensity score matched population

Of all selected patients, 159 of 161 (99%) patients with OM could be matched to patients without OM. After propensity score matching, a significantly lower occurrence of distant lymph node metastases was found in patients with OM - 14% (n=22) compared to 60% (n=95) in patients without OM, p<0.0001. No other significant differences between the two samples were found (Table 1). However residual imbalances existed regarding age, comorbidity, period of diagnosis, N stage, differentiation grade, liver metastases, distant lymph node metastases and resection of the primary tumour (Table 1).

Overall, the crude median overall survival length for the propensity score matched sample was 12.5 months. The three-year overall survival rate did not show a significant

difference between patients with OM (6.3%) and patients without OM (6.9%) (p =0.135) (Fig. 3). Also in multivariable analysis, there was no statistically significant difference between patients with OM and patients without OM (median OS 13.7 vs 9.5 months, adjusted HR 0.81, 95% CI 0.61-1.09, Table 2). Multivariable adjusted hazard ratios for other characteristics are presented in the supplementary table.

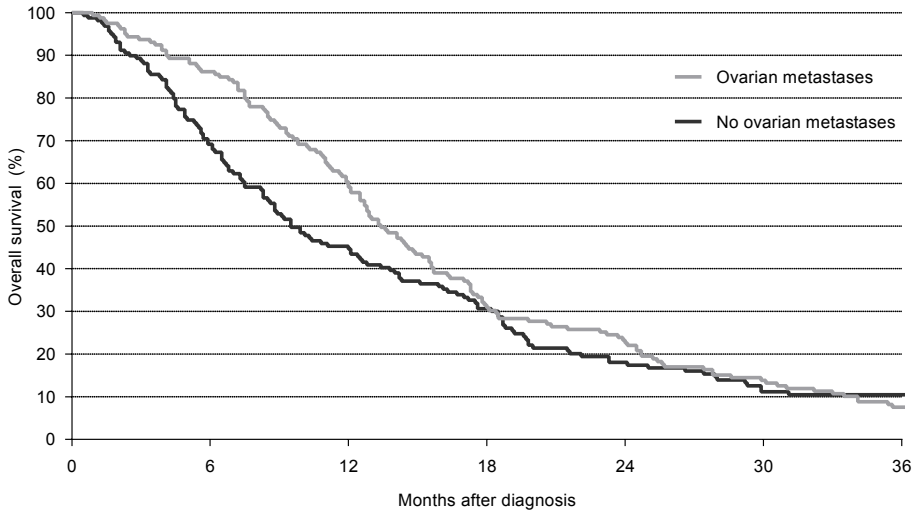

Fig. 3 Three-year overall survival propensity score matched sample. *Log-Rank test:* p=0.135

Discussion

Our propensity score matched analysis using the Netherlands Cancer Registry showed that in selected patients with stage IV CRC treated with systemic therapy with palliative intent, the presence of synchronous OM was not associated with decreased three-year overall survival when compared to patients without OM.

This result contrasts with our hypothesis that the presence of OM, which have frequently been reported to be resistant to systemic treatment,[4-10] would result in a shortened overall survival. Furthermore, various studies previously showed that the prognosis of patients with OM was poorer when compared to patients with other metastatic sites.[4,5,7] One study by Tong et al.[10] (n=50), reported a detrimental effect of OM when compared to other metastatic sites. However, some other studies, like the current one, did not find a worse prognosis in patients with OM compared to patients without OM.[4,21-24] Unfortunately, the majority of studies that reported on relatively chemo-resistant OM, did not make any statements regarding its impact on overall survival compared to patients with unaffected ovaries and vice versa.

However, the results of the present study should be interpreted with caution, due to the selection criteria that were used and the observational character of the study.

With regard to the selection criteria, it must be emphasized that the study population represents a highly selected group of patients in which no metastasectomies were performed, while a metastasectomy is actually commonly performed in patients with for example solitary liver or ovarian metastases. Unfortunately, reasons to refrain from metastasectomy were unknown, and could vary from irresectable metastases to frailty or preference of the patient. It could be hypothesized though, that probably a more vulnerable group of patients with extensive disease is included in the sample without OM, which impacts the comparison of both samples. Several retrospective studies suggest that ovarian metastasectomy or palliative surgery may positively affect survival in patients suffering from OM.[4,25-28] Even when cure is no longer possible, it has been suggested that a 'palliative oophorectomy' could improve survival or prevent large symptomatic OM.[5-7,26,29] Since no patient in the current study had an oophorectomy, no statements for this specific subgroup can be made. However, in order to test our hypothesis, we needed to evaluate patients that only received systemic treatment as an ovarian metastasectomy generally improves overall survival.[4,25,30-32] As far as we know, this is also the first study that investigated the impact of OM in a selected group of stage IV CRC patients with non-resected metastases treated with systemic therapy.

Regarding the observational character, it must be acknowledged that this leads to selection bias, as represented by the differences between the two samples. Propensity score matching was used to overcome several differences, but some differences remained and it is likely that other differences were present as well, for which no adjustment or matching was possible. These include amongst others patient and treatment characteristics such as the specific agents and the number of lines of systemic treatment, the presence of comorbidities and the performance status of the patient.

Neither the specific agents nor the number of lines of systemic treatment that patients received were known in this study. Our results could therefore be biased since these are predictive factors for survival. Moreover, for the past 20 years, systemic treatment has progressed in efficacy by molecular targeted therapy.[33] This evolution could unfortunately not be assessed in this study, but it could be assumed that therapeutic efficacy is equally divided since the period of diagnosis was also included as a matching variable in the propensity score matching analysis (Table 1). In addition, an immortal time bias might exist since follow-up began at the date of diagnosis as no information was available regarding the date of first exposure to systemic treatment.

Furthermore, the presence of comorbidities was only known for a small number of

patients, and no information was available for the performance status (i.e., Karnofsky Performance Score). Because of the absence of both the Charlson Comorbidity Index for the majority of patients and Karnofsky Performance Score (for all patients), both unselected and propensity score matched analyses may have been unbalanced for these parameters.

According to the current study, it seems that primary tumor resection has the most impact on OS (supplementary table). This finding is in accordance with the earlier finding from Boer et al.[34] who found that palliative resection of the primary tumor is associated with improved overall survival in incurable stage IV CRC (18.4 months vs. 9.5 months for no resection) in a retrospective study. However, the randomized controlled trial from Kanemitsu et al.[35] showed no superiority for primary tumour resection in addition to chemotherapy for CRC patients with asymptomatic primary tumours and synchronous unresectable metastases. Our results may therefore be biased as a result of our patient selection criteria. Furthermore, the exact mechanism of dissemination from the colon to ovary is unknown, although several metastatic pathways have been proposed including hematogenous, peritoneal and lymphatic spread.[36] Some studies found that OM occur independently from lymphatic dissemination.[37,38] The present data showed that after propensity score matching, a significant difference between the two samples was found regarding the presence of positive lymph nodes. However, since the two samples in the (original) total study population, before propensity score matching, were not significantly different and no impact on survival was found within the multivariate analyses, this finding seems to be of minor clinical relevance.

The present study focused on patients with synchronous metastases. Information on patients with metachronous metastases is still lacking, although they account for 0.9-7% of OM, according to previous single centre studies.[17,36,39,40] Some studies found a better survival for metachronous OM compared to synchronous OM.[25,38,41] Other previous studies, that focused on different metastatic sites in CRC patients, found that survival for metachronous metastases is equivalent or better compared to synchronous metastases.[42-45] Therefore, based on those studies, no further decrease in overall survival for patients with OM compared with patients with unaffected ovaries would be expected if patients with metachronous metastases had been added to the present data.

Since only clinically visible OM were included in this study, patients with synchronic – but microscopic – OM might have been missed and not included in our analysis. According to different cohort studies that performed prophylactic salpingo-oophorectomies, this incidence varied from 0-23.5%.[37,46-51] Our results could therefore be biased since patients with normal appearing ovaries during primary tumour resection could still have microscopically OM, or as the result of inadequate inspection of the

pelvic cavity during surgery.

In lack of any prospective studies that researched the current issue nationwide, this study provides useful information despite the mentioned limitations. However, future prospective studies are needed to validate our findings since our results are still based on retrospective data and represent a highly selected group of patients. In anticipation of such a prospective study, independent database validation, like the US Surveillance, Epidemiology, and End Results Program (SEER), may help test the external validity of our findings. Furthermore, the effect of different therapeutic agents on radiological response and overall survival needs further exploration.

Conclusion

The current study showed that the presence of synchronous OM was not associated with decreased three-year overall survival in a selected group of patients treated with systemic therapy for stage IV CRC. However, the results of the present study should be interpreted with caution, due to the selection criteria that were used and the observational character of the study.

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Supplementary material

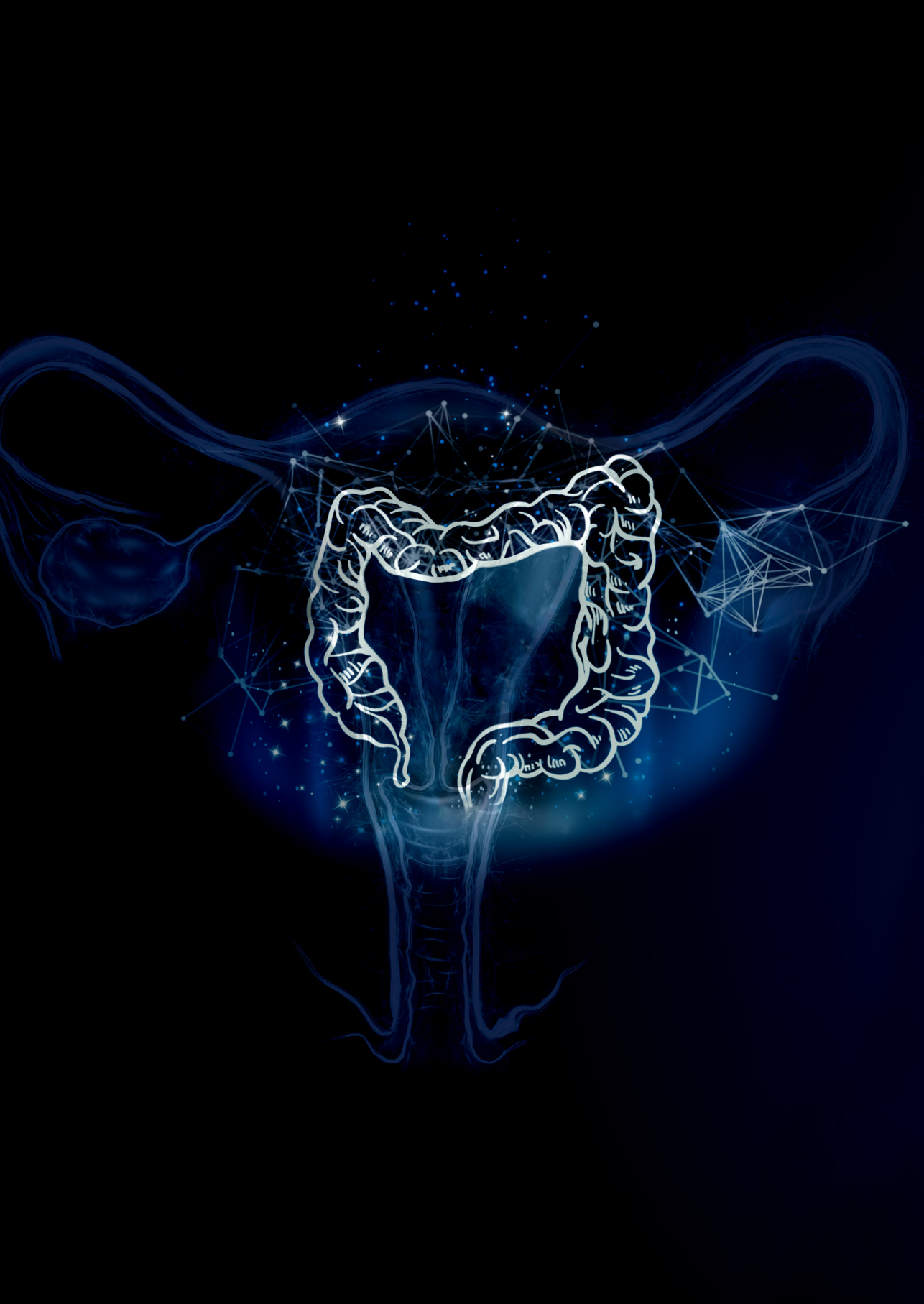
Supplementary table Crude median overall survival and multivariable adjusted hazard ratios for mortality for the total study population and the propensity score matched sample

	Total study population N=5,253		**Propensity score matched sample** N=318	
	Median OS (months)	Adjusted^ HR (95% CI)	Median OS (months)	Adjusted HR (95% CI)
Age				
≤55	15.1	1.00 (reference)	15.5	1.00 (reference)
56-75	13.3	**1.11 (1.03-1.20)**	12.0	1.15 (0.88-1.50)
≥76	10.8	**1.43 (1.30-1.56)**	8.0	1.68 (0.96-2.93)
Period of diagnosis				
2008-2011	13.9	1.00 (reference)	14.5	1.00 (reference)
2012-2015	12.9	1.01 (0.94-1.08)	11.0	0.99 (0.73-1.33)
2016-2018	12.5	0.98 (0.90-1.07)	12.1	0.82 (0.57-1.17)
T stage				
0-3	16.1	1.00 (reference)	14.1	1.00 (reference)
4	13.7	**1.19 (1.11-1.29)**	14.9	1.31 (0.96-1.78)
N stage				
0	14.3	1.00 (reference)	12.7	1.00 (reference)
1	13.5	**1.15 (1.06-1.25)**	12.2	1.05 (0.72-1.54)
2	13.9	**1.19 (1.09-1.31)**	13.6	1.05 (0.73-1.52)
Location primary tumour				
Right-sided colon	11.4	1.00 (reference)	11.1	1.00 (reference)
Left-sided colon	16.4	**0.77 (0.72-0.82)**	16.3	**0.70 (0.53-0.93)**
Colon other/NOS	8.9	**1.18 (1.02-1.37)**	6.8	1.00 (0.60-1.65)
Rectum	15.1	**0.73 (0.67-0.80)**	12.3	0.96 (0.63-1.48)
Morphology				
Adenocarcinoma	13.5	1.00 (reference)	12.8	1.00 (reference)
Mucinous adenocarcinoma	12.7	**0.89 (0.80-0.99)**	11.1	1.09 (0.73-1.63)
Signet ring cell carcinoma	8.5	**1.67 (1.34-2.09)**	7.2	**2.29 (1.32-3.97)**
Differentiation grade				
Well/moderate	16.6	1.00 (reference)	8.9	1.00 (reference)
Poor/undifferentiated	9.5	**1.42 (1.30-1.55)**	9.5	128 (0.89-1.66)
Liver metastasis				
Yes	12.9	**1.35 (1.20-1.51)**	12.1	1.30 (0.93-1.82)
No	14.3	1.00 (reference)	13.3	1.00 (reference)
Peritoneal metastasis				
Yes	11.3	1.07 (0.96-1.20)	11.3	1.30 (0.93-1.81)
No	14.0	1.00 (reference)	14.6	1.00 (reference)
Lung metastasis				
Yes	13.9	**0.88 (0.79-0.98)**	15.2	0.84 (0.58-1.21)
No	12.9	1.00 (reference)	12.0	1.00 (reference)
Distant lymph node metastasis				
Yes	10.8	0.95 (0.84-1.06)	10.3	0.95 (0.67-1.36)
No	13.8	1.00 (reference)	12.9	1.00 (reference)
Number of metastatic sites				
1	14.6	**0.84 (0.75-0.93)**	22.9	0.91 (0.51-1.62)
2	12.7	1.00 (reference)	13.8	1.00 (reference)
3	10.6	**1.21 (1.08-1.36)**	11.5	1.21 (0.87-1.69)
≥4	10.2	1.18 (0.97-1.43)	10.9	1.25 (0.75-2.06)

Supplementary table Continued

	Total study population N=5,253		Propensity score matched sample N=318	
	Median OS (months)	Adjusted^ HR (95% CI)	Median OS (months)	Adjusted HR (95% CI)
Resection of the primary tumour				
Yes	18.5	**0.55 (0.50-0.60)**	18.4	**0.57 (0.39-0.83)**
No	11.0	1.00 (reference)	9.5	1.00 (reference)

T stage unknown, N stage unknown, morphology other/NOS and differentiation grade unknown are included in the analyses but results not shown.
^Adjusted for all variables listed and ovarian metastasis
n.a.: not applicable
Bold characters represent statistically significant P-values.



CHAPTER 6

Biomarker concordance between primary colorectal cancer and ovarian metastases: a Dutch cohort study

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Abstract

Purpose

The genetic characteristics and mismatch repair (MMR) status of the primary tumor and corresponding metastases in colorectal cancer (CRC) are generally considered to be highly concordant. This implies that either the primary or metastatic tumor can be used for testing gene mutation and MMR status. However, whether this is also true for CRC and their ovarian metastases is currently unknown. Ovarian metastases generally show a poorer response to systemic therapy compared to other metastatic sites. Differences in biomarker status between primary CRC and ovarian metastases could possibly explain this difference in therapy response.

Methods

The study cohort was selected from CRC patients treated in two Dutch hospitals. Eligible patients with CRC and ovarian metastasis who were surgically treated between 2011 and 2018 were included. CRC and corresponding ovarian metastatic tissues were paired. Gene mutation status was established using next-generation sequencing, while the MMR status was established using either immunohistochemistry or microsatellite instability analysis.

Results

Matched samples of CRC and ovarian metastasis from 26 patients were available for analysis. A biomarker concordance of 100% was detected.

Conclusion

Complete biomarker concordance was found between MMR proficient CRC and their matching ovarian metastasis. Biomarker testing of MMR proficient CRC tissue appears to be sufficient, and additional testing of metastatic ovarian tissue is not necessary. Differences in therapy response between ovarian metastases and other metastases from CRC are thus unlikely to be caused by differences in the genetic status.

Introduction

Worldwide, colorectal cancer (CRC) ranks third in terms of incidence and second in terms of cancer-related mortality.[1] Stage IV disease is present in about 15-30% of patients at the time of diagnosis, and approximately 20-50% of the remaining patients will develop metachronous metastases.[1] The overall 5-year survival for patients with metastatic CRC is approximately 15%.[2]

Molecular genetic analysis is considered essential for the choice of treatment, especially in metastatic CRC.[1] The main predictive (and prognostic) biomarkers for CRC are mutation status, as well as the status of the DNA mismatch repair system (MMR; either proficient (pMMR) or deficient (dMMR)).[1] In addition, the presence of NRAS and KRAS mutations correlate with resistance to epidermal growth factor receptor (EGFR)-directed treatment, while BRAF mutations are associated with worse prognosis and poor response to combined treatment with EGFR and BRAF inhibitors.[1] Metastatic dMMR CRCs are treated with checkpoint inhibitors such as pembrolizumab as the first line of treatment.[1]

The biomarker status of the primary tumor and corresponding distant metastases in CRC is generally considered to be highly concordant,[3-5] meaning that tissue from either site can be used for testing. The majority of studies to date have focused mainly on pulmonary, hepatic, lymphatic, peritoneal, and/or brain metastases, However, the extent of biomarker concordance between primary CRC and ovarian metastases (OM) is less clear.[4,5] Several studies have reported that, compared to other metastatic sites, OM from CRC are predominantly sanctuary sites due to their decreased sensitivity to systemic chemotherapy, with or without targeted therapy.[6-12] We hypothesized that biomarker discordances between OM and their primary CRC might explain the difference in therapy response.

The aim of this study was, therefore, to investigate concordance for the main predictive biomarkers (gene mutation and MMR status) by analyzing matched samples of primary CRC and their OM.

Materials and methods

Patients and tissue samples

The study cohort was selected from two Dutch hospitals. Pathology reports were reviewed for all patients with CRC who were surgically treated for OM at the Máxima Medical Center Veldhoven/Eindhoven and at the Catharina Cancer Institute Eindhoven from January 2011 to December 2018. Eligible patients had tissues available from both

the primary CRC and their OM, thus allowing comparison of the biomarker status. Tissues that were taken during surgery in other hospitals were retrieved using the national archive of pathology (PALGA) database. In cases where double primary tumors occurred, both tumors were analyzed.

The following demographic and clinicopathologic characteristics were evaluated: age, anatomical subsite of the primary tumor (right colon: caecum, ascending colon, hepatic flexure, and transverse colon; left colon: splenic flexure, descending colon, sigmoid and rectosigmoid), tumor and nodal stage, ovarian metastatic site (left, right or bilateral), occurrence of metastases (synchronous: within 6 months after primary diagnosis; metachronous: after 6 months), time between resection of the primary tumor and metachronous OM (months).

Mutation analysis using next-generation sequencing (NGS)

Formalin-fixed and paraffin-embedded tissue samples of CRC and their OM were collected and stained with hematoxylin eosin. If multiple primary tumors were present, all were included in the study in order to identify which of them was clonally related to the OM. This allowed accurate comparison of the primary CRC and their matching OM at the genetic level.

Tumor regions selected for DNA isolation were identified by a dedicated pathologist and contained a tumor load of at least 20%. A crude proteinase K lysate (proteinase K heat inactivated) was used for mutation analysis with next-generation sequencing (NGS). The AmpliSeq Colon and Lung Cancer Panel v2 and the AmpliSeq for Illumina Library kit (Illumina) were used as described by the manufacturer with minor modifications. Subsequently, sequencing by synthesis was performed using the iSeq 100 system (Illumina). The sensitivity of this assay was at least 5% mutant allele when using a coverage of > 500x, > 10% tumor cell content, and > 1 ng/µl DNA. Only samples and NGS results that met these criteria were used in the current study.

The Colon and Lung Cancer Panel v2 NGS panel used here encompasses 92 fragments from 22 cancer-relevant genes and includes (gene–exon numbers) AKT1-4, ALK-22-23-25, BRAF-11-15, CTNNB1-3, DDR2-5-8-12-13-14-15-17, EGFR-12-18-19-20-21, ERBB2-19-20-21, ERBB4-3-4-6-7-8-9-15-23, FBXW7-4-7-8-9-10, FGFR1-5-8, FGFR2-6-8-11, FGFR3-6-8-13-15-17, KRAS-2-3-4, MAP2K1-2, MET-2-14-16-19, NOTCH1-26-27, NRAS-2-3-4, PIK3CA-10-14-21, PTEN-1-3-6-7-8, SMAD4-3-5-6-8-9-10-11-12, STK11-2-5-6-7-9, TP52-2-4-5-6-7-8-11.

