Case series

Staging surgery in early-stage ovarian mucinous tumors according to expansile and infiltrative types

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ABSTRACT

The aim of this study is to determine the value of surgical staging for the two histologic types (expansile or infiltrative) of apparent stage I mucinous ovarian carcinoma. We retrospectively analyzed patients treated from 1976 and 2016 for apparent macroscopic stage I ovarian mucinous carcinoma. Extra-ovarian disease and tumors that metastasized to the ovaries were excluded. Two expert pathologists performed pathologic reviews of tumor data, according to 2014 WHO classification criteria. Tumors were typed as expansile or infiltrative and clinical and histologic characteristics were studied. The value of staging procedures (peritoneal and nodal) was based on the rate of microscopic involvement in macroscopically normal specimens.

Of 114 cases reviewed, 46 were excluded (26 with macroscopic stage > I; 20 inaccessible for pathologic review). Of 68 patients included, 29 had expansile and 39 had infiltrative types. 27 patients received one-step surgery and 41 received restaging surgery. 52 patients received "complete" peritoneal surgical staging (including cytology, peritoneal biopsies, and an omentectomy or large omental biopsies). 24 underwent appendectomies and 31 underwent lymphadenectomies (8 expansile and 23 infiltrative). Before histologic analyses of staging specimens, 35 had "initial" stage IA and 33 had IC disease. After histologic analyses of lymph nodes, 4 cases (17%, all infiltrative) had nodal involvement, and 2 showed microscopic peritoneal disease (1 omentum and 1 right diaphragm peritoneum). Three patients were upstaged based on isolated positive peritoneal cytology.

To conclude, peritoneal staging procedures are required for both types of mucinous ovarian carcinoma. Lymphadenectomy could be omitted in expansile, but required in infiltrative type.

1. Introduction

Mucinous ovarian carcinoma (mOC) is a complex group of tumors frequently associated within a single "malignant" ovarian disease. These tumors exhibit varying transitional histologic patterns that include benign cystadenoma, borderline patterns, and invasive disease (Kurman et al., 2014; Lee & Scully, 2000; Rodríguez & Prat, 2002). Within the last four decades, different classifications of mucinous tumors have been described (Kurman et al., 2014; Lee & Scully, 2000; Rodríguez & Prat, 2002; Hauptmann et al., 2017). Conventionally, the cut-off between borderline and malignant ovarian tumors is based on the absence/presence of "frank" stromal invasion. In 2000, Lee and Scully introduced the expansile and infiltrative types of mOC based on morphological and prognostic differences (Lee & Scully, 2000). In 2014, the WHO proposed to standardize pathological reports of mOC (and also borderline disease) by classifying primary mucinous cancers as expansile or infiltrative, according to the growth pattern (Kurman et al., 2014). The expansile type has a better prognosis than the infiltrative type (Lee & Scully, 2000). Nevertheless, to our knowledge, only one previous study (which included 44 cases) specifically addressed the
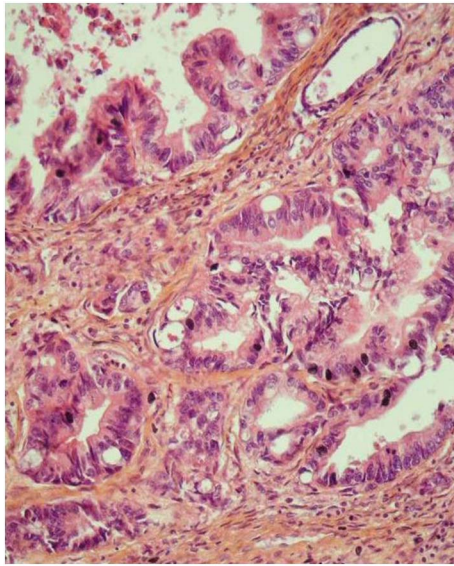
Fig. 1. Morphology of infiltrative mucinous carcinoma (hematoxylin-eosin-safran staining × 200).

value of peritoneal and nodal staging surgery for the expansile and infiltrative types of mOC.

