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**FERTILITY-SPARING SURGERY AND OUTCOME IN FERTILE WOMEN WITH
OVARIAN BORDERLINE TUMORS AND EPITHELIAL INVASIVE OVARIAN
CANCER.**

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Condensation

Women with Stage Ia epithelial ovarian cancer and borderline tumors may have successful fertility sparing surgery. Several of these patients do not accept the recommendation of prophylactic oophorectomy.

Abstract

Objective: The aim was to evaluate the outcome of fertility sparing treatment in ovarian borderline tumors and early invasive ovarian cancer.

Materials and Methods: All women diagnosed with ovarian borderline tumor or early invasive ovarian cancer and treated with fertility-sparing surgery at the University Hospital in Lund during 1988 to 2002 was identified and included, n=23.

Results: During the follow-up period of median 92 months, range 11-185 months, no relapse was found in the patients with stage Ia tumors including both the borderline tumors (n=12) and the invasive well (n=9) and moderately (n=1) differentiated ovarian cancers. One patient with poorly differentiated ovarian cancer stage Ic was pregnant at 13 weeks at the primary operation. Although, unilateral oophorectomy was performed she insisted in continuing the pregnancy. At 37 weeks she had a caesarian section and the ovarian cancer was disseminated. Chemotherapy was given but she died less than a year later. No other patient received chemotherapy. In total 30 children was born by 15 patients. Prophylactic removal of the remaining ovary +/- hysterectomy was accepted only in six of the women after completing their desire to have more children.

Conclusions: Young women with Stage Ia epithelial ovarian cancer and borderline tumors do not have to give up their fertility in order to receive successful and safe treatment of their disease. However, several of these patients do not accept the recommendation of prophylactic oophorectomy of the contra lateral ovary and hysterectomy after completion of childbearing age.

Introduction

Ovarian cancer is the sixth most frequent type of cancer among Swedish women and the fourth leading cause of death in cancer among women 45-64 years of age. These figures are comparable to other western countries [1]. Due to mild symptoms ovarian cancer is usually diagnosed in advanced stages of the disease, which is reflected in the generally poor outcome [2]. Below the age of 40 years, the incidence of ovarian cancer is 3/100 000 per year for women in Sweden [1]. Since the women tend to be older when they give birth to their first child, in Sweden at 28 years of age nowadays, there is an increasing demand among young women with early stage ovarian cancer to maintain their reproductive capability. The question is if it is possible to use fertility sparing surgery without compromising survival. Studies evaluating unilateral oophorectomy in the treatment of patients with ovarian germ cell tumors and borderline epithelial ovarian tumors have reported excellent patient outcome while preserving reproductive and endocrine function [3, 4]. Furthermore, selected patients with early stage invasive epithelial ovarian cancer Stage IA has also shown to be successfully managed with fertility sparing surgery [5].

The aim of this retrospective study was to evaluate the outcome of fertility sparing treatment at our institution. We analyzed the number of children born after primary treatment, the number of women having had prophylactic surgery after completing childbirth, progression free survival and overall survival.

Materials & Methods

All women diagnosed with ovarian cancer or borderline ovarian tumor under the age of 45 years at the University Hospital in Lund from 1988 to 2002 was identified with the help of the Regional Oncological Center (OC). The Regional OC includes all invasive and pre-malignant tumors in the Southern part of Sweden. Women with epithelial ovarian tumors and fertility-sparing surgery were included (N=23); women with radical surgery (N=46) or with ovarian stromal or germ cell tumors (N=12) were excluded. Two women with their primary surgery at a small local hospital who were referred for their second look operation was also included. The policy of the department during the study-period was to perform bilateral salpingo-oophorectomy, hysterectomy, omentectomy, peritoneal washing and several peritoneal biopsies in patients with suspicious ovarian malignancy or if the frozen section showed borderline tumor or invasive cancer. Lymph-node sampling or lymphadenectomy was not routinely performed. In patients with desire to preserve their fertility the ovarian lesion was removed and the final histo-pathological report was awaited. Thereafter the discussion with the patient and the final decision about saving the patients fertility was made. All patients were postoperatively examined, both clinically and with transvaginal ultrasonography, twice during the first year and then once a year. At the follow-up consultations the issue about the remaining ovary and prophylactic oophorectomy were discussed.

