Staging with Unilateral Salpingo-Oophorectomy and Expert Pathological Review Result in No Recurrences in a Series of 81 Intestinal-Type Mucinous Borderline Ovarian Tumors

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Keywords

Borderline ovarian tumor · Mucinous · Recurrence ·
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Abstract

Objective: Recent studies suggest that mucinous borderline ovarian tumors (MBOTs) belong to a high-risk group that is more likely to develop an invasive recurrence. The objective is to determine these risk factors. **Methods:** A monocentric retrospective review of all consecutive patients with intestinal-type MBOT diagnosed between 1993 and 2013. All tumors were evaluated by one pathologist without knowledge of clinical outcome. Extensive surgical staging and pathological tumor sampling (1 block/cm diameter in tumors <10 cm and 2 blocks/cm diameter in tumors >10 cm) were performed in all cases. **Results:** A total of 81 patients were included. Patients with micro-invasion were also included. None of the patients recurred. No bilateral tumors, nor tumors with International Federation of Gynecology and Obstetrics stage II or higher, were diagnosed. Median follow-up was 87 months. **Conclusions:** In our series of pure intestinal-type MBOT, including micro-invasion, no recurrences were observed. Given the heterogeneity of these tumors staging

with at least unilateral salpingo-oophorectomy, extensive pathological sampling, and expert pathological review are of paramount importance to be able to diagnose a pure intestinal-type MBOT and excluding gastrointestinal mucinous tumors and more important, excluding an invasive focus, defining a mucinous ovarian carcinoma. When these conditions are fulfilled, the prognosis of pure intestinal-type MBOT is excellent.

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Introduction

Borderline ovarian tumors (BOTs) represent between 10 and 20% of all epithelial ovarian cancer [1, 2]. Up to 95% of all BOTs are mucinous or serous, of which the mucinous represent 42.5–52% [3]. Mucinous BOTs (MBOTs) are categorized into 2 different histological groups: the intestinal (85–90%) and seromucinous type (also known as Müllerian or endocervical type) [4, 5]. These 2 MBOT entities differ not only pathologically, but also clinically [6].

The intestinal subtype is known to be more frequently unilateral, is not associated with the presence of endome-

triosis and is rarely diagnosed with extra-ovarian implants. No well-documented cases have been reported of invasive peritoneal implants in patients with MBOT of the intestinal type [7, 8]. Mucinous tumors are well-known for their heterogeneity; all phenotypes from completely benign to frankly invasive can be present in one tumor. This makes the pathological evaluation challenging. Confirmed risk factors for disease recurrence are a higher International Federation of Gynecology and Obstetrics (FIGO) stage, residual tumor, and age [3, 4]. Recent studies have shown MBOT (all types) recurrence rates from 3.5% (10 of 290, 5-year follow-up) up to 12% (17 of 140, mean follow-up of 3.7 years) [9, 10]. Prognosis is extremely good, with 5-year survival rates near 100% for stage I MBOTs in general. However, the prognostic factors for invasive recurrence are still not clearly defined. The mucinous histological subtype as a risk factor for invasive recurrence is still controversial [11–13]. Uzan et al. [10] concluded recently that MBOT are at high-risk to develop an invasive recurrence after fertility sparing surgery. We therefore conducted an analysis of intestinal-type MBOT patients treated in our institution.

Methods

Patients

For this study, we retrospectively included all consecutive patients diagnosed with a primary diagnosis of MBOT during the 21-year period (152 months) from January 1993 until and including December 2013. All patients were diagnosed and surgically staged at our institution. Active follow-up of all patients till the date of analysis was performed. Only patients with the diagnosis of a pure intestinal-type MBOT were included. Diagnosis was defined and classified according to the WHO criteria: an unusual degree of epithelial cellular proliferation (seen as cellular stratification, nuclear atypia, and mitotic activity) and characterized by the absence of either expansile or destructive stromal invasion, except for micro-invasion [14]. All patients with a mixed borderline diagnosis such as seromucinous, endometrioid-mucinous, and others were excluded. All tumors were pathologically evaluated by one expert pathologist, experienced in gynecological pathology (PhM) without knowing the clinical outcome of the patients. Tumors with a diameter less than 10 cm were sampled with at least one biopsy block per cm. Tumors larger than 10 cm were sampled with at least 2 blocks per cm diameter [15, 16]. Stromal micro-invasion was defined as the presence of one or more foci with infiltrative stromal invasion less than 5 mm in greatest dimension or $<10 \text{ mm}^2$ in area [14]. Patients with micro-invasion were included.