2. Patients and methods

We retrospectively identified patients with mOC that were referred or treated in our institution between 1976 and 2016. Patients were included when they met the following inclusion criteria:

1. Sufficient data available for a centralized pathologic review of the ovarian tumors, performed by two expert pathologists (CG and MDS), according to the 2014 WHO classification guidelines (Figs. 1 & 2). Patients were excluded when data on the initial ovarian tumor were not available for pathologic review (i.e., for patients treated outside our institution or for some of the oldest cases).
2. Primary mOC; tumors that had metastasized to the ovaries were excluded.
3. Macroscopic stage I disease only (no extra-ovarian disease identified in the surgical exploration).
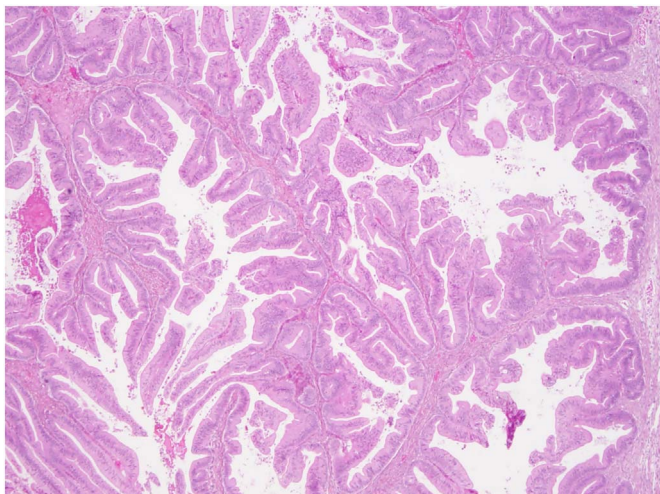

Fig. 2. Morphology of expansile mucinous carcinoma (hematoxylin-eosin-safran staining × 40).

4. Sufficient surgical and histological data available to determine the precise surgical procedures carried out and their histologic results.

"Complete" peritoneal surgical staging was defined as, at minimum, the acquisition of peritoneal cytology, multiple peritoneal biopsies, and an omentectomy or omental biopsies. An appendectomy was not included in the minimum requirements for a "complete" staging surgery in this series. Similarly, lymph node resection and uterine curettage (in case of conservative surgery) were optional for a complete staging surgery. In some cases, ovarian tumor surgery and staging (when performed) were performed in a one-step surgery, when the malignancy could be diagnosed during the surgery with a frozen section analysis. In others cases, the staging surgery was performed in two steps (restaging surgery). These surgeries were carried out with laparoscopic or laparotomic approaches, according to the judgment of the surgical teams. A "radical" surgery was defined as the removal of both adnexae. Conservative surgery was defined as the preservation of at least part of one ovary and the uterus.

Tumors were typed as expansile or infiltrative, according to the 2014 WHO classification criteria (Kurman et al., 2014). Clinical and histologic characteristics were studied for both histotypes. According to consensus, the grading system used for serous cancers is not applicable to mucinous subtypes. The 2014 WHO classification does not include recommendations about tumor grading in mOC. Thus, in the present series, for expansile subtype, we implemented the nuclear grading system recommended by Rodriguez & Prat (Rodríguez & Prat, 2002).

We evaluated the value of peritoneal (and nodal) staging procedures, based on the rate of microscopic involvement histologically determined for macroscopically normal specimens. The 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system was implemented; in particular, this system included 3 new classes of stage IC disease (Prat & Committee, 2014). According to local regulation, no IRB was required in such retrospective study.

3. Results

We reviewed 114 cases. Forty-six were excluded because the macroscopic disease severity was greater than stage I (n = 26 cases: 2 stage II, 18 stage III, 4 stage IV, and 2 unknown) or the lack of accessibility for a pathologic review (n = 20). The final analysis included 68 cases: 29 expansile and 39 infiltrative mOC types. The characteristics of the 68 patients are detailed in Table 1.

