World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v2.i4.109

World J Gastrointest Surg 2010 April 27; 2(4): 109-116
ISSN 1948-9366 (online)

GUIDELINES FOR BASIC RESEARCH

Clinicopathologic and immunohistochemical profile of ovarian metastases from colorectal carcinoma

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Received: December 22, 2009 Revised: January 28, 2010
Accepted: February 4, 2010
Published online: April 27, 2010

Abstract

Metastasis of colorectal adenocarcinoma of the ovary is not an uncommon occurrence and ovarian metastases from colorectal carcinoma frequently mimic endometrioid and mucinous primary ovarian carcinoma. The clinical and pathologic features of metastatic colorectal adenocarcinoma involving the ovary is reviewed with particular focus on the diagnostic challenge of distinguishing these secondary ovarian tumors from primary ovarian neoplasm. Immunohistochemical stains that may be useful in the differential diagnosis of metastatic colorectal tumors to the ovary and primary ovarian tumors are detailed.

Key words: Ovary; Colon; Metastatic carcinoma; Mucinous carcinoma; Colorectal carcinoma; Immunohistochemistry; Endometrioid adenocarcinoma

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Kir G, Gurbuz A, Karateke A, Kir M. Clinicopathologic and immunohistochemical profile of ovarian metastases from colorectal carcinoma. *World J Gastrointest Surg* 2010; 2(4): 109-116 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i4/109.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i4.109

INTRODUCTION

The ovary is a common site of metastases[1]. Secondary tumors account for 17.4%-30% of all ovarian malignancies[2-4] of which nongenital cancer metastases to the ovaries constitute 9%-14.6%[3-6]. Primary colon cancer has been identified in 10%-33% of metastatic ovarian tumors in various series[2-10]. In the literature, patients with metastatic colon cancer to the ovary (MCCO) range between 19 and 87 years (median 51 years) with 24%, younger than 40 years[11,12]. 1.2%-14% of women with intestinal cancer have ovarian metastases at sometime during the course of their disease[13-16]. Estimates of true incidence of ovarian metastases from a colorectal primary varies depending on whether autopsy data or clinical series are examined. At autopsy of women dying of colorectal cancer, 6%-14 % are found to have ovarian metastases[17,18]. Up to 45 % of MCCO are thought to be clinically primary ovarian tumors, even though most of the colonic tumors are of Dukes stage B or C[11,19-21]. These tumors may spread to the ovary *via* blood-borne or lymphatic routes, transperitoneal or by direct extension[13,22,23].

In this review, clinical and pathological status of MCCO are discussed with special focus on the diagnostic challenge of distinguishing these secondary ovarian tumors from primary ovarian neoplasms. Studies on useful immunohistochemical stains for the differential diagnosis are also discussed in detail.

CLINICAL FEATURES

Common presenting symptoms are usually related to ovarian involvement. Pelvic mass, abdominal and pelvic pain are the most common presenting symptoms[11,12,24].

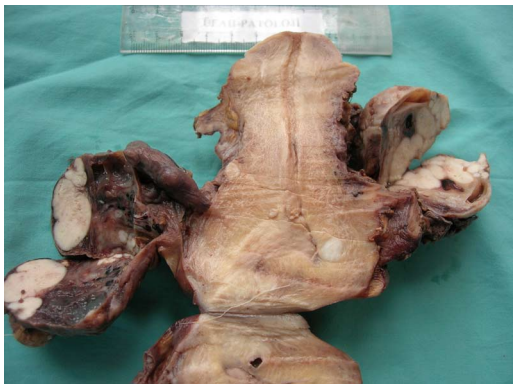

Figure 1 Gross appearance of bilateral ovarian metastasis from a colonic adenocarcinoma. The tumor has a nodular growth pattern.

Most patients have changes in bowel habits, rectal bleeding, feeling of abdominal fullness or bloating. Less frequently, patients present with abnormal vaginal bleeding, nausea, vomiting and constitutional symptoms such as fatique or weight loss. Stromal luteinization is most frequently found in MCCO and increased steroid hormone production in these patients often results in endocrine manifestations[25]. However significantly younger age of the women, uniform presentation as pelvic masses with few bowel symptoms, elevated CA-125 levels, and occasional presentation as large clinically unilateral tumor can all contribute to misclassification of these metastases as primary ovarian neoplasms[26,27]. The frequency of metastatic colorectal carcinoma in the ovary relative to primary ovarian neoplasms is sufficient to justify colonoscopy as a preoperative test in women younger than 50 years, even in pregnant women with adnexal masses lacking clinical symptoms referable to the lower intestinal tract[26,28].

PRIMARY COLORECTAL TUMORS

Colorectal tumors with ovarian metastases are predominantly distal lesions and most of them originate from the rectosigmoid colon[11,13,29]. Transvers colon, ascending colon, cecum and descending colon are affected with decreasing frequency[11,13]. Mean size of the primary tumor is less than that of the ovarian metastatic lesion[16,30]. MCCO are usually associated with advanced metastatic disease[11,12,15,20]. In a study, out of 19 colorectal tumors with ovarian metastases the stage of the primary tumors was as follows : Dukes stage : B1: 2 ; B2: 7 (Stage B: 47%); C2: 8 (Stage C: 42%); D: 2(Stage D:11%)[13]. In a report by Lash *et al*[20]; none of the intestinal primary tumors were Dukes stage A, 32% were B and 68% were C. In a study by Lewis *et al*[11], 86 cases of MCCO were reviewed. Primary tumor invaded the full thickness of the bowel wall in 58 cases (pT3), while in 17 cases, perforation of visceral peritoneum or direct invasion of other structures was noted (pT4). Nodal status was reported in 62 cases, of which 87% nodal involvement was documented at the time of resection; 29 (47%) had involvement of four or more nodes (pN2). Eighty one percent of patients had metastatic involvement of nonovarian sites either at or after the time of colectomy, with omental and/or other peritoneal involvement being the most common. Twenty five patients (40%) had liver metastases at some point during the course of their disease[11].