The 2014 FIGO classification was used for staging. FIGO stage was established combining the surgical staging and pathological report and was documented combining initial and restaging procedures. Staging was considered complete when consisting of at least unilateral salpingo-oophorectomy (USO), peritoneal cytology, omentectomy, multiple peritoneal biopsies, inspection and pal-

pation of the whole abdominal cavity, and appendectomy [3, 17]. Appendectomy was performed to exclude the possibility of ovarian metastasis of mucinous tumors of the appendix. However, none of the patients had a primary tumor of the appendix; hence, the necessity to perform a routine appendectomy in patients with intestinal type MBOT can be questioned. Furthermore, in the current series, none of the patients developed intestinal-type MBOT during follow-up carcinomas of the intestines; hence, we do not believe that a routine gastroscopy or colonoscopy is indicated in patients with intestinal-type MBOT. Neither lymphadenectomy nor biopsies of the contralateral ovary in fertility sparing approach were required for a patient to be classified as completely staged. The role of a lymphadenectomy has been a point of discussion for a long time now. However, according to the results of multiple studies, a pelvic and aortic lymphadenectomy does not improve the disease-free time or overall survival rate for women with BOT [18]. Staging could be complete in fertility sparing and non-fertility sparing surgery. Non fertility-sparing surgery or radical surgery was defined as a hysterectomy with bilateral salpingo-oophorectomy (BSO). Fertility preservation was achieved by conserving the uterus and one ovary or as a BSO without hysterectomy with oocyte cryopreservation. Follow-up consisted of clinical examination including vaginal palpation, and ultrasound scan in case of fertility sparing approach, every 6 month for 2 years and then yearly. The study protocol was approved by the local ethics committee of our hospital and a written informed consent of all patients was obtained granting access to their medical records and tissues.

Results

A total of 81 patients were included, none of whom suffered from recurrence ($n = 0$). Median age of the cohort was 51 (17–81) years, with 17 patients (21.0%) <40 years and 64 patients (79.0%) ≥ 40 years. Median follow-up was 87 months (1–214). Of these, 4 patients (4.9%) died of intercurrent disease. All patients were diagnosed in FIGO stage I, no bilateral tumors, nor tumors with FIGO stage II or higher, were diagnosed. A total of 65 patients (80%) were diagnosed in stage IA, 15 patients (19%) IC1, and 1 patient (1%) in stage IC2. Histopathologically, 12 tumors (15%) were classified as being micro-invasive, 10 (12%) with multiple foci, and 2 (3%) with only one focus. A total of 30 patients expressed elevated CA 125 levels at diagnosis (Table 1).

A separate 12 patients originally diagnosed as intestinal-type MBOT were at pathological review diagnosed as invasive mucinous ovarian carcinomas and were not included. These patients had a small invasive focus of stromal invasion more than 5 mm in greatest dimension or $>10 \text{ mm}^2$ in area, in otherwise mucinous borderline tumors. Of them, 8 (67%) patients were diagnosed in FIGO stage IA, 3 (25%) patients stage IC1, and 1 (8%) IC3. Staging was complete in 10 (83%) patients, 1 (8%) patient

Table 1. Clinical and histological patient characteristics

	Total (<i>n</i> = 81), <i>n</i> (%)
Age at diagnosis, years	
Median (range)	51 (17–81)
Age <40	17 (21)
FIGO stage	
IA	65 (80)
IC1	15 (19)
IC2	1 (1)
II–IV	0 (0)
Stromal micro-invasion	12 (15)
Single focus	2 (3)
Multiple foci	10 (12)
CA 125 levels preoperative	
Elevated*	30 (37)
Normal	49 (61)
Unknown	2 (3)

FIGO, International Federation of Gynecology and Obstetrics; CA, cancer antigen.