Mutation analysis was performed using SEQNEXT (JSI medical systems) with the same setting used for our diagnostic testing. Detected mutations are reported

according to the following reference sequences: AKT1 ENST00000349310.3, BRAF ENST00000288602.6, DDR2 ENST00000367921.3, ERBB4 ENST00000342788.4, FBXW7 ENST00000263981.5, KRAS ENST00000395977.1, NRAS ENST0000369535.5, PIK3CA ENST00000263967.3, SMAD4 ENST00000342988.3, and TP53 ENST00000420246.2. The pathogenic effect of detected mutations was verified using the Catalogue of Somatic Mutations in Cancer (COSMIC) database.

Mismatch repair (MMR) analysis

The status of the DNA MMR system was identified as either deficient (dMMR) or proficient (pMMR). Analysis of the MMR status was performed using immunohistochemistry (IHC) or microsatellite instability (MSI)-polymerase chain reaction (PCR) analyses.[13] The absence of MMR protein expression as observed by IHC corresponds to a defective DNA MMR system. This leads to MSI at the DNA level that can be detected by MSI-PCR, meaning that either of these two assays can be used to detect dMMR.

MSI-PCR analyses were performed using the following microsatellite markers: BAT-25, BAT-26, Mono-27, NR-21, NR-24 or BAT-25, BAT-26, BAT-40, D17S250, D2S123, and D5S346. When the MSI status was not stated in the pathology report, the sample was tested using IHC for all four MMR proteins: mutL homolog 1 (MLH1), mutS homologs 2 and 6 (MSH2, MSH6), and postmeiotic segregation increased 2 (PMS2). The lack of expression of at least one of these MMR proteins results in dMMR. This usually manifests as the absence of expression of 1) MLH1 and PMS2, 2) MSH2 and MSH6, 3) MSH6 alone, or 4) PMS2 alone.

Data analysis of included variables

Results from matched samples of primary CRC and OM were compared directly. Categorical variables were presented as numbers (frequencies) and percentages, while continuous variables were presented as the median and range. Data were analyzed and presented quantitatively.

Ethics approval

The regional Medical Research Ethics Committee of the Máxima Medical Center approved this study (protocol number: *2021-MMC-022)* and confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply. The study was also approved by the institutional review boards of the Catharina Cancer Institute and the national archive of pathology (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief, PALGA).

Results

Study population

Thirty-four CRC patients were surgically treated for ovarian metastases during or after CRC surgery between January 2011 and December 2018. Eight patients were excluded because of lack of availability of the primary tumor (n=4), direct extension of the primary tumor into the ovary (n=2), no vital residual tumor at the metastatic site (n=1), or pseudomyxoma peritonei (n=1)). Therefore, 26 patients had histologically verified OM and were selected for additional analysis. Sufficient tumor tissue in both the primary CRC and their OM was available in 24 of these 26 patients (insufficient tumor load was found in patient number 9 and 18, respectively). Detailed baseline characteristics of the study cohort are shown in Table 1.

Table 1 Overview of patient and tumor characteristics

Total number of patients	**26**	
Median age at colorectal cancer diagnosis (range)	**54.5**	(29-80)
Tumor location		
Right	**12**	(46%)
Left	**14**	(54%)
Tumor stage at diagnosis		
T3	**10**	(38%)
T4	**16**	(62%)
N stage at diagnosis		
N0	**6**	(23%)
N1	**13**	(50%)
N2	**7**	(27%)
Unilateral ovarian metastases	**16**	(62%)
left/right	*5/11*	
bilateral	**10**	(38%)
Synchronous ovarian metastasis	**8**	(31%)
Metachronous ovarian metastasis	**18**	(69%)
Median time (months) between resection of primary tumor and resection metastasis (range)	**16,5**	(7-106)

Mutation analysis

Clonally related primary tumors and OM were found in 23 of the 24 patients, as described below. Comparison of the mutation status of these clonally related OM with their matching primary CRC (n=23) revealed that all mutations were detected in both tumors (Table 2 and Fig. 1).

Multiple primary tumors were present in one patient (patient 20). TP53 mutation status is commonly used to identify the clonal relation between metastases and their primary carcinoma, as this mutation is an early oncogenic event and the mutations are highly variable.[14] However, for patient 20, the clonal relation between the two primary tumors and the OM remained inconclusive. The TP53 mutations detected in both primary tumors and in the OM were different. Since all three tumors showed dMMR, it is not clear whether these TP53 mutations occurred as an early event (allowing analysis of the clonal relationship between the two tumors), or later during oncogenesis as a result of the dMMR status. The variant allele frequency of these TP53 mutations was comparable to that detected for BRAF mutation in these samples, suggesting they occurred heterozygously as a result of dMMR. The detected BRAF mutation is a hotspot mutation in CRC and is, therefore, not informative for the clonal relationships of the tumors.

DNA mismatch repair status

Full concordance (26/26, 100%) was found for all patients with respect to the MMR status of primary tumors and their matching OM (Table 2). Only two tumors (both from the same patient) out of 27 primary tumors originating from 26 individual patients showed dMMR. Thus, dMMR was detected in 7% (2/27) of the primary tumors and in 4% (1/26) of the CRC patients.

Table 2 Mutation and mismatch repair analysis in primary colorectal tumors and paired ovarian metastases

Sample	MMR status		Mutated gene		Mutation annotation		VAF	VAF	Tumor cell %	
	CRC	OM	CRC	OM	NT change	AA change	CRC	OM	CRC	OM
1	pMMR	pMMR	KRAS	KRAS	c.34G>T	p.Gly12Cys	16%	26%	30%	70%
			TP53	TP53	c.818G>A	p.Arg273His	48%	83%		
2	pMMR	pMMR	SMAD4	SMAD4	c.1544G>C	p.Arg515Thr	42%	21%	60%	70%
3	pMMR	pMMR	BRAF	BRAF	c.1799T>A	p.Val600Glu	35%	28%	40%	50%
			TP53	TP53	c.797G>T	p.Gly266Val	60%	33%		
4	pMMR	pMMR	NRAS	NRAS	c.181C>A	p.Gln61Lys	38%	42%	70%	60%
			TP53	TP53	c.733G>A	p.Gly245Ser	40%	71%		
5	pMMR	pMMR	FBXW7	FBXW7	c.1273C>T	p.Arg425Cys	12%	17%	50%	40%
6	pMMR	pMMR	KRAS	KRAS	c.34G>T	p.Gly12Cys	43%	45%	50%	70%
7	pMMR	pMMR	-	-	-	-	-	-	40%	80%
8	pMMR	pMMR	KRAS	KRAS	c.35G>A	p.Gly12Asp	54%	50%	60%	40%
			PIK3CA	PIK3CA	c.1636C>A	p.Gln546Lys	37%	35%		
			TP53	TP53	c.743G>A	p.Arg248Gln	60%	51%		
9	pMMR	pMMR	*NA*	*NA*					-	-
10	pMMR	pMMR	BRAF	BRAF	c.1799T>A	p.Val600Glu	23%	15%	60%	80%
			ERBB4	ERBB4	c.503G>A	p.Arg168Gln	5%	14%		
			TP53	TP53	c.559+2T>G	splicing	32%	32%		
11	pMMR	pMMR	TP53	TP53	c.*129delT	3' UTR	41%	52%	40%	40%
12	pMMR	pMMR	AKT1	AKT1	c.49G>A	p.Glu17Lys	12%	16%	40%	70%
			BRAF	BRAF	c.1799T>A	p.Val600Glu	12%	13%		
			SMAD4	SMAD4	c.1587dupA	p.His530Thrfs*47	20%	25%		
13	pMMR	pMMR	TP53	TP53	c.814G>T	p.Val272Leu	60%	45%	40%	50%
14	pMMR	pMMR	BRAF	BRAF	c.1799T>A	p.Val600Glu	34%	43%	60%	70%
			SMAD4	SMAD4	c.1052A>T	p.Asp351Val	42%	63%		
			TP53	TP53	c.524G>A	p.Arg175His	57%	74%		
15	pMMR	pMMR	TP53	TP53	c.880G>T	p.Glu294Ter	14%	42%	60%	80%
16	pMMR	pMMR	BRAF	BRAF	c.1799T>A	p.Val600Glu	26%	14%	30%	20%

Table 2 Continued

Sample		MMR status		Mutated gene		Mutation annotation		VAF	VAF	Tumor cell %	
		CRC	OM	CRC	OM	NT change	AA change	CRC	OM	CRC	OM
17		pMMR	pMMR	NRAS	NRAS	c.35G>A	p.Gly12Asp	43%	47%	70%	80%
				PIK3CA	PIK3CA	c.1633G>A	p.Glu545Lys	38%	38%		
18		pMMR	pMMR	*NA*	*NA*					-	-
19		pMMR	pMMR	BRAF	BRAF	c.1799T>A	p.Val600Glu	23%	31%	40%	80%
				TP53	TP53	c.524G>A	p.Arg175His	43%	80%		
20	P1	dMMR[§]		BRAF	-	c.1799T>A	p.Val600Glu	25%		30%	
				TP53[#]	-	c.220G>A	p.Ala74Thr	30%			
				TP53[#]	-	c.322G>A	p.Gly108Ser	26%			
	P2	dMMR		BRAF	-	c.1799T>A	p.Val600Glu	26%		50%	
				DDR2	-	c.779G>A	p.Arg260Gln	25%			
				FBXW7	-	c.1273C>T	p.Arg425Cys	25%			
				TP53	-	c.216delC	p.Val73Trpfs*50	28%			
	OM		dMMR	-	BRAF	c.1799T>A	p.Val600Glu		38%		90%
				-	DDR2	c.779G>A	p.Arg260Gln		32%		
				-	TP53	c.701A>G	p.Tyr234Cys		40%		
21		pMMR	pMMR	KRAS	KRAS	c.37G>T	p.Gly13Cys	33%	40%	60%	60%
				KRAS	KRAS	c.188A>C	p.Glu63Ala	28%	40%		
				TP53	TP53	c.788delA	p.Asn263Ilefs*88	50%	71%		
22		pMMR	pMMR	TP53	TP53	c.524G>A	p.Arg175His	65%	90%	40%	80%
23		pMMR	pMMR	BRAF	BRAF	c.1780G>A	p.Asp594Asn	33%	41%	70%	80%
				KRAS	KRAS	c.57G>C	p.Leu19Phe	27%	55%		
				SMAD4	SMAD4	c.344G>T	p.Cys115Phe	45%	81%		
				TP53	TP53	c.742C>T	p.Arg248Trp	47%	78%		
24		pMMR	pMMR	KRAS	KRAS	c.35G>A	p.Gly12Asp	34%	26%	30%	20%
				TP53	TP53	c.376-1G>A	splicing	38%	32%		
25		pMMR	pMMR	KRAS	KRAS	c.35G>T	p.Gly12Val	36%	22%	60%	50%
				PIK3CA	PIK3CA	c.1634A>G	p.Glu545Gly	20%	14%		

Table 2 Continued

Sample	MMR status		Mutated gene		Mutation annotation		VAF	VAF	Tumor cell %	
	CRC	OM	CRC	OM	NT change	AA change	CRC	OM	CRC	OM
26	pMMR	pMMR	CTNNB1	CTNNB1	c.121A>G	p.Thr41Ala	72%	87%	50%	60%
			KRAS	KRAS	c.35G>T	p.Gly12Val	30%	31%		
			TP53	TP53	c.524G>A	p.Arg175His	47%	69%		

MMR = mismatch repair; pMMR = proficient MMR as tested by MSI PCR analysis (MSI-stable) or immunohistochemical expression of all four MMR proteins (MSH6, PMS2, MLH1 and MSH2); dMMR = deficient MMR as indicated by microsatellite instability (MSI-High) or the absence of MSH6, PMS2, MLH1 and/or MSH2 expression. P = primary tumor (P, P1 or P2); CRC = colorectal cancer; OM = ovarian metastasis; NGS = next generation sequencing; NT change = nucleotide change (DNA); AA change = amino acid change (protein); VAF = variant allele frequency

[#]Both TP53 mutations are located on different alleles

[$]Tested positive also for MLH1 hypermethylation.

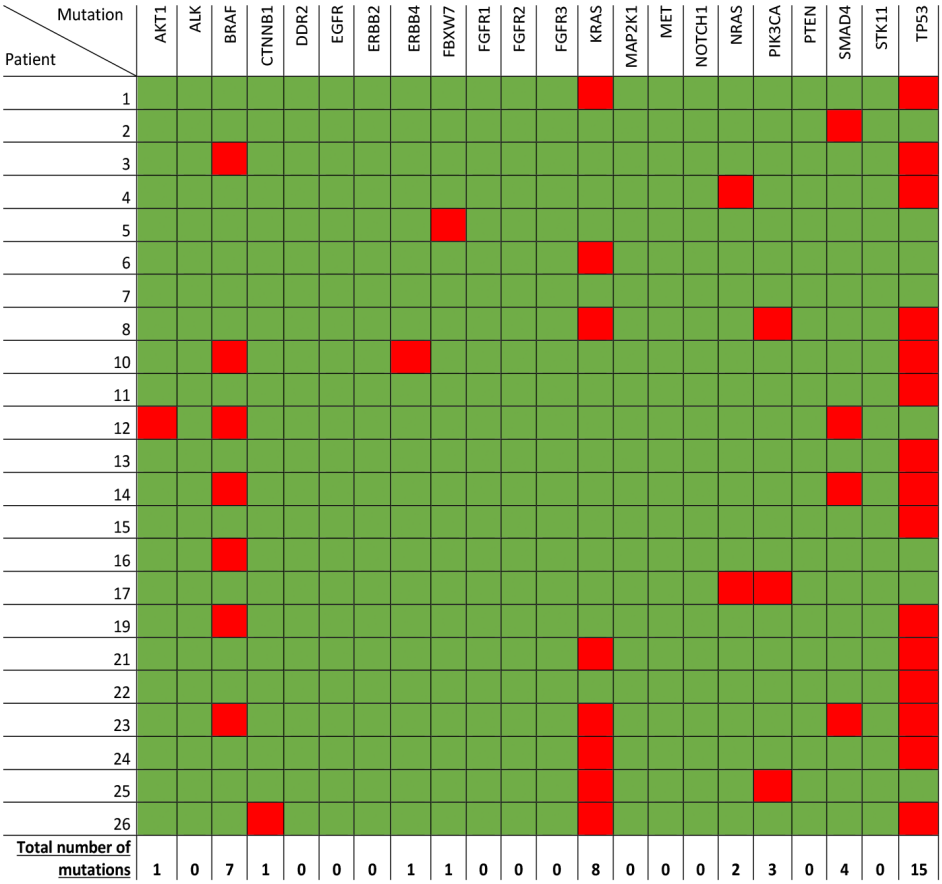

Fig 1 Concordance for the mutation status of 22 genes in primary colorectal cancer and matched clonal related ovarian metastases (n=23). Green color indicates wildtype genes in both primary colorectal tumor and metastasis. Red color indicates the presence of mutated genes in both the primary tumor and metastasis. White color indicates discordant gene mutations. No discordant gene mutations were found.

Discussion

This study found complete concordance in gene mutation status in all 23 primary CRC for which matching (clonal related) OMs were available for NGS. Similarly, full concordance for the MMR status was observed in all 26 sets of paired primary CRC and OM.

The most frequently detected mutations in this cohort of primary CRC occurred in TP53 (67%, 18/27), KRAS (37%, 10/27), BRAF (33%, 9/27), SMAD4 (19%, 5/27), NRAS (15%, 4/27), and PIKC3CA (11%, 3/27). This mostly concurs with previous studies that have reported similar frequencies for TP53 (68%), KRAS (44%), PIK3CA (18%), BRAF

(11%), SMAD4 (10%), and NRAS (5%),[15,16] with the exception of BRAF mutations that were more frequent in the current study cohort.

Previous studies have focused on the biomarker concordance between primary CRC and any metastatic site. The present study is the first and largest to thoroughly explore the concordance of biomarker status in CRC patients with OM. Two reviews have reported a high concordance of more than 90% for the most important biomarkers (e.g., KRAS, NRAS, and BRAF) between primary CRC and the corresponding metastasis from any site.[4,17] Bhullar et al.[4] reported a median concordance for any metastasis of 81% for a combination of different biomarkers, including KRAS, NRAS, BRAF, PIK3A, TP53, PTEN, SMAD4, EGFR, AKT, MET, FBXW7, STK11, FGR3, and NOTCH mutations. Although neither of these two reviews focused on OM, several other studies have evaluated the concordance between primary CRC and corresponding OM. However, these had a small sample size (n=1 to n=26) and mostly included only a subset of the genes analyzed in the current study.[10,18-22] Overlapping genes were KRAS, NRAS, BRAF, FBXW7, PTEN and TP53, and the overall concordance in studies that evaluated at least two patients ranged from 62% to 100%.[10,18,19,21,22] Furthermore, a comparison of the primary tumor and matching OM that included clonal analysis appears to be absent in most of these previous studies.

Table 3 Studies that researched the genetic mutation concordance rates from colorectal tumors and corresponding ovarian metastases

Study	Number of patients with OMs	Reported mutation(s) in relation to OMs	(Overall) concordance rate
Current study	23	Colon and Lung Cancer Panel[a]	100% (23/23)
Park et al.[18] [2019]	3	TP53	100% (3/3)
Mori et al.[10] [2018]	18	KRAS, BRAF	83% (15/18)
Crobach et al.[19] [2016]	26	KRAS, NRAS, BRAF, FBXW7, PTEN, PIK3CA[b]	62% (16/26)
Kim et al.[20] [2015]	1	APC, TP53	0% (0/1)
Brannon et al.[21] [2014]	2	KRAS	100% (2/2)
Kim et al.[22] [2012]	11	KRAS	82% (9/11)

OMs ovarian metastases

[a]Included genes in the Colon and Lung Cancer Panel are: AKT1, ALK, BRAF, CTNNB1, DDR2, EGFR, ERBB2, FBXW7, FGFR1, FGFR2, FGFR3, KRAS, MAP2K1, MET, NOTCH1, NRAS, PIK3CA, PTEN, SMAD4, STK11, and TP53

[b]Reported mutations of the most significant genes in relation to (future) targeted therapy

In our view, the best approach for investigating the concordance between primary tumors and OM is to compare them in matching sets, as used in the current cohort. With the exception of one case (patient 20), all sets contained identical mutations in the primary CRC and their matching OM. Patient 20 was found to be dMMR, which may have caused the differences in mutations observed between the OM and both of the primary

tumors. Therefore, the clonal relationship between the OM and both primary CRC in this case remained inconclusive because it was unclear whether the TP53 mutations occurred as an early event, or later during oncogenesis as a result of the dMMR status.

Matching sets were also investigated by Crobach et al.[19] However, these authors reported a high discordance because none of the sets showed identical mutation profiles between the primary CRC and matching OM. They reported discordance in 10 of the 26 sets that were evaluated for mutations in genes used in targeted therapy, thus resulting in only 62% concordance (Table 3). The concordance was even lower when genes included in the current study were also compared, since only 4/26 (15%) sets showed identical mutations. As these sets showed identical TP53 status, it is likely the investigated sets indeed consisted of a primary CRC with a clonal related OM. dMMR may cause the accumulation of mutations and possibly result in differences between primary CRC and their metastases. However, since dMMR is detected in approximately 15% of primary CRCs,[23] this cannot explain the reported differences. The differences are more likely to be caused by the variant calling parameters, which were set relatively low. Crobach et al.[19] reported this was done in order to allow identification of passenger mutations. However, this may not be helpful for the identification of mutations that are specifically associated with OM, as passenger mutations are not usually oncogenic. Furthermore, if passenger mutations were present in the disseminated tumor cells, they would appear at a higher frequency in OM and be detected even when stricter variant calling parameters were used. As this was not the case with our sets, we concluded that no relevant mutations were missed using our stricter (diagnostic) settings. Apart from being true passenger mutations, variants that are only detected with lower variant calling values could be caused by factors unrelated to the tumor, such as poor quality of the isolated DNA, or formalin-induced artifacts in the DNA. Therefore, poor DNA quality or dMMR could explain why some of the tumors in the study by Crobach et al.[19] showed a relatively high number of discordances between the primary tumor and matching OM.

Since a concordance of 100% was observed in the present study for all of the known predictive biomarkers, the mutation status could be determined from either the primary tumor or the metastatic tissue. This may be especially applicable for gene sequencing in cases where the tumor load is adequate for mutation analysis (at least 20% for the current study). It has been suggested that for cases of persistent and unresponsive OM, their resection may be the only option to prevent large symptomatic disease and to potentially improve survival.[7-9,24,25] Nevertheless, the high concordance found in the current study indicates it is highly unlikely that, for pMMR tumors at least, the apparently lower sensitivity of OM to systemic therapy can be attributed to discordant gene mutations.

The treatment strategy for OM varies from (prophylactic) surgery to systemic therapy

with or without (palliative) ovarian metastasectomy.[18,26-30] Since all female CRC patients can develop OM,[31] and dissemination frequently occurs within the first 2 years after CRC diagnosis,[24,32] choosing the most effective treatment is essential. It could be hypothesized that specific discordant gene mutations, when present, may be an extra argument in support of prophylactic or palliative salpingo-oophorectomy. However, this view is not supported by the current study due to the high observed biomarker concordance between pMMR primary tumors and OM.

To our knowledge, this is the largest study to have investigated the concordance in MMR status between CRC and their matching OM. A previous study compared MMR status in CRC with metastases at different sites, including four OM samples.[33] Since all four patients showed pMMR in the OM but dMMR in their primary CRC, the authors concluded that a rebiopsy might be needed during the course of anti-PD 1 therapy to evaluate MMR status. However, as dMMR is an early event in the development of CRCs with dMMR, it is unlikely that dMMR CRC gives rise to pMMR OMs. The reported differences in MMR status might therefore rather suggest the absence of a clonal relation between both tumors which could be explained by the presence of different primary tumors. Nevertheless, our results show that a rebiopsy is not required in CRC with pMMR which is underlined by the study from Mori et al.[10] who reported pMMR status in all primary tumors and OMs (n=18). Therefore, the concordance in patients with dMMR CRC requires further investigation.