GROSS FEATURES OF INVOLVED OVARIES

MCCO may form solid or, more commonly, partially or predominantly cystic masses[11,15,22,29,31,32]. They are often friable due to extensive necrosis[15,32] and tend to be associated with surface implants. Careful gross and microscopic inspection of the external ovarian surface for fibrous plaques containing infiltrating carcinoma is helpful in recognition of metastatic colorectal neoplasms[33]. In the study by Lewis *et al*[11], among 46 cases for which data were available, 21 featured an ovary with evidence of surface involvement by tumor and 7 showed evidence of surface rupture. Nodular growth pattern (Figure 1) and hilar involvement[33] are less frequently seen but also highly correlated with metastatic carcinoma. In different series, the size of tumors ranges from 1 to 27 cm with a median of 10-11 cm[11,15,25,31,33-36]. MCCO are bilateral in more than 80% of the reported cases[11,12,15,29,31,33-36]. Unilateral metastasis is more frequent in the right ovary[11,29]. Most commonly, MCCO mimic primary ovarian mucinous or endometrioid adenocarcinoma[10-12,15,22,29,32-36]. Mucinous carcinomas are reported to comprise 6%-25% of ovarian carcinomas (mean 12%), although recent regimens in the interpretation of histologic features of noninvasive and metastatic mucinous carcinomas suggest that this may be an overestimate. Mucinous carcinomas in the ovaries are commonly metastatic, but the proportion of primary versus metastatic mucinous carcinoma in unselected patients is unknown[35]. In Seidman's[35] report, among 52 cases of mucinous carcinoma in the ovaries, 40 (77%) were metastatic and 12 (23%) were primary.

In another report on 74 cases of mucinous carcinomas, 16 were primary ovarian; 52 metastatic, and 6 of indeterminate origin[34]. An algorithm has been proposed to assist diagnosis in which all bilateral mucinous and those unilateral tumors < 10 cm are classified as metastatic carcinomas whereas unilateral tumors ≥ 10 cm are classified as primary ovarian mucinous carcinomas[35]. In Khuramornpong's[34] series, when 6 tumors of indeterminate primary site were excluded, the proposed algorithm correctly classified primary and metastatic tumors in 84% of 68 cases. Of 21 unilateral mucinous adenocarcinomas ≥ 10 cm, 62% were primary ovarian. Of 5 unilateral tumors < 10 cm, 80 % were metastatic. Of 42 bilateral mucinous carcinomas, 95% were metastatic. By adjusting the size criteria to 12 cm, performance of the algorithm is both maintained for primary ovarian tumors and improved for metastases, giving correct classification of 86% of tumors overall including 100% primary tumors and 80% of metastases[37].

HISTOLOGIC FEATURES

In general, features which assist in distinguishing metastatic

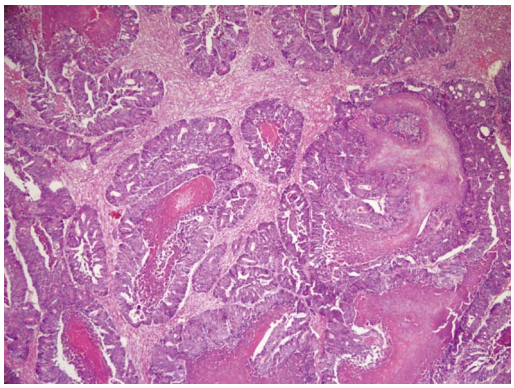

Figure 2 Garland histologic growth pattern with abundant intraluminal "dirty" necrosis and segmental destruction of glands (HE stain, × 100).

colorectal adenocarcinoma from primary ovarian adenocarcinoma are similar to those which apply to other metastatic adenocarcinomas (e.g. bilaterality, nodular pattern of ovarian involvement, surface tumour deposits and extensive lymphovascular permeation especially in hilar and paraovarian vessels, single cell invasion, signet-ring cells) all favour metastatic rather than primary neoplasm. However none of these features is specific[22,33].

Metastatic colorectal carcinoma involving the ovary may closely mimic primary ovarian endometrioid or mucinous neoplasm[7,11,12,15,20,22,29,31,32,36,38]. Young *et al*[1] introduced a classification of histological aspects of metastatic ovarian carcinomas. They observed the prevalence of glandular endometrioid-like pattern and mucinous-like pattern[11,15,22,31,32,36].

The following histological features are classic and characteristic of pseudoendometrioid metastases from large intestine; garland and cribriform histologic growth patterns, abundant intraluminal "dirty" necrosis, segmental destruction of glands and absence of mullerian features (squamous differentiation, adenofibromatous components or association with endometriosis)[11,15,22,30,32,36]. The garland pattern is typified by multiple large cystic glandular structures containing necrotic debris encircled by an array of rounded glands, often with segmental necrosis of their walls (Figure 2). Typically, dirty necrosis consists of densely eosinophilic, coarsely granular necrotic debris containing abundant karyorrhectic material of sloughed carcinoma cells[20]. Necrosis and intraluminal cellular debris also may occur in primary ovarian carcinoma[32,33] but often the intraluminal debris consists of thin secretions and degenerating neutrophils[39]. Thus although dirty necrosis is characteristic of but not specific for colorectal adenocarcinoma, additional histologic features may be helpful in arriving at correct diagnosis. Classic cytological criteria such as marked cytologic atypia (2+ or 3+) and high mitotic index may be considered helpful in the diagnosis of colorectal ovarian metastases[15,22,29,36].

Other metastatic colorectal adenocarcinomas involving the ovary may mimic ovarian mucinous neoplasm. Some may be cystic, closely mimicking the gross appearance of a primary ovarian neoplasm[7,11,15,22,29,31]. Histologically there may also be a close resemblance to primary ovarian mucinous cystadenoma as well as obviously malignant areas with destructive stromal invasion. Analogous to the situation with other metastatic mucinous carcinomas, those morphologically bland foci (maturation phenomenon) have been erroneously interpreted as evidence of primary ovarian neoplasm[11,15,22]. In a recent study, frequent findings strongly favoring metastatic mucinous adenocarcinoma were; bilaterality, surface implants and an infiltrative pattern of stromal invasion[33]. Findings that strongly favor primary ovarian mucinous carcinoma were; an "expansile" pattern of invasion and complex papillary pattern[33]. Stromal luteinization that may occur with any mass lesion in the ovary appears to be more common in metastatic colorectal adenocarcinoma than other metastatic neoplasms[22]. Rare adenocarcinomas metastatic from the intestine may contain cells with abundant clear cytoplasm, simulating either clear cell carcinoma or the secretory variant of endometrioid carcinoma[39]. In a recent study the clinical and pathological features of 86 cases of metastatic colorectal adenocarcinoma involving the ovary were reviewed[11]. Glandular and papillary architecture, "dirty necrosis", desmoplasia, garland pattern, surface involvement, single infiltrative cells, extracellular mucin, "incomplete glands", infiltrative nests of cells, cystic glandular dilatation, small glands, low malign potential -like areas, multimodularity and goblet cells were observed in decreasing frequency[11]. In 19% of cases, foci with benign or low malignant potential appearance were seen. One point worthy of emphasis is the anecdotal experience of Hart[31] who observed "microscopic nests of carcinoma within corpora lutea or corpora albicantia also points the metastasis".