The details of the surgical procedures are given in Table 2. Twenty-seven patients underwent a one-step surgery, and 41 underwent a restaging surgery. Sixty-seven patients had data for at least peritoneal cytology during the initial and/or restaging surgery. "Complete" peritoneal surgical staging was carried out in 52 cases. Twenty-four patients underwent an appendectomy (23 others had a previous history of appendectomy). Lymphadenectomy was carried out in 31 patients (one patient received a pelvic lymphadenectomy alone); of these, 8 had expansile and 23 had infiltrative mOC. Twenty-seven of these lymphadenectomies were done during a restaging surgery. Before histologic analyses of the staging specimens, 35 patients had "initial" stage IA, and 33 had stage IC disease.

The histologic analyses demonstrated that three patients had isolated positive cytology. Of these, two were upstaged from stage IC1 (perioperative rupture) to IC3, and one was upstaged from macroscopic stage IA to IC3. Two exhibited the expansile mOC type. Two patients were treated with 2-step surgeries (1 exhibited positive cytology during the 1st surgery, and the other exhibited positive cytology during the restaging surgery). One patient received a one-step surgery.

After the histologic analysis of the peritoneal specimens, two patients exhibited microscopic peritoneal spread: one in the omentum, and the other in a random biopsy of the right diaphragm. After a histologic analysis of the lymph nodes, four patients had nodal involvement. The correlations between the initial stage, nuclear grade, and

Table 1
Characteristics of patients according to the type of mucinous tumor.

Characteristic	Expansile n = 29	Infiltrative n = 39
Median age, years (range)	40 (14–83)	35 (16–78)
Menopausal patients		
No	18	29
Yes	5	6
Undetermined	6	4
Body mass index, kg/m^2	22 (19–34)	23 (17–34)
Previous history		
Borderline[a]	0	1
Cancer[b]	0	2
Previous appendectomy	12	11
Median tumor size (diameter), cm (range)	14 (7–26)	12 (4–30)
Bilateral		
Yes	1	1
No	26	36
FIGO stage		
IA	13	22
IB	0	0
IC1	9	9
IC2	5	7
IC3	2	1
Nuclear grade		
Grade 1	11	–
Grade 2	10	–
Grade 3	0	–
Undetermined	8	–

Data are the number of patients in each group, unless otherwise indicated.
FIGO: International Federation of Gynecology and Obstetrics.
[a] Borderline mucinous.
[b] Breast cancer.

Table 2
Surgical procedures according to histologic type of mucinous carcinoma.

Procedure	Expansile n = 29	Infiltrative n = 39
One-step surgery (ovary and staging procedures)	15	12
Laparotomy	9	6
Laparoscopy	1	0
Unknown	5	6
Two-step surgery	14	27
Median delay, months	2	2
Laparotomy only	6	14
Laparoscopy only	1	1
Both procedures	6	6
Unknown	1	6
Tumor rupture	14	13
Preoperative	6	6
Perioperative	8	6
Conservative surgery		
Yes	12	15
No	17	24
Peritoneal staging		
Cytology	29	38
Peritoneal biopsies	23	34
Omentectomy or omental biopsies	25	36
Appendectomy	10	14
Complete peritoneal staging	23	29
Lymph node staging		
Pelvic only	1	0
Pelvic and para-aortic	7	23
Median number of nodes removed (range)	28 (1–35)	13 (2–63)

Data are the number of patients in each group, unless otherwise indicated.

nodal status are detailed in Table 3. All four of these patients had in-filtrative mOC (4/23 that underwent lymphadenectomy: 17%). No nodal metastasis was observed among eight patients with expansile mOC that underwent lymph node sampling. Among the four patients with nodal spread, two had a single nodal metastasis (without capsular

Table 3
Nodal status according to tumor stage (before analyzing staging specimens) and nuclear grade in expansile and infiltrative tumor types.

