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# Perioperative Outcomes of Postmenopausal Women with Colorectal Cancer Undergoing Prophylactic Salpingo-oophorectomy

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## Abstract

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**Objectives** Women with colorectal cancer have an increased risk of developing ovarian malignancies, which have a poor prognosis. Shared decision making on the possibility of prophylactic salpingo-oophorectomy (PSO) during colorectal cancer surgery in postmenopausal women has, therefore, been implemented. Effects of PSO on perioperative parameters are unknown. This study therefore compares perioperative parameters between women with and without PSO.

**Materials and Methods** Women undergoing colorectal cancer surgery between January 2020 and March 2023 in four centers in the Netherlands offering the possibility of PSO were included. Perioperative parameters were compared between the group with and without PSO.

**Statistical Analysis** Continuous data were analyzed with independent *t*-tests or nonparametric tests when applicable. Categorical variables were analyzed with chi-square tests. Propensity score matching was performed to control for potential confounders. The variables age, American Society of Anesthesiologists classification, TNM stages, and type of surgery were used as respective covariates. Perioperative data were again analyzed between the matched groups. A sensitivity analysis including all participants was performed to evaluate the effect of PSO on duration of admission and on complications.

**Results** The present study included 112 women who underwent PSO and 28 who did not. The PSO group was significantly younger (median: 74 vs. 79 years, $p = 0.002$), had a shorter hospital stay (median: 4 vs. 6 days, $p = 0.006$), and experienced less overall postsurgical complications (31 vs. 64%, $p = 0.002$). These differences were neither observed after propensity score matching nor after sensitivity analysis. Malignant adnexal tissue was identified in three patients.

**Keywords**

- prophylactic salpingo-oophorectomy
- shared decision making
- ovarian malignancies
- colorectal cancer
- surgical outcomes

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**Conclusion** PSO in combination with elective colorectal cancer surgery in postmenopausal women does not lead to different or worse perioperative outcomes compared with the group without PSO. Nonetheless, the decision to undergo this combined surgery should be made on individual basis. Future research needs to focus on long-term follow-up and generalizability.

## Introduction

Colorectal cancer (CRC) is the third most common cancer in men and women.[1] For women, there is a 1 in 35 chance to develop CRC during lifetime. Women with a history of CRC display an elevated likelihood of developing an ovarian malignancy. These might develop as synchronous or metachronous metastases, but also as second primary cancer.[2,3] Ovarian malignancies are one of the most complex cancers to treat, with high mortality rates placing them at number five for the causes of death for women.[4] Symptoms of ovarian malignancies often present at a very advanced stage. Moreover, since ovarian metastases often are considered to be resistant to systemic treatments, these patients have a poor prognosis.[5,6] Although prognosis often depends on the stage of cancer, research has shown that ovarian metastases from CRC have an even worse prognosis than primary ovarian cancer.[7]

Given the onerous nature of diagnosing and treating ovarian malignancies, prophylactic salpingo-oophorectomy (PSO) for individuals undergoing surgery for CRC is debatable.[8,9] PSO is especially interesting for postmenopausal women, considering they are not physiologically dependent on their ovaries anymore. These patients could potentially be spared any chance of later presenting ovarian malignancies and additional treatment with all its risks included.[8]

The U.S. guidelines for CRC state that "*It is reasonable to offer prophylactic oophorectomy to all postmenopausal patients.*"[10] This shared decision making possibility about PSO has been implemented in the Dutch guideline for CRC management in 2019 as well. Máxima Medical Center (MMC; Veldhoven, The Netherlands) has developed an information module to inform patients about PSO. The use of this module for postmenopausal CRC patients was implemented in 2020. Nowadays, 15 Dutch hospitals implemented this same information module. Since the short-term and long-term effects of PSO in postmenopausal CRC patients are unknown, the effect of PSO with surgery for CRC in this population will be evaluated by a large prospective observational study in the future.[9] In addition, an evaluation of perioperative outcomes is warranted to correctly counsel future patients about the pros and cons of PSO.