IMMUNOHISTOCHEMICAL FEATURES

When the characteristic gross and microscopic distinguishing features are lacking between primary ovarian adenocarcinoma and metastatic colorectal adenocarcinoma, immunohistochemistry may be very useful[15,40-46]. Tumors with pseudoendometrioid histological pattern are most readily identified by immunophenotyping. However when the tumor is of mucinous type immunostains are less useful. This is due to the high frequency of intestinal differentiation in most primary ovarian mucinous neoplasms which results in considerable overlap in immunophenotype with metastatic mucinous neoplasms[47]. Use of a panel of antibodies provides the most accurate immunophenotype and can usually assist in correct identification of the site of origin (Table 1). Based on the immunohistochemistry results obtained from recent studies a decision flow chart has been constructed (Figure 3).

Cytokeratin 7 and 20

Use of coordinate expression of cytokeratins 7 and 20 (CK 7/20) for distinguishing primary ovarian tumors from colorectal metastases has been evaluated in large number of studies[39,42,45,46,48-51]. Combined use of CK 7 and 20 allows discrimination of most metastatic colorectal carcinoma from nonmucinous adenocarcinoma of the ovary[40].

Nonmucinous ovarian adenocarcinomas are almost always diffusely CK 7 positive and CK 20 negative whereas

Table 1 Primary *vs* metastatic colorectal carcinoma to the ovary: immunohistochemical profiles

	Primary ovarian carcinoma mucinous type	Primary ovarian carcinoma nonmucinous type	Metastatic colorectal carcinoma
CK 7	+/-	+	-/+
CK 20	-/+	-	+
CEA	-/+	-	+
CA 125	+/-	+	-/+
MUC 2	+/-	?[1]	+
MUC5AC	+	?	-/+
CDX2	+	-/+	+
P504S	?	?	+/-
β-Catenin	-/+	-/+	+
Vimentin	?	-/+	-
ER/PR	-/+	?	-

[1]Not known. CK 7, CK 20: Cytokeratin 7 and 20; CEA: Carcinoembryonic antigen; CA 125 : Cancer antigen 125; MUC 2, MUC5AC : Mucin gene products.

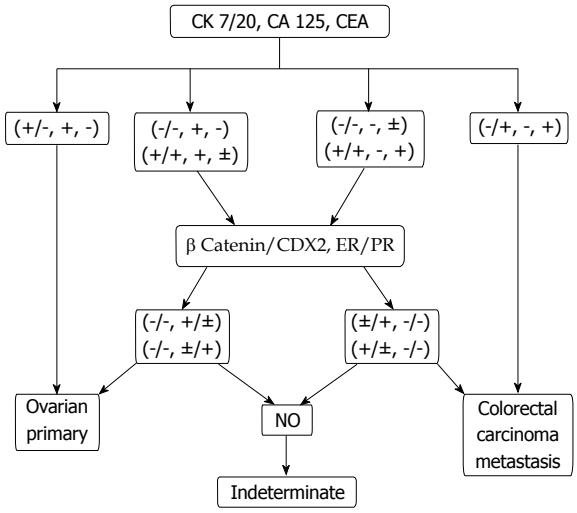

Figure 3 Flow chart showing the decision tree that was constructed based on the immunohistochemistry results. CK 7/CK 20: Cytokeratin 7 and 20; CEA: Carcinoembryonic antigen; CA 125: Cancer antigen 125; ER/PR: Estrogen and progesterone receptors.

the majority of colorectal carcinomas are usually negative for CK 7 and uniformly positive for CK 20[42,45,46,48-50,52]. A caveat is that a small percentage of colorectal carcinomas, particularly those that are right-sided and high grade, have CK 7 positive and CK 20 negative immunophenotype[48,53]. Ovarian mucinous tumors are almost always positive for CK 7 but show variable positivity for CK 20 which is often patchy in distribution[42,45,46,48,49,54]. However, mucinous tumors arising in ovarian mature cystic teratomas which were morphologically and immunohistochemically familiar with gastrointestinal tract-type mucinous tumors were negative for CK 7 and positive for CK 20[51,52,55]. Intestinal-type mucinous epithelial neoplasm of low malignant potential, intraepithelial carcinomas and invasive adenocarcinomas more frequently had a CK 7-/CK 20+ phenotype (56%, 50% and 100%) respectively. A CK 7+/CK 20- phenotype was rare in these later 3 morphologic groups (6%)[56].

Carcinoembryonic antigen

Carcinoembryonic antigen (CEA) is a highly glycosylated cell surface protein overexpressed in a variety of tumors such as colorectal, ovarian, pancreatic, breast and nonsmall cell carcinomas[57]. When evaluating ovarian tumors its greatest utility is in distinguishing metastatic colorectal carcinoma with pseudoendometrioid pattern from primary endometrioid carcinoma. These pseudoendometrioid metastatic tumors typically demonstrate strong and diffuse staining for CEA especially along the glycocalyceal border, apical cytoplasm or throughout the cytoplasm[20,58]. However several studies have demonstrated that CEA immunostaining is of no value in the differentiation between secondary ovarian tumors showing a mucinous pattern and primary ovarian mucinous adenocarcinomas because both show equally strong staining[20,54]. In recent studies 67%-85% of primary ovarian mucinous carcinomas were CEA positive compared to 95%-100% of metastatic colorectal carcinomas[44,50,54]. It is, however, possible to use CEA in combination with other tumor markers.

Cancer antigen 125

Cancer antigen (CA) 125 shows strong and diffuse staining of serous and endometrioid ovarian carcinomas with positivity ranging from 0-50% in mucinous tumors[40,50,54,59]. 4%-15 % of colorectal carcinomas are immunoreactive for CA 125 although staining may be weak and focal and the pattern may be cytoplasmic rather than membranous[15,50,54]. CA 125 may be helpful as a part of a diagnostic panel but its' use as a single test in identifying ovarian adenocarcinoma is not reliable.

