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Ovarian metastases from colorectal cancer: prognostic role of prophylactic oophorectomy. A single center experience

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Summary

Background: The incidence of ovarian metastases (OM) from colorectal cancer (CRC) is uncommon but women with OM from CRC had poorer quality of life and decreased survival. *Materials and Methods:* The authors retrospectively categorized women submitted to surgery for CRC from January 2004 to December 2012 considering previous mono- or bilateral-oophorectomy, oophorectomy performed during colorectal resection, and oophorectomy performed after surgery for CRC and its cause. The analysis focused on two groups: women who underwent surgery for CRC before menopause and after menopause. Survival outcome in terms of overall survival (OS) and disease-free survival (DFS) were assessed and appearance of OM was also evaluated. *Results:* In postmenopausal women with CRC who underwent left hemicolectomy or anterior resection of the rectum the incidence of OM was 4 % with a statistical significance ($p < 0.05$). The mean OS of patients with metachronous OM was 26 months and the patients' age ranged from 60 to 70 years. *Conclusion:* The authors suggest prophylactic oophorectomy in postmenopausal women with an age between 60 and 70 years with cancer of left colon or rectum; in these patients there was an increased risk of metachronous OM with related decrease of OS.

Key words: Ovarian metastases; Colorectal cancer; Prophylactic oophorectomy; Menopause.

Introduction

Colorectal cancer (CRC) is an important cause of morbidity and mortality in Western World, and in Europe it is the most common cancer in non-smoking people. It is also the first most frequently diagnosed cancer in Italy. In 2014, an estimated 52.000 new cases of CRC will occur in this country [1]. It is the third cancer diagnosed in men, following prostate and lung, and second in women following breast cancer [1, 2].

CRC presents hopeful and increasing prognosis: five-year overall survival rate was 50–51% in the first years of 1990 and increased to 63–64 % from 2005-2007 [1]. In Italy and in Europe, mortality due to CRC decreased thanks to earlier diagnosis (CRC screening) and improvement in surgical and medical treatments [2].

Approximately 20% of patients with CRC have metastatic disease at diagnosis, and 25% will develop metastases during follow-up [3]. These metastases have a predilection for liver (50%) and lung (20%), but rarely affect ovaries, adrenal gland, and brain [4]. Ovarian metastases (OM) differ from lesions at other metastatic sites because they are frequently associated with peritoneal carcinomatosis [3-5]. Ovary is a site of metastasis for many cancers and primary tumor can originate in bowel (gastric or colonic), breast, thyroid, adrenal, and bladder tissue [6-8]. Most series showed that primary CRC is the most common primary malignancy resulting in metastatic tumor to the ovary with the prevalence of colon rather than rectum [3]. The incidence of metastases to the ovaries from CRC is relative uncommon: synchronous OM are reported in 1–9% of the women undergoing surgical resection of a primary CRC, and metachronous OM occur only in 1–7%, but women with ovarian metastases from CRC had poorer quality of life and decreased survival [3, 5, 9-11].

The role of prophylactic oophorectomy during primary resection for CRC was debated. The aftermaths of oophorectomy are related to loss of estrogen levels and include increase of cardiovascular diseases, osteoporosis, urinary incontinence, and weight gain; in literature some Authors showed that OM from CRC occur in 3–4% of cases and prophylactic oophorectomy during surgery for CRC decreases morbidity and improves the quality of survival [12, 13].

This study aimed at investigating the incidence of OM from CRC and to define the role of prophylactic oophorectomy in postmenopausal women.