The present study therefore aims to evaluate perioperative outcomes of PSO in postmenopausal women undergoing surgery for CRC. We hypothesized that there will be no significant differences in perioperative parameters due to PSO being a short, low-risk procedure.

## Materials and Methods

### Study Population

The present observational cohort study included preliminary data from the Dutch PSO evaluation study.[9] It includes prospectively collected data from four Dutch hospitals: MMC, Catharina Hospital Eindhoven, St. Jans Gasthuis Weert, and Dijklander Hospital Hoorn. Postmenopausal women (60 years or older) scheduled for curative CRC surgery between January 2020 and February 2023 who were informed with the information module and who gave informed consent were eligible for this study. The choice to perform a PSO was based on the patient's preference. Surgeries, including the PSO procedure, were all performed by experienced CRC surgeons. Approval of the medical ethics committee was requested but formal approval was deemed unnecessary, according to Dutch law (METC Máxima MC). The study procedure was approved by the institutional review board of each participating hospital.

### Baseline and Perioperative Parameters

Baseline characteristics included age, body mass index (BMI), comorbidities, American Society of Anesthesiologists (ASA) classification, and CRC TNM stage. Perioperative parameters included type of surgery, surgical approach, duration of surgery, and duration of admission. If surgical conversion applied, the surgical approach was considered as an open procedure. Blood loss and blood transfusion during admission were evaluated for MMC patients only ($n = 91$). Any transfusions preoperatively or weeks to months after the surgery were not considered in this analysis. Surgical complications were labeled using the Clavien–Dindo Classification (CDC).[11] The highest scored complication was initially used to assign a single CDC score. This score was converted to two different dichotomous variables: one variable indicating the presence of any complication, defined as CDC grade $\geq$1; the other variable indicating the presence of a severe complication, defined by CDC grade $\geq$3a.

### Pathology

The pathologist reports about the extirpated adnexa were scored as follows: no adnexa available, no suspect or malignant anomaly, and suspect or malignant anomaly. This information solely referred to macroscopic and microscopic findings by the pathologist.

### Statistical Analysis

SPSS version 22 was used for the analyses.[12] Perioperative data were compared between the two groups; PSO versus the

 

group without PSO (nPSO). Normally distributed data were analyzed with independent *t*-tests. Not normally distributed data were analyzed with nonparametric tests. Categorical variables were analyzed with chi-square tests. Propensity score matching was performed to control for potential confounders. The variables age, ASA classification (clustered), TNM stages (clustered), and type of surgery (clustered) were used as respective covariates. Perioperative data were also analyzed between the matched groups. To exclude the presence of bias due to matching, sensitivity analyses including all participants were performed. In two regression analyses (linear and logistic), the effect of PSO on duration of admission and on complications was evaluated. These outcomes were selected, since they initially showed a significant difference between groups. In addition to PSO execution, the same independent variables from propensity score matching were included in this regression analyses as covariates (age, ASA classification, TNM stage, and surgery type). Python version 3.8.13 was used for propensity score matching.[13] Data about gross pathology were investigated in a descriptive manner.

## Results

### Baseline and Perioperative Parameters

In total, 140 women were included, of which 112 women underwent PSO, and 28 women did not. ►Table 1 shows the baseline characteristics and perioperative parameters of both groups. The PSO group had a significantly lower median age of 74 years compared with 79 years for the nPSO group ($p = 0.002$). No significant differences were observed regarding BMI, ASA classification, or TNM stages. Neoadjuvant therapy was received in 10% of the PSO group. Previous salpingo-oophorectomy was observed in 21% of the women in the nPSO group. There was no significant difference among the groups regarding surgery type ($p = 0.176$) and surgical approach ($p = 0.56$). Conversions were needed in four (3.6%) cases of the PSO group and four (14.3%) cases of the nPSO group. Surgery duration did not differ between both groups (PSO: median 142 minutes, nPSO: median 144 minutes, $p = 0.82$). Comparing the available blood loss data showed no significant difference ($p = 0.90$). Around 3% of the PSO group and 7% of the nPSO group required blood transfusion. The PSO group had shorter hospital admission than the nPSO group (PSO: median 4 days, nPSO: median 6 days, $p = 0.006$). The PSO group appeared to generally have less postsurgical complications than the nPSO group ($p = 0.002$), but not significantly less severe complications ($p = 0.18$). The amount of complications related to intestinal damage was not different between the PSO and nPSO groups (6.2 vs. 7.1%, respectively). These included three bleedings, four colon perforations, and one spleen injury in the PSO group, and one bleeding and one unresectable gut in the nPSO group. No specific ureter injuries were noted in the PSO group.

