

Conservative Fertility-Sparing Surgical Treatment of Invasive Epithelial Ovarian Cancer: When Is It Acceptable?

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Ovarian cancer is the most lethal gynecologic malignancy. Most patients with invasive epithelial ovarian cancer are diagnosed at an advanced stage. The standard initial surgical treatment of EOC is cytoreductive surgery, which includes total abdominal hysterectomy and bilateral salpingo-oophorectomy. The consideration of a more conservative surgical approach in selected EOC patients dates back to the previous century. In 1969 Munnell et al. [1] reported 46 EOC patients with unilateral tumors, i.e., apparently stage I tumors, in whom the opposite grossly normal ovary and frequently the uterus were preserved. They mentioned several reports of conservative surgery dating back to 1933.

The current International Federation of Gynecology and Obstetrics (FIGO) classification system [2] defines stage I EOC as follows:

- Stage I: Growth limited to the ovaries
- IA: Growth limited to one ovary; no ascites present containing malignant cells. No tumor on the external surface; capsule intact
 - IB: Growth limited to both ovaries; no ascites present containing malignant cells. No tumor on the external surfaces; capsules intact
 - IC: Tumor either Stage IA or IB, but with tumor on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings

Patients with tumors macroscopically apparently confined to one ovary (apparent stage I) should undergo, in addition to

hysterectomy and bilateral adnexectomy, meticulous surgical staging, which includes peritoneal washings for cytological examination, multiple peritoneal biopsies, omentectomy, and lymph node sampling in order to be classified as FIGO stage IA. Grade of differentiation is the most powerful prognostic indicator in stage I ovarian cancer [3]. Surgically staged patients with stage IA grade 1 disease do not require adjuvant chemotherapy.

While most EOC patients are elderly and are diagnosed at an advanced stage, the malignancy may also occur at an early stage in younger women. According to the FIGO 26th annual report on the results of treatment in gynecological cancer [2], 7.2% of EOC patients are younger than 40 and 2.7% are younger than 29. Among those younger than 40 about 60% are diagnosed in stage I (39% in stage IA). It should also be mentioned that today couples are increasingly delaying child-bearing [4]. Maternal age at first birth is increasing and women in their late thirties and forties are attempting to get pregnant. In the United States the percentage of first birth for women 40–44 years old increased by 70%. Therefore, in young EOC patients with early EOC, fertility-sparing conservative surgery, i.e., conserving an uninvolved ovary and/or the uterus may be of great importance. Furthermore, a fertility-sparing procedure prevents the complications of more extensive surgery, and conservation of the apparently uninvolved ovary maintains

hormonal function. The aim of conservative surgery is to preserve fertility without compromising outcome.

The purpose of the present report is to review currently available data regarding the results of fertility-sparing conservative surgery in EOC.

A PubMed search of investigations published during the last 20 years containing the terms “fertility-sparing surgery” and “conservative surgery” in combination with “epithelial ovarian cancer/carcinoma” was conducted. The relevant articles were reviewed and abstracted. Case reports and abstracts were not included in the present review.

Fertility-sparing conservative surgery in stage IA grade 1 (and possibly grade 2) ovarian cancer does not significantly compromise survival and allows future fertility