Materials and Methods

The authors retrospectively categorized 523 women submitted to surgery for CRC at OU General Surgery and Organ Transplantation, University Hospital of Parma, from January 2004 to December 2012. Exclusion criteria included: distant metastasis, postoperative death (within 30 days from surgery), palliative surgery, and primary appendiceal tumor (the authors did not consider the phenomenon of pseudomyxoma peritonei). Of 523 patients, 439 were included in this study while 84 were excluded for the following reasons: eight lost at follow-up, four incomplete pathology reports, two deaths within 30 days after surgery, seven inop-

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Table 1. — *Incidence of oophorectomy performed before, during and after surgery for CRC in the two groups analyzed.*

	N	Bilateral oophorectomy performed before surgery for CRC	Monolateral oophorectomy performed before surgery for CRC	Monolateral oophorectomy performed during surgery for CRC*	Bilateral oophorectomy performed during surgery for CRC*	Monolateral oophorectomy performed after surgery for CRC **	Bilateral oophorectomy performed after surgery for CRC **
Premenopausal women	28	3 (13.6 %)	0	2 (9 %)	2 (9 %)	2 (9 %)	1 (4.5 %)
Postmenopausal women	411	35 (9.3 %)	6 (1.6%)	20 (5,3 %)	16 (4,2 %)	3 (0.8 %)	5 (1.3 %)

* Synchronous oophorectomy was performed because of neoplastic infiltration, metastases, macroscopic pathological findings or increased ovarian volume.
** Metachronous oophorectomy was performed because of high clinical and/or radiological suspicion of metastases.

erable, and 63 with distant metastasis.

The following data were recorded: age, tumor site, type of surgical procedure (laparoscopic or laparotomic resection), AJCC 7th Edition TNM stage, previous mono- or bilateral-oophorectomy, oophorectomy performed during colorectal resection, oophorectomy performed after surgery for CRC and its cause, and synchronous or metachronous OM.

Survival status was collected through the Parma's Registry of Tumors and some data were recorded by contacting the patients directly; follow up was completed in June 2015. Survival outcome in terms of overall survival (OS) and disease-free survival (DFS) were assessed. OS was defined as the period from surgery to the last follow up or death; DFS was defined as the period from surgery to the time of clinical or radiological evidence of disease relapse.

The authors analyzed radiological exams (abdominal ultrasonography, computed tomography scan, magnetic resonance scan, and PET) performed after surgery for CRC to evaluate recurrence of disease. The analysis focused on two groups: women who underwent surgery for CRC before menopause (premenopausal patients or group A) and women who underwent colorectal resection after menopause (postmenopausal patients or group B).

The Chi-square test was used for comparison of qualitative data. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the Statistical Product and Service Solution, SPSS version 17.0.

Results

The most common site of CRC was right colon (182 cases, 41.5%) followed by left colon (145 cases, 33%), rectum (92 cases, 20.9%), and transverse colon (15 cases, 3.5%). In five patients (1.1%) tumor had multiple location. Laparoscopic resections were performed in 124 patients (28%) and conventional open surgical resections in 315 patients (72%). Table 1 shows the incidence of oophorectomy performed before, during, and after surgery for CRC in the two groups analyzed.

Patients underwent oophorectomy during surgery for CRC because of neoplastic infiltration, metastases, macroscopic pathological findings or increased ovarian volume. Metachronous oophorectomy were performed in 11 patients because of high suspicion of metastasis: clinical presentation or new ovarian masses on imaging follow-up. Only one synchronous OM occurred in postmenopausal group and no one was diagnosed in group A. Six postmenopausal women who underwent colorectal resection developed metachronous OM; no OM after surgery for CRC were diagnosed in premenopausal patients and there was a statistical significant difference between two groups analyzed ($p < 0.05$). The women who developed metachronous OM presented these clinical and pathological features: the patient's age ranged from 60 to 70 years at the time of colorectal resection, cancer site was left colon or rectum, time between primary CRC resection and oophorectomy was about 24 months (range 15–48). These cases included one patients with pT3N0, two patients with pT3N1, and three patients with pT4N1 stage measured by AJCC 7th Edition TNM stage.

In this work, the incidence of OM in postmenopausal women was 1.5 % and if we consider only women of group B who underwent left hemicolectomy or anterior resection of the rectum, the incidence was 4% with a statistical significance ($p < 0.05$). The mean OS of patients with metachronous OM was 26 months.