The main limitation of the present study was the possibility of selection bias due to the inclusion of patients with only fully resected OMs. As a result, it provides no insight into biomarker concordance for non-resected and systemically resistant (or unresponsive) OMs. Tissue samples from patients with “unresponsive” and unresected metastases could be especially interesting. However, it is difficult to study a large number of cases from this population because needle aspiration of an ovarian mass carries the potential safety risk of tumor seeding.[34] This type of additional diagnostic test is, therefore, rarely used.

Based on the present results we conclude that the biomarker status in pMMR tumors are highly correlated between primary CRC and metastatic ovarian sites. The poor response of OM to systemic therapy is thus unlikely to be due to biomarker discordance of the main driver genes. Therefore, genetic testing of OM tissue additional to that of the primary tumor does not appear to be warranted for clinical purposes. However, further evaluation of dMMR tumors, or the analysis of other markers not used in routine diagnostic setting (e.g., larger next-generation sequencing panels, and epigenetic markers) could provide additional insights.

Conclusion

In summary, this study found a high concordance in biomarker status between primary pMMR CRC and their matching OM. This agrees with previous systematic reviews that examined concordance at other metastatic sites. We, therefore, conclude that biomarking testing for pMMR CRC can be performed on either the primary tumor or the OM. Further studies are needed to determine if other gene mutations or biologic mechanisms can account for the non-responsiveness of OM to systemic therapy.

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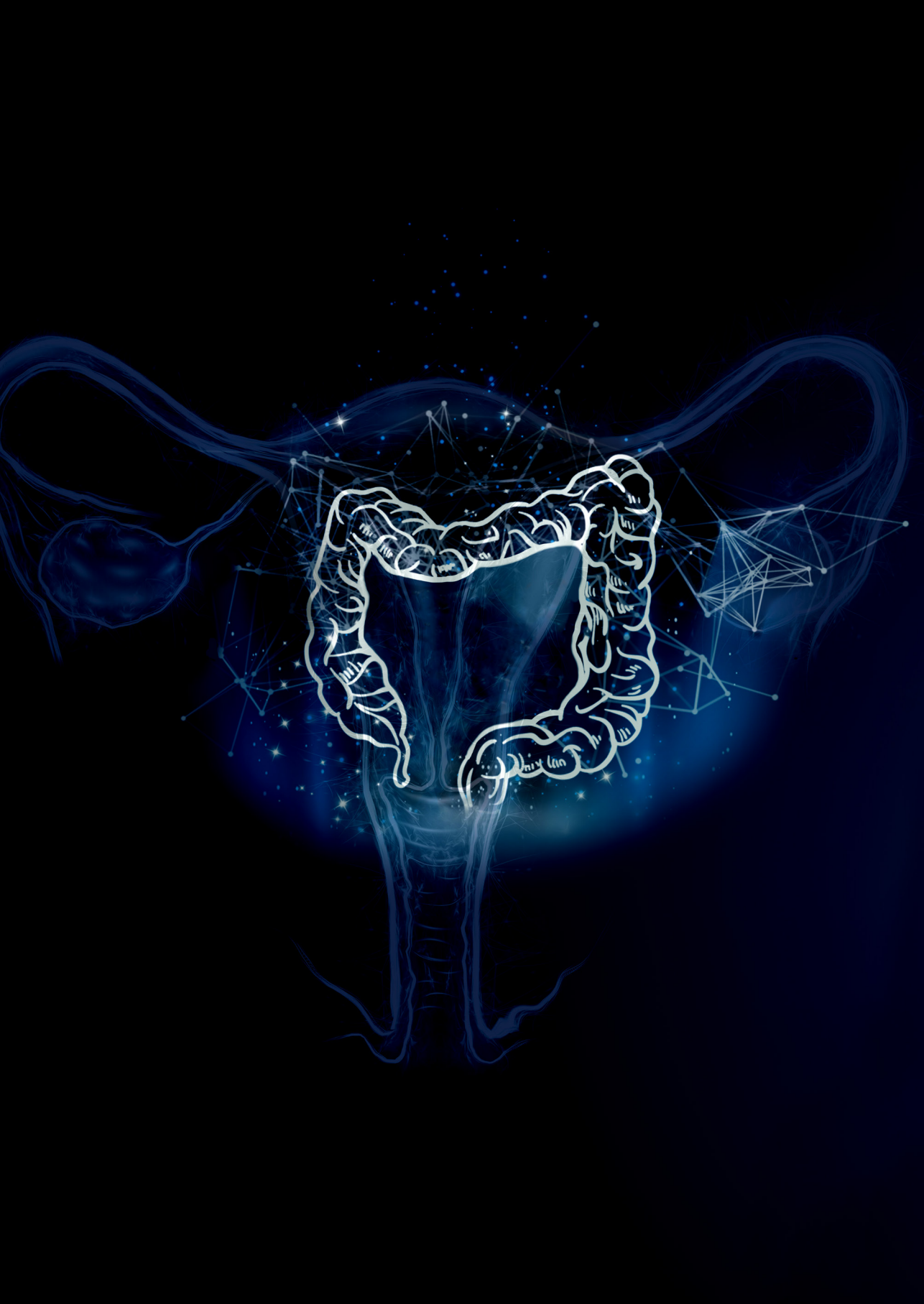

CHAPTER 7

Primary ovarian cancer after colorectal cancer: a Dutch nationwide population-based study

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Abstract

Background and purpose

Women with colorectal cancer (CRC) are not only at risk of developing ovarian metastases, but also of developing a primary ovarian malignancy. Several earlier studies have in fact shown a link between the development of primary ovarian cancer and CRC. The purpose of this study was therefore to determine the risk of developing a primary ovarian cancer in women with prior CRC compared to the general population.

Methods

Data from the Netherlands Cancer Registry were used. All women diagnosed with invasive CRC between 1989-2017 were included. Standardized incidence ratios (SIRs) and absolute excess risks (AERs) per 10,000 person-years were calculated.

Results

During the study period, 410 (0.3%) CRC patients were diagnosed with primary ovarian cancer. Women with CRC had a 20% increased risk of developing ovarian cancer compared to the general population (SIR=1.2, 95% CI: 1.1-1.3). The AER of ovarian cancer was 0.9 per 10,000 person-years. The risk was especially increased within the first year of a CRC diagnosis (SIR=3.3, 95% CI: 2.8-3.8) and in women aged ≤55 years (SIR=2.0, 95% CI: 1.6-2.6).

Conclusion

This study found a slightly increased risk of primary ovarian cancer in women diagnosed with CRC compared to the general population. However, this may be partly attributable to surveillance or detection bias. Nevertheless, our findings could be helpful for patient counseling, as CRC patients do not currently receive information concerning the increased risk of ovarian cancer.

Introduction

Colorectal cancer (CRC) is the second most frequently diagnosed cancer in women, with approximately 800,000 new cases worldwide in 2018.[1] Women with CRC are at risk of developing synchronous or metachronous ovarian metastases, with a mean incidence rate of 3.4%.[2] In addition to the development of ovarian metastases, women diagnosed with CRC are also at risk of developing a primary ovarian malignancy. These so-called secondary primary malignancies or multiple primary malignancies may develop due to genetic predisposition (especially Lynch syndrome, or hereditary non-polyposis colorectal cancer (HNPCC) syndrome), lifestyle factors, environmental exposures, immunological deficiencies or specific treatment modalities for the primary malignancy.[3-6] Several previous studies have reported a link between the development of ovarian cancer and CRC. Compared with the general population, the incidence rate can be up to 3-6 times higher.[3,4] Generally, secondary or multiple primary malignancies, including ovarian cancer, have a negative influence on survival and cancer-specific mortality.[7,8] Prophylactic salpingo-oophorectomy or risk-reducing salpingo-oophorectomy of macroscopically normal ovaries and fallopian tubes during primary surgery for CRC may be a valuable option to prevent ovarian metastases. However, this is still controversial and remains a subject of ongoing debate.[9-11] If the Dutch CRC population were also to show an increased incidence of ovarian cancer, this would confirm the results from several previous studies. Consequently, this could provide an additional argument for prophylactic- or risk-reducing salpingo-oophorectomy since it could potentially reduce the incidence of primary ovarian cancer in this population.

The aim of the present study was therefore to determine the risk of developing primary ovarian cancer in Dutch patients with prior CRC in comparison to the general population using a nationwide population-based dataset.

Methods

Data collection

Data were obtained from the Netherlands Cancer Registry (NCR). This is a population-based registry covering all newly diagnosed malignancies in the Netherlands as notified by the automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnoses. Information on patient and tumor characteristics, diagnosis and treatment is routinely extracted from the medical records by trained NCR administrators. Anatomical site of the tumor is registered according to the International Classification of Disease – Oncology (ICD-O). The tumor-node-metastasis (TNM) classification is used for stage notification of the primary tumor, according to the current edition at

the time of diagnosis. For ovarian cancer, the International Federation of Gynecology and Obstetrics (FIGO) stage is derived from the registered TNM staging system. For CRC, information on microsatellite status has been recorded in the NCR since 2015. However, the microsatellite status was not always determined at the initial diagnosis in clinical practice. Therefore, the NCR information on microsatellite status is incomplete. The patients' vital status was obtained by annual linkage of the NCR to the Municipal Personal Records Database, which records information on the vital status of Dutch inhabitants. Follow-up on vital status was complete up to February 1, 2020.

Study population

All women diagnosed with invasive CRC (ICD-O C18-C20) between 1989 and 2017 were included. Tumors located in the appendix (C18.1) and neuroendocrine tumors were excluded. Location of the colorectal tumor was classified as right-sided colon (caecum, ascending colon, hepatic flexure, transverse colon: C18.0, C18.2-C18.4), left-sided colon (splenic flexure, descending colon, sigmoid: C18.5-C18.7), colon other/not otherwise specified (C18.8-C18.9), and rectum (C19.9-C20.9). Furthermore, all histological subtypes for ovarian cancer, both invasive and borderline tumors, were included. The topographies were ICD-O C56.9, C57.0, C48.1 and C48.2.

Statistical analyses

Standardized incidence ratios (SIR) were computed to determine the risk of developing primary ovarian cancer in CRC patients compared to the general population and by using data from the Netherlands Central Bureau of Statistics (CBS). The number of expected ovarian cancer cases was calculated by matching with incidence rates for the general population according to age and year of diagnosis. SIRs were calculated as the ratio of observed to expected number of cases with primary ovarian cancer. Poisson distribution was used to compute 95% confidence intervals (CI).

The overall excess burden of primary ovarian cancer was measured by calculating the absolute excess risk (AER). This represents the additional incidence among CRC survivors beyond the background incidence in the general population. AER was defined as the difference between the observed and expected number of women with primary ovarian cancer, divided by the number of person-years at risk, and multiplied by 10,000. Person-years at risk represents the cumulative follow-up time of all individual follow-up times from CRC diagnosis until the occurrence of primary ovarian cancer, the end of follow-up (February 1, 2020) or death, whichever occurred first.

SIRs and AERs were calculated for the total study population and for groups classified according to: the number of years after CRC diagnosis (0-1, 2-10, >10 years), age (≤55 and >55 years, with women ≤55 years being considered as premenopausal)[12-15],

anatomical origin of the CRC (right-sided colon, left-sided colon, colon other/not otherwise specified, rectum), TNM stage (I, II, III, IV, unknown), tumor histology (adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, other/not otherwise specified), grade of differentiation (well/moderate, poor/undifferentiated, unknown), microsatellite status (stable, unstable) and radiotherapy treatment for CRC (yes, no). A sensitivity analysis was performed in which all primary ovarian cancer cases diagnosed within 3 months of CRC diagnosis were excluded. Statistical analyses were performed using SAS 9.4 and StataSE 16.1.

Results

The study population consisted of 140,403 women with CRC. Of these, 410 (0.3%) developed primary ovarian cancer during the study period. The mean age at CRC diagnosis was 70.6 years for the total study population and 70.5 years for those who developed primary ovarian cancer. For the overall CRC patient cohort, the majority were older than 55 years (88.3%), had a right-sided colon tumor (38.2%), had TNM-stage II disease (30.4%), and had an adenocarcinoma (82.1%) (Table 1). Off note, only nineteen (4.6%) tumors were described as "borderline" ovarian tumors. The microsatellite status was unknown in 95.2% of patients. Furthermore, most patients (*n*=121,308, 86.4%) did not receive radiotherapy for CRC, and their CRC was most often diagnosed between 2009-2017 (38.5%).

Table 1 Characteristics of women diagnosed with colorectal cancer in the Netherlands, 1989-2017

	n	%
Age at CRC diagnosis		
≤55 years	16,431	11.7
>55 years	123,972	88.3
Anatomical site		
Right-sided colon	53,633	38.2
Left-sided colon	42,734	30.4
Colon, other/NOS	2,970	2.1
Rectum	41,066	29.3
TNM stage		
I	25,247	18.0
II	42,695	30.4
III	37,704	26.8
IV	27,242	19.4
Unknown	7,515	5.4
Histology		
Adenocarcinoma	115,279	82.1
Mucinous adenocarcinoma	18,430	13.2
Signet ring cell carcinoma	1,467	1.0
Other/NOS	5,227	3.7

Table 1 Continued

	n	%
Differentiation grade		
Well/moderate	89,133	63.5
Poor/undifferentiated	21,218	15.1
Unknown	30,052	21.4
Microsatellite status[a]		
Stable	5,557	4.0
Unstable	1,144	0.8
Unknown	133,702	95.2
Radiotherapy for CRC		
No	121,308	86.4
Yes	19,095	13.6
Year of CRC diagnosis		
1989-1998	38,567	27.5
1999-2008	47,798	34.0
2009-2017	54,038	38.5

CRC colorectal cancer, *NOS* not otherwise specified, *TNM* tumor node metastasis
[a]Only available for a small percentage of the study population

Of the 410 CRC patients who developed primary ovarian cancer, 370 (90.2%) were diagnosed with non-epithelial ovarian carcinoma (C56.9), 29 (7.1%) with extra-ovarian carcinoma (C48.1-2), and 11 (2.7%) with tuba carcinoma or non-epithelial tuba tumors (C57.0) (Table 2). The most frequently diagnosed FIGO stage was stage III (35.1%) and tumor verification occurred by histological confirmation in 363 patients (88.6%). Ovarian cancer was diagnosed within 0-1 years after CRC in 42.0% (n=172) of patients, within 2-10 years in 41.2% (n=169) of patients, and after 10 years in 16.8% (n=69) of patients.

Overall, women with CRC had a 20% increased risk of developing ovarian cancer compared to the general population (SIR=1.2, 95% CI: 1.1-1.3) (Table 3). The excess number of ovarian cancer cases was 0.9 per 10,000 person-years. The risk was highest in the first year after CRC diagnosis, lower during years 2-10, and then not detectable more than 10 years after CRC diagnosis. Furthermore, the risk was higher in patients aged ≤55 years and in those with primary tumors located in the colon or that were TNM stage III-IV, mucinous adenocarcinomas, well or moderately differentiated, microsatellite stable, or in patients who were not treated with radiotherapy.

Sensitivity analysis showed that CRC patients had a 20% lower risk of developing ovarian cancer compared to the general population if ovarian cancer cases diagnosed within 3 months after the CRC diagnosis were excluded (SIR = 0.8, 95% CI: 0.7-0.9, AER -0.9). Moreover, the risk was no longer higher in the first year after CRC diagnosis but was actually lower if the ovarian cancer cases diagnosed within 3 months of the CRC diagnosis were excluded (SIR = 0.7, 95% CI: 0.5-1.0, AER -1.3).

Table 2 Characteristics of women diagnosed with second primary ovarian cancer after colorectal cancer in the Netherlands, 1989-2017

	n	%
Topography		
(Non-)epithelial ovarian carcinoma (C56.9)	370	90.2
Extra-ovarian carcinoma (C48.1-2)	29	7.1
Tuba carcinoma or non-epithelial tuba tumors (C57.0)	11	2.7
FIGO stage		
I	103	25.1
II	45	11.0
III	144	35.1
IV	46	11.2
Unknown	72	17.6
Type of verification		
Histological confirmation	363	88.6
Cytological confirmation	28	6.8
Other[a]	19	4.6
Years after CRC diagnosis		
0-1	172	42.0
2-10	169	41.2
>10	69	16.8

FIGO International Federation of Gynecology and Obstetrics, *CRC* colorectal cancer
[a]Biochemical/immunological lab research or clinical-diagnostic research

Table 3 Standardized incidence ratios (SIRs) and absolute excess risks (AERs) per 10,000 person-years for primary ovarian cancer in women diagnosed with colorectal cancer in the Netherlands from 1989-2017

	Observed (*n*)	Expected (*n*)	SIR	95% CI	AER
Overall	410	339	**1.2**	1.1-1.3	0.9
Years after CRC diagnosis					
0-1	172	52	**3.3**	2.8-3.8	9.9
2-10	169	216	**0.8**	0.7-0.9	-1.0
>10	69	71	1.0	0.8-1.2	-0.1
Age at CRC diagnosis					
≤55 years	70	34	**2.0**	1.6-2.6	2.8
>55 years	340	305	1.1	1.0-2.0	0.6
Anatomical location					
Colon[a]	307	234	**1.3**	1.2-1.5	1.4
Rectum	103	106	1.0	0.8-1.2	-0.1
TNM stage					
I	86	92	0.9	0.7-1.2	-0.3
II	158	135	1.2	1.0-1.4	0.8
III	117	89	**1.3**	1.1-1.6	1.4
IV	32	15	**2.1**	1.5-3.0	4.3
Unknown	17	8	**2.3**	1.3-3.6	5.3
Histology					
Adenocarcinoma	329	286	1.2	1.0-1.3	0.7
Mucinous adenocarcinoma	71	49	**1.5**	1.1-1.8	2.1
Signet ring cell carcinoma	3	2	1.5	0.3-4.4	2.2
Other/NOS	7	3	2.1	0.9-4.4	4.4

Table 3 Continued

	Observed (*n*)	Expected (*n*)	SIR	95% CI	AER
Differentiation grade					
Well/moderate	298	243	**1.2**	1.1-1.4	1.0
Poor/undifferentiated	48	44	1.1	0.8-1.5	0.5
Unknown	64	64	1.2	0.9-1.6	1.0
Microsatellite status[b]					
Stable	6	2	**2.9**	1.1-6.3	6.2
Unstable	1	1	1.8	0.0-9.9	3.2
Radiotherapy for CRC					
No	375	293	**1.3**	1.2-1.4	1.3
Yes	35	47	0.8	0.5-1.0	-1.1
Period of diagnosis					
1989-1997	186	125	**1.5**	1.3-6.8	2.3
1998-2008	157	147	1.1	0.9-4.9	0.3
2009-2017	67	68	1.0	0.8-4.5	0.0

SIR standardized incidence rate, *CI* confidence interval, *AER* absolute excess risk, *CRC* colorectal cancer, *TNM* tumor node metastasis, *NOS* not otherwise specified

[a]Combination of right-sided colon / left-sided colon / colon, other/NOS

[b]Only available for a small part of the study population

Discussion

During the 28-year study period, 0.3% of women diagnosed with CRC developed an ovarian malignancy. This represents a 20% increase compared with the general population.

A remarkably elevated SIR of 3.3 within the first year after CRC diagnosis has been found. This result may be attributed to adnexal masses found during surgery for CRC, to surveillance bias due to imaging modalities used during the follow-up period, or because of increased attention when abdominal symptoms occur. Of note, the present study did not find a significantly increased risk of ovarian cancer if patients who developed this disease within 3 months of their CRC diagnosis were excluded. Nevertheless, there was a significant increase when the first year was combined with all other periods. This result concurs with the large population-based study by Hemminki et al.[16], who found a high SIR of 7.4 within the first year after CRC. Other explanations could be the presence of detection bias, and incorrect classification of the ovarian tumors as being primary ovarian malignancies.

Young women (≤55 years of age) are the most often affected, with a significantly elevated SIR of 2.0. Other studies have also reported a higher incidence of ovarian cancer in the young CRC population.[3,17,18] This may be due to a lower threshold for performing additional imaging, or to immediate referral to a gynecologist when specific or vague symptoms appear in younger CRC patients. An additional explanation could

be that such patients live longer and therefore have a longer follow-up period. This appears to be supported by the median follow-up time of 6.4 years for women aged ≤55 years compared to 4.0 years for women aged >55 years. Our results also agree with the findings of several previous reports. Evans et al.[17] reported an increased incidence of ovarian cancer in women aged <65 years (SIR of 2.6) in a large cohort of cancer patients from South East England. Two similar large, population-based cohort studies from Taiwan found a SIR of 2.0 for ovarian cancer in all women diagnosed with CRC,[18] and a SIR of 4.5 in those aged <50 years.[19]

Several population-based studies of CRC patients have shown the SIR for any second primary malignancy ranged from 1.02 to 4.03 compared to the general population.[20-23] However, the development of ovarian cancer is especially relevant clinically because women with prior CRC are also at risk of developing colorectal ovarian metastases. To reduce the risk of developing ovarian metastases, prophylactic resection of macroscopically normal ovaries/fallopian tubes during surgery for CRC may be considered, but is still the subject of ongoing debate.[9-11] An additional argument in favor of implementing risk-reducing salpingo-oophorectomy in this specific CRC group is that it reduces the risk of developing ovarian cancer. This is especially relevant when the CRC population has an increased risk of primary ovarian cancer within the first three months post-surgery. Alternatively, pre- and postoperative screening for the detection of ovarian cancer could be performed as part of a surveillance program, although the efficacy of surveillance in high-risk patients seems questionable.[24]

A known risk factor for the development of double primary malignancies is a high level of tumor microsatellite instability (MSI-H).[25] MSI-H is the result of a deficient mismatch repair (dMMR) system.[26] Mismatch repair is the predominant mechanism used by cells use to repair insertions, deletions and mis-incorporations that are introduced into DNA during the process of replication.[26] In a minority of CRC patients the dMMR is due to Lynch syndrome, while in the remaining patients it is due to somatic mutations in the MMR genes. Unfortunately, the number of patients with Lynch syndrome in the current study population was unknown, and MSI status was only determined for a small percentage of cases. Approximately 3% of the CRC population suffers from Lynch syndrome and the average risk of developing ovarian cancer in patients with Lynch syndrome is 8% compared with 0.7% in the general population.[27,28] MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), Muts homolog 6 (MSH6) and postmeiotic segregation 2 (PMS2) are the MMR genes associated with Lynch syndrome. Although PMS2 mutations are the most prevalent in the overall population, mutations in MLH1 and MSH2 are the most frequent in the CRC population.[29] The lifetime risk of ovarian cancer is highest in the MSH2 group and could be up to 38%.[29] Therefore, the 20% increased risk for ovarian cancer observed in the present study could have been due

to a selected population in which Lynch syndrome was more prevalent. In a separate analysis (not presented) we therefore excluded the hypothetically expected number of patients suffering from CRC and ovarian cancer due to Lynch syndrome (0.03 x 0.4 x 410) and still found a significantly higher SIR of 1.2 [95% CI: 1.1-1.3]. An association could still be attributed to Lynch-like syndrome or to "familial colorectal cancer type X". Buksch et al.[30] found no association between either of these conditions and ovarian cancer. We therefore conclude that our finding with ovarian cancer in CRC patients is unlikely to be due to the presence of Lynch syndrome in this population.