**Table 1** Baseline and perioperative parameters before propensity score matching

| | | PSO, $n = 112$ | nPSO, $n = 28$ | *p*-Value |
|---|---|---|---|---|
| **Baseline characteristics** | | | | |
| Age in years (median, IQR) | | 74 (68, 79) | 79 (73, 84) | **0.002** |
| BMI (median, IQR) | | 25 (22, 28) | 25 (22, 28) | 0.915 |
| ASA classification (*n*, %) | ASA-1 and ASA-2<br>ASA-3 and ASA-4 | 82 (73%)<br>30 (27%) | 16 (57%)<br>12 (43%) | 0.079 |
| TNM stages (*n*, %) | Stage 1<br>Stage 2<br>Stage 3 and Stage 4 | 37 (33%)<br>33 (30%)<br>42 (38%) | 7 (25%)<br>14 (50%)<br>7 (25%) | 0.118 |
| Neoadjuvant therapy (*n*, %) | | 11 (10%) | – | – |
| Previous salpingo-oophorectomy (*n*, %) | | – | 6 (21%) | – |
| **Perioperative parameters** | | | | |
| Surgery type (*n*, %) | Right colon<br>Left colon<br>Rectum | 57 (51%)<br>26 (23%)<br>29 (26%) | 19 (78%)<br>6 (21%)<br>3 (11%) | 0.176 |
| Surgical approach (*n*, %) | Laparoscopic<br>Open | 97 (87%)<br>15 (13%) | 24 (86%)<br>4 (14%) | 0.555 |
| Surgery duration in min (median, IQR) | | 142 (119, 167) | 144 (107, 173) | 0.823 |
| Blood loss in mL (median, IQR) | | 0 (0, 100) | 0 (0, 75) | 0.900 |
| Duration of admission in days (median, IQR) | | 4 (3, 6) | 6 (4, 8) | **0.006** |
| Complications (CDC ≥ grade 1) (*n*, %) | | 35 (31%) | 18 (64%) | **0.002** |
| Serious complications (CDC ≥ grade 3) (*n*, %) | | 19 (17%) | 8 (29%) | 0.184 |

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CDC, Clavien–Dindo Classification; IQR, interquartile range; nPSO, group without PSO; PSO, prophylactic salpingo-oophorectomy.
Note: *p*-Values in bold indicate significance. A significance level of $p < 0.05$ was chosen.

 