Discussion

Menopause is usually a natural change and it occurs because of the natural or surgical cessation of estradiol and progesterone production by the ovaries. Surgical menopause, in particular oophorectomy, is often assimilated to physiological one, although the endocrine environment is different in the two conditions [14].

Premenopausal oophorectomy is associated with several negative outcomes; in particular, studies have revealed an increased risk of premature death, cardiovascular disease, cognitive impairment or dementia (neuro-protective effect of estrogens on the brain), parkinsonism, osteoporosis and bone fractures, decline in psychological well-being (anxiety and depression), and decline in sexual function (loss of libido, hypoactive sexual desire) [15-20]. Estrogen therapy is efficacious in preventing osteoporotic fractures and in decreasing the risk of cardiovascular disease; androgen co-administration may be useful for reduced libido [21], but not all negative outcomes are solved. Ovariectomy after menopause may also be associated with higher risk of cardiovascular disease. In physiological menopause, ovarian activity de-

creases during the years and ovarian androgen production lessens bit by bit [22]. After menopause, estrogen continues to be produced in other tissues such as in bones, blood vessels, and even in the brain and the production of androstendione and testosterone continues. In physiologic menopause there is no sudden decrease of ovarian androgens because their production drops gradually in premenopausal period [22, 23]; androstenedione and testosterone levels are 50% lower than in young women, but they continue to be produced by the ovaries with an increasing production [23]. Women who have their ovaries surgical removed experience a sudden drop in blood androgens because levels of estrone and testosterone are lower than in physiological menopause with negative consequences; for example lumbar spine bone mineral density (BMD) decrease of 21.5 % in women who underwent bilateral oophorectomy and 16.8 % in women with physiological menopause [24].

The true incidence of OM from primary CRC is unclear and it is reported to occur in 5% (1–9%) of women undergoing colorectal resection; between 6–14 % of women dying with CRC are found at autopsy to have OM [25]. Haematogenous spread seems a rather likely way of diffusion; other hypotheses are the direct implantation of malignant cells within the peritoneal cavity or, alternatively, the retrograde lymphatic spread after malignant obstruction of the primary draining channels [13].

In literature no clear benefits in terms of OS were demonstrated for prophylactic oophorectomy during primary surgery for CRC, especially in the premenopausal patients, even if women with ovarian metastases from CRC had poorer quality of life and decreased survival [12, 26, 27]; in case of synchronous OM or direct invasion of ovary from the CRC, oophorectomy can be performed with curative aim and the radical oophorectomy improved OS [26]. Banerjee *et al.*, with an accurate review of the literature, suggested that all women undergoing surgical resection for CRC should be counselled about the possibility of therapeutic unilateral- or bilateral-oophorectomy, in particular postmenopausal patients with family history of ovarian cancer [12]. Surgical complications attributable to oophorectomy appear to be highly rare and include haemorrhage from the ovarian pedicle and ureteric injury [12, 27].

In our paper all metachronous OM occurred, with a statistical significance ($p < 0.05$), in postmenopausal women with an age between 60 and 70 years who underwent surgery for cancer of left colon or rectum. The present series confirmed literature: metachronous OM had a negative impact on OS; four of six women who developed metachronous OM died within three years from this finding ($p < 0.05$). It would seem appropriate to consider prophylactic oophorectomy in every woman older than 60 years undergoing surgery for cancer of left colon or rectum.

Conclusions

There are no guidelines for prophylactic oophorectomy during surgery for primary CRC to prevent OM. In the present paper the authors suggest prophylactic oophorectomy in postmenopausal women with an age between 60 and 70 years with cancer of left colon or rectum; in these patients the authors analyzed an increased risk of metachronous OM with related decrease of OS. In premenopausal women, oophorectomy causes premature menopause with many adverse consequences and the present authors do not suggest oophorectomy during surgery for left colon or rectum cancer to prevent metachronous OM.

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