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Review Article

Fertility-sparing Surgery for Early Stage Epithelial Ovarian Cancer

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Running head: Fertility-sparing surgery for ovarian cancer

Abstract

Discussion of fertility-sparing treatment is an important part of pretreatment counseling for young patients with early epithelial ovarian cancer. As a result of late childbearing nowadays, fertility preservation has become a major issue in ovarian cancer patients. The purpose of this review is to update current knowledge on fertility-sparing treatment for early stage epithelial ovarian cancer, which may be useful for pretreatment counseling for reproductive-age patients. The multicenter study data on the fertility-sparing treatment published by Japan Clinical Oncology Group (JCOG) in 2010 confirmed that fertility-sparing surgery is a safe treatment for stage IA patients with non-clear cell histology and grade 1 or 2 and suggested that stage IA patients with clear cell histology and stage IC patients with non-clear cell histology and grade 1 or 2 can be candidates for fertility-sparing surgery followed by adjuvant chemotherapy. In the current review, we added the recent case series and review, and discussed the fertility-sparing treatment on young patients with early epithelial ovarian cancer. We need not to change the proposal by the JCOG study, but we should wait the results of an ongoing prospective study to strongly recommend the proposal of the JCOG study.

Mini-abstract

Fertility-sparing surgery (FSS) with optimal staging followed by adjuvant chemotherapy can be considered for patients with stage IC non-clear cell carcinoma (CCC) and grade 1 or 2 disease and patients with stage IA CCC, though FSS with optimal staging not followed by adjuvant chemotherapy is recommended for stage IA non-CCC and grade 1 or 2 disease. FSS cannot be recommended for patients with stage IC CCC or stage I non-CCC and grade 3 disease.

Key words: epithelial ovarian cancer, fertility-sparing surgery, patients selection

INTRODUCTION

Preservation of fertility is an important issue for reproductive-age patients with epithelial ovarian cancer. The first reports of fertility-sparing surgery (FSS) for epithelial ovarian cancer started to appear in the 1960-70s (Munnell EW, Is conservative therapy ever justified in stage IA cancer of the ovary? Am J Obstet Gynecol 103; 641, 1969). However, only fewer than 60 patients had been reported in each case series undergoing FSS for stage I EPITHELIAL OVARIAN CANCER until the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG) carried out a multicenter study of 30 institutions (the JCOG-FSS study) in 2010, which analyzed 211 cases of FSS for stage I EPITHELIAL OVARIAN CANCER including 30 patients with clear cell carcinoma (CCC) (1). The JCOG-FSS study confirm that fertility-sparing surgery is a safe treatment for stage IA patients with non-CCC and grade 1 or 2 (G1/G2) and suggest that stage IA patients with CCC and stage IC patients with non-CCC and G1/G2 disease can be candidates for FSS followed by adjuvant chemotherapy. After the publication of the JCOG-FSS study, Hu *et al.* summarized 94 cases in 2011 (2), Fruscio *et al.* 237 cases in 2013 (3), and Kajiyama *et al.* 94 cases in 2014 (4). The addition of these cases has now enabled a more detailed discussion regarding fertility-sparing treatment in reproductive age patients with early stage ovarian cancer. The pooled analyses using Medline database by Nam *et al.* (5) and Zapardiel *et al.* (6) supported the conclusion of JCOG-FSS study.

In Japan, JCOG launched a non-randomized confirmatory study of fertility-sparing surgery for patients with epithelial ovarian cancer (JCOG1203) in 2014 (7). This is a prospective study for confirming the conclusion of the JCOG-FSS study that FSS with optimal staging followed by adjuvant chemotherapy can be considered for stage IA patients with CCC and stage IC patients with non-CCC and G1/G2 disease. Since this FSS is an experimental treatment, patients are enrolled preoperatively before stage of disease,

histological type and grade are determined. For this reason, subjects are divided by their final pathology results into a primary analysis group (stage IA patients with CCC or stage IC patients with non-CCC and G1/G2 disease) and a non-primary analysis group comprising patients other than these. Both groups except patients with benign disease are followed up for at least five years. The primary endpoint for the primary analysis group is five-year survival rate.