Patients with stage IV CRC appeared to have the highest SIR (2.1) for ovarian cancer. This is somewhat surprising because no common pathway for stage IV CRC and ovarian cancer is known. Unfortunately, the diagnostic accuracy cannot be verified and hence synchronous ovarian metastases, which develop in about 1% of CRC patients,[31,32] could have been misdiagnosed as primary ovarian malignancies. For the present data, it is unknown whether differences in the diagnostic performance of immunohistochemistry or genetic mutations exist between colorectal tumors and ovarian malignancies. Our results could therefore show a detection bias as these primary ovarian tumors could actually be ovarian metastases. Nevertheless, these patients would then be even more interesting in terms of their oncologic outcome, since the prognosis of patients with ovarian metastases originating from gastro-intestinal tumors is generally considered worse than that of primary ovarian tumors.[33,34]

Although the precise mechanism or relationship is unclear, colon cancer appears to be associated with a higher absolute excess risk for all primary second malignancies compared to rectal or rectosigmoid tumors.[21] Lee et al.[19] reported a SIR of 2.8 for colon cancer and ovarian cancer, compared with just 0.9 for rectal cancer and ovarian cancer. The present study also showed a significantly increased SIR (1.3, 95% CI: 1.2-1.5) and elevated AER (1.4) for colon cancer compared to a non-significant SIR (1.0, 95% CI 0.8-1.2) and negative AER (-0.1) for rectal cancer. Different biological characteristics have been found between colon and rectal cancers, but no direct relationship with the occurrence of ovarian cancer has been described to date.[35] However, radiotherapy is more frequently administered in patients with rectal tumors. The increased risk might be related to radiotherapy since almost all (33 out of 35) patients who received radiotherapy had rectosigmoid or rectal cancer. The SIR for patients who received radiotherapy showed a trend towards a protective effect. Moreover, Lehrer et al.[36] concluded that beam radiation to the rectum and rectosigmoid that also reached the ovaries reduced the subsequent risk of ovarian cancer by 44%. It has been hypothesized this effect could occur because of a potentially favorable biological response to low-dose irradiation.[36,37]

The strength of the present nationwide study is the inclusion of a large number of

CRC patients. Furthermore, almost all ovarian malignancies were histologically or cytologically verified, resulting in a high diagnostic accuracy for the presence of malignant cells.

Our study also has some weaknesses. Firstly, the number of patients with Lynch syndrome was unknown and therefore it is unclear whether the increased incidence of ovarian malignancy was due to this genetic condition. However, it could be anticipated that any possible effect would be quite small given the low incidence of Lynch syndrome. Secondly, non-operated patients for primary ovarian cancer could be missed. It could be expected, however, that the calculated SIR would increase if such patients were included in the present analysis. This is because a newly discovered ovarian mass after CRC could be misdiagnosed as an incurable ovarian metastasis, resulting in palliative non-surgical treatment. Finally, as previously mentioned there was also the possibility for detection bias in our study.

The mean incidence rate of ovarian cancer in the general Dutch population is 4.5 per 10,000 person-years. The observed AER of 0.9 in the CRC population represents an incidence rate of 5.4 per 10,000 person-years. When this number is translated to a 10-year follow-up period for 1,000 patients diagnosed with CRC, approximately one additional case of ovarian cancer will be found compared to the general population. Although this number seems small, risk-reducing salpingo-oophorectomy during CRC is a potentially simple way to reduce the detrimental effect of a subsequent primary ovarian malignancy. Risk-reducing salpingo-oophorectomy would also abolish the need for second surgeries for primary ovarian cancers and for any ovarian metastases that may develop. Women diagnosed with CRC should therefore be informed of this procedure because risk reduction is easily achieved. The potential side effects of risk-reducing salpingo-oophorectomy should of course be considered, but this mostly affects premenopausal women as it induces a surgically induced menopause. Instead of a risk-reducing salpingo-ooporectomy, a thorough inspection of the ovaries during CRC surgery is, to our opinion, strongly advised.

Conclusion

This population-based study found a 20% increase in the risk for developing primary ovarian malignancy in women diagnosed with CRC as compared to the general population. The possibility of surveillance and detection bias cannot be ruled out, however. Nevertheless, these findings will be helpful for improving patient counseling, as CRC patients do not currently receive information on this increased risk. Future studies should focus on whether specific genetic predispositions, such as Lynch syndrome,

can account for the higher incidence of ovarian cancer after CRC, and whether risk-reducing salpingo-oophorectomy is effective in reducing the development of ovarian malignancies in CRC patients.

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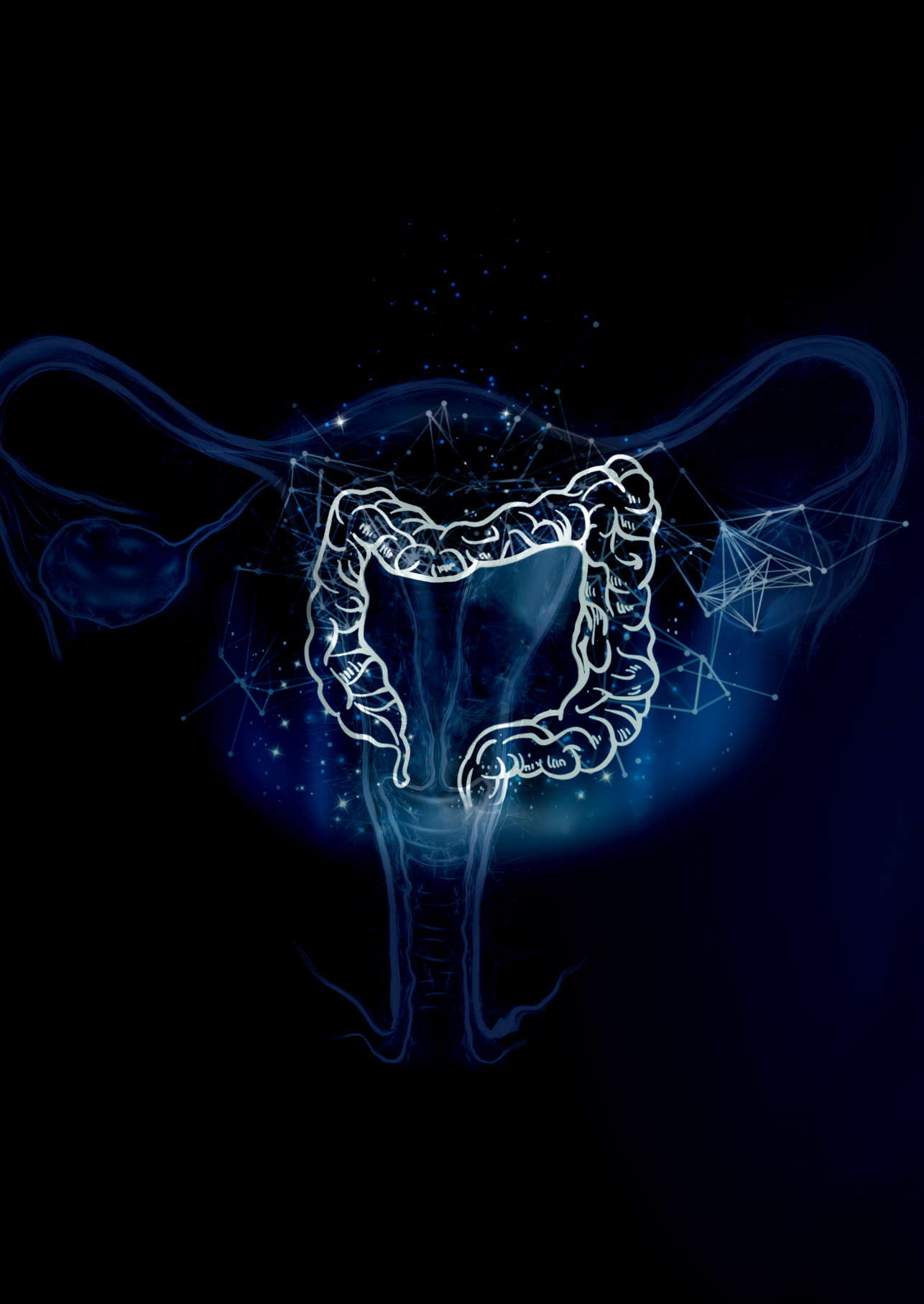

CHAPTER 8

Salpingo-oophorectomy to prevent ovarian metastases in women suffering from colorectal cancer: open for discussion[1]

[1]*Translated publication, original article was written in Dutch*

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Abstract

Prophylactic salpingo-oophorectomy (PSO) is a potential treatment option to limit ovarian metastasis (OM) in patients with colorectal cancer. Arguments in favor of PSO, are: 1. A better prognosis could potentially be achieved for the colorectal cancer patient; 2. PSO in the colorectal cancer patient is mentioned in various treatment guidelines; 3. Other disciplines, such as gynecology and urology, offer or routinely perform PSO during abdominal surgery; 4. Systemic therapy has rather limited effects on OM since ovaries are considered 'sanctuary sites'; 5. In postmenopausal women, the negative side effects of PSO are predicted to be very low; 6. PSO for prevention of OM is viewed as a cost-effective oncological procedure; 7. Reducing the risk of primary ovarian cancer could be viewed as a positive side effect; and 8. Treatment by PSO is part of shared decision making.

In two Dutch hospitals, Máxima Medical Center (Veldhoven/Eindhoven) and the Catharina Hospital (Eindhoven), prophylactic salpingo-oophorectomy (PSO) is offered to colorectal cancer (CRC) patients, and other hospitals are invited to follow this strategy. However, what are the arguments in favor of performing PSO on CRC patients?

Case study

A 57-year-old woman presented for surgery with an obstructing colorectal tumor that necessitated an acute sigmoidal resection. This patient appeared to have both synchronic lymphatic- and hepatogenic metastases resulting in a final tumor stage of pT4N1M1. Following the operation, a cure for this malignancy seemed achievable and systemic chemotherapy was administered resulting in decrease of the hepatogenic metastases. Following this, the following procedures were performed: 1. metastasectomy of the left hepatic segments 3 and 4b; 2. portal vein embolization; and 3. right hemihepatectomy. Several months later, this patient suffered from constipation and bloating, and upon physical examination a palpable mass was found. Computed tomography (CT) of the thorax-abdomen revealed a multilocular mass in the left side of her lesser pelvis. This mass had the appearance of an ovarian malignancy (Fig. 1). Subsequently, an abdominal hysterectomy and bilateral salpingo-oophorectomy was carried out on this patient. During the surgery, no evidence for peritoneal dissemination was observed. Histopathologic analysis of the ovaries revealed a metastasis from colorectal origin located in the left ovary.

Unanswered questions

Several questions are raised by this case. For example, what would have happened if PSO was performed during the primary surgery? Although the hepatic metastases responded well to the chemotherapy, the ovarian metastasis (OM) – which was perhaps already present during the primary surgery as a micrometastasis – continued to grow. As subsequent diagnosis and treatment of this patient was detrimental, these circumstances prompt the question if this outcome could have been prevented.

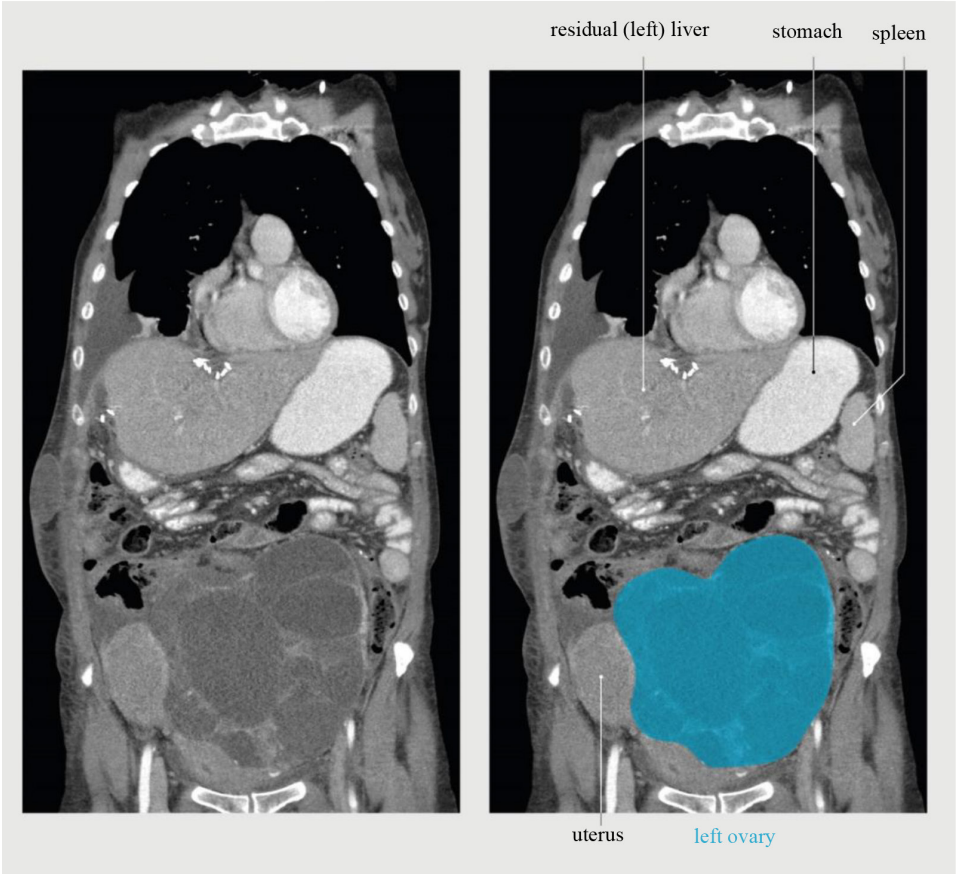

Fig. 1 Ovarian malignancy. Coronal view of the CT scan of the thorax and abdomen of a 57-year-old woman treated for lymphatic- and hepatic-metastasized sigmoid carcinoma, stage pT4N1M1. A multilocular mass is observed in the left side of the lesser pelvis, and this mass has the appearance of an ovarian malignancy

Background and epidemiology

In recent years, colorectal cancer (CRC) has been diagnosed in approximately 14,000 persons each year, with a male-to-female ratio of 4 to 3 (Table 1). Women with CRC may present with ovarian metastases (OMs) at diagnosis (synchronous), or such lesions may be diagnosed during follow-up period (metachronous). The mean incidence of OMs in CRC patients is 3.4% (range: 0-9.7%) and even higher incidence rates, up to 20%, are found in younger or premenopausal CRC patients.[1,2] The prognosis of CRC patients with OMs is dismal as these patients exhibit a 5-year overall survival of 25-27%.[3,4] When compared to CRC patients with hepatic metastases, who are treated with curative intent and in which liver surgery is included in the treatment plan, a 5-year overall

survival of 40-50% has been reported.[5] This supports the idea that CRC patients could potentially benefit from PSO during initial CRC surgery.

Table 1 Epidemiological background of women that potentially could benefit from prophylactic salpingo-oophorectomy

number of Dutch CRC patients between 2017-2019*	41,178
male-to-female ratio*	4:3
female CRC patients ≥ 60 years of age‡; %	81.6
mean incidence of ovarian metastases in female CRC patients;[1] % (range)	3.4 (0-9.7)
proportion of CRC ovarian metastases for female CRC patients aged ≤ 55 years;[6] %	5
conceivable number of Dutch CRC patients with ovarian metastases per year	> 200
5-year overall survival of CRC patients with ovarian metastases;[3,4] %	25-27
response of extra-ovarian CRC metastases to systemic therapy;[4] %	42-58
response of CRC ovarian metastases to systemic therapy;[4] %	5
lifetime risk of primary ovarian cancer in the general population;[7] %	1.3

CRC = colorectal cancer

* *Based on data from the Netherlands Caner Registry between 2017-2019; data from 2018 and 2019 were partially complete.*

‡ *Based on data from the Netherlands Caner Registry 1989-2019; data from 2018 and 2019 were partially complete*

Guidelines and differences in clinical practice

In daily clinical practice, differences exist in the discussion of prophylactic surgery in various cancer patients to prevent OMs. These differences are largely based on historical approaches, ideas, and assumptions, and are less frequently based on validated scientific research.

Until 2019, PSO was not mentioned in the Dutch treatment guideline for CRC, which is in contrast with the American CRC guideline.[8] The American guideline proposes consideration of prophylactic oophorectomy in postmenopausal patients. Moreover, this guideline also mentions that prophylactic oophorectomy might be considered in premenopausal patients who have already completed their families. The most recent Dutch guideline for CRC mentioned that physicians could consider discussing PSO in patients at risk for ovarian cancer, for example patients with hereditary predisposition for BRCA- or MSH-2 mutations, as well as in postmenopausal patients.[9]

It bears notice that bilateral salpingo-oophorectomies are routinely performed by urologists in patients with muscle-invasive bladder cancer to reduce the risk of OMs.[10,11] However, following this operation, OMs are found in less than 1% of all patients of whom all reproductive organs are resected 'en bloc'.[10] The ovaries are, for similar reasons, resected by gynecologists in patients undergoing surgical treatment for endometrial cancer.[12] In these patients, post-surgical histopathology revealed that, at most, 5-6% had OMs.[12]

Biological background

The ovaries are generally considered a sanctuary site for ovarian (micro)metastases from primary CRC because they frequently are unresponsive to systemic treatment. Specifically, according to Kim et al.[4], the response rate from systemic therapy in CRC patients is 5% for OM compared to 42-58% for extra-ovarian sites. Additionally, ovarian stromal cells are essential for the progression of many cancers, including metastatic lesions.[13] High angiogenetic capability, the presence of growth factors in ovarian tissue, as well as the large production of cyclooxygenases and prostaglandins which favor tumor cell growth, all offer additional support for a potential preference of colorectal tumor cells to metastasize to the favorable tissue environment of the ovaries.[14] This biological background could also contribute to the unresponsiveness of OMs following systemic therapy.

The consequences of prophylactic salpingo-oophorectomy

According to the Netherlands Cancer Registry (NCR), 18.4% of female CRC patients are 0-59 years of age. Thus, over 80% are above 60 years of age and, presumably, are postmenopausal. We fully expect that the benefits of a PSO outweigh the disadvantages in postmenopausal patients. Potential benefits include the treatment of ovarian (micro) metastases and the prevention of the development of metachronous metastases. Disadvantages include increased length of surgery and accompanying additional risk of surgical complications, including increased intraoperative blood loss and/or injury to the ureter. Such complications, fortunately, rarely occur during prophylactic surgery.[15,16] Further, since the ovaries in postmenopausal patients continue to produce androgens, removal of these organs could affect hormone balance.[17] Decreased satisfaction with sexual functioning could occur when this source of androgens has been extinguished.[18] Of note, it is known that androgens promote the development of polyps and carcinogenesis and decreased androgen could, therefore, potentially reduce the development of additional colorectal tumors.[19,20] Higher androgen levels in men might be the underlying reason for the increased prevalence of CRC in men compared to women.

Beyond the pros and cons discussed above, premenopausal patients have additional disadvantages related to PSO. One such disadvantage is that these patients will need to navigate the results of surgical induced menopause. Known short-term effects of surgically induced menopause are sexual dysfunction, which may also be a long-term complication, infertility, hot flashes, night sweats, and sleeping problems.[21,22] Long-term effects include vaginal problems because of vaginal atrophy, osteopenia or osteoporosis, dementia, and cardiovascular disease.[21,22] A previous study concluded that patients who underwent

prophylactic bilateral oophorectomy below the age of 45 showed an increased mortality rate when compared to older patients.[23] However, it is expected that many of these negative consequences may be overcome by the use of hormone replacement therapy.[21]

Treatment cost-effectiveness

PSO could represent a cost-effective oncological procedure. In support of this view is the price for one extra year of good health, which is generally expressed as quality-adjusted life year (QALY). According to the report of the Dutch Health Council, a price of €20,000 for one QALY is considered cost-effective; and €80,000 per treatment is the absolute maximum price for one QALY.[24] The estimated cost for one QALY in CRC patients receiving adjuvant chemotherapy, is expected to lie between €30,000 and €50,000.

Next, when one calculates the potential price for one QALY in postmenopausal CRC patients in relation to PSO, these costs are expected to be low. The itemized expected costs for this population are: 1. The operation duration will be extended by 15-20 minutes (one hour of surgery equals €900-1000); 2. Additional costs for histopathology (€200-300) and; 3. incidentally, gynecologic consultations and/or hormone replacement therapy for the consequences of an early-induced menopause (the latter for premenopausal women only). We presume that 50 patients will need a PSO in order to treat or prevent one ovarian (micro)metastases, resulting in ten additional years of good health. We also calculate that the estimated cost per QALY, based on this presumed situation, is expected to be approximately €2500. The cost per QALY would reduce in case additional years in good health are increased by this procedure. This would be also the case when ovarian micrometastases are more frequently found than expected or when PSO would result in a significant reduction of primary ovarian cancer. The cost per QALY would, almost certainly, increase when premenopausal women are included in this calculation.