EOC = epithelial ovarian cancer

FIGO = International Federation of Gynecology and Obstetrics

During the period reviewed the following studies were published. Colombo et al. published two series of conservatively treated EOC patients [5,6]. In the first [5] they reported the treatment results of 99 patients below the age of 40 with stage I ovarian cancer. Conservative surgery was performed in 56 patients (56%). Of these, 36 patients were in stage IA, one in stage IB, and 19 in stage IC. Adjuvant chemotherapy was given to 16 patients, 8 of them in stage IA. Relapse occurred in three stage IA patients (one each with grade 1, 2, and 3), but only one occurrence was in the residual ovary and the patient was rescued by surgery. The other two patients who relapsed in distant sites died as a result of their tumors. In the second series [6] they reported the results of conservative surgery in 24 patients. Nine were in stage IA (all grades), 11 in stage IC (all grades), one in stage IIC and 3 in stage III. Recurrence occurred in three patients – one each in stage IC, IIC and IIIC. These authors also summarized the European experience of conservative surgery and found that of a total of 152 patients diagnosed in stages I to III, recurrence occurred in 18 (11.8%). Of 51 patients in stage IC, 5 recurred and of 6 patients in stage IIIC just one recurred. Morice and collaborators [7,8] also published two series of conservative treatment in EOC patients. In the first series [7] of 25 patients, 19 had stage IA (9 with grade 1, 10 with grade 2), one had stage IC, 2 had stage II, and in 3 the initial stage was unknown. The recurrence rate in this series was high. In seven patients (28%) the cancer recurred. The disease-free survival rate at 5 years for patients with stage IA grade 1 and 2 tumors were 89% and 71%, respectively. The second series [8] consisted of a multicenter retrospective study performed by members of two French groups and comprised 34 surgically staged patients. Of these, 30 had stage IA disease; 3 had stage IC and one had stage IIA. Recurrence occurred in 10 patients (one with stage IA grade 1, four with stage IA grade 2, one with stage IA grade 3 and four with stage IC or greater). In both series the authors emphasize that all patients with stage higher than IA experienced recurrence. In a retrospective study, Zanetta et al. [9] reported 99 surgically staged patients of whom 56 underwent fertility-sparing surgery and 43 more radical surgery. Of those treated conservatively, 32 were in stage IA (grades 1 to 3) and the remaining were in stage IB and IC. Conservative treatment was given in 62% of grade 1 tumors, in 48% of grade 2, and 50% of grade 3 tumors. With a median follow-up of 7 years, they observed five recurrences (9%) in women treated conservatively. Interestingly, they noted five (12%) recurrences in those treated more radically as well. Two women (one in each treatment arm) were saved after recurrence. In a retrospective multi-institutional study during

The effect of adjuvant chemotherapy on outcome after conservative surgery is unclear

Favorable results have also been reported in conservatively treated patients with higher stage and grade, but their number is too small to draw any conclusions

the years 1965–2000, Schilder and co-authors [10] identified 52 stage I patients treated with fertility-sparing surgery (42 in stage IA and 10 in stage IC). Among the 52 patients, 5 had clear cell carcinoma and 14 had grade 1-2 cancer. Adjuvant chemotherapy was given to 20 patients. After a median follow-up of 68 months, five patients recurred and the estimated 5 year survival was 98%. Park et al. [11] treated 62 EOC patients conservatively. Thirty-six were in stage IA, 23 were in stages IB, and IC, and one each was in stage IIB, IIIA, and IIIC; 48 were grade I and 14 were grades 2 and 3. Forty-eight patients received platinum-based adjuvant chemotherapy. At a median follow-up of 56 months (range 6–205 months), 11 patients had tumor recurrence and 6 died of disease. Of the 11 patients with recurrence, 4 had initial stage IA, grade 3 tumors; 2 had stage IC, grade 3; and one each had stage IA, grade 1; stage IC, grade 1; stage IC, grade 2; stage IIIA, grade 1; and stage IIIC, grade 3 tumors. Of these 11 tumors, 7 were mucinous, 2 were clear cell, and one each were endometrioid and mixed. For all patients, the 5 and 10 year disease-free survival rates were 80% each and the 5 and 10 year overall survival rates were 88% each. For patients with stage I disease, the 5 and 10 year disease-free survival rates were 82% each, and the 5 and 10 year overall survival rates were 91% each. Patients with stage greater than IC or with grade 3 tumors had significantly poorer survival ($P = 0.0014$ and $P = 0.0002$ respectively). Schlaerth et al. [12] reported 20 stage I EOC patients who had preservation of the uterus and contralateral ovary at the time of surgical staging. Platinum-based chemotherapy was administered to 50% of these patients postoperatively. Three patients (15%) recurred in the retained ovary at 9, 20, and 22 months, and all died of their disease. At a median follow-up of 122 months, 17 (85%) of 20 patients treated with fertility-sparing surgery were alive without disease. Cheng et al. [13] reported the outcome of conservative surgery in 17 young patients, 13 (76.5%) with mucinous tumors. Ten patients (58.8%) were in stage IA, 6 in stage IC and one in stage IIIA. The great majority (15 of 17) had grade 1 disease. Platinum-based chemotherapy was given to 16 patients. After a median follow-up of 61 months all 17 patients were alive. In a review from 2003, Morice and co-workers [14] mention, among others, 6 previous case reports and small series comprising 12 patients or less. These series included 36 stage IA-IC (grade 1-3) patients and three stage III patients treated conservatively. In these patients, of whom nine received postoperative chemotherapy, two recurrences and one death occurred. Several recent small studies of conservative surgery in early EOC consisting of 20 or less patients have also been published [15-18]. Overall they

comprise a total of 42 patients. While the follow-up periods in these studies varied greatly, the outcome was very favorable.

