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STUDIES ON THE ROLE OF OVARIAN METASTASES IN COLORECTAL CANCER

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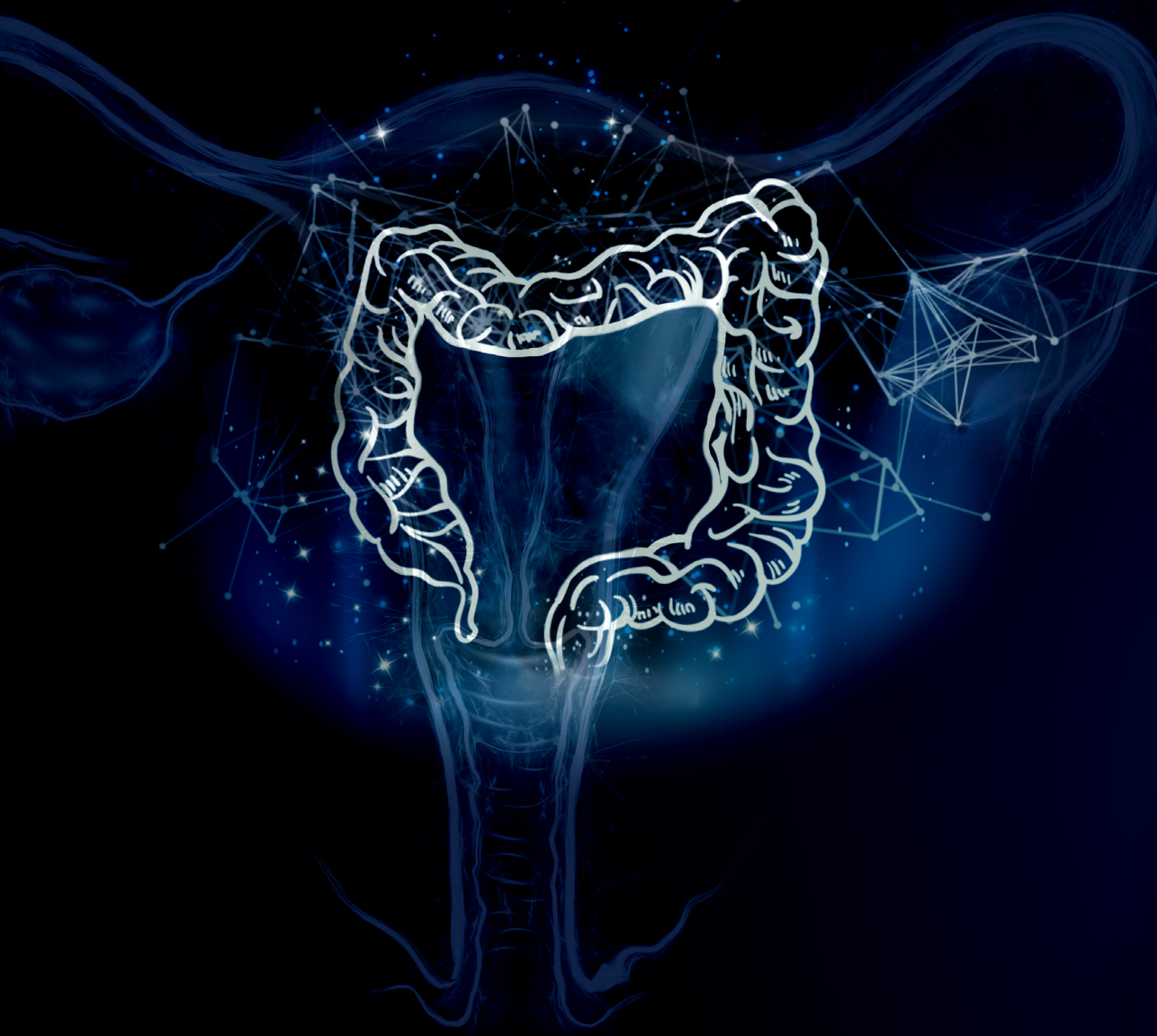

CHAPTER 10

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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