Lynch syndrome and additional benefit

Lynch syndrome, which is also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common cause of inherited CRC.[25,26] Lynch syndrome accounts for approximately 3 percent of all newly diagnosed CRC cases.[25,26] Lynch syndrome is an autosomal dominant disorder that is caused by mutations in various mismatch repair (MMR) genes.[25] In women, it is known that this genetic disorder is also associated with endometrial- and ovarian cancer.[27] Moreover, beyond the risk of ovarian cancer in patients associated with Lynch syndrome, several studies showed an extra increased risk

for ovarian cancer in CRC patients.[28,29]

An additional benefit of PSO is the option for ovarian cancer risk reduction. A Dutch gynecologic study, the 'Stop Ovarian Cancer trial' (STOPOVCA-trial), investigates the effect of an opportunistic salpingectomy to reduce the number of new ovarian cancer cases. The lifetime risk to develop ovarian cancer is approximately 1 out of 80 women.[7] The 5-year overall survival of these patients is approximately 50%,[7] because they generally initially present with an advanced cancer stage.

Based on the above, it is reasonable to presume that the use of PSO, especially in CRC patients, could lower the incidence of ovarian cancer, although it is expected that this additional benefit would be small.

CRC patient counseling

At present, the treatment of choice for CRC is generally decided by patients and their treating physicians through the process of shared decision making. All women with CRC should, in our view, be informed of the potential benefits (see Table 2 for arguments in favor of PSO) and disadvantages of PSO especially as the risk for complications is expected to be small.

Table 2 Arguments to offer prophylactic salpingo-oophorectomy to colorectal patients

1.	a better prognosis could potentially be achieved for the colorectal cancer patient
2.	other disciplines, such as gynecology and urology, offer or routinely perform prophylactic salpingo-oophorectomy during abdominal surgery
3.	prophylactic salpingo-oophorectomy in the colorectal cancer patient is mentioned in various treatment guidelines
4.	systemic therapy has rather limited effects on ovarian metastases, since ovaries are considered 'sanctuary sites'
5.	in postmenopausal women, the negative side effects of prophylactic sapingo-oophorectomy are predicted to be very low
6.	prophylactic salpingo-oophorectomy for prevention of an ovarian metastasis is viewed as a cost-effective oncological procedure
7.	reducing the risk of the occurrence of primary ovarian cancer could be viewed as a positive side effect
8.	treatment by PSO is part of shared decision making

What's next?

The prognosis of a small, but very relevant, number of female CRC patients could potentially benefit from PSO. Moreover, given rising healthcare costs in general, this could represent a cost-effective procedure. Two Dutch hospitals, Máxima Medical Center (Veldhoven/Eindhoven) and the Catharina Hospital (Eindhoven), currently offer PSO to postmenopausal CRC patients within the context of a clinical study. Information on the pros and cons of this procedure is provided during surgical consultation and this includes an information bulletin and decision guide. Eligible patients are included in a prospective observational cohort study in which the effects of such prophylactic surgery on oncologic outcome will be analyzed. Other hospitals are invited to join this initiative.

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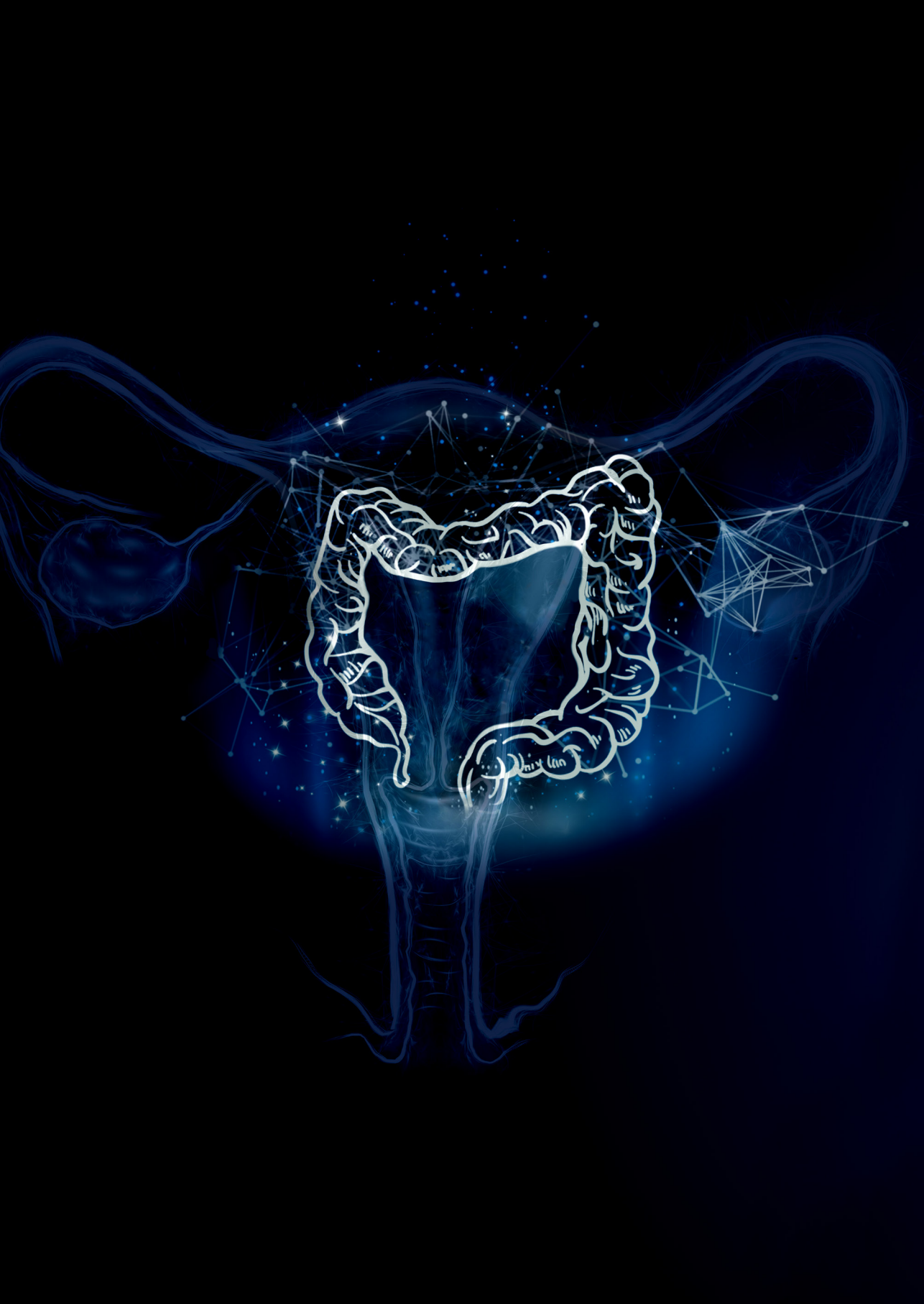

CHAPTER 9

Role Of Ovarian Metastases In Colorectal Cancer (ROMIC): a Dutch study protocol to evaluate the effect of prophylactic salpingo-oophorectomy in postmenopausal women

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Abstract

Background

The mean incidence of ovarian metastases (OM) in patients with colorectal cancer (CRC) is 3.4%. The 5-year survival of these patients, even when operated with curative intent, is remarkably low. The lifetime risk of ovarian cancer is approximately 1.3%. Prophylactic salpingo-oophorectomy (PSO, or surgical removal of the ovaries and fallopian tubes) could reduce the number of CRC patients that develop OM after removal of the primary tumor, as well as preventing the occurrence of primary ovarian cancer. Recently, the care pathway for CRC has been changed in several hospitals in line with the updated Dutch guideline. The possibility of PSO is now discussed with postmenopausal CRC patients in these hospitals. The aims of the current study are firstly to estimate the incidence of OM and primary ovarian cancer in postmenopausal patients with CRC, and secondly to evaluate the effect of PSO in these patients.

Methods

An information bulletin and decision guide on this topic was implemented in several Dutch hospitals in 2020. Post-decision outcomes will be collected prospectively. The study population consists of postmenopausal (≥ 60 years of age) patients that are operated with curative intent for CRC. Based on their own preference, patients will be divided into two groups: those who choose to undergo PSO and those who do not. The main study parameters are the reduction in incidence of ovarian malignancies (metastatic or primary) following PSO, and the number needed to treat (NNT) by PSO to prevent one case of ovarian malignancy.

Discussion

This will be the first study to evaluate the effect of PSO in postmenopausal CRC patients that is facilitated by an altered CRC care pathway. The results of this study are expected to provide relevant information on whether PSO adds significant value to postmenopausal patients with CRC.

Introduction

Intra-abdominal relapse of colorectal cancer (CRC), including ovarian metastases (OM), is a serious event leading to high morbidity and mortality and to a significant loss in quality of life.[1,2] For CRC patients with OM, including those who are operated with curative intent, the reported median survival is between 12-18 months,[1,3-5] and the 5-year survival rate is about 12-27%.[2,6-10]

Occurrence of ovarian metastases

The risk of developing OM in patients with CRC has been reported as between 1-8%,[1,3-5,8,11-16] with postmortem studies showing a higher incidence of 5-10%.[2] Review of the literature by Pitt et al.[17] revealed the mean risk for development of synchronous and metachronous OM is 3.4%. The risk of developing OM is considerably higher in young or premenopausal patients, with a mean incidence of 5% (range 3 to 50%).[1,7,12,18–21]

Guideline, evidence for prophylactic surgery, and current practice

The Dutch guideline for CRC management was updated in 2019 and includes discussing the role of prophylactic salpingo-oophorectomy (PSO) to reduce the risk of developing OM and primary ovarian cancer in *postmenopausal* patients.[22]

To date, only one randomized controlled study (n=155) has investigated the impact of prophylactic surgery by randomizing patients into one of two groups: prophylactic oophorectomy or non-oophorectomy.[11] This study found no significant difference between the two groups in terms of disease-free survival at 5 years: 78% for the prophylactic oophorectomy group versus 68% for the non-oophorectomy group (p=0.16). Furthermore, no significant difference in overall survival was found between the two groups (p=0.79). However, the statistical power of this study was quite low and hence no firm conclusions could be drawn.

In accordance with the updated Dutch guideline, PSO is now regularly discussed with postmenopausal (≥60 years of age) CRC patients in several Dutch hospitals.

Consequences of PSO

The removal of ovaries in postmenopausal patients can affect the hormone balance. Following oophorectomy, the concentrations of androstenedione and testosterone decrease by 50%, but this does not lead to significant clinical complaints.[23,24] A recent study showed that postmenopausal status was a risk factor for the development of CRC and adenomas, due mainly to the production of androgens by the ovaries.[25] This hormonal influence may be the reason why CRC is more prevalent in males, with a male-to-female incidence ratio of 4:3.[26]

The removal of ovaries in postmenopausal patients has several potential disadvantages:
1) introduction of extra risk during operation, including bleeding or damage to nearby structures such as ureters. However, this risk appears to be low according to a number of mainly gynecological-focused studies,[27–29]
2) decreased satisfaction with sexual functioning.[30]

Proposed benefits of PSO include:[31]
1) resection of microscopic ovarian metastases,
2) reduced risk of disease recurrence,
3) prevention of primary ovarian cancer, which has a lifetime risk of approximately 1.3% in the general population.[32]

Explanation for the choice of comparators and efficacy of PSO
The primary goal of implementing PSO is to improve the health of individual women by preventing the development of ovarian malignancies (primary or metastatic), thus improving disease-free survival, preventing additional treatment-related morbidity, and ultimately improving overall survival. As such, PSO could potentially be a cost-effective procedure, especially from an oncological point of view.[26]

Fear of cancer recurrence is an important issue for CRC survivors.[33] A patients' ability to choose additional prophylactic surgery could be helpful in reducing their fear, since the risk of subsequent metastatic or primary ovarian cancer is removed. Moreover, this supports the practice of "shared decision making". Beginning in 2020, counseling for PSO (preference of "yes" or "no" to PSO) started to be implemented in the CRC care pathway in several Dutch hospitals. Consequently, the impact of PSO can be prospectively evaluated.

Protocol items
The protocol has been written following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance.[34]

Objectives and outcomes (Table 1)

Primary Objective
- The main aim of this study is to determine whether prophylactic bilateral salpingo-oophorectomy conducted in postmenopausal patients aged ≥60 years during surgery for primary CRC reduces the incidence of ovarian malignancies (metastatic or primary) during a three-year follow-up period. Moreover, this study will provide the data necessary to calculate the number needed to treat (NNT) in order to prevent one case of ovarian cancer (metastatic or primary).

Secondary Objectives

- What is the effect of PSO on disease-free survival (DFS) after 3-years of follow-up? What is the concomitant NNT to gain one year of DFS, according to the method of Lubsen et al.[35]?
- What is the effect of PSO on surgery-related morbidity?
- In the non-PSO group, what is the incidence and pattern of intra-abdominal relapse, including CRC ovarian metastases and primary ovarian cancer, requiring renewed surgical intervention?
- During primary surgery, how often are abnormal ovaries found that require resection?
- What is the incidence of (micro)metastatic disease in the ovaries of patients with primary CRC?

Table 1 Primary and secondary outcomes of the study

Outcome	Metric	Time point/period
Primary		
Occurrence of ovarian cancer (primary or metastatic)	Incidence	36 months
Number needed to treat to prevent one case of ovarian cancer (primary or metastatic)	NNT	36 months
Secondary		
Disease-free survival	DFS	36 months
Number needed to treat with PSO to prevent one case of ovarian cancer (primary or metastatic)	NNT	36 months
Surgery-related morbidity of PSO	Number	36 months
Subsequent intra-abdominal relapse pattern in the non-PSO group	Number	36 months
Abnormal ovaries found during surgery	Number	During surgery
Incidence of ovarian (micro)metastatic disease	Incidence	36 months
Quality of life (EORT QLQ-C30 and EORTC QLQ-CR29)	SUM score	Baseline, 3-, 12-, 24- and 36 months
Repeat surgery for complications (i.e., adhesions)	Numbers	36 months
Long-term overall survival	OS in days	60 months
Preference for PSO	Numbers	36 months
Reversal of decision	Numbers	36 months
Baseline characteristics	Numbers	Before surgery
Other parameters		
Type of surgery	Number per type of surgery	During surgery
Operation duration	Minutes	During surgery
Blood loss	Milliliters	During surgery
Pre- and postoperative treatment strategies	Number per type of treatment strategy	Before surgery and 36 months

NNT, number needed to treat; DFS, disease free survival; SUM, Single Usability Metric; OS, overall survival; PSO, prophylactic salpingo-oophorectomy; EORT QLQ, European Organization for Research and Treatment of Cancer European Union Quality of Life Questionnaire

- What is the effect of PSO on quality of life as assessed using health-related quality of life (HRQL) questionnaires, and effects such as surgery for abdominal adhesions occurring within 3 years?
- What is the effect of PSO on 5-year overall survival?
- What is the percentage of patients who have a preference for PSO (or no PSO) when scheduled for surgery for primary CRC? Within 3 years of their index surgery, how many patients revise their initial decision of no PSO and subsequently undergo PSO?
- Are there differences in the baseline characteristics between patients who choose PSO compared to those who do not? (The baseline patient characteristics include age, ASA-classification, BMI, previous unilateral oophorectomy, comorbidities, and neo-adjuvant therapy (Table 2))

Table 2 Baseline characteristics of study patients

Baseline characteristic	PSO	Non-PSO
Age, mean (SD) or median (IQR), years		
ASA classification, No. (%)		
ASA-1		
ASA-2		
ASA-3		
ASA-4		
BMI, mean (SD), median (IQR), kg/m^2		
Previous (unilateral) oophorectomy		
Yes, unilateral		
Yes, bilateral		
No		
Comorbidities, No. (%)		
Smoking (yes/no)		
Chronic pulmonary disease (yes/no)		
Hypertension (yes/no)		
Diabetes mellitus (yes/no)		
Myocardial infarction (yes/no)		
Transient ischemic attack (yes/no)		
Cerebral vascular accident (yes/no)		
Central arterial disease (yes/no)		
Peripheral arterial disease (yes/no)		
Severe kidney disease (GFR <30 mg/mmol) (yes/no)		
Neo-adjuvant therapy		
No		
Yes, chemotherapy		
Yes, radiotherapy		
Yes, chemoradiotherapy		

SD, standard deviation; *IQR,* interquartile range; *y,* year; *ASA,* American society of anesthesiologists; *no,* number; *BMI,* body mass index; *GFR,* glomerular filtration rate

Other study parameters
Other information will be collected on the type of surgery (colon *vs* rectum, laparoscopic *vs* open), operative duration, intraoperative blood loss, adjuvant treatment strategies, and pTNM classification. Preoperative data are collected during admission to the surgical and/or gynecology department. Data collected during operation is noted in the operative report. Quality of life after the operation is evaluated by questionnaires (part of the standard follow-up / value-based healthcare) given at 3 months and at 1-, 2- and 3-year(s) after surgery. Data collection is performed centrally.

Methods/Design

This prospective, observational cohort study will evaluate short- and long-term effects in post-menopausal patients given the choice to undergo PSO or not during surgery for CRC. As such, two separate cohorts are studied based on the patient's preference. Cohort 1 includes all patients who had PSO, while cohort 2 includes all patients who did not choose PSO. All patients are followed up prospectively.

Current practice and study setting
In 2020 an information bulletin and decision guide (supplementary file 1) on PSO was implemented in several Dutch hospitals for female patients ≥60 years of age. In patients that opted for PSO, prophylactic surgery during CRC will be performed by surgeons, gynecologists, or both (depending on the surgeons' experience and local hospital policies).

Post-decision outcomes are collected prospectively with standardized variables and data are stored in electronic patient files. These variables will be used for various statistical analyses and will provide evidence as to whether or not PSO adds significant value to postmenopausal CRC patients.

The following website lists all hospitals that contributed patients to this study: https://romic.surgery/ziekenhuizen/.

Study population and eligibility criteria
All female patients with CRC who received the information bulletin and decision guide and who signed informed consent (IC) for use of follow-up data are included in this study cohort. Patients are also included when they answered positively to the 'opt-in' question for research and education within their electronic health record. Fig. 1 shows schematic representation of the study cohort.

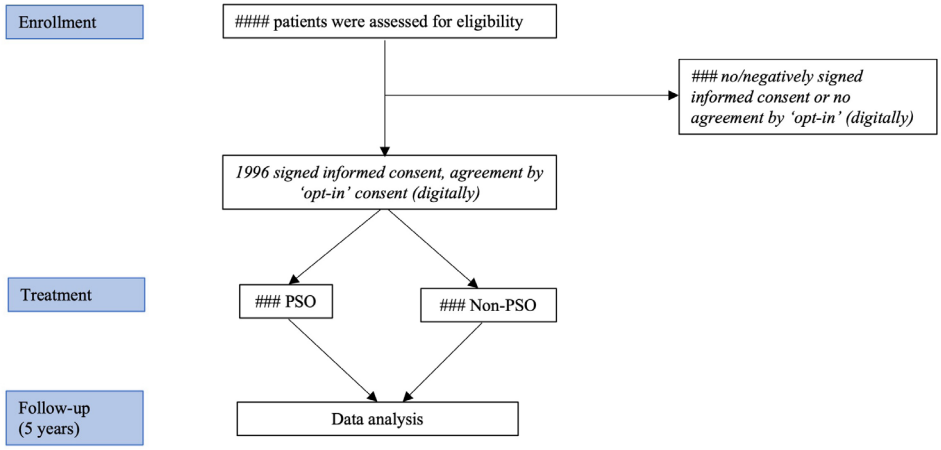

Fig. 1 Schematic representation of the cohort. PSO = prophylactic salpingo-oophorectomy

Inclusion criteria

- Female sex
- Age ≥60 years at the time of CRC diagnosis
- Intended curative resection of colon or rectal cancer, with no evidence of incurable distant metastases
- Informed consent (supplementary file 2) or consent by opt-in form (for research and education)
-

Exclusion criteria

- No signed informed consent and no consent by opt-in form (for research and education)
- Surgery with palliative intent
- Known distant metastases preoperatively, or evidence of distant or intraperitoneal metastases during operation, except when curative metastasectomy is considered possible (e.g., for hepatic metastases)

Who will obtain informed consent and how

Written, informed consent to participate will be obtained from all participants or, in cases where a positive answer for opt-in (for research and education) exists, data can be used without a written informed consent form. Researchers, registration officers, case managers and/or surgeons will obtain the informed consent.

Additional consent provisions for collection and use of participant data and biological specimens

Not applicable

Intervention description

This study protocol is not designed for the implementation of a procedure. However, it will be used to evaluate the effect of an existing procedure implemented in the local CRC pathway as follows: PSO *vs*. non-PSO in a female population with CRC. The following items are therefore not applicable: criteria for discontinuing or modifying allocated interventions, strategies to improve adherence to interventions, relevant concomitant care permitted or prohibited during the trial and provisions for post-trial care.

Randomization, blinding and treatment allocation

Because this study will evaluate the effects of PSO that are facilitated by an altered CRC care pathway, randomization and blinding are not applicable. The two different patient groups are formed based on patient preferences.

Study procedures

Complications will be scored according to the Clavien-Dindo classification.[36,37] Furthermore, the Comprehensive Complication Index[38] is a composite score that summarizes the patients' postoperative wellbeing regarding complications based on the Clavien-Dindo classification. Both scores will be determined after surgery.

Health-related quality of life (HRQL) will be measured using EORTC QLQ-C30 for cancer patients in general, and EORTC QLQ-CR29 specifically for CRC patients. The outcomes will be measured at baseline, at 3 months, and at 1-, 2-, and 3-year(s) after surgery. Differences in outcomes between the two groups will be analyzed statistically.

Participant timeline

Patients in this study will be enrolled during the period from 07/01/2020 to 07/01/2025. The follow-up period will be 5 years. When a patient withdraws from the study, only the data collected until that time will be used.

Sample size

The primary study outcome is the occurrence of either CRC metastases in the ovaries or primary ovarian cancer within 3 years after resection of the (primary) colorectal tumor. Based on previous studies, we assume the incidence of synchronous and metachronous colorectal metastases in the ovaries will be 2.0% during the follow-up period.[15,17,21] The incidence of primary ovarian cancer is expected to be 0.1% in this period.[39] This gives an overall incidence of 2.1% in cases where PSO is not performed (non-PSO group).

Following PSO, colorectal tumors can no longer metastasize to the ovaries, while the incidence of primary ovarian malignancy should presumably be 0% (PSO group). However, a small risk of primary ovarian malignancy still exists after PSO due to the

development of 'ovarian remnant syndrome' (ORS).[40–42] This risk is estimated to be approximately 0.01% for the PSO group.

Based on these assumptions and an alfa of 0.05 with power of 80%, a sample size calculation was performed using an online sample size calculator for comparison of two proportions.[43] This gave a sample size of 371 patients per group, or 742 in total.