Mucin gene products: MUC 2, MUC5AC

In recent studies, 100% of primary mucinous adenocarcinomas were shown to express MUC5AC whereas 0-33% of metastatic colorectal carcinomas expressed the same marker[45,60]. MUC2 reactivity was found in 90% of metastatic colorectal adenocarcinomas, in 70% of primary mucinous cytadenocarcinomas and all borderline tumors of intestinal type but in none of the cystadenomas or endocervical-like borderline tumors[58].

CDX2

The CDX2 gene encodes an intestine-specific transcription factor belonging to the homeobox family that plays an important role in the regulation of proliferation and

differentiation of intestinal epithelial cells[61]. Diffuse and strong CDX2 protein expression is reported in almost all MCCO[41,43,54,59,62-64]. CDX2 expression is observed in up to 70% of primary ovarian tumors[41,54,62,64,65]. Gaggero *et al*[66] reported that all 47 endocervical-type mucinous cystadenomas stained negative for CDX2 and two of three intestinal-type cystadenomas stained positive. They concluded that the expression of CDX2 in mucinous tumors is likely to be dependent on the cell type (endocervical or intestinal). In view of the findings of these recent studies, positive CDX2 expression in a tumor involving the ovary should be interpreted with caution as although it may be a primary ovarian adenocarcinoma the possibility of metastatic tumor needs to be carefully excluded. Conversely, none-expression of CDX2 in a tumor would strongly support an ovarian primary.

β-Catenin

A frequently observed genetic change in colorectal carcinoma is an inactivating mutation of the adenomatosis coli gene[67]. This leads to the accumulation of the protein β-Catenin in the nucleus. In several recent studies, 59%-83% of MCCO showed nuclear expression of β-Catenin[41,44]. In one study, nuclear expression of β-Catenin was noted in only 9% of primary ovarian mucinous carcinomas[44]. In Logani *et al*[41] nuclear expression was found in 19% of 23 primary ovarian adenocarcinomas with only one tumor (5%), an endometrioid carcinoma, having a diffuse pattern of expression. Two endometrioid adenocarcinomas had strong nuclear immunoreactivity in foci of squamous metaplasia.

α-methyl-coenzyme a racemase

α-methyl-coenzyme a racemase, also known as P504S, is a mitochondrial and proximal enzyme involved in the metabolism of fatty acids[68]. Overexpression of P504S has been observed in several tumors, most notably prostate and colorectal carcinoma[69,70]. Some authors have found that the frequency of P504S expression is decreased in poorly differentiated colonic adenocarcinomas[60,71]. In Logani's[41] study, 32% of MCCO showed diffuse expression of P504S as versus none in primary ovarian tumors. Although there seems to be value of using P504S in the differential diagnosis of primary ovarian and MCCO, its' expression in primary ovarian tumors requires further evaluation.

Vimentin and estrogen/Progesterone receptors

In the current literature some controversy exist about Vimentin expression in mucinous carcinomas. Van Niekerk *et al*[72] described rather high expression. Viale *et al*[73] could only show it at a low level in some samples while Moll *et al*[74] did not find it at all. In a recent publication, Vimentin was found to be substantially present (except for one sample) in colonic carcinomas but was present in only 18% of mucinous ovarian carcinomas[50]. Therefore it combines a low sensitivity with high specificity.

Estrogen receptor (ER) and progesterone receptor (PR) expression in primary ovarian mucinous tumors and the utility of these markers for distinguishing MCCO from primary ovarian mucinous tumors have not been extensively investigated. In one study, all atypical proliferative mucinous tumors of gastrointestinal type, primary ovarian mucinous carcinomas and metastatic mucinous carcinomas (including 24 metastasis from colorectal primary) were negative for ER and PR with the exception of three metastatic endocervical adenocarcinomas[8]. The authors concluded that immunohistochemical assesment of hormone receptor expression is of no value in distinguishing the common types of primary ovarian mucinous tumors from the vast majority of mucinous tumors metastatic to the ovary.

FOLLOW-UP

In premenopausal women ovaries have rich blood supply owing to both direct origin of ovarian arteries from the aorta and anastomosis through ovarian branches of the uterine arteries. Approximately ten arterial branches from this arcade penetrate the ovarian hilus, becoming markedly coiled and branched as they course through the medulla[75]. It is also reported that ovarian metastases from primary colorectal cancer may involve haematogenous spread as the main pathway[16]. This vascular-rich histology of the ovaries may be the main reason why colorectal tumor metastasis to the ovaries often expand rapidly, resulting in significant size increase compared to the mean size of the primary tumour[16]. In Judson's study[26], mean size of the colorectal tumor and ovarian metastasis were 5.1/5.0 cm and 12.8/14.1 cm in undiagnosed and known colorectal adenocarcinoma groups respectively. The large metastatic sizeis the main reason why patients need resection for this disease in spite of poor prognosis[24,76,77].

Ovarian metastasis are associated with advanced metastatic disease. In a report of 624 patients with colorectal adenocarcinoma, 19 (7.7%) had ovarian metastasis. They were divided into two groups according to the diagnostic time; Group A: syncronous (9 patients), Group B: metachronous (10 patients)[13]. 5 year survival in group A was 16% while it was 0 in goup B. The authors concluded that resection of primary tumor plus bilateral oophorectomy is suitable for syncronous ovarian metastasis and as palliative treatment for metachronous disease. Miller *et al*[24] reported on 23 patients with MCCO at the time of initial diagnosis. Surgical treatment consisted of colon resection in all but one patients, bilateral or unilateral salpingoophorectomy in 22 patients and hysterectomy in nine patients. Only one patient survived 5 years. Sixteen patients died of colon cancer. The median survival time was 17.8 mo, with a range from 1 to 86 mo. Tumor size was of no prognostic importance. Median survival time of patients with peritoneal disease (10.8 mo) was significantly shorter than for patients without peritoneal disease (25.2 mo). In the presence of liver metastasis , the median survival time was,likewise, significantly reduced from 20.1 to 8.1 mo. Some recent reports show that bilateral oophorectomy for MCCO has a good impact on disease-free and overall survival (OS) for patients with isolated ovarian metastasis[78]. McCormick *et al*[79] observed that patients with metastatic disease confined to the ovaries had a median OS of 61 mo (range 15-120 mo) compared to 17 mo (range 0.5-73 mo) for those with more extensive metastases (P = 0.0428).