In many of the above mentioned series a conservative surgical approach was also undertaken in EOC patients with unfavorable grades and patients with disease not confined to one ovary. Several reports included patients in stages IB and IC and with grades 2 and 3 disease [5-7,9-11] and even patients with stage II and III disease [6,7,11]. Such patients would usually undergo radical surgery. However, even in such patients the recurrence rate was low. Noteworthy is the small series presented by Raspagliesi et al. [19] who reported 10 young patients with invasive epithelial ovarian cancer and high grade or limited extra-ovarian disease who were treated with conservative surgery. Two patients had stage IA grade 3, two had stage IC, two had stage IIIA and 4 had IIIC disease. Eight patients were given adjuvant therapy (radiotherapy in one and chemotherapy in seven). All patients were alive and disease free at a median follow-up time of 70 months (range 24–138 months). Nine patients were menstruating regularly and three conceived. Some authors [5,6,9,11,13] reported that the outcome data in patients who underwent conservative surgery are similar to those who underwent radical surgery. Altogether, these data were taken to suggest that conservative surgery may be applied to patients with stage higher than IA grade 1 disease [5,9,11].

TUMOR SPILL

The possible occurrence of cyst rupture during surgery in EOC apparently confined to one ovary is of concern when a conservative approach is considered, since spillage of malignant cystic contents may result in intra-peritoneal dissemination of malignant cells. According to the FIGO classification, rupture of a malignant tumor apparently confined to one ovary during surgery advances the disease to stage IC. Nevertheless, the effect of such an occurrence on the prognosis is inconsistent. In some studies intraoperative capsule rupture was not found to be prognostically significant [20-22]. In other studies [23,24], it was found to be significant only in univariate analysis but not in multivariate analysis [23]. Higashi et al. [25] found in a large number of stage I clear cell carcinomas of the ovary that the capsule status was an independent prognostic factor of a poor overall and disease-free survival. Other recent reports also found that capsule rupture and spillage are independent predictors of poorer disease-free survival [26-28]. It is therefore generally agreed that rupture and spillage should be avoided.

Today laparoscopic surgery is often used in the surgical management of ovarian cysts. It has been shown that during this procedure the rate of cyst rupture and spillage of its content is higher than during laparotomy, about 6% and 2% respectively [29]. This and the effect of pneumoperitoneum should be taken

into account when laparoscopic conservative management of suspected malignant ovarian cysts is contemplated.

INVOLVEMENT OF THE CONTRALATERAL OVARY

An additional concern when conservative surgery is performed is the possibility of very small or microscopic foci in a normal-appearing contralateral ovary. Biopsy, wedge resection and bivalving are all unreliable methods for detection of occult disease and may even be harmful. Thus, involvement of the normal-appearing contralateral ovary cannot be ruled out with certainty. Involvement of the contralateral ovary may differ according to histological type of the tumor. Generally it may be as high as 33% in serous tumors [30] but is much lower in other histological types of EOC. Benjamin et al. [31] assessed specifically the frequency of occult metastases in normal-looking ovaries of 118 EOC patients who underwent bilateral adnexectomy. The stage of these tumors was IA in 79, IB in 4 and IC in 35 patients. In only 3 (2.5%) patients was microscopic involvement in the contralateral normal-appearing ovary found. None of them were in stage IA.

RECURRENCE IN THE CONTRALATERAL RESIDUAL OVARY

The site of recurrence after conservative surgery is not recorded in most series. It may occur in the contralateral preserved ovary. The number of patients with recurrence in the residual ovary after conservative surgery is mentioned in four studies (5,7,9,12) and is shown in Table 1. Of a total of 209 conservatively treated patients 14 (6.7%) recurred in the contralateral ovary. Some authors [14] suggest that radical surgery should be considered after completion of childbearing. The risk of recurrence in the contralateral ovary is low but not negligible and seems to support this approach.

FERTILITY RESULTS

Future fertility is the main objective of conservative surgery in EOC. Candidates for fertility-sparing surgical treatment should be assessed for the realistic probability of achieving

Table 1. Number of patients with recurrence in the residual ovary after conservative fertility-sparing surgery

Author [ref]	No. of patients	Recurrence in residual ovary
Colombo et al. [5]	56	1
Morice et al. [7]	25	5
Zanetta et al. [9]	56	2
Schlaerth et al. [12]	20	3
Total	209	14 (6.7%)

Table 2. Fertility outcome in EOC patients who underwent conservative surgical treatment

Author, year [ref]	No. of patients	No. wanting to conceive	Conceptions	Deliveries
Colombo et al., 1994 [5]	56	17	25	NI
Zanetta et al., 1997 [9]	56	NI (?)	20	17
Jobo et al., 2000 [15]	11	10	6	11
Morice et al., 2001 [7]	25	NI	4	NI
Schilder et al., 2002 [10]	52	24	17	26
Morice et al., 2005 [8]	23	NI	10	NI
Borgfeldt et al., 2007 [16]	10	NI	7	14
Park et al., 2008 [11]	62	19	NI	22
Ghaemmaghami et al., 2010 [18]	10	NI	6	7
Cheng et al., 2012 [13]	17	8	5	6

NI = not indicated

conception and should be made aware that they may require assisted reproduction technology to achieve this. They should also be informed that conservative surgical management is associated with a small risk for recurrence of the disease.

