



Case report

Is uterine preservation combined with bilateral salpingo-oophorectomy to promote subsequent fertility safe in infiltrative mucinous ovarian cancer?



Sebastien Gouy^a, Marine Saidani^a, Amandine Maulard^a, Matthieu Faron^b, Slim Bach-Hamba^c, Enrica Bentivegna^a, Alexandra Leary^{c,d}, Patricia Pautier^c, Mojgan Devouassoux-Shisheboran^e, Catherine Genestie^f, Philippe Morice^{a,g,h,*}

^a From Department of Gynecologic Surgery, Gustave Roussy, Villejuif, France

^b Department of Gastro-intestinal Surgery, Gustave Roussy, Villejuif, France

^c Department of Medical Oncology, Gustave Roussy, Villejuif, France

^d INSERM U981, Gustave Roussy, Villejuif, France

^e Department of Pathology, Hospices Civils de Lyon, Lyon, France

^f Department of Pathology, Gustave Roussy, Villejuif, France

^g Unit INSERM 1030, Villejuif, France

^h University Paris Sud, 94805 Villejuif, France

ARTICLE INFO

Keywords:

Expansile
Infiltrative
Mucinous
Ovarian cancer
Recurrence
Staging
Uterine preservation

ABSTRACT

According to the latest World Health Organization classification (2014), mucinous ovarian cancers should be classified histologically as being either expansile or infiltrative. Compared to other epithelial cancers, both of these mucinous patterns are diagnosed, in the main, at an early stage, although they can affect relatively young patients. The infiltrative subtype is characterized by a morphologically and clinically more aggressive disease versus the expansile form. Consequently, even in young patients who would prefer fertility sparing management, the removal of both ovaries (even for a unilateral tumor) remains a common recommendation. However case reports describing the preservation of the uterus for a further potential pregnancy (following oocyte donation) have now been described. In this series, we present six patients treated for stage I mucinous infiltrative cancer using bilateral salpingo-oophorectomy with uterine preservation. All but one patient underwent 1-step ($n = 1$) or 2-step ($n = 4$) surgery, including peritoneal and nodal (4 patients) procedures. Disease stages were IA ($n = 2$), IC1 ($n = 1$), IC2 ($n = 2$), or IC3 ($n = 1$). While two patients subsequently became pregnant, two patients also suffered disease recurrence. For one patient, recurrence was at the pelvic peritoneum. For the second patient, an ultimately lethal disease recurrence involved the uterine serosa with nodal involvement. The results of this short series lead us to question the safety of this uterine-preserving strategy.

SBH was recipient of a DUERTECC/EURONCO grant (Diplôme Universitaire Européen de Recherche Translationnelle Et Clinique en Cancérologie).

1. Introduction

Within the last 4 decades, various classifications of mucinous tumors have been proposed (Rioped et al., 1999; Lee & Scully, 2000; Rodríguez & Prat, 2002; Hauptmann et al., 2017). In 2000, the expansile and infiltrative types of mucinous ovarian carcinoma (mOC) were described by Lee & Scully (2000). In 2014, in order to standardize pathology-reporting for mOCs (including borderline disease), the World Health Organization (WHO) harmonized its classification of primary

mucinous cancers as either the expansile or infiltrative subtypes, as categorized by their growth patterns (Kurman et al., 2014); the more favorable prognosis is the expansile type.

Compared to other epithelial cancers, mOCs are often diagnosed early, but can affect young patients. This scenario raises the question of fertility sparing surgery which is conventionally based on the preservation of the uterus and ovary contralateral to the initial tumor (Bentivegna et al., 2016). According to a new FIGO classification, this conservative approach appears to be oncologically safe in early disease stages (grades 1 and 2, up to stage IC1 (IC2?)) (Prat and Committee, 2014). However, in patients with poor prognoses (stage IA or IC1/2, but with grade 3 disease) the removal of both ovaries should be considered as the conventional strategy with which to reduce the risk of

* Corresponding author at: Gustave Roussy Cancer Campus Grand Paris, 114 rue Edouard Vaillant, 94805 Villejuif, France.
E-mail address: philippe.morice@gustaveroussy.fr (P. Morice).

