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International Journal of Colorectal Disease (2022) 37:1865–1873
https://doi.org/10.1007/s00384-022-04217-4

RESEARCH

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

R. van der Meer[1] · C. Bakkers[2] · J. A. Wegdam[3] · T. Lettinga[4] · E. G. Boerma[5] · F. Aarts[6] · I. H. J. T. de Hingh[2,7] · R. M. H. Roumen[1,7]

Accepted: 8 July 2022 / Published online: 20 July 2022

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.

Keywords Colorectal cancer · Ovarian metastases · Young women

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, and in women [5], 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].

✉ R. van der Meer
romic.resurge@mmc.nl; richard.van.der.meer@mmc.nl

1 Department of Surgery, Máxima Medical Center, P.O. Box 7777, 5500 MB Veldhoven, The Netherlands

2 Department of Surgery, Catharina Cancer Institute, Eindhoven, The Netherlands

3 Department of Surgery, Elkerliek Hospital, Helmond, The Netherlands

4 Department of Surgery, Sint Jans Gasthuis, Weert, The Netherlands

5 Department of Surgery, Zuyderland Hospital, Geleen, The Netherlands

6 Department of Surgery, VieCuri Medical Center, Venlo, The Netherlands

7 GROW - School for Oncology and Development Biology, Maastricht University, Maastricht, Netherlands

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 was 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 to 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, IL, 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

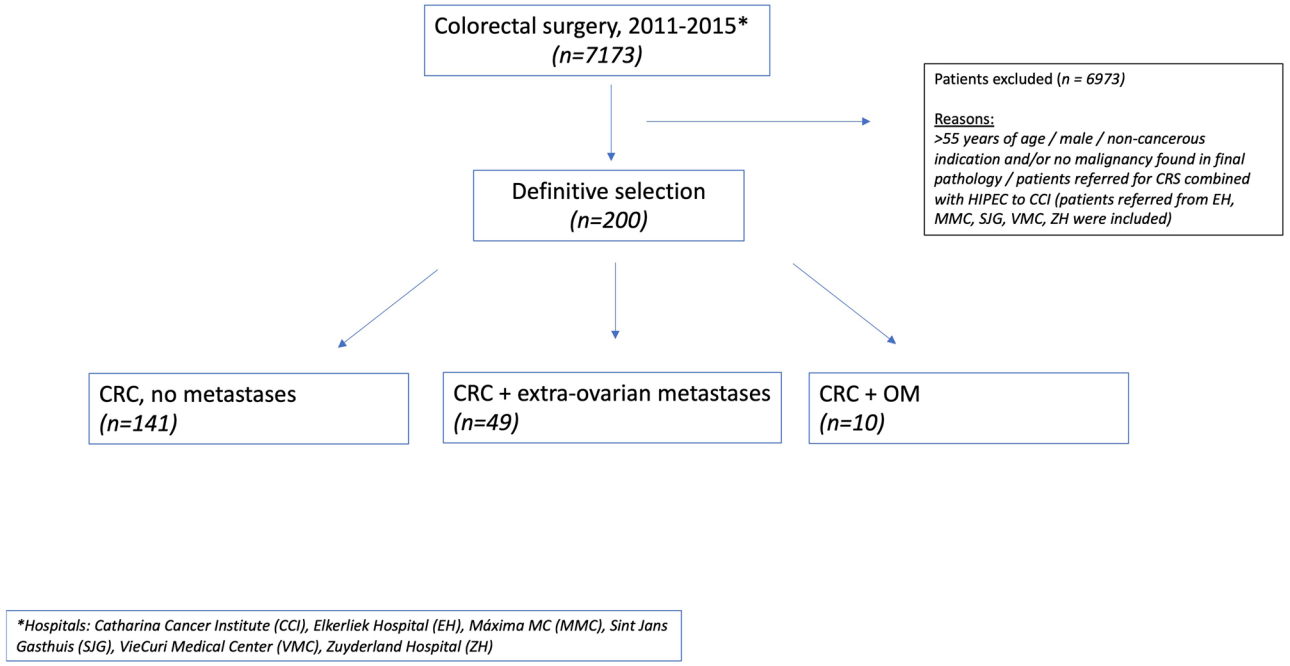

Fig. 1 Flowchart of patient selection

metastases to the ovary. The median time of the occurrence of metachronous metastases was 19 months (range 11–62 months).

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.

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 was not statistically significant different (*p-values* of 0.701 and 0.665, respectively).