* Elevated, above the upper normal limit (30 kU/L)

lacked peritoneal biopsies, and 1 (8%) patient lacked an appendectomy. Out of these 12 patients, 10 patients were treated with a hysterectomy and BSO, 5 of whom received 6 cycles of chemotherapy (carboplatin). In this group, 1 pulmonary metastasis after 94 months was observed and this patient died 100 months after primary diagnosis. All other patients did not recur and are alive. Two patients underwent fertility sparing treatment. No completion surgery was performed yet. Mean follow-up was 82 months (25–173).

In the borderline population, radical surgery consisting of a hysterectomy with BSO was performed in 65 patients (80%). In 4 of these 65 patients, this was performed laparoscopically. One patient underwent a BSO without hysterectomy because of comorbidity. A total of 15 patients (19%) underwent fertility sparing surgery, 14 of whom were <40 years. Three of these 15 patients were solely treated laparoscopically. One patient diagnosed with intestinal type MBOT after a USO was later treated with a contralateral salpingo-oophorectomy and cryopreservation of oocytes, followed by a completion hysterectomy after 5 years.

After final surgical management (1- or 2-step procedure), nobody was treated exclusively with a cystectomy. Four patients with intestinal-type MBOT diagnosis after initial cystectomy (4.9%), underwent all 4 immediate completion surgery: 1 case with USO, the 3 others BSO + hysterectomy. No residual MBOT nor invasive tumor could

be demonstrated at pathological examination. In 8 cases, a diagnostic laparoscopic staging procedure was performed (9.9%), before surgical therapy. All 8 diagnostic procedures were followed by a hysterectomy + BSO (Table 2).

In total, 49 patients had an optimal staging (60.5%), 7 out of the 15 fertility sparing treated patients were optimally staged (50.0%). Considering the EORTC surgical staging categories, 77 of all patients (95%) meet the modified staging criteria, and in the fertility sparing population, all patients fulfilled these criteria [19]. Lymphadenectomy was performed in 3 (4%) patients: 1 pelvic lymphadenectomy and 2 pelvic- with para-aortal lymphadenectomies. All 3 were negative.

Discussion

In our series of pure intestinal-type MBOT, no recurrences were observed (not as borderline, nor as invasive mucinous carcinoma). This finding is in contrast to recent studies concluding that MBOT are a high-risk group for invasive recurrence and associated with poorer overall survival in comparison with other borderline subtypes [10, 12]. As the other published series on BOT, this is also a retrospective study, but with a central pathological review performed by one pathologist with a 35-year expertise in gynecological pathology. Bias is also minimized by including all consecutive patients, all disease stages and all surgical managements during the study period.

Literature often defines prognostic factors for BOTs in general. However, we are convinced that the separate categories of BOT represent completely different entities with specific pathological and clinical characteristics, underlining the importance of correct and expert pathology in these cases [12]. Even within the subgroup of MBOT, a further classification dividing into intestinal- and endocervical-subtypes is important [6, 8, 15, 16, 20, 21]. The latter are more related to serous BOT than the intestinal-type MBOTs [22, 23].

Nowadays it is accepted that fertility sparing surgery can be performed in younger patients [5, 9, 24, 25]. Yet, the mode of fertility sparing intervention continues to fuel the debates. Several recommendations have been made to perform an USO as fertility sparing approach, while a cystectomy is still considered adequate by others [3, 5, 25]. A recent large meta-analysis of 5,105 women with BOT confirmed that USO is advisable in MBOT [21]. Several studies found a significant decrease of progression-free survival when cystectomy was performed instead of USO [2, 13, 26].