<http://dx.doi.org/10.1016/j.gore.2017.09.011>

Received 18 July 2017; Received in revised form 21 September 2017; Accepted 25 September 2017

Available online 28 September 2017

2352-5789/ © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

recurrence.

Occasionally, the possibility of oocyte donation has led to a different approach for patients with poor prognoses: that of preserving the uterus in order to support future pregnancies. This option has been reported in several case reports (Gallot et al., 2000; Navot et al., 1991; Lawal and B-Lynch, 1996; Pouly et al., 1997), three of which involved serous borderline tumors with peritoneal spread and/or bilateral ovarian involvement (with the option to become pregnant after oocyte donation or the transfer of embryos frozen prior to ovarian surgery). The fourth case report involved a stage IC serous cancer with a successful pregnancy. Other than these cases, we lack a relevant larger series with which to evaluate the outcome of “isolated” uterine preservation with removal of both adnexae in ovarian cancers, particularly the mucinous subtype that is most frequently encountered in this situation. This is the aim of the current analysis, using a larger number of cases.

2. Patients and methods

Patients with mucinous ovarian carcinoma referred or treated in our institution between 1976 and 2016 were retrospectively identified. Patients were included if they met the following additional inclusion criteria:

1. A centralized pathologic review of the tumor could be undertaken by 2 expert pathologists (CG and MDS) according to the criteria of the 2014 WHO classification. The patient was excluded if the initial ovarian tumor was “unavailable” for review (i.e. patients treated at other facilities or older cases).
2. Primary mOC. Metastatic tumors (to ovaries) were not included.
3. Macroscopic stage I disease (the absence of extra-ovarian disease during surgical exploration).
4. Surgical, histological, and outcome data were available to determine the precise surgical procedures conducted, the histology, and subsequent recurrence or pregnancy.
5. Surgical procedures comprising 1-step (in cases of malignancy recognized by frozen-section analyses) or 2-step surgery (initial followed by restaging), based on bilateral salpingo-oophorectomy with uterine preservation.

“Complete” peritoneal surgical staging was defined as (at least) peritoneal cytology, multiple peritoneal biopsies, omentectomy or omental biopsies. The option to take a laparoscopic and/or laparotomic approach was at the discretion of the surgical team. Tumors were typed as being either expansile or infiltrative, according to the 2014 WHO classification criteria (Rioped et al., 1999).

Histology in terms of peritoneal (and nodal) staging procedures were analyzed (rate of histologic involvement of macroscopically normal specimens). The 2014 FIGO staging system was used, including its description of 3 new classes of stage IC disease (Pouly et al., 1997).

3. Results

Sixty-eight patients with stage I disease, for whom a review of their tumor pathology was possible, were studied. Twenty-one patients underwent conservative treatment, preserving a single ovary and the uterus, and six patients underwent bilateral salpingo-oophorectomy with uterine preservation.

The details of these latter six cases are provided in Table 1, with all demonstrating infiltrative subtypes. One patient (patient 5) had a previous history of ovarian surgery (cystectomy for benign cyst). Five patients manifested a unilateral tumor, and all but two patients (patients 1 and 3) underwent 2-step surgery. Patient 3 underwent 1-step staging surgery, and patient 1 was followed for 240 months without recurrent disease, and without having undergone complete staging surgery. Four patients had nodal surgery (negative nodes). The final disease-stages were IA (2 patients), IC1 (1 patient), IC2 (2 patients), and

IC3 (1 patient).

After a median time of follow-up of 97 (range 27–262) months, 2 patients 4-5 experienced recurrent disease. Patient 4 had stage IC2 disease treated exclusively with surgery, without nodal dissection. Six months later she recurred on the uterine serosa and iliac nodes under the form of high grade mucinous carcinoma and underwent a radical surgery, with pelvic and para-aortic lymphadenectomy, followed by chemotherapy (carboplatin & paclitaxel). She later died from her disease (eighteen months post recurrence).