The observation that optimal cytoreduction was associated with prolonged progression-free survival and OS in both patients with localized ovarian and widespread metastases of colon cancer suggests a role for the management of metastatic colon cancer in women. Chung *et al*[80] analysed the clinicopathological and follow-up data on 34 patients who underwent surgical resection of metastatic tumors originating from colorectal cancer. They concluded that surgical resection may be beneficial in selected patients with ovarian metastasis limited to the pelvis. Another report suggested that ovarian metastases are less responsive to chemotherapy compared to other sites and that surgical resection should always be considered for ovarian metastases even in the case of associated extraovarian metastases[81]. In conclusion, macroscopic metastatic disease to the ovary is a poor prognostic factor in colon cancer. In selected patients who can be rendered disease-free by surgery, prolonged survival is possible and an aggresive aproach is recommended.

Controversies exist regarding the role of prophylactic oophorectomy for improving outcome following colorectal cancer surgery. While clinical series report rates of 1.2% to 14% of patients with colorectal carcinoma having ovarian metastasis[13-16] it is impossible to speculate how many, if any, could have been cured by oophorectomy on the premise that ovarian metastases were initially isolated and therefore treatable. These figures would suggest that a proportion of women with colorectal cancer would benefit from prophylactic oophorectomy. However recent studies have been unable to confirm this hypothesis[82-84]. Tentes *et al*[83] divided the patients into two groups; in 70 of 124 (56.6 %) patients, the ovaries were preserved during surgery and in 54 (43.4%), synchronous prophylactic oophorectomy during primary tumor resection was performed. Seilezneff *et al*[84] offered bilateral oophorectomy to all postmenopausal women in a consecutive series of 92 patients. Forty-one agreed to undergo oophorectomy. In both studies comparison of both groups revealed no difference in overall survival.

CONCLUSION

From 1.2% to 14% of women afflicted by colorectal adenocarcinoma are found to have ovarian involvement at some point in the course of their disease[13-16]. In many of these cases diagnosis of colorectal carcinoma has been established prior to the recognition of the ovarian lesion although in a minority of cases, ovarian mass is the initial manifestation of the disease[19,24]. In such cases preoperative differential diagnosis centers on the primary ovarian neoplasm. If the possibility of metastatic carcinoma is not raised either at the time of intraoperative consultation or in the final pathology report, clinical management may be adversely affected. Correct classification is important from both therapeutic and prognostic point of view. Unfortunately there is significant overlap between metastatic colorectal adenocarcinoma and those of primary epithelial ovarian neoplasms especially endometrioid and mucinous adenocarcinomas regarding the gross and histologic features[11,12,15,22,30,32,34-38]. Bilaterality, high-stage disease, multimodularity, surface implants, infiltrative pattern of invasion, invasion of hilar structures and vascular invasion are strong markers for metastatic ovarian tumors[11,33,35]. Prominent intraluminal dirty necrosis with a garland and cribriform pattern is characteristic of metastatic colorectal carcinomas[19]. Features favoring primary ovarian endometrioid or mucinous neoplasm include; unilateral involvement, large size, an expansile pattern of invasion, complex papillary pattern and presence of Mullerian features[11,22,33]. A recently reported adjusted algorithm for mucinous carcinomas in which bilateral tumors and those unilateral tumors smaller than 12 cm are classified as metastatic has proved to be correct in 86% of cases[35,37].

Selected immunostains may be helpful in identifying MCCO. Tumors with a pseudoendometrioid histologic pattern are most readily identified by immunophenotyping. However when the tumor is of mucinous type, immunostains are less useful. A panel comprising of CDX2, β-Catenin and P504S is helpful in distinguishing primary mucinous or endometrioid adenocarcinoma from colorectal metastasis to the ovary in the majority of cases and is a useful adjunct to the already established role of differential staining with CK 7/CK 20, CA 125, CEA in this differential diagnosis[15,41].

Ovarian metastases are associated with advanced stage disease[13]. Median survival time is 17.8 mo (1-86 mo)[25] and 5 years survival rates are 16% and 0% in groups with oophorectomy and without oophorectomy respectively[13].

It is important to reemphasize that both gynecologist and pathologist should have a high level of suspicion of metastasis from another organ when they encounter a mucinous tumor in the ovary in order to prevent misdiagnosing a metastatic neoplasm as primary tumor.

REFERENCES

1 **Young RH**, Scully RE. Metastatic tumors in the ovary: a problem-oriented approach and review of the recent literature. *Semin Diagn Pathol* 1991; **8**: 250-276
2 **Khunamornpong S**, Suprasert P, Chiangmai WN, Siriaunkgul S. Metastatic tumors to the ovaries: a study of 170 cases in northern Thailand. *Int J Gynecol Cancer* 2006; **16** Suppl 1: 132-138
3 **Yada-Hashimoto N**, Yamamoto T, Kamiura S, Seino H, Ohira H, Sawai K, Kimura T, Saji F. Metastatic ovarian tumors: a review of 64 cases. *Gynecol Oncol* 2003; **89**: 314-317
4 **Ayhan A**, Tuncer ZS, Bükülmez O. Malignant tumors metastatic to the ovaries. *J Surg Oncol* 1995; **60**: 268-276
5 **Ayhan A**, Guvenal T, Salman MC, Ozyuncu O, Sakinci M, Basaran M. The role of cytoreductive surgery in nongenital cancers metastatic to the ovaries. *Gynecol Oncol* 2005; **98**: 235-241
6 **Moore RG**, Chung M, Granai CO, Gajewski W, Steinhoff MM. Incidence of metastasis to the ovaries from nongenital tract primary tumors. *Gynecol Oncol* 2004; **93**: 87-91
7 **Demopoulos RI**, Touger L, Dubin N. Secondary ovarian carcinoma: a clinical and pathological evaluation. *Int J Gynecol Pathol* 1987; **6**: 166-175
8 **Vang R**, Gown AM, Barry TS, Wheeler DT, Ronnett BM. Immunohistochemistry for estrogen and progesterone receptors in the distinction of primary and metastatic mucinous tumors in the ovary: an analysis of 124 cases. *Mod Pathol* 2006; **19**: 97-105
9 **Petru E**, Pickel H, Heydarfadai M, Lahousen M, Haas J, Schaider H, Tamussino K. Nongenital cancers metastatic to the ovary. *Gynecol Oncol* 1992; **44**: 83-86
10 **Chang TC**, Changchien CC, Tseng CW, Lai CH, Tseng CJ, Lin SE, Wang CS, Huang KJ, Chou HH, Ma YY, Hsueh S, Eng HL,