Table 2. Surgical characteristics

	Total (<i>n</i> = 81), <i>n</i> (%)
Surgical approach	
1-Step procedure	50 (55)
2-Step procedure*	30 (37)
Radical completion after fertility sparing surgery	1 (1)
Fertility sparing approach	19 (17)
Primary approach	
Laparoscopic	19 (24)
Converted (laparoscopy to laparotomy)	5 (6)
Laparotomy	57 (70)
Primary intervention	
Diagnostic laparoscopy, no intervention	8 (10)
Unilateral cystectomy	3 (4)
Bilateral cystectomy	1 (1)
USO	23 (28)
BSO	3 (4)
HT + BSO	43 (53)
Secondary approach (restaging)	31 (38)
Laparoscopic	13 (16)
Converted (laparoscopy to laparotomy)	1 (1)
Laparotomy	17 (21)
Secondary intervention	31 (38)
Staging	7 (9)
Contralateral USO	1 (1)
Hysterectomy	2 (3)
HT + contralateral USO	9 (11)
USO after cystectomy	1 (1)
HT + BSO after cystectomy	3 (4)
HT + BSO	8 (10)
End result	
HT + BSO	65 (80)
Solely laparoscopic approach	4 (5)
BSO	1 (1)
USO	14 (17)
Optimal staging	49 (61)
Modified staging	77 (95)
Omentectomy	78 (96)
Cytology	80 (99)
Abdominal cavity description in surgery report	81 (100.0)
Random biopsies	60 (74)
Appendectomy	62 (77)

USO, unilateral salpingo-oophorectomy; BSO, bilateral salpingo-oophorectomy; HT, hysterectomy.

* 2-Step procedure: surgical completion within 6 weeks of initial treatment.

A possible explanation can be found in the histopathological characteristics of MBOT. MBOT are known to be bulky tumors. Different tumor characteristics often coexist in one tumor specimen: a continuum of all degrees of malignancy from frankly benign to clearly invasive can be found in one and the same tumor [5, 6, 10, 15, 27]. Because of this heterogeneous composition, this type of tumor is particularly prone to pathological sampling error. This is why the internationally recommended extensive pathological sampling of MBOT is tremendously important. The current directive to sample at least 1 section for every cm in diameter in MBOT <10 cm and a minimum of 2 sections for all MBOT ≥10 cm is indicated to detect an invasive focus, thus minimizing the risk of possible sampling error.

This heterogeneity is one of the reasons why MBOT is a difficult pathological diagnosis [15, 22]. This is shown in the series of du Bois et al. [13] with discrepancies between the external and reference pathologists' diagnosis in 122 patients, stressing the importance of expert pathologic review. It is important to note that in large multicenter studies a central pathological review by an expert pathologist does not rule out the possibility of sampling error [10]. This can be minimized if the initial sampling was performed in all patients according to the WHO guidelines, hereby minimizing the risk of classifying invasive mucinous carcinomas as mucinous borderline tumors. This should be taken into account when evaluating the larger earlier reported studies. The heterogeneity of these tumors could also explain why a simple cystectomy results in a higher recurrence rate in other studies. An inadequate "in toto" resection is a possible explanation for the higher invasive recurrence rates after fertility sparing surgery including cystectomy [10, 11]. In our study, none of the patients were treated with a cystectomy only, which might also be a reason for the fact that we did not observe any recurrence.

Another remarkable finding in our series is the absence of any FIGO stage higher than stage I although this was not an exclusion criteria. This is in line with the literature stating that implants are very rare in true intestinal-type MBOT [28]. Hence, one can conclude that if a higher FIGO stage is found, it is likely that the diagnosis will not be an intestinal-type MBOT and that another type of BOT (for example, a serous or a seromucinous BOT) or a metastatic extra-ovarian primary [3, 4, 22]. Earlier reports describing stage III BOT were associated with pseudomyxoma peritonei and almost certainly not primary ovarian tumors, hence the importance of appendectomy for complete staging [22]. Likewise, bilateral

neoplasms are very rare in pure intestinal-type MBOT. Also, in bilateral mucinous tumors, one should always exclude extra-ovarian metastatic ovarian spread of a primary gastrointestinal carcinoma [14]. On the other hand, endocervical-like MBOT is known to be bilateral in as many as 40% of cases [5].

Conclusion

In conclusion, in our series of pure intestinal-type MBOTs, no recurrences were observed nor bilateral tumors nor tumors in FIGO stage II or higher. Given the

heterogeneity of these tumors staging with at least USO, extensive pathological sampling of the tumor, and an expert pathological review are of paramount importance to be able to make the diagnosis of a pure intestinal-type MBOT and excluding mucinous tumors originating in gastrointestinal tract and more important excluding an invasive focus defining a mucinous ovarian carcinoma.

Disclosure Statement

The authors have declared no conflict of interest.

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