Tumor characteristics	Expansile n = 8		Infiltrative n = 23	
	N −	N +	N −	N +
Disease stage (2014 FIGO classification)				
IA	2	–	9	3
IC1	3	–	5	1
IC2	2	–	4	–
IC3	1	–	1	–
Nuclear grade				
Grade 1	3	–	–	–
Grade 2	5	–	–	–
Grade 3	–	–	–	–

N −, negative nodal metastasis; N +, positive nodal metastasis FIGO: International Federation of Gynecology and Obstetrics.

rupture); one was in the pelvic area, and one was in the para-aortic supra-mesenteric area. The third patient had 5 metastatic nodes (among 63 removed), all in para-aortic nodes (without capsular rupture). The fourth patient had pelvic and para-aortic nodal metastasis (number and size of nodes undetermined). Of these four patients, two also had microscopic peritoneal disease (patients previously described). The final FIGO staging classes of these patients were stages IIIA1 (n = 2) and IIIA2 (n = 2). No other case of microscopic peritoneal spread was observed. No appendiceal tumor was observed.

4. Discussion

This study raised the complex issue of the value of peritoneal staging surgery, in terms of histologic detection rate (how many patients had histologic spread whereas macroscopic exploration is normal). We also investigated the question of how staging contributed to overall cancer management; we determined the percentage of patients that required adjuvant treatment, based only on the histologic results of staging surgery.

Among epithelial ovarian cancers, mOC is one of the least frequently observed. It can be characterized on the basis of 3 points: 1: It is diagnosed frequently in stage I (in contrast to other subtypes/3–5). 2: It is observed in younger patients, compared to the other types of ovarian cancer. 3: When observed at a more advanced stage, the prognosis is worse than that of the other types of ovarian cancer. A key issue in mOC is that characterization is crucial for the differentiation between a primary ovarian tumor and metastatic disease from a non-gynecologic primitive tumor.

Because mOC is frequently observed at a limited stage and in the youngest patients, the quality of the staging surgery is a key factor. On the other hand, this group of tumors involves different entities, and previous studies on the histologic classifications have provided widely variable results; consequently, it is difficult to compare the results from different series previously published on this topic. Many studies that investigated the value of staging surgery included a mixture of mOC types (Cho et al., 2006). Others studies that distinguished between the types were mainly focused on the histologic characteristics of the tumors, but not clinical management (Lee & Scully, 2000; Rodríguez & Prat, 2002). The only study that discussed this topic was published by Muyldermans et al. They studied 44 mOC cases (including 20 with lymph node sampling) (Muyldermans et al., 2013). However, that interesting paper did not focus on other staging procedures (Muyldermans et al., 2013). Thus, the present study was the first that specifically focused on studying the different staging procedures for both histologic types of mOC.

The two most important strengths of this study are firstly the number of stage I mOC cases (collecting the largest number of stage I

mOC with characterization of expansile and infiltrative types); and secondly the accuracy of the histological analysis. This quality is increased by conducting the pathologic review with expert pathologists that have considerable experience in gynecological tumors. This point is particularly a corner stone in series about mucinous ovarian diseases mixing different patterns inside the same tumor. In the current series, the pathologic review was conducted by two senior pathologists, both with substantial expertise in these diseases. The two weaknesses of this study are its retrospective nature (but that is the methodology of a vast majority of studies about rare tumors) and its length (nearly 40 years). But this last potential weakness has an impact mainly on the discrepancy of the pathologic analysis within 4 decades, that have been corrected with the centralization of pathologic review previously mentioned.