Fan HA. Retrograde lymphatic spread: a likely route for metastatic ovarian cancers of gastrointestinal origin. *Gynecol Oncol* 1997; **66**: 372-377
11 **Lewis MR**, Deavers MT, Silva EG, Malpica A. Ovarian involvement by metastatic colorectal adenocarcinoma: still a diagnostic challenge. *Am J Surg Pathol* 2006; **30**: 177-184
12 **Daya D**, Nazerali L, Frank GL. Metastatic ovarian carcinoma of large intestinal origin simulating primary ovarian carcinoma. A clinicopathologic study of 25 cases. *Am J Clin Pathol* 1992; **97**: 751-758
13 **Luna-Pérez P**, Alvarado I, Labastida S, Sosa J, Barrientos FJ, Herrera L. [The mechanisms of the dissemination and the treatment of ovarian metastases in colonic adenocarcinoma] *Rev Gastroenterol Mex* 1994; **59**: 290-296
14 **Birnkrant A**, Sampson J, Sugarbaker PH. Ovarian metastasis from colorectal cancer. *Dis Colon Rectum* 1986; **29**: 767-771
15 **Hart WR**. Diagnostic challenge of secondary (metastatic) ovarian tumors simulating primary endometrioid and mucinous neoplasms. *Pathol Int* 2005; **55**: 231-243
16 **Kim DD**, Park IJ, Kim HC, Yu CS, Kim JC. Ovarian metastases from colorectal cancer: a clinicopathological analysis of 103 patients. *Colorectal Dis* 2009; **11**: 32-38
17 **Abrams HL**, Spiro R, Goldstein N. Metastases in carcinoma; analysis of 1000 autopsied cases. *Cancer* 1950; **3**: 74-85
18 **Köves I**, Vámosi-Nagy I, Besznyák I. Ovarian metastases of colorectal tumours. *Eur J Surg Oncol* 1993; **19**: 633-635
19 **Harcourt KF**, Dennis DL. Laparotomy for "ovarian tumors" in unsuspected carcinoma of the colon. *Cancer* 1968; **21**: 1244-1246
20 **Lash RH**, Hart WR. Intestinal adenocarcinomas metastatic to the ovaries. A clinicopathologic evaluation of 22 cases. *Am J Surg Pathol* 1987; **11**: 114-121
21 **Banerjee S**, Kapur S, Moran BJ. The role of prophylactic oophorectomy in women undergoing surgery for colorectal cancer. *Colorectal Dis* 2005; **7**: 214-217
22 **McCluggage WG**, Wilkinson N. Metastatic neoplasms involving the ovary: a review with an emphasis on morphological and immunohistochemical features. *Histopathology* 2005; **47**: 231-247
23 **Herrera LO**, Ledesma EJ, Natarajan N, Lopez GE, Tsukada Y, Mittelman A. Metachronous ovarian metastases from adenocarcinoma of the colon and rectum. *Surg Gynecol Obstet* 1982; **154**: 531-533
24 **Miller BE**, Pittman B, Wan JY, Fleming M. Colon cancer with metastasis to the ovary at time of initial diagnosis. *Gynecol Oncol* 1997; **66**: 368-371
25 **Scully RE**, Young RH, Clement PB. Tumors of the Ovary, maldeveloped gonads, fallopian tube and broad ligament. Atlas of tumor pathology. third series. Fascicle 23. Washington: Armed Forces Institute of Pathology, 1998: 81-105
26 **Judson K**, McCormick C, Vang R, Yemelyanova AV, Wu LS, Bristow RE, Ronnett BM. Women with undiagnosed colorectal adenocarcinomas presenting with ovarian metastases: clinicopathologic features and comparison with women having known colorectal adenocarcinomas and ovarian involvement. *Int J Gynecol Pathol* 2008; **27**: 182-190
27 **Lewis MR**, Euscher ED, Deavers MT, Silva EG, Malpica A. Metastatic colorectal adenocarcinoma involving the ovary with elevated serum CA125: a potential diagnostic pitfall. *Gynecol Oncol* 2007; **105**: 395-398
28 **Gurbuz A**, Kir G, Karateke A, Haliloglu B, Kabaca C. Metastatic ovarian carcinoma one year after surgical removal of colon carcinoma during pregnancy: a case report. *Int J Gynecol Cancer* 2006; **16** Suppl 1: 330-333
29 **Dionigi A**, Facco C, Tibiletti MG, Bernasconi B, Riva C, Capella C. Ovarian metastases from colorectal carcinoma. Clinicopathologic profile, immunophenotype, and karyotype analysis. *Am J Clin Pathol* 2000; **114**: 111-122
30 **Stewart CJ**, Brennan BA, Hammond IG, Leung YC, McCartney AJ. Accuracy of frozen section in distinguishing primary ovarian neoplasia from tumors metastatic to the ovary. *Int J Gynecol Pathol* 2005; **24**: 356-362
31 **Hart WR**. Mucinous tumors of the ovary: a review. *Int J Gynecol Pathol* 2005; **24**: 4-25
32 **DeCostanzo DC**, Elias JM, Chumas JC. Necrosis in 84 ovarian carcinomas: a morphologic study of primary versus metastatic colonic carcinoma with a selective immunohistochemical analysis of cytokeratin subtypes and carcinoembryonic antigen. *Int J Gynecol Pathol* 1997; **16**: 245-249
33 **Lee KR**, Young RH. The distinction between primary and metastatic mucinous carcinomas of the ovary: gross and histologic findings in 50 cases. *Am J Surg Pathol* 2003; **27**: 281-292
34 **Khunamornpong S**, Suprasert P, Pojchamarnwiputh S, Na Chiangmai W, Settakorn J, Siriaunkgul S. Primary and metastatic mucinous adenocarcinomas of the ovary: Evaluation of the diagnostic approach using tumor size and laterality. *Gynecol Oncol* 2006; **101**: 152-157
35 **Seidman JD**, Kurman RJ, Ronnett BM. Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. *Am J Surg Pathol* 2003; **27**: 985-993
36 **Prat J**. Ovarian carcinomas, including secondary tumors: diagnostically challenging areas. *Mod Pathol* 2005; **18** Suppl 2: S99-S111
37 **Yemelyanova AV**, Vang R, Judson K, Wu LS, Ronnett BM. Distinction of primary and metastatic mucinous tumors involving the ovary: analysis of size and laterality data by primary site with reevaluation of an algorithm for tumor classification. *Am J Surg Pathol* 2008; **32**: 128-138
38 **Ulbright TM**, Roth LM, Stehman FB. Secondary ovarian neoplasia. A clinicopathologic study of 35 cases. *Cancer* 1984; **53**: 1164-1174
39 **Young RH**, Hart WR. Metastatic intestinal carcinomas simulating primary ovarian clear cell carcinoma and secretory endometrioid carcinoma: a clinicopathologic and immunohistochemical study of five cases. *Am J Surg Pathol* 1998; **22**: 805-815
40 **Baker PM**, Oliva E. Immunohistochemistry as a tool in the differential diagnosis of ovarian tumors: an update. *Int J Gynecol Pathol* 2005; **24**: 39-55
41 **Logani S**, Oliva E, Arnell PM, Amin MB, Young RH. Use of novel immunohistochemical markers expressed in colonic adenocarcinoma to distinguish primary ovarian tumors from metastatic colorectal carcinoma. *Mod Pathol* 2005; **18**: 19-25
42 **Vang R**, Gown AM, Barry TS, Wheeler DT, Yemelyanova A, Seidman JD, Ronnett BM. Cytokeratins 7 and 20 in primary and secondary mucinous tumors of the ovary: analysis of coordinate immunohistochemical expression profiles and staining distribution in 179 cases. *Am J Surg Pathol* 2006; **30**: 1130-1139
43 **Groisman GM**, Meir A, Sabo E. The value of Cdx2 immunostaining in differentiating primary ovarian carcinomas from colonic carcinomas metastatic to the ovaries. *Int J Gynecol Pathol* 2004; **23**: 52-57
44 **Chou YY**, Jeng YM, Kao HL, Chen T, Mao TL, Lin MC. Differentiation of ovarian mucinous carcinoma and metastatic colorectal adenocarcinoma by immunostaining with beta-catenin. *Histopathology* 2003; **43**: 151-156
45 **Ji H**, Isacson C, Seidman JD, Kurman RJ, Ronnett BM. Cytokeratins 7 and 20, Dpc4, and MUC5AC in the distinction of metastatic mucinous carcinomas in the ovary from primary ovarian mucinous tumors: Dpc4 assists in identifying metastatic pancreatic carcinomas. *Int J Gynecol Pathol* 2002; **21**: 391-400
46 **Tot T**. Cytokeratins 20 and 7 as biomarkers: usefulness in discriminating primary from metastatic adenocarcinoma. *Eur J Cancer* 2002; **38**: 758-763
47 **Lin X**, Lindner JL, Silverman JF, Liu Y. Intestinal type and endocervical-like ovarian mucinous neoplasms are immunophenotypically distinct entities. *Appl Immunohistochem Mol Morphol* 2008; **16**: 453-458
48 **Park SY**, Kim HS, Hong EK, Kim WH. Expression of cytokeratins 7 and 20 in primary carcinomas of the stomach and colorectum and their value in the differential diagnosis of