Tumors were classified according to the World Health Organization (WHO) System and were staged according to the International Federation of Gynecology and Obstetrics (FIGO) System. In 16 of the 23 cases the pathology slides had been reviewed twice at the time for diagnosis and were re-examined according to the WHO-terminology revised in 2003 by one pathologist (AM) in 2005 (see discussion). All patient data were extracted from the patient journals (n=81). Survival status of all patients, i.e. alive or dead including date of death was obtained on March 15, 2005 from the Swedish Population Register (OC).

The Regional Ethical Committee Lund University, Sweden approved the study.

The statistical analyses were performed using SPSS™ (11.5.1).

Results

Twelve patients with borderline tumors in one ovary and eleven patients with invasive epithelial ovarian cancer Stage I a-c treated with fertility preserving surgery who met the eligibility criteria were included. Clinical and histological characteristics of the patients studied and their follow-up results are illustrated in Table 1. The mean age of the patients was 30.3 years (range 18-43 years). The tumor cell types were as follows: mucinous 14, serous 8 and endometrioid 1. Histological differentiation of the tumors studied was as follows: borderline tumors 12, well differentiated (G1) 9, moderately differentiated (G2) 1, and poorly differentiated (G3) 1.

Eight patients underwent second look surgery within a year from primary surgery either to remove the whole ovary after ovarian resection (n=3), lymph node sampling (n=1), removing another benign cystic lesion (n=1), diagnostic second look surgery (n=2), or in order to perform caesarian section (n=1).

In total 30 children has been born by 15 out of 23 women after fertility sparing surgery. Seven patients with borderline tumors have given birth to 15 children and seven patients with invasive ovarian cancer stage Ia have given birth to 14 children. One patient was pregnant at 13 weeks at the primary operation. She had a unilateral oophorectomy performed and the histology showed poorly differentiated mucinous ovarian cancer with positive cytology in the peritoneal washing. She insisted in continuing the pregnancy until 37 weeks when a caesarian section was performed. The child was in good shape but the ovarian cancer had disseminated and the woman died less than a year after the caesarian section even though she received chemotherapy. No other patient received chemotherapy. One patient died 46 months after her primary surgery due to an accident.

Prophylactic removal of the remaining ovary +/- hysterectomy has been performed in six of the women after completing their desire to have more children (median time 58 months, range 22-100 months). Twelve out of 18 women with born children have not yet decided to perform prophylactic surgery.

During the follow-up period of median 92 months, range 11-185 months, no progression has been found in the patients with stage Ia tumors including both the border line tumors (n=12) and the invasive well (n=9) and moderately (n=1) differentiated ovarian cancers.

Discussion

This study indicates that selected patients with Stage Ia epithelial ovarian cancer and borderline tumors may be safely treated with fertility sparing surgery. The results are in agreement with other studies [5-8] in both early ovarian cancer and borderline tumors [9]. There has always been a demand for less radical surgery and fertility sparing surgery if the treatment is reasonably safe. Women tend to give birth to their first child at older age. An increasing part of well-educated women with access to Internet and the latest published knowledge want to take part in discussion of their illness. Those facts will probably increase the demand for fertility preserving surgery at early stage ovarian cancer and borderline tumors in the ovaries.

Only two of the women with invasive ovarian cancer Stage Ia in this study were properly staged. It is important to emphasize that patients selected for conservative surgery should have complete surgical staging, including pelvic/para-aortic lymph node sampling, multiple peritoneal biopsies, washings, and omentectomy [7]. For mucinous tumors, appendectomy is also recommended [10].