Since all eligible patients are not randomized, it is necessary to correct for possible confounders. According to the one-in-ten rule, at least 10 events (of ovarian malignancies) are needed per factor studied in order to achieve sufficient statistical power.[44] Besides PSO, correction will also be made for age as another possible confounder.

Based on current clinical practice, we estimate that about half of all postmenopausal CRC patients undergo PSO during resection of their colorectal tumor. Therefore, we expect the two study groups to be approximately equal in size. The estimated incidence of ovarian malignancies in the total study population will thus be 1.055% (average of 2.1% and 0.01%), thus requiring a sample size of at least 1896 patients (20/0.01055). Finally, after taking into account a dropout rate of 5%, at least 1996 patients should be recruited into the study.

Recruitment

Consecutive CRC patients will be checked for eligibility by their surgeons once they are scheduled for tumor resection surgery. Either the surgeon or the case manager (depending on local logistics) will inform eligible patients about the study at their next visit to the outpatient clinic and provide them with written information. All patients will receive the same written information on the specific issues concerning the study.

Written informed consent for inclusion in follow-up will then be sought from the patient by the involved surgeon or case manager. After informed consent is given, patients are registered with a code (no personal identifiers) in an online case record form using Research Manager.[45]

Data collection and management

Plans for assessment and collection of the outcomes

Standardized variables used in the pre-operative records and standardized items during surgery will be used to record the outcomes. An electronic data collection form will be used to capture the information. Participants will be followed up at 3 months and at 1-, 2-, and 3 year(s) after surgery. At each follow-up time, the physician will note whether complications (within ≤3 months postoperatively) or recurrent disease have occurred.

Plans to promote participant retention and to complete follow-up

There are no additional strategies to promote participant retention since follow-up is the standard of care. In cases where the participant withdraws informed consent, only previously collected data will be used for this study.

Data management

Data will be managed by local investigators and local data managers, and local supporting researchers/research assistants. using the online data management system 'Research Manager'.[45] Each patient receives a unique study number generated by the data management system. The study number is linked to patient details and is stored in a password-secured file that can only be accessed by the research investigators.

Confidentiality

All analyses of study data during the trial period will be carried out in compliance with the relevant regulations for data protection. Personal identifiers will be replaced by a study number generated in 'Research Manager'. The study data is only accessible by the investigators. Research data that needs to be taken away from the research center will not contain any personal information of the participants. If necessary, government regulatory authorities or ethics committees may access patient data from the study. At the end of the trial, permission from the participants for further storage or for the use of any specimens is already available, since this is included in the signed informed consent form (supplementary file 2). Finally, the study results will be published with non-identifiable personal data once the trial has ended.

Additional consent provisions for the collection and use of participant data and biological specimens

The collection, processing, and storing of biological specimens will be carried out in accordance with the applicable institutional policies. The use of specimens is described in the patient's informed consent form (supplementary file 2).

Statistical methods

General statistical analysis

Categorical variables will generally be presented as numbers (frequencies) and percentages. Continuous variables will be presented as the mean and standard deviation, or as the median and interquartile range in case of a skewed distribution. The data will only be analyzed and presented quantitatively. Missing data will not be replaced.

Statistical analysis of the primary study parameters

For each group, the number of patients who are alive and without evidence of disease relapse after 3 years of follow-up will be determined. Kaplan-Meier curves with the

end-point of disease-free survival will be constructed and the log-rank test will be used to compare 3-year disease-free survival rates between groups.

In the case of differences in baseline variables between the two groups, Cox regression analyses including these variables will be performed. Univariate analysis will first be used to identify possible confounders. Multivariate Cox regression analysis will then be performed including 'group' (PSO or no PSO), with possible confounders as independent variables and disease-free survival as the dependent variable.

The NNT to prevent one case of ovarian cancer will be calculated according to the method of Lubsen et al.[35]. NNT describes the number of patients required to undergo PSO in order to gain 1 year of disease-free survival.

Statistical analysis of secondary study parameters

The proportion of abnormal ovaries found during primary surgery that necessitate resection (based on the opinion of the operating surgeon) will be presented as a number and percentage of the total group of study patients. This specific group of patients will be analyzed separately since the need for resection is established before the intervention (PSO) takes place.

Per- and post-operative complications will be presented as numbers and percentages. The number of patients with any complication and the number of patients with a more severely complicated course (Comprehensive Complication Index > 20) will be compared between groups using chi-square tests or Fisher exact tests, as appropriate. In the case of differences in baseline variables between the groups, the number of patients with complications or with a severely complicated course will also be compared using logistic regression analyses that include these variables.

The occurrence of *metastatic spread* to the ovaries (based on pathology reports) will be presented as a number and percentage. Because this can only be assessed in the intervention group, comparison between the groups cannot be made.

The occurrence of relapse of intra-abdominal tumors and the occurrence of primary ovarian cancer are compared between groups using Kaplan Meier analysis and log-rank tests. In the case of differences in baseline variables between the groups, the occurrence of relapse or of primary ovarian cancer will be compared using logistic regression analyses that include these variables.

Generic and disease-specific, health-related quality of life will be measured using the EORTC QLQ-C30 and QLQ-CR29 questionnaires. These will provide continuous

variable data that are compared between groups using the student's t-test or Mann Whitney U-test, as appropriate. Furthermore, linear mixed models for repeated measures will be used to estimate the effect of PSO on the quality of life over time.

Other study parameters and methods for additional analyses
All baseline parameters will be compared between groups using either chi-square tests for categorical variables and t-tests, or Mann-Whitney U-tests for continuous variables.

In addition, the surgical substrate (colon *vs* rectum), type of surgery (laparoscopic *vs* open) and use of adjuvant treatment are compared between groups using chi-square tests.

Oversight and monitoring
Composition of the coordinating center and trial steering committee
The data management team consists of local investigators and local data managers.

Composition of the data monitoring committee, its role and reporting structure
There will be a research coordinator at each hospital to monitor the trial.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethics committees)
Important protocol modifications will be communicated by e-mail to all relevant parties.

Ethics and disseminations
Dissemination policy
The results of this study will be communicated to all participating hospitals and published in peer-reviewed journals. In addition, the results will be presented at gynecological and surgical conferences.

Discussion

Up until 2019, there was no explicit focus on the role of the ovaries in CRC patients. In our view, however, patients with CRC could gain a benefit from PSO. Apart from the possibility of developing metastases in the ovaries, the risk of developing ovarian cancer at a later stage in life makes PSO a highly relevant issue.

The outcomes of this study will result in continued discussion of the role of PSO. It should also increase awareness among surgeons for the ovaries and salpinges and stimulate them to check the ovaries for possible abnormalities.

In the case of successful completion of this study, evidence should be obtained on different aspects of ovarian malignancies in CRC patients and on the clinical consequences of prophylactic surgery. We will be able to evaluate the impact of recurrent colorectal malignancy, particularly intra-abdominal, as well as the occurrence (or prevention) of ovarian cancer. In addition, we will gain further insights into the disease-free and overall survival of postmenopausal patients with CRC. Based on this new information, we should be able to conclude whether offering PSO to all postmenopausal patients with CRC is beneficial for their oncologic outcome. This conclusion could eventually be incorporated into the CRC guidelines.

Finally, we will gain insight into the long-term effects of both of these operating strategies (PSO or no PSO) on patient quality of life and on complications. Only then will it be possible to balance the considerations that allow informed individual decision-making on this specific issue.

Within the selected hospitals that have altered their CRC care pathway, younger or premenopausal patients are excluded. Therefore, no conclusions can be drawn for this specific group. Since OM appears to be more prevalent in premenopausal patients, research into the effects of PSO on the oncologic outcome of these patients would also be valuable. However, for such a study to be considered, more comprehensive informed consent should be obtained due to the consequences of surgically induced menopause.

At last, the added value of PSO in patients that developed CRC caused by Lynch syndrome, which is the case in approximately 2-4% of all CRC patients,[46,47] remains unanswered by the current study. Although, it is expected that the number needed to treat in this specific population is a lot smaller compared with the general population, because of a lifetime risk of 3-14% for the development of ovarian cancer in patients with Lynch syndrome.[48] A separate substudy regarding this specific population is therefore in preparation.

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Supplementary material

Supplementary file 1 Information bulletin and decision guide

General information
Soon you will be operated for colorectal cancer. During this surgery, the tumor and some surrounding (healthy) tissue will be removed. The surgeon will inspect the abdominal cavity for signs of potential metastatic disease during the procedure. However, metastases are not always visible at the time of surgery. Sometimes there are small metastases present within the ovaries that are not detected by the surgeon or by medical imaging with ultrasound or CT-scan. These metastases can later grow during the follow-up period. One option is to undergo a prophylactic resection of the ovaries and fallopian tubes (adnexa). After this procedure, it is no longer possible for any existing metastases to grow within the ovaries, or for new metastases to develop within the ovaries. It is also possible that the adnexa are not affected by metastatic disease and are therefore removed for no reason. Prophylactic resection of the ovaries does not affect the development of metastases elsewhere in the body.

Why has this information bulletin been developed?
The adnexa are not routinely prophylactically resected in colorectal cancer patients. However, we believe that patients should be informed about the possibility of developing ovarian metastases, so that a decision regarding prophylactic surgery can be made.

In cases where the surgeon suspects (during surgery) that malignant ovarian disease is present, the ovaries are resected as standard procedure. The new situation concerns resection of the adnexa when there is no sign of malignant ovarian disease.

Specifics on the decision guide in this information bulletin
The decision guide helps you to choose the best therapy that is suitable for your situation. The advantages and disadvantages of each therapy are discussed and should prove helpful in making your choice. In this way, you will be well prepared for the next meeting with your physician. Together, you will choose one of the two therapy options.

How can this information bulletin help you?
This information bulletin has been developed for female patients with colorectal cancer who are aged 60 years or more. In these patients, the adnexa can be surgically removed in order to prevent the (further) development of ovarian metastases.

The final decision for prophylactic surgery is made by you. Your medical specialist or nurse practitioner may also be of assistance in making this decision. This information

bulletin discusses the advantages and disadvantages of prophylactic surgery.

This information bulletin is not offered to female patients who are younger than 60 years of age.

Background information

Metastases in the ovaries

Colorectal cancer metastases within the ovaries are uncommon. It is estimated that subsequent ovarian metastases occur in only 2 or 3 out of 100 women with colorectal cancer. These metastases mean that another operation must be performed in which the ovaries (and some surrounding tissue) are removed and/or treatment with chemotherapy is necessary.

The consequences of metastases in the ovaries are serious, and only about 1 out of every 5 patients is still alive after 5 years.

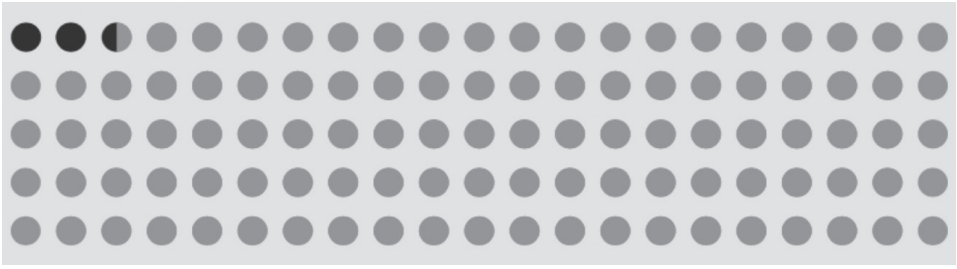


Fig. 1 Schematic representation of how much 2-3 in 100 women means

Women before menopause

Removal of the ovaries has more physical consequences for women who are still menstruating (before menopause, also called premenopausal) compared to women who no longer menstruate (after menopause, also called postmenopausal). For this reason and on the advice of the Dutch Society for Obstetrics and Gynecology (NVOG), women under the age of 60 years will not receive this information bulletin. This information is only applicable to women aged 60 years or more.

The treatment and your options

What options do you have?

You will receive the treatment of your choice:

1. Surgery in which only the colorectal tumor is removed
2. Surgery in which the colorectal tumor is removed, as well as the ovaries and

fallopian tubes (prophylactically)

The operation
The removal of the ovaries and fallopian tubes takes place during the same operation in which the colorectal tumor is removed. The duration of the operation will therefore be increased by an average of 10-15 minutes. The removal of the ovaries and fallopian tubes is a relatively simple procedure that is performed regularly, and the risk of complications is very small.

Potential disadvantages and complications
Removing the ovaries can have adverse effects. Due to the operation, there is a risk of damage to nearby tissues and organs (such as the ureters) and bleeding can occur. This is estimated to occur in less than 1 in 100 patients, and the possible burden is limited.
In addition, surgical removal of the ovaries can lead to a decreased libido (= sexual arousal).

Option 1:
Surgery in which only the colorectal tumor is removed, with no additional treatment
Important: the ovaries and/or fallopian tubes will be removed if they are visibly abnormal at the time of surgery. This is standard care.

- You will receive the care which is currently offered as standard
- Advantages:
  - The operation duration is not extended
  - There is no risk of complications arising from ovarian and fallopian tube removal
- Cons:
  - There is a risk of developing colorectal cancer metastases to the ovaries later on, estimated at 2-3 in 100 women with colorectal cancer

Option 2:
Surgery in which the colorectal tumor and (prophylactically) the ovaries and fallopian tubes are removed

- The fallopian tubes and ovaries are removed prophylactically to prevent colorectal cancer metastases in the ovaries
- Advantages:
  - Prevents the growth of colorectal cancer metastases in the ovaries
  - No additional surgery is needed later on to remove the ovaries and fallopian tubes, because metastases can no longer occur at these sites
- Cons:
  - Extended operation time (an extra 10-15 minutes on average)

- o There is a risk of complication following the removal of ovaries and fallopian tubes, such as injury to surrounding organs or bleeding. This is estimated to affect less than 1 in 100 women
- o Potentially decreased libido

Compare treatments

	Option 1: No additional treatment	Option 2: Prophylactic removal of the ovaries and fallopian tubes
Advantages	1. No extended operation time	1. Prevents the growth of colorectal cancer metastases in the ovaries
	2. No risk of complications from removal of the ovaries and fallopian tubes	2. No additional surgery is needed later to remove the ovaries and fallopian tubes because metastases can no longer occur at these sites
Cons	1. Risk of developing colorectal cancer metastases to the ovaries later on, estimated at 2-3 in 100 women with colorectal cancer	1. Extended operation time of 10-15 minutes on average
		2. Risk of complications following removal of ovaries and fallopian tubes (injury to surrounding organs or bleeding, estimated to affect less than 1 in 100 women)
		3. Potentially decreased libido

Important points

- If you do not undergo the additional treatment, you will not have any direct disadvantages from the removal of the ovaries and fallopian tubes, but there is a risk of developing colorectal cancer metastases within the ovaries later on
- Prophylactic removal of the ovaries and fallopian tubes prevents the growth of any colorectal cancer metastases within this organ. Colorectal cancer metastases can still occur elsewhere in the body after prophylactic ovarian resection.

Your preference (what matters to you)
You can discuss the following questions (and answers) with your medical specialist and/or nurse practitioner.

1. I would like to prevent colorectal ovarian metastases
□ Yes □ No □ No opinion

2. I am afraid of the risks related to the surgical removal of my ovaries and fallopian tubes
□ Yes □ No □ No opinion

3. I value not getting cancer more than the disadvantages of prophylactic removal of my ovaries and fallopian tubes
□ Yes □ No □ No opinion

4. I am very worried about the possible loss of libido as a result of ovary removal
□ Yes □ No □ No opinion

Your preference

- Which side effects and/or late effects are you most concerned about?
  _____
  _____
  _____

- What is still unclear to you?
  _____
  _____
  _____

Your choice
What will your definitive treatment choice be?
O No additional treatment
O Preventive removal of ovaries and fallopian tubes

How sure are you of your choice?

Very uncertain					Neutral					Very sure
5	**4**	**3**	**2**	**1**	**0**	**1**	**2**	**3**	**4**	**5**

Final questions

- Do you know enough about the advantages and disadvantages of the different treatments?
  □ Yes □ No

- Are you able to determine what is most important to you?
  □ Yes □ No

- Do you feel that you can make a good and well-balanced decision?
  □ Yes □ No

- Do you have any additional concerns or questions? Is something still unclear to you?
  □ Yes □ No

End of information bulletin and decision guide

Authors of this information bulletin

- Máxima Medical Center: Dr. R. Roumen (surgeon), R. van der Meer (PhD candidate), L. Janssen (trial coordinator)
- Other: Surgeons (Prof. Dr. I. De Hingh, Dr. J. Bloemen), gynecologists (Dr. S. Coppus, Dr. P. Geomini), nurse practicioners (D. Lurling, S. v Lankvelt, J. Ophorst), communication and marketing consultant (N. Hermans)

Glossary

- Adnexa: ovaries and fallopian tubes
- Libido: sexual arousal
- Postmenopausal: time after menopause
- Premenopausal: time before menopause
- Prophylactic: preventive

Supplementary file 2 Informed consent form

Evaluation of prophylactic salpingo-oophorectomy in postmenopausal patients with colorectal cancer

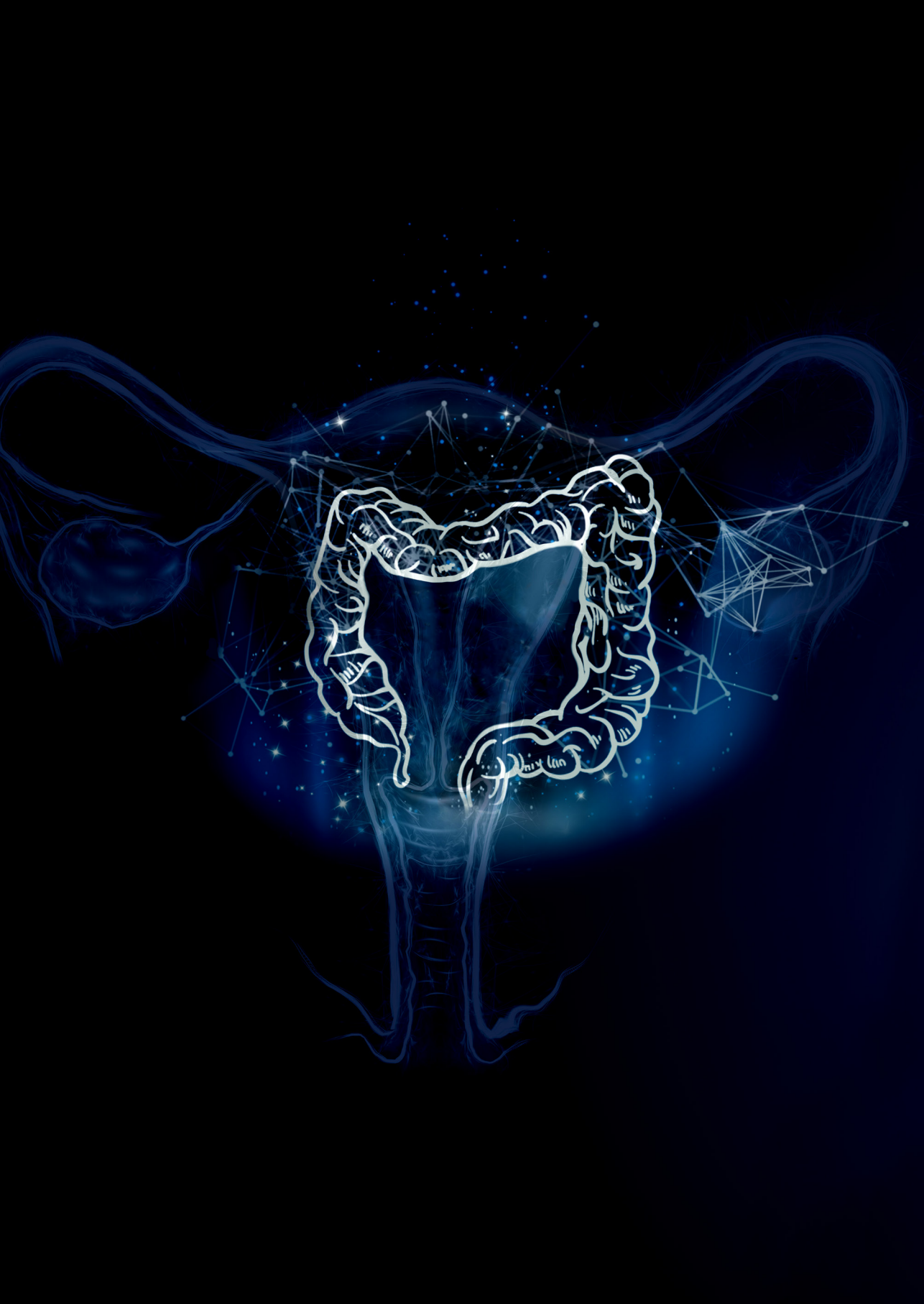
Background
Recently the colorectal cancer care pathway has been changed and postmenopausal women can choose for prophylactic surgery (salpingo-oophorectomy) to prevent ovarian malignancies. By this study, we will investigate whether prophylactic salpingo-oophorectomy will be of added value in postmenopausal patients with colorectal cancer. And finally, we will be able to get well-grounded evidence on the real size of this problem and the nature of ovarian malignancies in these patients.

Data protection and confidentiality
- I give permission for the gathering of information and the use of my personal data for scientific research
- I know my biological samples will be used and stored for a longer period for scientific research
- I agree that my official cause of death can be requested by the Dutch Central Bureau of Statistics (CBS)
- I know that all collected data will be accessed by all researchers that are involved in this study

I do agree with all statements that are written below 'Data protection and confidentiality'
□ Yes
□ No

Name participant:
Signature: Date: __ / __ / __

I hereby declare that I have fully informed the participant about this study.
Name researcher:
Signature: Date: __ / __ / __



CHAPTER 10

Summary, general discussion, and future perspectives

This thesis emphasizes the necessity for increased awareness of ovarian malignancies in CRC patients. This increased recognition is warranted because of 1. the development of ovarian metastases (OMs), which may occur in CRC patients; 2. the development of primary ovarian cancer, which seems more prevalent in female CRC patients compared to the general female population; and 3. potentially reduced risk of developing OMs and ovarian cancer by prophylactic or 'so-called' risk-reducing (bilateral) salpingo-oophorectomy (PSO) during CRC surgery.