Two aspects of the staging surgery must be evaluated: the peritoneal procedures and the lymphadenectomy. First, the peritoneal staging procedures appeared to provide low value, because previous studies in "macroscopic" stage I ovarian cancers indicated that mucinous cancer had the lowest rate of extra-ovarian microscopic spread (Cho et al., 2006; Powless et al., 2009; Lee et al., 2014; Garcia-Soto et al., 2012). The series of Lee et al. showed that, in eight cases of stage I disease that were upstaged to IIIA, no mucinous tumor was found (out of 92 cases included in the series) (Lee et al., 2014). In the series of Cho et al., which included 60 cancer cases, no patients were upstaged to stage II or III disease (Cho et al., 2006). However, in the series of Powless et al., all eight patients upstaged to stage III disease exhibited pelvic spread on the peritoneum (stage II) (Powless et al., 2009). However, only two of the eight in the latter series were mucinous tumors (Powless et al., 2009). Interestingly, in the series of Cho et al., five cases of mucinous tumors were upstaged to stage IC3 disease, solely on the basis of positive cytology (Cho et al., 2006). Thus, the question has arisen: Can we simply skip the staging (or restaging) surgery in mOC? This is a crucial question because, although these staging procedures have low morbidity risk when the malignancy is detected during surgery, in cases where the initial diagnosis is mistaken (either no frozen section analysis/FSA or false negative results), the question is whether to perform a new surgery for adequate staging. Our results suggested that, although the detection rate is low, microscopic peritoneal spread could be observed even during (re)staging surgery in cases of macroscopically normal peritoneal cavity. In the present series, three patients were upstaged to stage IC3 based on isolated positive cytology, and two exhibited microscopic involvement in the omentum and in a right diaphragm biopsy. In a recent study by Garcia-Soto et al., three mucinous cancers that were upstaged had spread to similar locations (Garcia-Soto et al., 2012). Our two patients upstaged to stage III disease initially had the infiltrative tumor type. No extra-ovarian spread was found among expansile subtype tumors, but one patient exhibited isolated positive cytology. These results suggested that peritoneal staging surgery should be conducted, regardless of the type of mOC.

The second question concerns the need for a lymph node resection. For 15 years, we have known that, in mOC, the rate of nodal spread is very low in an apparent stage I tumor (Schmeler et al., 2010; Morice et al., 2003; Powless et al., 2011; Hoogendam et al., 2017; Van Baal et al., 2017). Over the last 10 years, some authors have suggested omitting lymph node resections in staging procedures for mOC (Morice et al., 2003). However, a recent study by Muyldermans et al. found that, among 10 infiltrative mOC cases that underwent lymph node sampling, 4 exhibited nodal spread (Muyldermans et al., 2013). That study was the first to analyze the lymph node spread specifically in both mOC subtypes. We found similar results in the present study. Among 31 patients that underwent lymphadenectomy (including pelvic and para-aortic lymphadenectomies), we found positive nodes in 4 out of 23 patients (17%) in the infiltrative group. Moreover, among these four patients, two exhibited peritoneal metastasis. In contrast, we found no nodal metastasis in the expansile group. These crucial results demonstrated that, although we might omit the lymphadenectomy in

expansile mOC cases, this procedure is required for infiltrative mOC cases, during either the initial or the restaging surgery. Ideally, can we use a FSA to determine between both subtypes and to carry out the lymphadenectomy during a single-step surgery only in infiltrative cases? As mOC are frequently bulky tumors (sometimes > 25 cm), mixing different histologic components (from benign cystadenoma, to borderline aspects, intra-epithelial carcinoma and frankly invasive patterns) accuracy of FSA to determine the degree of malignancy (borderline disease or cancer) in mucinous tumors is particularly complex and need expert pathologists. To ask furthermore to the pathologist to determine between expansile or infiltrative in case of mOC "confirmed" during FSA, is really challenging and impossible. No specific papers had been published about this specific point. So, pragmatically, if a (midline) laparotomic approach is used (due to the volume of the tumor) and FSA confirms a mOC during the primary surgery, lympadenectomy could be used (as the laparotomy done) in patient with no co-morbidity (obesity, previous history of vascular disease…). If a laparoscopic approach used to remove the ovarian tumor, we can wait the permanent histologic analysis to decide a potential secondary surgery (using a mini-invasive approach).

However, in truth, although we demonstrated the diagnostic value of the lymphadenectomy, we did not demonstrate its therapeutic value, as many of patients with infiltrative subtypes received an adjuvant treatment, whatever the lymph node status. This therapeutic effect of the lymph node resection itself in apparent stage I Ovarian Cancer remains currently an unsolved debate with endless discussions. Only a large randomized trial comparing systematic lymphadenectomy and no lymph node resection in exclusively macroscopic stage I disease, could theoretically answer to this important topic but its feasibility, according to the number of patients required, remains doubtful.

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