Lymph node metastases appear in patients with clinically apparent Stage I ovarian cancer in around 10 to 15%. [11, 12]. Lymph node metastases are mainly found in patients with poorly differentiated tumors but rarely in patients with well differentiated tumors [11, 12]. All the patients in this study in clinically stage Ia had either a borderline tumor or a well differentiated tumor, which may explain why there is no woman so far with any known recurrence despite not all patients in this study had a thorough staging operation.

In this material one patient had endometrioid ovarian carcinoma Stage Ia. Patients with endometrioid ovarian cancer may have coexisting endometrioid carcinoma of the endometrium as

well, why uterine curettage should be performed in patients with endometrioid ovarian carcinoma Stage I if hysterectomy is not performed.

There are controversies related to the diagnosis of borderline tumors and the management of these tumors [13-16]. The definitions for borderline ovarian tumor have changed over the years.

According to WHO 2003, to diagnose carcinoma, invasion has to be identified. The rule of four or more epithelial cell layers as a sign of malignancy is questioned and in borderline tumors it is acceptable with a stromal micro invasion in up to 5 mm of greatest linear measurement in any single focus and non-invasive peritoneal implants [13, 17]. One pathologist (AM) reevaluated the histological specimens in 2005 by using these newer definitions for borderline ovarian tumor. Using these broader criteria's seven of the carcinomas should have been classified as borderline tumors. Some of these criteria's have yet limited experience in the literature and additional studies are warranted to resolve the clinical significance of e.g. small foci of micro invasion.

No one of the patients with invasive Stage Ia ovarian cancer or borderline tumors received chemotherapy. The ICON 1 study indicated that adjuvant chemotherapy improves survival and delays recurrence in patients with early-stage invasive ovarian cancer [18, 19]. However, the ACTION trial concluded that optimally staged early epithelial ovarian cancers patients do not benefit from the use of adjuvant chemotherapy [20, 21] The conflicting results indicates that properly staged invasive ovarian cancer stage Ia should not receive adjuvant chemotherapy, but not properly staged stage Ia patients should undergo a thorough staging procedure in order to avoid adjuvant chemotherapy. Borderline tumors have a very low risk of recurrence and they rarely respond to chemotherapy or irradiation [22]. Thus, adjuvant treatment with chemotherapy or irradiation should not be offered patients with borderline tumors [9].

Wedge biopsies are still controversial if the contra lateral ovary is macroscopically normal. One of the most common policies is that a frozen section microscopy should always be performed when a suspicious ovarian tumor is removed. If a serous borderline tumor or an invasive serous cancer is found, a wedge biopsy of the contra lateral ovary is recommended because of the risk of occult disease in the contra lateral ovary [23, 24]. In non-serous borderline tumors or early cancer, wedge biopsy of a normally looking contra lateral ovary is not necessary or recommended since there is a risk of impairing fertility [10].

In the present investigation 30 children was born which indicates that successful reproduction in patients with Stage I ovarian cancer or borderline tumors treated by conservative surgery is not only possible but also probable. This confirms other reports which have documented successful reproductive function following fertility sparing surgery [5, 7]

If prophylactic surgery removing the contra-lateral ovary and the uterus should be undertaken following completed desire for children is debatable. No prospective study has so far been designed and powered to evaluate the relevance of prophylactic secondary surgery and it is doubtful if it ever will be possible to perform such study. Sparing the uterus should be an option even in true stage Ib if no peritoneal tumor spread is found in order to later be able to perform embryo transfer with donated eggs. At our institution the recommendation has so far been to suggest prophylactic oophorectomy of the contra lateral ovary and hysterectomy after completion of childbearing due to the reported recurrence rate and late recurrences found in other retrospective reports [3, 6, 7, 25, 26]. Nevertheless, not all patients accept this recommendation which is shown in this study where 66% of the women with born children so far prefer to continue their clinical check ups. The reasons to keep the remaining ovary and the uterus varies among the patients but several women express that they feel safe and rely on the regular check-ups even though they are

told the increased risk of having a new tumor. If the patient has had a diploid borderline tumor expectant management may be reasonable [9]. But in patients with invasive ovarian Stage I tumors clinical check ups beyond childbearing age is doubtful because of a risk of contra lateral ovarian pre-neoplastic phenotypes in these high-risk women is high [27, 28].