Summary and general discussion

In **Chapter 2**, a nationwide population-based study is described. This study investigates 53,883 females diagnosed with CRC between 2008 and 2016. Synchronous metastases (stage IV disease) were found in 11,343 patients; of these, 471 (4.2%) were diagnosed with OMs. Of those with OMs, we found that patients who underwent CRS-HIPEC had an improved median overall survival compared to those who underwent resection only (34.1 vs. 17.5 months, respectively). Additionally, this study revealed that patients with other metastases had the lowest median overall survival (11.7 months) compared to those with OMs (25.5 months) and ovarian and other metastases combined (14.2 months). It could, however, be questioned whether these diagnosed OMs are actually peritoneal implants on the surface of the ovary or whether these ovaries are (fully) invaded by malignant cells due to lymphatic or hematogenic spread. Future studies are needed to clarify whether this improved overall survival is due to a lesser aggressive biology of OM, a 'HIPEC-sensitive' peritoneal or transcoelomic dissemination on the ovary, or because of the resection of the ovaries (with or without the fallopian tubes). Another finding was that OMs were more frequently diagnosed in younger patients. We therefore explicitly focus on the younger CRC population in the next chapters. In **Chapter 3**, we present a retrospective multicenter cohort study on 200 young (≤ 55 years of age) female CRC patients. Within this population, 5% (n=10) had synchronous or metachronous OMs. This result appears to be clinically relevant and demonstrates the need for improved surveillance of young CRC patients. This is supported by the fact that the actual risk of OMs in this population is likely underestimated: The actual risk could be higher since the calculated proportion only includes patients who were operated on for CRC and metastatic disease; patients with an inoperable condition because of tumor size or poor performance status were thus excluded. Additionally, the number of patients with micrometastatic disease located in the ovaries is unknown. In **Chapter 4**, we present a systematic review studying the literature on the presence of OMs in young (≤ 55 years of age) CRC females. We found that 4.6% 95% CI [4.0, 5.4] (157 of 3379 patients) were reported to have OMs. This risk may be underestimated since not all reviewed studies (n=14) included both synchronous and metachronous

metastases.[1-14] Nevertheless, the cohort study (Chapter 3) corroborates the review's findings and further confirms that approximately one in twenty young female CRC patients will present with or develop ovarian metastasis (OM). Since the ovaries are considered sanctuary sites due to the lesser sensitivity to systemic therapy compared to other metastatic sites,[15-21] it is suggested that the presence of an OM in CRC patients might be a negative prognostic factor. In **Chapter 5**, we, therefore, studied the impact of OM in stage IV CRC in a nationwide population-based study using a propensity score-matched analysis. All patients that received systemic treatment were categorized into two groups based on the presence of OM: patients with OM (one or more metastatic sites) and those without OM. Consequently, a subsample was created using propensity score matching to create comparable groups. This study, however, showed that the presence of OMs was not associated with decreased overall survival. Unfortunately, due to the design of this study, we were unable to evaluate the radiological response of all used therapeutic regimens. This, therefore, must be evaluated in future drug-oriented studies. Moreover, future prospective studies are needed to validate our findings since our results are still based on retrospective data and represent a highly selected group of patients. In anticipation of such a prospective study, independent database validation, like the US Surveillance, Epidemiology, and End Results Program (SEER), may help test the external validity of our findings. In **Chapter 6**, we describe a cohort study in which we aim to find an explanation for the alleged lesser sensitivity to systemic therapy for OMs and report on different predictive biomarkers in CRC patients. This study found a very high concordance rate in biomarker status for primary CRC and OM comparable with other metastatic sites. The lesser sensitivity to systemic therapy is, therefore, most likely not attributed to biomarker discordances. Additionally, the results suggest that testing on metastatic ovarian tissue is not necessary for deciding whether systemic therapy should be initiated. It could be speculated that the use of the consensus molecular subtype pathological classification system is superior for deciding the most suitable therapy since this classification is based on RNA expression patterns.[22-24] Consequently, patients could be stratified into biological subgroups associated with distinct disease outcomes and responses to therapy.[24] Another nationwide population-based study is described in **Chapter 7**. We reported a 20% increased risk for the development of primary ovarian malignancies in CRC patients compared to the general population. This study, therefore, confirmed the results of previous studies. Both the present and previous studies, however, might misinterpret these malignancies as primary ovarian cancer instead of CRC OM as a result of detection bias. The likelihood of this bias is high since 1. diagnostic accuracy could not be assessed; 2. the diagnosis was generally made in the earliest evaluated period (1989–1997), ergo before the introduction of immunohistochemistry staining by pathology; and 3. younger patients (≤ 55 years of age) were more frequently diagnosed. Additionally, a surveillance bias might exist since all ovarian malignancies are mainly found within the first evaluation period 0–1 year following CRC diagnosis.

Nevertheless, this higher incidence of ovarian cancer in CRC patients must be confirmed by prospective studies. One such study has already been prepared by our study group and is outlined in Chapter 9.

PSO could be offered to CRC patients to prevent (the outgrowth of) synchronous or metachronous OM or the occurrence of primary ovarian cancer. The rationale for this is described in **Chapter 8**, in which we mainly review the potential advantages and disadvantages of PSO. The following arguments in favor of PSO are described: 1. a better prognosis could possibly be achieved for the CRC patient; 2. other disciplines, such as gynecology and urology, offer or routinely perform PSO during abdominal surgery (for endometrial and muscle-invasive bladder cancers, respectively);[25–27] 3. PSO in the CRC patient is mentioned in various treatment guidelines; 4. systemic therapy has rather limited effects on OMs since ovaries are considered 'sanctuary sites'; 5. in postmenopausal patients, negative side effects of PSO are predicted to be low; 6) PSO for prevention of OM is viewed as a cost-effective oncological procedure; 7. reducing the risk of primary ovarian cancer may be a positive side effect; and 8. treatment by PSO is part of 'shared decision making'. On the other hand, disadvantages involve an increased length of surgery and accompanying additional risk of surgical complications, including increased intraoperative blood loss and injury to the ureter. Moreover, decreased satisfaction with sexual functioning may follow, as androgens are no longer secreted by the ovaries.[28,29] Younger or premenopausal patients have additional disadvantages related to PSO. One such disadvantage is that these patients must then navigate the results of surgical-induced menopause.[30–34] Known short-term effects are sexual dysfunction – which may also be a long-term complication – infertility, hot flashes, night sweats, and sleeping problems.[32,35] Long-term effects include vaginal problems because of vaginal atrophy, osteopenia or osteoporosis, dementia, and cardiovascular disease.[32,35] A published study concluded that patients below the age of 45 who underwent prophylactic bilateral oophorectomy for benign conditions showed an increased mortality rate compared to older patients.[33] However, it is expected that many negative consequences may be overcome by the use of hormone replacement therapy.[32,34,36,-38] To implement this knowledge into clinical practice, information (on the advantages and disadvantages of PSO) has been given during consultation at the surgical department in several Dutch hospitals since 2020, and an information bulletin and decision guide is offered to postmenopausal patients. Further clarification for this change in clinical practice and its evaluation are presented in the next chapter.

A study protocol for a prospective multicenter cohort study (evaluation of care) is outlined in **Chapter 9.** This study aims to estimate the incidence of OMs and primary ovarian cancer in postmenopausal patients with CRC through the prospective evaluation of all patients that received the information bulletin and decision guide regarding

PSO. The final study population is divided into patients who underwent PSO and those who did not. Consequently, the number number needed to treat to prevent one ovarian malignancy can be estimated. Secondary study outcomes mainly focus on other effects of PSO and include the occurrence of PSO-related morbidity and the evaluation of the impact of PSO on overall survival and quality of life. The results of this study are therefore expected to provide relevant information on whether PSO adds significant value to postmenopausal CRC patients. However, this study will not provide information on the effects of PSO in younger/premenopausal patients. For such a study to be considered, a more comprehensive informed consent – whether carried out by a gynecologist or not – should be obtained due to the dismal consequences of surgically induced menopause, as described above.

Future perspectives

As previously mentioned, increased awareness of ovarian malignancies in CRC patients is needed in daily clinical practice. Although the advantages and disadvantages of PSO and a changed CRC pathway regarding PSO are explicitly described in Chapters 8 and 9, the ultimate goal of this thesis is not to encourage the performance of prophylactic surgery in all CRC patients. We merely want patients to be adequately informed, resulting in a shared decision-making process. Whether PSO should be offered to CRC patients that completed their families as well as to premenopausal patients with a strong preference for PSO is up to debate.

As discussed in Chapter 8, prophylactic surgery to prevent OMs from different primary tumors is routinely performed by gynecologists and urologists.[25–27] It also has been reviewed that a prophylactic oophorectomy bears no additional risk of post-operative complications or death in CRC patients.[39] Moreover, opportunistic salpingectomy or prophylactic tubectomy seems effective in the prevention of ovarian cancer,[40-43] and its short- and long-term adverse effects are currently being investigated by the prospective STOP OVarian CAncer (STOPOVCA) young projects (ClinicalTrials.gov Identifier: NCT04470921).[44] Tomasch et al.[45] evaluated and confirmed the feasibility and safety of prophylactic salpingectomy in females aged 45 years or older undergoing non-emergency laparoscopic cholecystectomy for benign indications. In addition, premenopausal PSO to reduce the occurrence of ovarian cancer appears to be extremely cost-effective in those with a $\geq$ 4% lifetime risk of ovarian cancer,[46] as is the case for individuals with BRIP1, RAD51C, RAD51D, MSH2, MLH1, BRCA1, and BRCA2 gene mutations.[38] The currently available literature combined with the findings of the presently ongoing prospective studies regarding prophylactic salpingectomy or PSO should lead to the continued discussion for prophylactic surgery in all CRC patients and for patients with

planned abdominal surgeries for other indications. The outcome of this discussion could ultimately result in an altered, shared decision-making process into which PSO is embedded.

Nevertheless, pending the results of the prospective studies described in Chapter 9 and the previous paragraph, in both pre- and postmenopausal CRC patients, an inspection of the peritoneal cavity is considered an (acceptable) alternative when abdominal surgery is performed. During the assessment of the abdomen, ovarian cystic lesions, ascites accumulation in Douglas pouch, or tethering of one or both ovaries to the primary tumor can be indicative of the presence of (micro)metastatic OM.[47] During the follow-up of these operated patients, the presence of anorexia, changes in stool or voiding pattern, an (palpable) abdominal mass, abdominal pain, abdominal distension, ascites, or abnormal uterine bleeding can indicate the presence of an ovarian malignancy.[48-51] If one or more of these symptoms occur, additional radiological examinations or referral to a gynecologist should be applied. Since OMs generally appear within two years after CRC diagnosis,[52,53] female CRC patients, especially premenopausal patients, may benefit from a closer follow-up performed by a gynecologist within the early (two-year) post-operative period.

While this thesis provides relevant insights into ovarian malignancies in CRC patients, various unanswered questions remain.

It is still unknown which route of dissemination (hematogenous, lymphogenous, or transcoelomic) results in OMs,[54-56] as mentioned in Chapter 2. It could be helpful to explore this in CRC patients that underwent CRS-HIPEC procedures since OMs are found more often in this population.[57-63] Additional evaluation of patients who are explicitly referred for CRS-HIPEC because of an enlarged ovary discovered during CRC follow-up could be relevant. Further analysis of this population could also include the evaluation of patients with supposed peritoneal disease, which is limited to the ovaries. Furthermore, reassessment of the pathology samples of all affected ovaries could further clarify the exact location – stromal, surface/capsular, or both – of the OM.[56,64,65] Besides, a growing group of experts perform bilateral prophylactic oophorectomy in CRS-HIPEC patients,[66] which periodically results in the detection of ovarian micrometastases.[58,61,62] According to different cohort studies in which PSO was performed, the incidence of micrometastatic metastases located in the ovaries varied from 0–23.5%.[13,14,47,67–70] It could be helpful to screen for occult micrometastases by multiple-level sectioning and immunohistochemistry of prophylactic resected ovaries, which has previously been done in the sentinel lymph nodes of breast cancer patients.[71-73] This evaluation could be applied to different CRS-HIPEC cohorts or the population of the prospective study described in Chapter 9. These future studies may give additional information on the

incidence of this form of (synchronous) metastatic disease. Such studies could also give further relevant information on the most likely route of ovarian metastatic dissemination and, perhaps, its most suited treatment. Additionally, it could be valuable to compare the overall survival of the previously described group of patients with micrometastases to a (retrospective) cohort with metachronous OM. The added value of PSO in patients with normal-appearing ovaries already affected by disseminated disease could be investigated by the comparison of these two groups.

The studies described in Chapters 5 and 6 aim to explain the cause of systemic treatment-resistant OMs and to evaluate its potential impact on overall survival. Unfortunately, the cause of treatment-resistant OMs is still unanswered, and its impact on overall survival is not fully evaluated in Chapter 5 (since this chapter describes patients with unknown responses to systemic treatment in the absence of patient-specific radiology response data). A future, combined drug-, radiology-, and pathology-oriented study must focus on the cause of this considered sanctuary site.

The role of the ovarian stroma in the development and outgrowth of metastases is an almost unexplored area. Ovarian stroma is known to be involved in different physiologic processes since it comprises blood vessels, nerves, lymphatic vessels, immune cells, and different ovary-specific components; additionally, specific phenotypic features, especially infiltrative patterns of stromal invasion and prominent stromal luteinization, seem to be present within the ovarian stroma in patients with OMs.[65,74-77] However, future studies need to focus on the – earlier described – precise location of the OM (in relation to the ovarian stroma) and which specific components of the stroma are responsible for the (rapid) progression of OMs. It could also be speculated that CRC OM results in the differentiation of the ovarian stroma into a pro-tumoral phenotype in the same way (primary) ovarian cancer does.[78]

In addition, combining our prospective cohort study with patient-specific outcomes from the Prospective Landelijk ColoRectaal Carcinoom (PLCRC) study and the Dutch Institute for Clinical Auditing (DICA) outcomes could provide a more thorough overview of patients that are prone to OM development and of the consequences of PSO.[79,80] Moreover, a substudy regarding quality of life affected by hormonal changes is currently ongoing using the Greene Climacteric Questionnaire.[81,82] The relevance of this study is substantiated by the fact that the ovaries in postmenopausal patients continue to produce androgens (see also Chapter 8), so the removal of these organs could potentially affect hormone balance and result in decreased satisfaction with sexual function.

This thesis highlights that CRC OMs are not uncommon since approximately one in twenty young female CRC patients develop this form of disseminated disease, and this

is most likely an underestimated number. This underestimation in younger patients – but also in patients > 55 years of age – arises because 1. most previous studies did not include both synchronous and metachronous metastases;[1-14] 2. micrometastases within the ovaries, which has a reported incidence up to 23.5% in female CRC patients (described previously), might be missed; and 3. OM are more frequently found in post-mortem studies, with an incidence ranging from 5% to 9.7%.[83] Although the two population-based studies described in Chapter 2 and Chapter 5 gave a clear overview of the proportion of synchronous OM in the Netherlands and its consequences, new population-based or prospective data on metachronous OMs are not provided by this thesis. In particular, new insights into the development of metachronous OMs would be helpful since this could result in a better risk assessment for those that are prone to metachronous OM development and thus improved pre-surgical considerations – in relation to PSO – for both the surgeon and the patient. The prospective study described in Chapter 9 could improve pre-operative risk assessment if the results support the development of a nomogram that predicts the development of metachronous OM. However, population-based data or data provided by a large prospective study in which younger females (≤ 60 years of age) are included are still needed for a pre-operative risk assessment in this population. Nevertheless, some guidance can be provided by the available data in this thesis: the risk for both synchronous and metachronous OM in all CRC females is increased in patients ≤ 55 years of age compared to patients > 55 years of age (4.1% and 0.8% respectively, derived from Chapter 4; table 1), and the risk for the development of only synchronous OM is increased for females with T4 tumors (compared to T0–T3 tumors, adjusted OR 5.76 [4.58-7.25]), tumors with lymph node involvement (compared to tumors without lymph node involvement, adjusted OR 2.23 [1.68-2.96]), and sigmoid tumor location (compared to ascending colon, descending colon, and rectum, OR 1.69 [1.11-2.58]). The results of this thesis must ideally be validated by prospective studies since all results are based on retrospective data.

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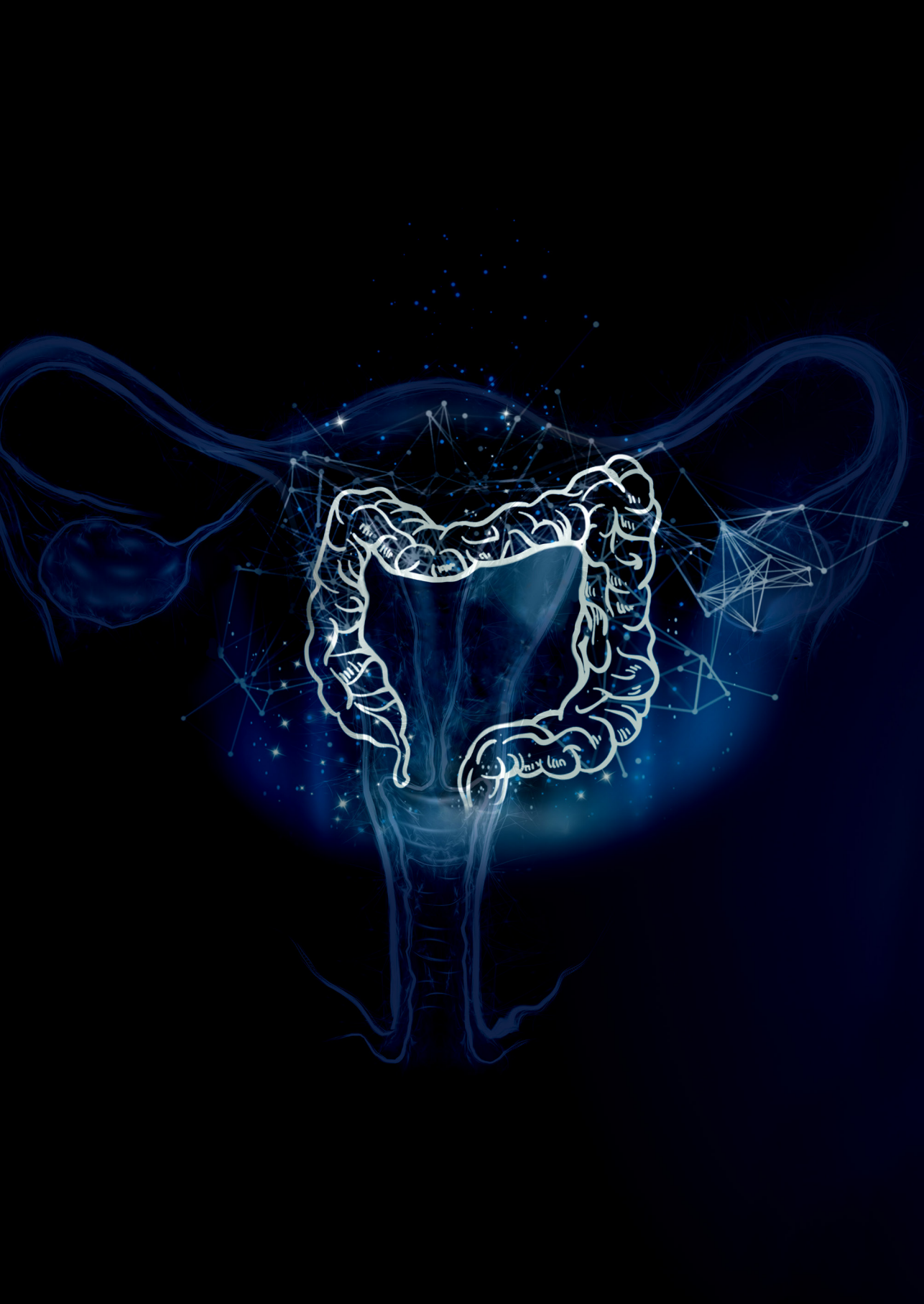


CHAPTER 11

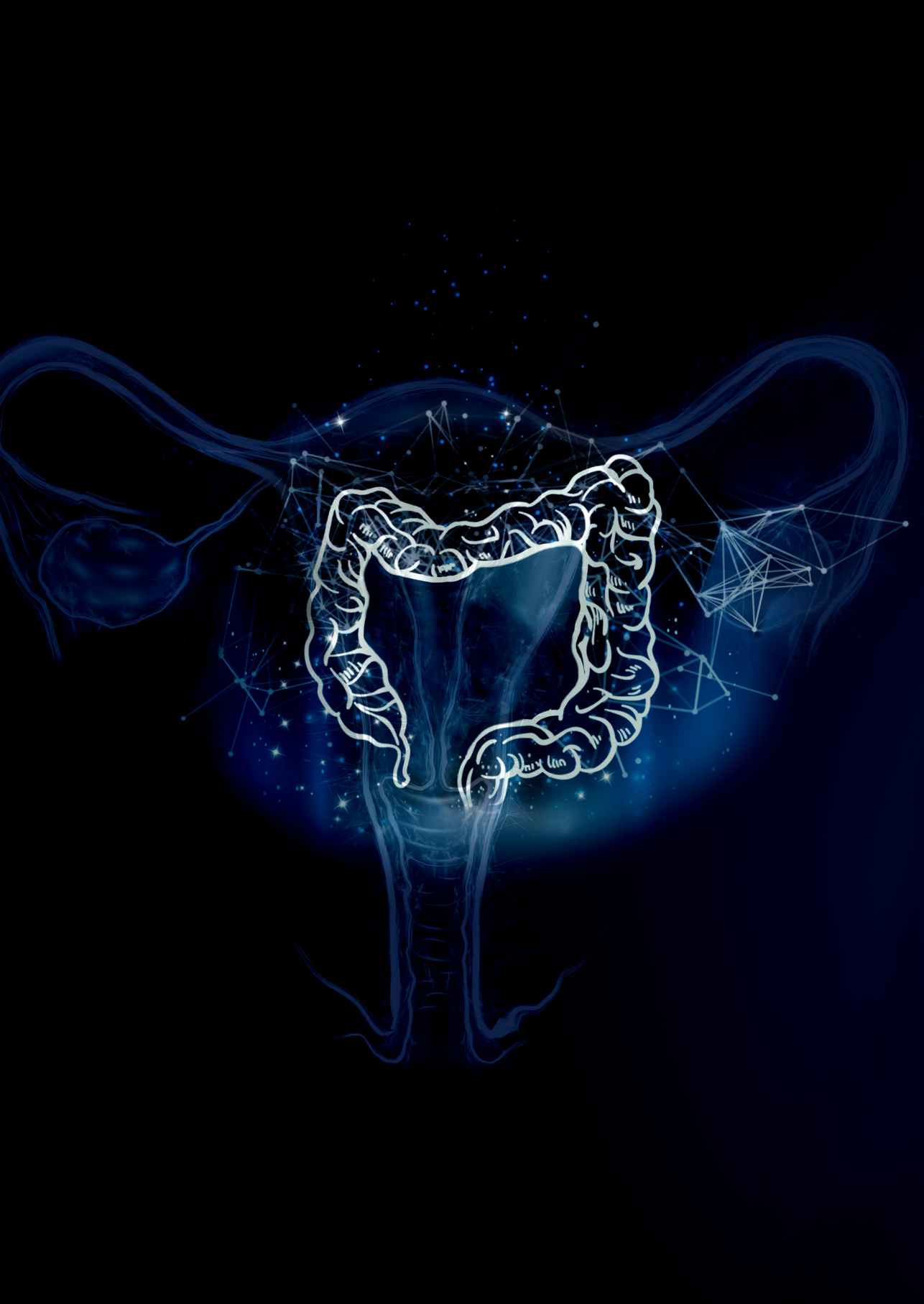
Impact

Impact

The main goal of this thesis is to evaluate the role of ovarian metastases in colorectal cancer patients. Moreover, we researched the rationale behind the need for increased awareness among physicians regarding the presence or development of ovarian malignancies in colorectal cancer patients. The relevance of this thesis is addressed by the fact that 1. ovarian metastases seem to occur more frequently in younger/premenopausal colorectal cancer patients as compared to older patients (Chapters 2, 3, & 4); 2. in a highly selected patient population ovarian metastases are not as harmful as previously expected (Chapter 5); 3. the ovaries are generally considered unresponsive to systemic therapy, which is unfortunately still poorly understood (Chapter 6); 4. cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy showed better overall survival in colorectal cancer patients with ovarian metastases compared with surgery alone (Chapter 2); 5. there is a higher incidence of (primary) ovarian cancer in colorectal cancer patients compared to the general population (Chapter 7); and 6. oncologic outcomes may improve following a prophylactic salpingo-oophorectomy in colorectal cancer patients (Chapters 8 & 9).