metastatic carcinomas to the ovary. *Hum Pathol* 2002; **33**: 1078-1085
49 **Cathro HP**, Stoler MH. Expression of cytokeratins 7 and 20 in ovarian neoplasia. *Am J Clin Pathol* 2002; **117**: 944-951
50 **Lagendijk JH**, Mullink H, Van Diest PJ, Meijer GA, Meijer CJ. Tracing the origin of adenocarcinomas with unknown primary using immunohistochemistry: differential diagnosis between colonic and ovarian carcinomas as primary sites. *Hum Pathol* 1998; **29**: 491-497
51 **Stewart CJ**, Tsukamoto T, Cooke B, Leung YC, Hammond IG. Ovarian mucinous tumour arising in mature cystic teratoma and associated with pseudomyxoma peritonei: report of two cases and comparison with ovarian involvement by low-grade appendiceal mucinous tumour. *Pathology* 2006; **38**: 534-538
52 **Ronnett BM**, Seidman JD. Mucinous tumors arising in ovarian mature cystic teratomas: relationship to the clinical syndrome of pseudomyxoma peritonei. *Am J Surg Pathol* 2003; **27**: 650-657
53 **Lee MJ**, Lee HS, Kim WH, Choi Y, Yang M. Expression of mucins and cytokeratins in primary carcinomas of the digestive system. *Mod Pathol* 2003; **16**: 403-410
54 **Raspollini MR**, Amunni G, Villanucci A, Baroni G, Taddei A, Taddei GL. Utility of CDX-2 in distinguishing between primary and secondary (intestinal) mucinous ovarian carcinoma: an immunohistochemical comparison of 43 cases. *Appl Immunohistochem Mol Morphol* 2004; **12**: 127-131
55 **Marquette S**, Amant F, Vergote I, Moerman P. Pseudomyxoma peritonei associated with a mucinous ovarian tumor arising from a mature cystic teratoma. A case report. *Int J Gynecol Pathol* 2006; **25**: 340-343
56 **McKenney JK**, Soslow RA, Longacre TA. Ovarian mature teratomas with mucinous epithelial neoplasms: morphologic heterogeneity and association with pseudomyxoma peritonei. *Am J Surg Pathol* 2008; **32**: 645-655
57 **Sikorska H**, Shuster J, Gold P. Clinical applications of carcinoembryonic antigen. *Cancer Detect Prev* 1988; **12**: 321-355
58 **Fleuren GJ**, Nap M. Carcinoembryonic antigen in primary and metastatic ovarian tumors. *Gynecol Oncol* 1988; **30**: 407-415
59 **Kim MJ**. The usefulness of CDX-2 for differentiating primary and metastatic ovarian carcinoma: an immunohistochemical study using a tissue microarray. *J Korean Med Sci* 2005; **20**: 643-648
60 **Albarracin CT**, Jafri J, Montag AG, Hart J, Kuan SF. Differential expression of MUC2 and MUC5AC mucin genes in primary ovarian and metastatic colonic carcinoma. *Hum Pathol* 2000; **31**: 672-677
61 **Suh E**, Chen L, Taylor J, Traber PG. A homeodomain protein related to caudal regulates intestine-specific gene transcription. *Mol Cell Biol* 1994; **14**: 7340-7351
62 **Tornillo L**, Moch H, Diener PA, Lugli A, Singer G. CDX-2 immunostaining in primary and secondary ovarian carcinomas. *J Clin Pathol* 2004; **57**: 641-643
63 **Werling RW**, Yaziji H, Bacchi CE, Gown AM. CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. *Am J Surg Pathol* 2003; **27**: 303-310
64 **Vang R**, Gown AM, Wu LS, Barry TS, Wheeler DT, Yemelyanova A, Seidman JD, Ronnett BM. Immunohistochemical expression of CDX2 in primary ovarian mucinous tumors and metastatic mucinous carcinomas involving the ovary: comparison with CK20 and correlation with coordinate expression of CK7. *Mod Pathol* 2006; **19**: 1421-1428
65 **Rabban JT**, Lerwill MF, McCluggage WG, Grenert JP, Zaloudek CJ. Primary ovarian carcinoid tumors may express CDX-2: a potential pitfall in distinction from metastatic intestinal carcinoid tumors involving the ovary. *Int J Gynecol Pathol* 2009; **28**: 41-48
66 **Gaggero G**, Sola S, Mora M, Fulcheri E. [Expression of the cdx2 gene in benign intestinal-type mucinous ovarian tumors] *Pathologica* 2003; **95**: 185-191
67 **Miyoshi Y**, Nagase H, Ando H, Horii A, Ichii S, Nakatsuru S, Aoki T, Miki Y, Mori T, Nakamura Y. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. *Hum Mol Genet* 1992; **1**: 229-233
