Long-term follow-up of patients with an isolated ovarian recurrence after conservative treatment of epithelial ovarian cancer: review of the results of an international multicenter study comprising 545 patients

Enrica Bentivegna, M.D.,[a] Robert Fruscio, M.D.,[b] Stephanie Roussin, M.D.,[a] Lorenzo Ceppi, M.D.,[b] Toyomi Satoh, M.D., Ph.D.,[c] Hiroaki Kajiyama, M.D., Ph.D.,[d] Catherine Uzan, M.D., Ph.D.,[a,e] Nicoletta Colombo, M.D., Ph.D.,[f] Sebastien Gouy, M.D., Ph.D.,[a] and Philippe Morice, M.D., Ph.D.[a,e,g]

[a] Department of Gynecologic Surgery, Institut Gustave Roussy, Villejuif, France; [b] Clinic of Obstetrics and Gynecology, San Gerardo Hospital, University Milano-Bicocca, Milan, Italy; [c] Department of Obstetrics and Gynecology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; [d] Nagoya University Graduate School of Medicine, University of Nagoya, Nagoya, Japan; [e] Unit INSERM 30-10, Villejuif, France; [f] Department of Surgery and Interdisciplinary Medicine, University Milano-Bicocca, Milan, Italy; and [g] University Paris Sud, Paris, France

Objective: To determine the long-term outcomes of patients with an isolated ovarian recurrence after fertility sparing surgery (FSS) for epithelial ovarian cancer (EOC) and to evaluate the recurrence rates (and location) according to the new 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system.
Design: Retrospective multicenter study.
Setting: Teams having reported recurrence after FSS for EOC.
Patient(s): Four series comprising 545 patients undergoing FSS and 63 (12%) recurrences.
Intervention(s): FSS (salpingo-oophorectomy for a majority of cases) for EOC.
Main Outcomes Measure(s): Recurrences rates and characteristics of recurrent disease.
Result(s): Among 63 recurrent patients, 24 (38%) recurrences were isolated on the spared ovary, and 39 (62%) arose at an extraovarian site. Among the patients with an isolated ovarian recurrence, three patients died after a median follow-up period of 186 months (range: 28–294 months). Among the patients with recurrent extraovarian disease, 24 died and 7 were alive with persistent disease after a median follow-up period of 34 months (range: 3–231 months). The overall rate of isolated ovarian and extrapelvic recurrences was higher for grade 3 tumors (compared with grades 1/2).
Conclusion(s): The long-term survival of patients with an isolated ovarian recurrence after FSS for EOC remains favorable. The prognosis of patients with an extraovarian recurrence is poor compared with those who have an isolated recurrent ovarian tumor. Grade 3 tumors (compared to grades 1/2) give rise to a higher rate of extraovarian recurrences. (Fertil Steril® 2015;104:1319–24. ©2015 by American Society for Reproductive Medicine.)
Key Words: Conservative surgery, epithelial ovarian tumor, extraovarian recurrence, prognosis, recurrence

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/bentivegnae-conservative-surgery-epithelial-ovarian-cancer/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Received March 11, 2015; revised and accepted June 5, 2015; published online July 3, 2015.
E.B. has nothing to disclose. R.F. has nothing to disclose. S.R. has nothing to disclose. L.C. has nothing to disclose. T.S. has nothing to disclose. H.K. has nothing to disclose. C.U. has nothing to disclose. N.C. has nothing to disclose. S.G. has nothing to disclose. P.M. is a consultant for Roche.
Presented at the European Cancer Congress (ECC 2015) Vienna, Austria, September 25-29, 2015.
Reprint requests: Philippe Morice, M.D., Ph.D., Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France (E-mail: morice@igr.fr).

Fertility and Sterility® Vol. 104, No. 5, November 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.06.008

Conservative treatment of epithelial ovarian cancer (EOC) is based on unilateral salpingo-oophorectomy and complete surgical staging. This is an option available to young women who present with an early-stage invasive tumor with a low

risk of recurrence (1–3). The outcomes for patients seem to be similar to those after conventional treatment of patients with stage IA (grades 1 and 2) and stage IC (grade 1) disease (1–3). In the case of patients with stages IA and IC grade 3 disease and stage IC grade 2 tumors, the results of conservative management continue to fuel debate (1). To have a complete overview of the different issues likely to exert an impact on oncologic results in this context, an analysis of the prognosis after a first recurrence after conservative treatment of EOC is crucial. A single study on this topic was published nearly a decade ago, which featured a short follow-up period (4). The long-term outcomes of such patients are unknown.