Patient 5 was initially diagnosed with stage IC3 disease that was treated with complete peritoneal and nodal staging, followed by 4 courses of adjuvant platinum-based chemotherapy (Folfox regimen). This patient had a pregnancy after oocyte donation. Sixty months after her initial management she suffered disease recurrence on the pelvic peritoneum (utero-sacral ligament) under the form of high grade mucinous carcinoma and was treated using radical surgery with chemo-hyperthermia. This patient is currently alive without disease 14 months after her management.

Two pregnancies were achieved after oocyte donation (patients 2 and 5); patient 5 became pregnant before disease recurrence. Outcomes of both pregnancies were normal with a term delivery.

During the same period of the study, 9 patients having an infiltrative mOC underwent a conservative treatment with preservation of the uterus and 1 ovary. Disease-stages were stage IA ($n = 4$), IC1 ($n = 2$) and IC2 ($n = 3$). One patient with a stage IA disease had recurrence with a mucinous borderline tumor on the contralateral ovary 44 months after her initial treatment and underwent a radical surgery. She showed a new “invasive” massive peritoneal recurrence 116 months later and is currently alive with progressive disease. Two patients obtained spontaneous pregnancy.

4. Discussion

This paper is, to our knowledge, the first dedicated to the study of the safety of uterine preservation in epithelial ovarian cancer. In their analysis of the SEER data-base, Wright et al. suggested that uterine (and ovarian) preservation was oncologically safe in stage IA and IC disease (Wright et al., 2009). Nevertheless, while of interest, the extent to which these data could be analyzed was limited given the large patient cohort with mixed clinical histories (based on registry data retrieved from different US states).

The main limitation of the current study is our small number of cases. Nevertheless, this is the first series (despite its limited size) to specifically address the safety of uterine preservation in the context of ovarian cancer.

All of the mucinous cancers included in the current analysis were infiltrative, given that these are the aggressive subgroup for which some clinical teams recommend a “radical treatment” (i.e. the removal of both ovaries). In mucinous cancers, tumors are mainly unilateral (Kurman et al., 2014). In rare cases of bilateral disease, metastases from the gastro-intestinal tract should be screened for (i.e. primitive bilateral ovarian mucinous cancer; patient 5), with the removal of both ovaries seen as the standard approach. For these cases of more advanced disease (higher grade cases, the infiltrative mucinous subtype, stages IB and IC, and eventually IC3?), the possibility of removing both adnexae to reduce the recurrence rate, while retaining the uterus, has been proposed as a fertility-sparing option (Pouly et al., 1997).

While this strategy allowed two of our patients to become pregnant after oocyte donation, the approach has yet to be robustly evaluated in terms of oncological safety. Two cases recurred, both in the pelvic cavity, with a potentially superior prognosis than recurrence in the form of extra-pelvic peritoneal carcinosis or distant metastasis. Despite this, one patient still died from her recurrent disease and the other is currently alive, but with progressive disease. Consequently, we can't rely on the potentially higher curability rate of “pelvic-cavity” recurrent disease.

Table 1
Patient characteristics for the current series.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	35	16	32	33	27	26
Previous surgical history	0	0	0	0	1	0
Previous appendectomy	0	0	0	1	0	1
Tumor diameter (cm)	10	6	15	Unknown	8	11
Laterality	1	1	1	1	2	1
Complete peritoneal staging ^a	0	1	1	1	1	1
Lymph node staging	0	1	1	0	1	1
Number of nodes	-	21	20	-	42	22
One-step surgery	1	0	1	0	0	0
Two-step surgery	0	1	0	1	1	1
Median delay (months)	-	4	-	3	2	2
FIGO stage	IA	IC1	IA	IC2	IC3	IC2
Recurrence	0	0	0	1	1	0
Follow-up (yrs.)	20	22	13	2 ^b	7 ^b	3
Previous history of infertility	0	0	1	0	0	0
Nulliparous (prior their diagnosis)	1	1	1	1	1	0
Pregnancy	0	1	0	0	1	0

^a Complete peritoneal staging inclusive of peritoneal cytology, peritoneal biopsy, and omentectomy or omental biopsy; ^bIn cases of recurrence, follow-up time since treatment for recurrent disease.