68 **Nassar A**, Amin MB, Sexton DG, Cohen C. Utility of alpha-methylacyl coenzyme A racemase (p504s antibody) as a diagnostic immunohistochemical marker for cancer. *Appl Immunohistochem Mol Morphol* 2005; **13**: 252-255
69 **Zhou M**, Chinnaiyan AM, Kleer CG, Lucas PC, Rubin MA. Alpha-Methylacyl-CoA racemase: a novel tumor marker over-expressed in several human cancers and their precursor lesions. *Am J Surg Pathol* 2002; **26**: 926-931
70 **Jiang Z**, Fanger GR, Woda BA, Banner BF, Algate P, Dresser K, Xu J, Chu PG. Expression of alpha-methylacyl-CoA racemase (P504s) in various malignant neoplasms and normal tissues: astudy of 761 cases. *Hum Pathol* 2003; **34**: 792-796
71 **Kuefer R**, Varambally S, Zhou M, Lucas PC, Loeffler M, Wolter H, Mattfeldt T, Hautmann RE, Gschwend JE, Barrette TR, Dunn RL, Chinnaiyan AM, Rubin MA. alpha-Methylacyl-CoA racemase: expression levels of this novel cancer biomarker depend on tumor differentiation. *Am J Pathol* 2002; **161**: 841-848
72 **Van Niekerk CC**, Ramaekers FC, Hanselaar AG, Aldeweireldt J, Poels LG. Changes in expression of differentiation markers between normal ovarian cells and derived tumors. *Am J Pathol* 1993; **142**: 157-177
73 **Viale G**, Gambacorta M, Dell'Orto P, Coggi G. Coexpression of cytokeratins and vimentin in common epithelial tumours of the ovary: an immunocytochemical study of eighty-three cases. *Virchows Arch A Pathol Anat Histopathol* 1988; **413**: 91-101
74 **Moll R**, Pitz S, Levy R, Weikel W, Franke WW, Czernobilsky B. Complexity of expression of intermediate filament proteins, including glial filament protein, in endometrial and ovarian adenocarcinomas. *Hum Pathol* 1991; **22**: 989-1001
75 **Stephen S**. Sternberg. Histology for pathologists. Philadelphia-New York: Lippincott Williams & Wilkins, 1997: 930-932
76 **Mason MH 3rd**, Kovalcik PJ. Ovarian metastases from colon carcinoma. *J Surg Oncol* 1981; **17**: 33-89
77 **Herrera-Ornelas L**, Mittelman A. Results of synchronous surgical removal of primary colorectal adenocarcinoma and ovarian metastases. *Oncology* 1984; **41**: 96-100
78 **Erroi F**, Scarpa M, Angriman I, Cecchetto A, Pasetto L, Mollica E, Bettiol M, Ruffolo C, Polese L, Cillo U, D'Amico DF. Ovarian metastasis from colorectal cancer: prognostic value of radical oophorectomy. *J Surg Oncol* 2007; **96**: 113-117
79 **McCormick CC**, Giuntoli RL 2nd, Gardner GJ, Schulick RD, Judson K, Ronnett BM, Vang R, Bristow RE. The role of cytoreductive surgery for colon cancer metastatic to the ovary. *Gynecol Oncol* 2007; **105**: 791-795
80 **Chung TS**, Chang HJ, Jung KH, Park SY, Lim SB, Choi HS, Jeong SY. Role of surgery in the treatment of ovarian metastases from colorectal cancer. *J Surg Oncol* 2009; **100**: 570-574
81 **Goéré D**, Daveau C, Elias D, Boige V, Tomasic G, Bonnet S, Pocard M, Dromain C, Ducreux M, Lasser P, Malka D. The differential response to chemotherapy of ovarian metastases from colorectal carcinoma. *Eur J Surg Oncol* 2008; **34**: 1335-1339
82 **Hanna NN**, Cohen AM. Ovarian neoplasms in patients with colorectal cancer: understanding the role of prophylactic oophorectomy. *Clin Colorectal Cancer* 2004; **3**: 215-222
83 **Tentes A**, Markakidis S, Mirelis C, Leventis C, Mitrousi K, Gosev A, Kaisas C, Bouyioukas Y, Xanthoulis A, Korakianitis O. Oophorectomy during surgery for colorectal carcinoma. *Tech Coloproctol* 2004; **8** Suppl 1: s214-s216
84 **Igor Sielezneff**, Etienne Salle, Kristina Antoine, Xavier Thirion, Christian Brunet, Bernard Sastre. Simultaneous bilateral oophorectomy does not improve prognosis of postmenopausal women undergoing colorectal resection for cancer. *Dis Colon Rectum* 1997; **40**: 1299-1302

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