**Table 2** Baseline and perioperative parameters of the matched study population

| | | PSO, $n = 28$ | nPSO, $n = 28$ | *p*-Value |
|---|---|---|---|---|
| **Baseline characteristics** | | | | |
| Age in years (median, IQR) | | 77 (70, 80) | 79 (73, 84) | 0.156 |
| BMI (median, IQR) | | 25 (21, 28) | 25 (22, 28) | 0.606 |
| ASA classification (*n*, %) | ASA-1 and ASA-2<br>ASA-3 and ASA-4 | 14 (50%)<br>14 (50%) | 16 (57%)<br>12 (43%) | 0.789 |
| TNM stages (*n*, %) | Stage 1<br>Stage 2<br>Stage 3 and Stage 4 | 10 (36%)<br>11 (39%)<br>7 (25%) | 7 (25%)<br>14 (50%)<br>7 (25%) | 0.641 |
| Neoadjuvant therapy (*n*, %) | | 1(4%) | – | – |
| Previous salpingo-oophorectomy (*n*, %) | | – | 6 (21%) | – |
| **Perioperative parameters** | | | | |
| Surgery type (*n*, %) | Right colon<br>Left colon<br>Rectum | 20 (71%)<br>5 (18%)<br>3 (11%) | 19 (78%)<br>6 (21%)<br>3 (11%) | 0.943 |
| Surgical approach (*n*, %) | Laparoscopic<br>Open | 22 (79%)<br>6 (21%) | 24 (86%)<br>4 (14%) | 0.729 |
| Surgery duration in min (median, IQR) | | 135 (122, 164) | 144 (107, 173) | 0.933 |
| Blood loss in mL (median, IQR) | | 0 (0, 75) | 0 (0, 100) | 0.620 |
| Duration of admission in days (median, IQR) | | 6 (4, 8) | 6 (4, 8) | 0.691 |
| Complications (CDC $\geq$ grade 1) (*n*, %) | | 12 (42%) | 18 (64%) | 0.180 |
| Serious complications (CDC $\geq$ grade 3a) (*n*, %) | | 6 (21%) | 8 (29%) | 0.758 |

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CDC, Clavien–Dindo Classification; IQR, interquartile range; nPSO, group without PSO; PSO, prophylactic salpingo-oophorectomy.
Note: *p*-Values in bold indicate significance. A significance level of $p < 0.05$ was chosen.

### Baseline and Perioperative Parameters after Propensity Score Matching

After propensity score matching, both groups included 28 women. The PSO group was matched to the nPSO group based on age, ASA classification, TNM stage, and type of surgery. ►Table 2 shows the baseline characteristics and perioperative parameters of both groups. As a result of the propensity score matching, there were no significant differences between the groups regarding baseline characteristics. After matching, the PSO group does neither have a significantly shorter duration of admission ($p = 0.69$) anymore, nor does the PSO group has less overall postsurgical complications ($p = 0.18$) and less severe complications ($p = 0.76$) than the nPSO group.

### Sensitivity Analysis of the Unmatched Population

The additional regression analysis included all 140 participants. The linear regression with duration of admission in days as outcome showed that PSO execution did not have a significant effect ($p = 0.33$). In contrast, age ($p = 0.02$) and TNM stage 1 compared with TNM stage 2 ($p = 0.002$) did have a significant effect on duration of admission. Further, the logistic regression showed that PSO execution also did not have a significant effect on the amount of complications ($p = 0.07$). In contract, ASA classification ($p = 0.003$) and TNM stage 1 compared with TNM stage 2 ($p = 0.04$) did have a significant effect on the amount of complications. These findings confirm the results after propensity score matching.

### Pathology

Adnexal tissue of 112 participants in the PSO group was analyzed macroscopically and microscopically without additional immunostaining. The reports showed two malignant adnexal tissues in two different patients; one tuba carcinoma and one ovarian cancer. In another patient, continued growth of the CRC was found in the adnexal tissue.

## Discussion

PSO in combination with elective CRC surgery is newly implemented for postmenopausal women in 15 hospitals in the Netherlands. So far, no studies have investigated the perioperative outcomes in these women. The present study shows that PSO performed during elective CRC surgery does not lead to more complications, a longer operating time or hospital admission and thus is a safe procedure.

The age difference before propensity score matching gives insight into the patient population that do not opt for PSO. Some reports show that older patients are hesitant to choose surgical interventions that can require longer anesthesia. The elderly worry more about cognitive or physical complications from longer anesthesia and have a more apparent fear

 

of not waking up.[14,15] One might also argue that elderly simply do not find it necessary to undergo this additional effort. It could also be that physicians do not recommend PSO because of the presence of various comorbidities. The pros and cons of PSO should be discussed on an individual basis with the surgeon or nurse practitioner, enabling a shared decision making process on this issue.