The outcome of patients with an extraovarian recurrence as the first event is poor (akin to that of patients with ovarian cancer and peritoneal spread) (4). But the long-term outcomes of patients with an isolated recurrence on the spared ovary as a first event remain undetermined. With the 2014 International Federation of Gynecology and Obstetrics (FIGO) classification modifications (particularly concerning early stage disease with the creation of the "IC" group), oncologic results of the different series published on this topic should be reevaluated in the light of the new FIGO system to identify the potential oncologic safety limits of conservative treatment within the stage IC group (5). Our study [1] determined the long-term outcomes of patients with an isolated recurrence on the spared ovary and [2] evaluated the recurrence rates (between ovarian and extraovarian sites) after conservative treatment according to the 2014 FIGO staging system (5).

MATERIALS AND METHODS

We reviewed the data of patients treated conservatively for an EOC and involving at least 10 cases as reported in the literature (6–24). We selected published series (excluding those published exclusively as abstracts with no full publication) that reported at least one isolated ovarian recurrence. In cases of repeated publication by the same team, only the most recent update (or the series by the same team reporting on the largest number of recurrences) was retained for further analysis. The studies derived from five different countries on three continents; the senior authors of these series were contacted to update the data on patients with recurrent disease (10, 14, 17, 22, 23). Among the five teams contacted who had published at least one article involving our criteria, four had updated the outcomes of their patients with recurrent disease (10, 17, 22, 23). Institutional review board (University Paris Sud) approval was obtained.

We analyzed the patient characteristics for each study. For stage IC disease, after reviewing the descriptions of the patients we reclassified them as having stage IC1 (peroperative rupture), IC2 (preoperative rupture), or IC3 (positive cytology or positive ascites) by the 2014 FIGO staging system (5). If the data were insufficient to classify the patients with IC disease, we classified them as having IC "unknown" disease (Table 1). Similarly, for some studies it was not possible to correlate the tumor grade and the FIGO classification; in these cases, the patients were classified as stage IA or IC with an "unknown grade" (Table 1).

The characteristics of the patients with recurrent disease were reanalyzed with a focus on our primary and secondary objectives. Our primary aim was to evaluate the long-term survival of patients with an isolated first recurrence on the spared ovary. Our two secondary objectives were [1] to classify the recurrent disease location (isolated ovarian recurrences on the remaining ovary or extraovarian recurrences with or without combined ovarian disease) according to the 2014 FIGO staging classification (with a correlation between the initial characteristics of the tumor and the location of these recurrences); and [2] to evaluate the survival of patients with an extraovarian recurrence.

The analyses were performed using the chi-square or Fisher exact tests for qualitative data. All analyses were performed with OpenStat for Windows (http://statpages.info/miller/OpenStatMain.htm). $P<.05$ was considered statistically significant for all analyses.

RESULTS

The four series analyzed comprised 545 patients. The characteristics of these patients are detailed in Table 1. Half of the patients (n = 280; 51%) had a mucinous tumor. Two-thirds of the patients (n = 357; 65%) had a grade 1 lesion, and 20% (n = 107) had grade 2 disease. The majority of patients had stage IA disease (n = 316; 58%), and 41% (n = 222) had stage IC. Logically, in this context a minority of patients had stage IB disease (see Table 1).

Among the 63 (11.6%) patients who developed a recurrence, in 24 (38%) it was isolated on the spared ovary, and in 39 (62%) it comprised an extraovarian site. The median time to the recurrence was 21 months (range: 2–172 months). Twenty-seven (6%) patients died of their recurrence. Thirty-seven patients had received adjuvant treatment during the initial treatment. The characteristics of the patients with recurrent disease are shown in Table 1.

The recurrence rate was higher for serous neoplasms at 20.6% compared with mucinous at 6.8% ($P<.001$) (see Table 1). This rate approached the level of statistical significance for stage IC (14%) compared with IA at 9.2% ($P=.08$). The recurrence rate was statistically significantly higher for grade 3 tumors (23.5%) compared with grades 1 (9%) and 2 (11.2%) ($P<.001$), and for stage IC grade 3 disease (27%) compared with IC grades 1 (10.7%) and 2 (10.2%) ($P=.01$). The recurrence rate was close to statistical significance for stage IC3 (18.6%) compared with IC1 (9.2%) ($P=.09$).

Among the 24 patients with an isolated ovarian recurrence, the median age at initial management was 26 years (range: 16–37 years). The median time to recurrence was 43 months (range: 2–172 months). The details of the adnexal surgery were available for 19 patients. Thirteen had undergone a salpingo-oophorectomy, and six had undergone a simple cystectomy. Eleven had undergone staging procedures. The histologic subtypes, tumor grade, and FIGO staging system are detailed in Table 2. None of these characteristics appeared to impact the outcomes of patients with an isolated ovarian recurrence. After a median follow-up of 186 months (range: 28–294 months), three patients had died, and one was alive with persistent disease. The patient who was alive with