Furthermore, as both instances of recurrent disease were located near (utero-sacral ligament) or on (serosa) the uterus, this naturally raises the question of the safety of uterine preservation. Arguing against this concern is the comparable lateness of one of our cases of disease recurrence (60 months), although it may be of relevance that this patient received an oocyte donation that required hormonal intervention prior to embryo implantation.

One patient manifested stage IC2 disease, and the other, stage IC3 disease (treated with adjuvant chemotherapy). Those recurrences might have been observed even after a radical surgery of both ovaries and the uterus. In other words, these disease recurrences might have been related to the natural history of the ovarian cancer rather than uterine preservation. However, in the absence of any conclusive evidence with which to make this determination, we would recommend extreme caution when preserving the uterus after removing both ovaries in mucinous ovarian cancer. With our current absence of more rigorous data, future work should more fully evaluate the oncological issues of uterine and unilateral ovarian preservation for expansile and infiltrative subtypes (i.e. allowing a spontaneous pregnancy without using hormones for oocyte/embryo implantation).

References

Bentivegna, E., Gouy, S., Maulard, A., Pautier, P., Leary, A., Colombo, N., Morice, P., 2016. Fertility-sparing surgery in epithelial ovarian cancer: a systematic review of oncological issues. *Ann. Oncol.* 27, 1994–2004.

- Gallot, D., Pouly, J.L., Janny, L., Mage, G., Canis, M., Wattiez, A., et al., 2000. Successful transfer of frozen-thawed embryos obtained immediately before radical surgery for a stage IIIa serous borderline ovarian tumour: Case report. *Hum. Reprod.* 15, 2347–2350.
- Hauptmann, S., Friedrich, K., Redline, R., Avril, S., 2017. Ovarian borderline tumors in the 2014 WHO classification: evolving concepts and diagnostic criteria. *Virchows Arch.* 470, 125–142.
- Kurman, R.J., Carcangiu, M.L., Herrington, C.S., Young, R.H., 2014. WHO Classification of tumours of female reproductive organs, 4th Edition. IARC, Lyon.
- Lawal, A.H., B-Lynch, C., 1996. Borderline ovarian cancer, bilateral surgical castration, chemotherapy and a normal delivery after ovum donation and in vitro fertilisation-embryo transfer. *Br. J. Obstet. Gynaecol.* 103, 931–932.
- Lee, K.R., Scully, R.E., 2000. Mucinous tumors of the ovary: a clinicopathologic study of 196 borderline tumors (of intestinal type) and carcinomas, including an evaluation of 11 cases with 'pseudomyxoma peritonei. *Am. J. Surg. Pathol.* 24, 1447–1464.
- Navot D, Fox JH, Williams M, Brodman M, Friedman F Jr, Cohen CJ. The concept of uterine preservation with ovarian malignancies. *Obstet. Gynecol.* 1991;78(3 Pt 2):566–8.
- Pouly, J.L., Janny, L., Pouly-Vye, P., Canis, M., Curé, A., Déchelotte, P., 1997. Successful oocyte donation after stage 1C serous ovarian cancer. *Hum. Reprod.* 12, 1589–1590.
- Prat, J., Committee, F.I.G.O., 2014. on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int. J. Gynaecol. Obstet.* 124, 1–5.
- Riopel, M.A., Ronnett, B.M., Kurman, R.J., 1999. Evaluation of diagnostic criteria and behavior of ovarian intestinal-type mucinous tumors: atypical proliferative (borderline) tumors and intraepithelial, microinvasive, invasive, and metastatic carcinomas. *Am. J. Surg. Pathol.* 23, 617–635.
- Rodríguez, I.M., Prat, J., 2002. Mucinous tumors of the ovary: a clinicopathologic analysis of 75 borderline tumors (of intestinal type) and carcinomas. *Am. J. Surg. Pathol.* 26, 139–152.
- Wright, J.D., Shah, M., Mathew, L., Burke, W.M., Culhane, J., Goldman, N., Schiff, P.B., Herzog, T.J., 2009. Fertility preservation in young women with epithelial ovarian cancer. *Cancer* 115, 4118–4126.