The findings provided by this thesis are thus relevant for women suffering from colorectal cancer and those involved in the care of these patients. Physicians that may particularly benefit from these findings are general practitioners, gastroenterologists, gynecologists, medical oncologists, and surgeons. Therefore, all findings described in Chapter 8 are presented in a Dutch scientific magazine that is generally read by a wide medical audience. In Chapter 8, we also address the social and economic impact of the implementation of prophylactic surgery by representing the cost-effectiveness of this oncological surgical procedure. This cost-effectiveness was calculated as the price for one additional year of good health, generally expressed in quality-adjusted life years (QALY). According to the Dutch Health Council, €20,000 for one QALY is considered cost-effective, while €80,000 per treatment is considered the absolute maximum. The approximate cost per QALY for postmenopausal patients receiving PSO is expected to lie below the cost-effective range. However, this analytic model is based on assumptions. Prophylactic salpingo-oophorectomy may, in fact, have no impact on quality of life or oncologic outcome in colorectal cancer patients or could potentially have more detrimental consequences than expected for the current population. Since all these aspects have not yet been systematically and prospectively investigated on a large scale, we can neither confirm nor negate the hypothesis of the potential benefits of prophylactic salpingo-oophorectomy. In the near future, the results of the ongoing prospective study described in Chapter 9 will be relevant for female colorectal cancer patients aged ≥ 60 years, their treating clinicians, and researchers from different countries worldwide. Ultimately, the findings of the latter study could expand awareness

of ovarian malignancies in colorectal cancer patients. Finally, this could lead to changes in colorectal cancer guidelines and potentially improve care for all female patients with colorectal cancer.



APPENDICES

12

I-Dutch summary
II-List of publications
III-Curriculum vitae auctoris
IV-Acknowledgements

Appendix I Dutch summary (*Nederlandse samenvatting*)

Uitzaaiingen naar de eierstokken, ook wel ovariële metastasen (OM), worden bij vrouwen met dikke darm- of endeldarmkanker (kortweg darmkanker) over het algemeen beschouwd als een zeldzaam fenomeen. Een eerdere landelijke patiëntenpopulatie-studie uit Zweden toonde aan dat OM ten tijde van de primaire darmkanker diagnose (synchroon), en metastasen die gedurende de follow-up werden gevonden (metachroon), bij respectievelijk 1,1 en 0,6% van de patiënten aanwezig waren. Deze getallen kunnen echter misleidend zijn omdat, zeer kleine, microscopische OM, in deze studie niet zijn meegenomen. Bovendien tonen autopsie data dat 5%-9,7% van de vrouwen met darmkanker OM hebben. Verder toonde de eerdergenoemde Zweedse studie aan dat OM vaker voorkomen bij premenopauzale – dus jongere – patiënten en wordt gesuggereerd dat OM zich potentieel agressiever gedragen dan metastasen elders in het lichaam. Omdat OM niet zelden gezamenlijk vóórkomen met peritoneale metastasen, of verkeerd kunnen worden geïnterpreteerd als eierstokkanker (ovariumcarcinoom), worden deze patiënten vaak doorverwezen naar een gespecialiseerd ziekenhuis.

De meest effectieve behandelstrategie van OM is vooralsnog onduidelijk. De behandeling kan variëren van (enkel) een chirurgische resectie, tot systemische therapie eventueel gecombineerd met een aanvullende chirurgische resectie of cytoreductieve chirurgie gecombineerd met hypertherme intraperitoneale chemotherapie (HIPEC). Operatieve ingrepen voor darmkanker kunnen daarnaast ook gecombineerd worden met een preventieve verwijdering van de eierstokken en eileiders (adnexextirpatie). Een preventieve adnexextirpatie zou daarnaast ook overwogen kunnen worden bij vrouwen met darmkanker ter preventie van eierstokkanker. Echter, de meerwaarde van deze procedure is vooralsnog niet aangetoond.

Dit proefschrift is allereerst bedoeld om meer inzicht te verschaffen in de patiënten die OM ontwikkelen en om de impact van deze vorm van metastasen te beschrijven. Ook wordt de plek van een preventieve adnexextirpatie in deze context verder onderzocht.

De concrete doelen van dit proefschrift zijn als volgt:

1. Beschrijven hoe vaak OM in de Nederlandse darmkankerpopulatie vóórkomen en de klinische consequenties hiervan verder verduidelijken
2. Door middel van een literatuurstudie uitzoeken in welke mate er sprake is van het vóórkomen van OM in de jonge darmkankerpopulatie
3. De achtergrond en impact van systemische therapie ongevoelige OM onderzoeken
4. Het beschrijven van het vóórkomen van eierstokkanker bij vrouwen met darmkanker
5. Uiteenzetten wat de klinische implicaties van een preventieve adnexextirpatie kunnen zijn binnen de vrouwelijke darmkankerpopulatie

In **Hoofdstuk 2** wordt een landelijke patiëntenpopulatie-studie beschreven. Deze populatie bestaat uit 53.883 vrouwen die tussen 2008 en 2016 zijn gediagnosticeerd met darmkanker. Darmkanker met gelijktijdige metastasen (stadium IV ziekte) waren aanwezig in 11.343 patiënten, van deze vrouwen hadden 471 (4,2%) synchrone OM. Bij vrouwen met OM werd aangetoond dat cytoreductieve chirurgie met HIPEC, in vergelijking tot chirurgie alleen, geassocieerd was met een betere mediane totale overleving (respectievelijk 34,1 en 17,5 maanden). Deze studie vond verder de hoogste mediane totale overleving voor patiënten met OM (25,5 maanden), in vergelijking met gecombineerde metastasen (ovariële en extra-ovariële metastasen) (14,2 maanden). De slechtste overleving werd gevonden voor patiënten met enkel extra-ovariële metastasen (11,7 maanden). Deze studie wekt daardoor de suggestie dat OM minder agressief zijn dan gedacht wordt (door andere auteurs).

In **Hoofdstuk 3** wordt een retrospectieve multicenter cohortstudie beschreven. Deze studie werd uitgevoerd bij 200 jonge vrouwen (≤55 jaar) met darmkanker. Van deze vrouwen hadden, c.q. ontwikkelden, 5% (n=10) OM. Wij concludeerden dat dit een klinisch relevante bevinding is en dat er een verbeterde surveillance moet komen voor jonge vrouwen met darmkanker. Dit wordt ondersteund door het feit dat het daadwerkelijke risico op het ontwikkelen van OM waarschijnlijk hoger ligt. Dit kan onder andere komen omdat patiënten die niet zijn geopereerd in verband met darmkanker en OM, vanwege bijvoorbeeld een te uitgebreide gemetastaseerde ziekte of een beperkt niveau van algemene fysieke fitheid, niet zijn geïncludeerd in deze studie. Wat verder bij kan dragen aan een onderschatting van het werkelijke risico is dat het aantal patiënten met microscopische uitzaaiingen in de ovaria binnen dit cohort onbekend was. De onderschatting van dit risico zou daarnaast ook aanwezig kunnen zijn in retrospectieve studies die de totale vrouwelijke darmkankerpopulatie – dus inclusief de oudere patiënten – hebben onderzocht. **Hoofdstuk 4** beschrijft een systematische review waarbij een overzicht wordt gegeven van de bestaande literatuur die het vóórkomen van OM bij jonge vrouwen (≤55 jaar) met darmkanker als uitkomst had. Uit de resultaten kwam naar voren dat gemiddeld 4,6% van de vrouwen met darmkanker [95% betrouwbaarheidsinterval: 4,0;5,4] (157 patiënten van de totaal 3379 patiënten) OM hadden of ontwikkelden. Aangezien niet alle studies (n=14) uit patiënten bestond met synchrone metastasen én metastasen welke gedurende follow-up werden gevonden, is het waarschijnlijk dat er sprake is van een onderschatting. Toch laat de cohortstudie uit Hoofdstuk 3 eenzelfde uitkomst zien als deze systematische review. Daarom kan geconcludeerd worden dat één op de twintig jonge patiënten met darmkanker OM hebben bij diagnose of deze ontwikkelen gedurende de follow-up.

Verschillende studies rapporteren dat OM in vergelijking met metastasen in andere organen minder gevoelig lijken te zijn voor systemische therapie. Om deze reden wordt

gesuggereerd dat de aanwezigheid van een ovariële metastase in patiënten met darmkanker een negatieve prognostische factor is. Daarom wordt in **Hoofdstuk 5**, eveneens aan de hand van een landelijke patiëntenpopulatie-studie, uitgezocht wat de impact is van OM in patiënten met stadium IV darmkanker die behandeld worden met systemische therapie. In deze studie werd gebruik gemaakt van een zogenoemde propensity-score gematchte analyse, hierdoor kon er op basis van verschillende patiënt eigenschappen (variabelen) twee grotendeels gelijkende patiëntengroepen (samples) gevormd worden. Hierbij was het enige verschil het wel of niet hebben van een OM. Het uiteindelijke resultaat toonde dat de aanwezigheid van een OM niet is geassocieerd met een slechtere totale overleving. Omdat de aanwezigheid van (het aantal) comorbiditeiten voor veel patiënten onbekend was, kan het zijn dat dit ongelijk verdeeld was over de twee patiëntengroepen. Daarnaast worden in deze studie alleen darmkankerpatiënten geëvalueerd die behandeld werden met systemische therapie. Het kan daarom zijn dat de resultaten hierdoor vertekend zijn door middel van een selectiebias. De resultaten moeten daarom voorzichtig worden geïnterpreteerd. Toekomstige 'medicijn georiënteerde' studies zijn verder nodig om de daadwerkelijke radiologische respons van verschillende metastasen, inclusief OM, met bijbehorende overlevingskans, te onderzoeken. In **Hoofdstuk 6** wordt naar een verklaring gezocht voor de oorzaak van de vermeende verminderde gevoeligheid voor systemische therapie van OM ten opzichte van metastasen in andere organen. Een verklaring hiervoor zou kunnen zijn dat er sprake is van een verschil in genexpressie en/of eiwit- en stofwisselingsprofiel (biomarkers) tussen de primaire tumor en de bijbehorende ovariële metastase. Echter, de biomarker-status tussen de primaire tumor en ovariële metastase blijkt op basis van deze studie volledig overeen te komen. De verminderde gevoeligheid voor systemische therapie wordt daarom zeer waarschijnlijk niet veroorzaakt door een verschil in biomarker-status. Op basis van deze studie kan ook gesuggereerd worden dat, ten aanzien van de te bepalen systemische therapie, de ovariële metastase geen aanvullend biomarker-onderzoek behoeft als de primaire tumor reeds is geanalyseerd.

Een derde landelijke patiëntenpopulatie-studie wordt beschreven in **Hoofdstuk 7**. In dit hoofdstuk wordt het vóórkomen van eierstokkanker in een darmkankerpopulatie vergeleken met het vóórkomen van eierstokkanker in de algemene populatie. De uiteindelijke resultaten toonden aan dat eierstokkanker 20% vaker voorkomt bij vrouwen met darmkanker in vergelijking met de algemene populatie. Eerdere studies worden daarom door dit onderzoek bevestigd. Wel werd de diagnose eierstokkanker het vaakst gesteld binnen het eerste jaar na de diagnose darmkanker. Er zou daarom sprake kunnen zijn van een vertekend beeld doordat eierstokkanker makkelijker gevonden kan worden door de (intensieve) follow-up bij vrouwen met darmkanker (surveillance bias). Daarnaast kan het zijn dat de OM bijvoorbeeld door een beperkte diagnostische accuraatheid aangezien zijn voor eierstokkanker (detection bias) terwijl het in feite om een colorectale metastase ging. De aanwezigheid van een detection bias wordt mede

waarschijnlijk geacht doordat: 1. eierstokkanker werd het meest gediagnosticeerd in de eerste geanalyseerde periode (1989-1997); en 2. jongere vrouwen (≤55 jaar) werden vaker gediagnosticeerd met eierstokkanker. Deze resultaten moeten daarom geverifieerd worden door prospectieve studies. Een prospectieve studie die onder andere kijkt naar het vóórkomen van ovariumkanker binnen een darmkankerpopulatie is reeds door onze studiegroep opgezet en wordt behandeld in Hoofdstuk 9.

Een preventieve adnexextirpatie kan aangeboden worden aan vrouwen met darmkanker om (de uitgroei van) OM en het ovariumcarcinoom te voorkómen. De rationale hierachter wordt beschreven in **Hoofdstuk 8**. In dit hoofdstuk worden de argumenten voor een preventieve adnexextirpatie beschreven met de bijbehorende (mogelijke) consequenties. De volgende argumenten voor een preventieve adnexextirpatie worden gegeven: 1. een preventieve adnexextirpatie zou de prognose van vrouwen met darmkanker substantieel kunnen verbeteren; 2. om vergelijkbare oncologische redenen wordt al jarenlang een preventieve adnexextirpatie uitgevoerd bij vrouwen met een endometriumcarcinoom of een urotheelcelcarcinoom van de blaas; 3. een preventieve adnexextirpatie wordt geadviseerd in de Nederlandse richtlijn 'Colorectaal carcinoom'; 4. ovariële (micro) metastasen zijn in de meeste gevallen ongevoelig voor systemische therapie; 5. de gevolgen van een adnexextirpatie zijn voor postmenopauzale vrouwen gering; 6. de behandeling zou zeer kosteneffectief kunnen zijn; 7. de behandeling zou de incidentie van het primair ovariumcarcinoom kunnen verlagen; 8. het hoort bij gezamenlijke besluitvorming om patiënten een keuze hierin te geven. Het nadeel van een aanvullende adnexextirpatie is dat de operatie in totaal langer duurt en gepaard kan gaan met een bijkomend risico op complicaties, zoals een bloeding of ureterletsel, hoewel het risico daarop laag is. Daarnaast kan het verwijderen van de adnexen een verandering in de hormoonproductie teweegbrengen, aangezien de ovaria bij postmenopauzale vrouwen nog androgenen produceren. Het wegvallen van deze androgeenproductie kan daardoor een negatieve invloed hebben op het libido. Voor jongere, premenopauzale vrouwen zijn er, naast de eerdergenoemde voor- en nadelen, extra negatieve gevolgen van een preventieve adnexextirpatie te verwachten. Bij deze vrouwen treedt de overgang vervroegd op. De nadelige effecten hiervan op de korte termijn zijn bekend: verlaagd libido – ook op de lange termijn –, infertiliteit, opvliegers, nachtzweten en slaapproblemen. Op de lange termijn bestaat er een verhoogd risico op vaginale klachten als gevolg van atrofie, osteopenie of osteoporose, dementie en hart- en vaatziekten. In de literatuur is beschreven dat vrouwen die vóór hun 45e levensjaar een preventieve dubbelzijdige verwijdering van de eierstokken hebben ondergaan, een verhoogd risico hebben om te overlijden. De verwachting is wel dat meerdere van de nadelige effecten van een preventieve adnexextirpatie door hormoonvervangende therapie kunnen worden tegengegaan. De huidige kennis over de voor- en nadelen van een preventieve adnexextirpatie wordt sinds 2020 in verschillende Nederlandse ziekenhuizen gedeeld tijdens het chirurgisch consult voorafgaand aan de

operatie. Hierbij wordt gebruik gemaakt van een informatie- en keuzemodule welke wordt aangeboden aan postmenopauzale patiënten. De evaluatie hiervan wordt verder uitgediept in het volgende hoofdstuk.

Het studieprotocol van een prospectieve multicenter cohortstudie wordt beschreven in **Hoofdstuk 9**. Deze studie heeft als beoogd doel het bepalen van de incidentie van zowel OM áls het ovariumcarcinoom bij postmenopauzale vrouwen met darmkanker. Na het doornemen van een informatie- en keuzemodule (zie eerder) kan er gekozen worden voor een preventieve adnexextirpatie. De studiepopulatie bestaat uit vrouwen die tijdens de darmkankeroperatie een preventieve adnexextirpatie ondergaan en vrouwen die enkel een darmresectie ondergaan waarbij de adnexen in situ worden gelaten. Hieruit volgend kan het aantal te behandelen patiënten om één ovariële maligniteit (inclusief micrometastase) te voorkómen, bepaald worden. De secundaire studie-uitkomsten zijn met name gericht op de gevolgen van de preventieve adnexextirpatie zoals gerelateerde morbiditeit en de impact van deze aanvullende chirurgie op de totale overleving en kwaliteit van leven. De verwachting is dat de resultaten van deze studie antwoord kunnen geven op de vraag of een preventieve adnexextirpatie van toegevoegde waarde is bij postmenopauzale vrouwen met darmkanker. In deze studie worden jonge/ premenopauzale vrouwen buiten beschouwing gelaten. Indien een soortgelijke studie voor deze jongere populatie overwogen wordt, zal er in ieder geval een uitvoeriger informed consent plaats moeten vinden, vanwege de eerder beschreven consequenties van een chirurgisch geïnduceerde menopauze. In dit geval zal mogelijk ook een extra gynaecologisch consult noodzakelijk zijn.

Samenvattend kan op basis van dit proefschrift gesteld worden dat ovariële maligniteiten – bij met name jonge vrouwen met darmkanker –, niet zeldzaam zijn. Ook wordt een onderschatting van OM in de totale darmkankerpopulatie aannemelijk gemaakt. Daarnaast is het mogelijk om een dergelijke maligniteit te voorkómen, waarbij de klinische meerwaarde vooralsnog onduidelijk is. Verder moet vermeld worden dat de gevonden en gepresenteerde resultaten en conclusies in deze hoofdstukken gebaseerd zijn op retrospectieve data en dat verdere validatie hiervan middels prospectieve studies wenselijk is. Hoewel de preventieve adnexextirpatie met bijbehorende voor- en nadelen expliciet worden beschreven in Hoofdstuk 8 en 9, is het niet het ultieme doel van dit proefschrift om een preventieve chirurgische ingreep standaard aan alle vrouwen met darmkanker aan te bieden. Ons doel is wel dat patiënten adequaat worden geïnformeerd over de kans op het ontwikkelen van ovariële maligniteiten waarbij, door middel van gezamenlijke besluitvorming ("shared decision making"), kan worden gekozen voor een preventieve adnexextirpatie. Op basis van onze opgezette prospectieve studie denken wij in de toekomst een uitspraak te kunnen doen over de verdere meerwaarde van een preventieve adnexextirpatie in postmenopauzale setting.

Appendix II List of publications

Bakkers C, van der Meer R, Roumen RM, Lurvink RJ, Lemmens VE, van Erning FN, de Hingh IH. Incidence, risk factors, treatment, and survival of ovarian metastases of colorectal origin: a Dutch population-based study. *Int. J. Colorectal Dis.* 2020;35:1035–1044. https://doi.org/10.1007/s00384-020-03555-5

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van der Meer R, Jeuken JWM, Bosch SL, van Erning FN, Simkens LHJ, de Hingh IHJT, Roumen RMH Biomarker concordance between primary colorectal cancer and ovarian metastases: a Dutch cohort study. *J. Canc. Res. Clin. Oncol.* 2022 [Online ahead of print] https://doi.org/10.1007/s00432-022-04502-3

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van der Meer R, de Hingh IHJT, Coppus SFPJ, van Erning FN, Roumen RMH. De ontwikkeling van het primair ovariumcarcinoom na een colorectale tumor; analyse van Nederlandse Kanker Registratie-data [short report]. *Medisch Journaal*. 2022:1:8-10

Appendix III Curriculum vitae auctoris

Richard van der Meer was born on the 23th of October 1990, in Harderwijk, the Netherlands. In his adolescence he developed an interest in sports, especially running and bike racing. After graduating in 2010 he enrolled in the Maastricht University Medical School. Following the completion of his bachelor and master he worked as a general surgery resident not-in-training in the St. Antonius Hospital, Nieuwegein for two years. After this period he enrolled as a PhD candidate in the Maastricht University under the guidance of Prof. Dr. Ignace de Hingh, Dr. Rudi Roumen, and Felice van Erning. The period as a PhD candidate was combined with clinical work at the Post-Surgical Care Unit and Intensive Care Unit as a resident not-in-training.

Richard currently works as an anesthesiology resident in training at the Radboud University Medical Center, Nijmegen.