The value of second-look surgery in patients with Stage I ovarian cancer treated initially with unilateral salpingo-oophorectomy has not been assessed in any study. Monitoring the patients with transvaginal ultrasonography and CA125 every third to six months has been proposed. However, screening by transvaginal ultrasonography and serum CA-125 measurement in women at increased risk of ovarian cancer is ineffective in detecting ovarian malignancy before spread from the ovaries and no study has showed any benefit in overall survival [29-31]. We recommend prophylactic oophorectomy of the contra lateral ovary and hysterectomy after completion of childbearing in patients with borderline tumors or early invasive cancer. The patient must be informed and involved in the discussion about the risks of not having radical surgery. There is no evidence based medicine to keep on monitoring these patients with CA-125 measurement, transvaginal ultrasonography or any other modality if the patient chooses not to have radical surgery after completed childbearing.

This study and other recent investigations have showed that patients with Stage Ia epithelial ovarian cancer treated with fertility-sparing surgery have an excellent prognosis. In the material published by Schilder et al including patients with ovarian cancer Stage I treated with fertility sparing surgery the 5-year and 10-year survival rates were 98 and 93%, respectively, which compares favorably to the ovarian cancer treated by more radical surgery [32, 33], These retrospective data points out the need of establishing a prospectively enrolling national registry

including Stage Ia ovarian cancer and borderline tumor patients who are treated with conservative surgery. The results of this and other studies [6, 7, 34] indicate that young women with Stage Ia epithelial ovarian cancer and borderline tumors do not have to lose their fertility in order to receive successful and safe treatment of their disease.

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Table 1

	Age	Histology	Cell type	Stage	Omentectomy	Lymphnode sampling	Second look surgery	Number of children	Prophylactic surgery at x months	Recurrence	Follow-up (months)
A	18	borderline	mucinous	1 a	no	no	yes	2	.	no	121
B	27	borderline	mucinous	1 a	yes	no	yes	1	.	no	154
C	31	borderline	mucinous	1 a	no	no	yes	1	22	no	66
D	31	borderline	mucinous	1 a	yes	no	no	0	.	no	76
E	33	borderline	mucinous	1 a	no	no	no	0	.	no	11
F	43	borderline	mucinous	1 a	yes	no	no	0	.	no	26
G	20	borderline	seropapular	1 a	no	no	yes	2	.	no	137
H	20	borderline	seropapular	1 a	no	no	no	2	.	no	66
I	29	borderline	seropapular	1 a	no	no	yes	4	.	no	149
J	30	borderline	seropapular	1 a	yes	no	no	3	.	no	56
K	40	borderline	seropapular	1 a	yes	no	yes	0	.	no	141
L	42	borderline	seropapular	1 a	no	no	yes	0	89	no	97
M	22	well differentiated	mucinous	1 a	no	no	no	4	.	no	50
N	22	well differentiated	mucinous	1 a	yes	no	no	2	.	no	51
O	28	well differentiated	mucinous	1 a	yes	no	yes	1	27	no	136
P	31	well differentiated	mucinous	1 a	yes	no	no	1	.	no	185
Q	31	well differentiated	mucinous	1 a	yes	yes	yes	3	.	no	60
R	36	well differentiated	mucinous	1 a	yes	no	yes	0	85	no	88
S	42	well differentiated	mucinous	1 a	no	no	yes	0	100	no	110
T	21	well differentiated	seropapular	1 a	yes	yes	yes	1	.	no	83
U	34	well differentiated	seropapular	1 a	yes	no	yes	2	.	no	138
V	36	moderately differentiated	endometrioid	1 a	no	no	yes	0	32	no	92
W	30	poorly differentiated	mucinous	1 c	no	no	yes	1	6	yes	16

* dead 46 months postoperatively in accident

** Pregnant 13 weeks at primary surgery, Caesarean Section at 37 weeks with disseminated disease