PSO for individuals undergoing surgery for CRC is still debatable.[8,9] Besides the logical beneficial effect PSO has on sparing any chance of ovarian malignancies and therefore also quality of life, the effectiveness of PSO could also be evaluated based on (long term) survival. A meta-analysis showed that there was no difference in survival between CRC patients with PSO and without PSO.[16] The four included studies, however, had a limited number of patients, and were often biased. So far, only one randomized controlled trial was performed.[17] In that report, CRC patients with PSO showed a 5-year recurrence-free survival of 80% compared with 65% in the nPSO group. This finding was, however, not significant due to the study being underpowered. Additional evidence for the effect of PSO on survival will be hard to get, since randomizing patients will be unethical, and a large number of patients and a long follow-up period are required. We therefore started a large prospective observational study to analyze the number needed to treat to prevent future ovarian malignancies and to see what the long-term outcomes of both patient groups will be.[9] In light of discrepancies in the literature regarding the potential role of adnexa in postmenopausal women, assessing hormonal effects in future studies could also offer valuable insights. It is worth noting that premenopausal CRC patients are more frequently diagnosed with ovarian metastases than postmenopausal women.[18,19] However, premenopausal women remain significantly reliant on the physiological role of their adnexa. This, of course, creates reservations about combining CRC surgery with PSO in their cases. While this discussion is beyond the scope of the current study, it is a pertinent aspect to consider for future studies.

In the PSO group, one tuba carcinoma, one ovarian cancer, and one continued growth of the CRC in adnexal tissue have been identified by the pathologists (~2%). This is less than we anticipated. Since there was no immunostaining of the tissues, micro-metastases could have been missed. Leydig cell hyperplasia and teratomas are rare in postmenopausal women.[20–22] However, in our PSO group two additional patients were found to have Leydig cell hyperplasia and one patient had a mature teratoma in the ovaries. Although Leydig cell hyperplasia is often benign, it can cause hormonal imbalances and a surgical intervention may be necessary in some cases.[20,21] A teratoma can cause androgen-related complications and explain some experienced hormonal symptoms.[22] These pathologic findings do not provide strong evidence to support PSO with colorectal surgery, but it should be considered in conjunction with the other findings. A more accurate assessment by immunostaining should be conducted to identify any potential presence of more micro-metastases.

For this study, most participants ($n = 91$) were treated at the same hospital, namely MMC. In the future, a larger sample size, with a more even distribution among different Dutch hospitals, would improve the generalizability of our findings. The propensity score matching ultimately resulted in excluding many participants belonging to the PSO group. Therewith, collected data are not only negated but it also does not represent the reality: women did choose PSO more frequently. Although regression analysis showed comparable results, it is desirable to have a larger group, especially nPSO.

## Conclusion

The present study provides valuable insights into the perioperative outcomes of postmenopausal women who choose to undergo PSO in addition to curative CRC surgery. PSO does not appear to have a significant negative impact on surgical outcomes. However, the decision to undergo PSO should be made on an individual basis, considering the potential benefits and risks, as well as personal preferences and values. Further research is needed to better understand the long-term effects of PSO on overall health and quality of life in postmenopausal women.

### Ethical Approval

Approval of the medical ethical committee was requested but formal approval was deemed unnecessary, according to Dutch law (METC Máxima MC). The study procedure was approved by the institutional review board of each participating hospital.

### Author's Contribution

The study concepts were developed by E.S., J.Z., M.H., J.B., and R.R., while the study design was created by E.S., J.Z., M.H., and R.R. Data acquisition was carried out by E.S., J.Z., M.H., J.B., T.L., J.W., and R.R. E.S. and M.H. were responsible for the quality control of data and algorithms, and data analysis and interpretation were conducted by E.S., M.H., and R.R. Statistical analysis was performed by E.S. and M.H. The manuscript was prepared by E.S., edited by E.S., M.H., and R.R., and reviewed by J.Z., M.H., J.B., T.L., J.W., and R.R.

### Conflict of Interest

None declared.

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