As shown in Table 2, conception and delivery can be achieved in many conservatively treated patients. Obviously not all patients who desire to become pregnant conceive. Thus, in the series by Schilder et al. [10], of 24 patients who attempted pregnancy 17 conceived.

SUMMARY

The disadvantages of the reviewed studies dealing with fertility-sparing conservative surgery in EOC reported during the last 20 years are inherent in their retrospective nature. Many of the studies include a limited number of patients. The follow-up periods in these studies vary greatly and in some [6] it is not indicated at all. Outcome is often given as the number of patients with recurrence or the number of patients alive at the end of follow-up and not as the probability of survival. The percentage of serous and mucinous carcinoma in stage I EOC in young patients is about equal [1]. Yet, in many of the studies the rate of patients with mucinous carcinomas treated conservatively exceeds by far that of other histological types and is as high as 62–76% (8,11,13), while serous tumors comprise only a small proportion of the cases [12]. In several studies the histological type is not given at all [5,17]. An assessment of outcome according to histologic type of the tumor was not done in many of the studies, probably because of the limited number of patients. In some of the studies adjuvant chemotherapy was administered after conservative surgery [11-13,17,19]. However, how this affected the outcome was not assessed.

Nevertheless, it seems that the presented data indicate that fertility-sparing conservative surgery in stage IA grade 1 (and possibly grade 2) EOC does not significantly compromise survival and allows future fertility. Although favorable results have been reported in many studies that included conservatively treated patients with higher stage and grade, their number is too small to draw any conclusion.

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Capsule

Mosaic PPM1D mutations are associated with predisposition to breast and ovarian cancer

Improved sequencing technologies offer unprecedented opportunities for investigating the role of rare genetic variation in common disease. However, there are considerable challenges with respect to study design, data analysis and replication. Using pooled next-generation sequencing of 507 genes implicated in the repair of DNA in 1150 samples, an analytical strategy focused on protein-truncating variants (PTVs) and a large-scale sequencing case-control replication experiment in 13,642 individuals. Ruark et al. show that rare PTVs in the p53-inducible protein phosphatase PPM1D are associated with predisposition to breast cancer and ovarian cancer. PPM1D PTV mutations were present in 25 of 7781 cases versus 1 of 5861 controls ($P = 1.12 \times 10^{-5}$), including 18 mutations in 6912 individuals with breast cancer ($P = 2.42 \times 10^{-4}$) and 12 mutations in 1121 individuals with ovarian cancer ($P = 3.10 \times 10^{-9}$). Notably, all of the identified PPM1D PTVs were mosaic in lymphocyte

DNA and clustered within a 370 basepair region in the final exon of the gene, carboxy-terminal to the phosphatase catalytic domain. Functional studies demonstrate that the mutations result in enhanced suppression of p53 in response to ionizing radiation exposure, suggesting that the mutant alleles encode hyperactive PPM1D isoforms. Thus, although the mutations cause premature protein truncation, they do not result in the simple loss-of-function effect typically associated with this class of variant, but instead probably have a gain-of-function effect. These results have implications for the detection and management of breast and ovarian cancer risk. More generally, these data provide new insights into the role of rare and of mosaic genetic variants in common conditions, and the use of sequencing in their identification.

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Capsule

A shift in cancer's inflammatory balance

One of the many factors that contribute to the initiation and progression of cancer is inflammation. Inflammation can support tumor development, both directly and indirectly, and tumors can promote a chronic inflammatory environment that results in immunosuppression, which benefits the tumor. In their review of the components of the immune system that contribute to the chronic inflammation seen in tumors, Coussens et al. found that potential therapies

might shift this inflammatory environment toward one more characteristic of an acute, resolving inflammation, similar to what is observed during a pathogenic infection. Such a shift would relieve immunosuppression and drive antitumor immunity that, when combined with other therapies, may ultimately result in tumor cell clearance.

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“Remorse is a violent dyspepsia of the mind”

Ogden Nash (1902-1971), American poet known for his light verse