Additional findings

Of all CRC patients with OM, 5 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

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]

Ten patients were diagnosed with OM. Five had synchronous OM and five other patients developed metachronous metastases to the ovary. The age at CRC diagnosis varied in a range of 29–55 years. The time between CRC diagnosis and the occurrence of metachronous metastases varied in a range of 11–62 months. Resection of the primary tumor was categorized curative (no residual disease) in nine patients and palliative in one patient. Tumor status was T3 and T4 in respectively three and seven patients. Nodal status was N0, N1, and N2 in one, five, and four 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.

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

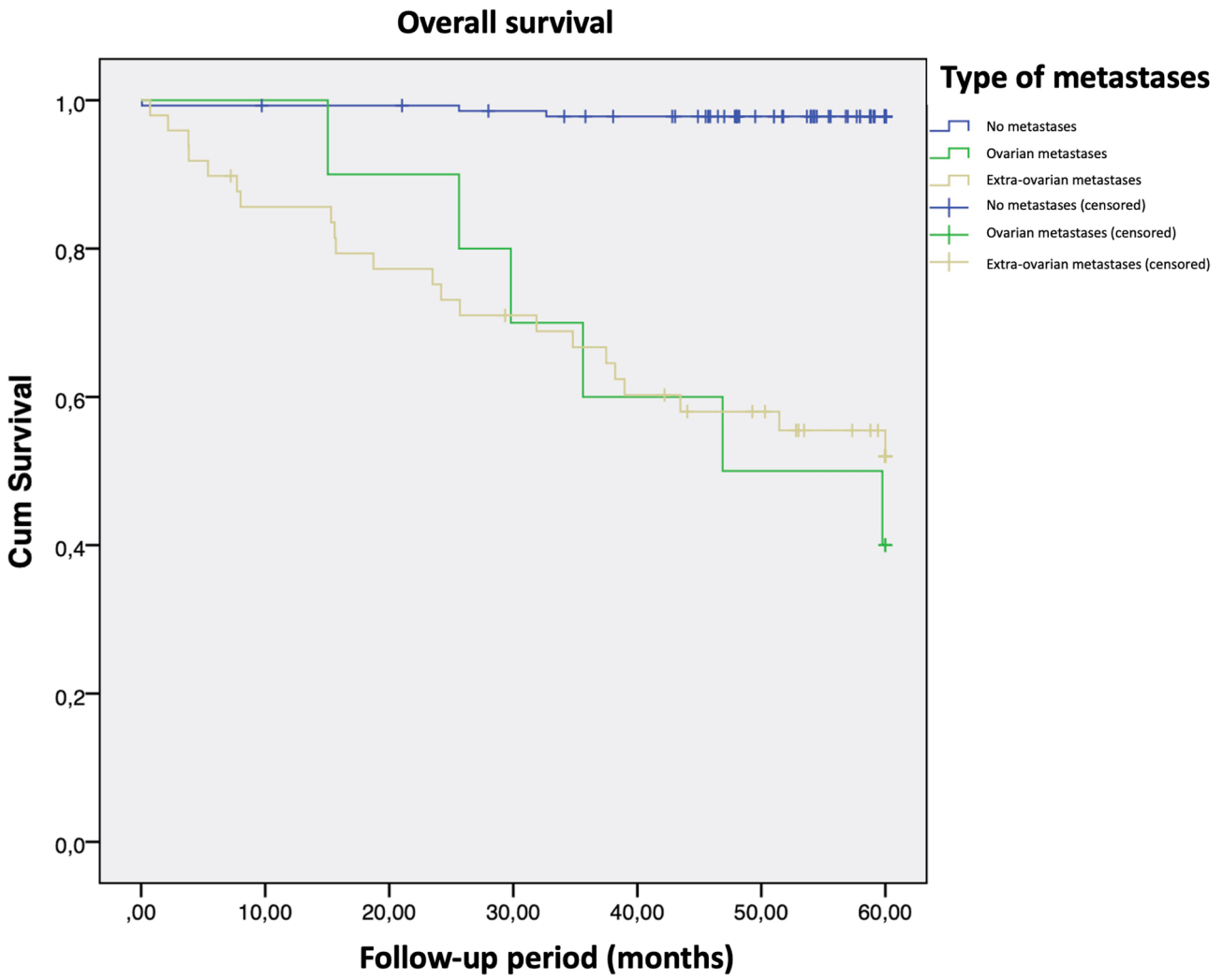

Fig. 2 Kaplan–Meier overall survival

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 the colon to the ovary is unknown; however, several metastatic pathways have been suggested. For example, direct spread from the primary tumor and 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, 34–38]) 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 and 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 prompt 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 min), 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.

Author contribution RM, RR, and IH contributed to the conception and design of this study. Material preparation, data collection, and data analysis were performed by RM. The first draft of the manuscript was written by RM, and all authors provided feedback on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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