The purpose of this review is to update current knowledge on FSS for early stage epithelial ovarian cancer, which may be useful for pretreatment counseling for reproductive-age patients. The search was restricted to articles describing relevant clinical and histologic factors such as stage of disease, surgical procedures, histological type and grade, site of recurrence, and survival. Fertility outcomes after FSS are not discussed in this review, because the good fertility outcomes have already been addressed in two previous reviews (5,6).

Evaluation of Survival and Relapse after Conservative Management of Ovarian Cancer

The conservative management should meet one of the following two requirements in survival. One requirement is an absolutely good prognosis after fertility-sparing treatment is performed, for example, which exceed 95% in five-year survival rate. Another requirement may be that fertility-sparing treatment is not inferior to radical treatment in survival irrespective of survival rates, because fertility-sparing treatment has an obvious advantage that the patient can bear children. However, there are no studies comparing the survival between fertility-sparing and radical treatments in early ovarian cancer. We can only compare the survival rate of fertility-sparing treatment in one case series with that of radical treatment in another case series.

The prognosis for patients with recurrence in the contralateral or residual ovary alone after FSS is much better than for patients with other patterns of recurrence. A review of seven papers (1,3, 8–12) that include clear details of patterns of recurrence and outcomes showed that the disease-free survival rate after salvage therapy was 82.1% (23/28) for patients with recurrence in the oppposite ovary alone, compared with 19.2% (10/52) for those with other patterns of recurrence (Table 1). Other studies have also found that patients with recurrence in the contralateral ovary alone have better outcomes (13,14). Recurrence pattern is an important factor that should be taken into account when considering the patient selection for FSS.

Conservative Management of Stage I Ovarian Cancer by Substage, Histology and Grade in Young Women

Stage IA, non-CCC, G1

FSS is recommended for patients with stage IA non-CCC and G1 disease. When data from ten papers containing sufficient information about patients with sIA non-CCC and G1 disease (1, 3, 9–12, 15–18) were combined, the recurrence-free rate was 93.4% (282/302), and the survival rate was 98.0% (296/302) (Table 2). FSS not followed by adjuvant chemotherapy is adequate treatment for patients in this group because the absolute prognosis is good.

Of the patients in the above ten case series, 12 developed recurrent mucinous adenocarcinoma after a median time of 17.5 months (range 9–172 months); the pattern of recurrence was in the contralateral ovary alone in 4 patients and elsewhere in 8. For the 8 patients with serous or endometrioid adenocarcinoma, the median time to recurrence was 62 months (range 23–83 months), and the recurrence occurred in the contralateral ovary alone in 7 patients and elsewhere in 1. The time to recurrence was shorter and recurrence was

common in locations other than the contralateral ovary in patients with mucinous adenocarcinoma. One reason may be that components consisting of anaplastic carcinoma or sarcoma are sometimes present in mucinous tumors with mural nodules, and this is known to be associated with a poor prognosis (19,10). Another reason may be that mucinous adenocarcinoma has been found to be metastatic in 70.3% (21) or 77% (22) of cases, and tumors removed during FSS may in fact have been metastatic carcinomas. These two points must be borne in mind when considering FSS for mucinous adenocarcinoma.

One study found that 24% of cases of ovarian cancer were genetic (23), and in such cases, it is quite possible that a new ovarian cancer may develop in the remaining ovary and tube. Taking a detailed family history may be important when considering FSS in ovarian cancer, not only for patients with stage IA non-CCC and G1 disease. If there is a family history of ovarian cancer, then greater caution may be required when choosing FSS. And it may be appropriate to consider the removal of the residual ovary and tube at the point when the patient no longer desires to have children.

Endometrioid and clear cell adenocarcinomas are known to develop from ovarian endometriosis (24, 25), and *de novo* carcinogenesis may be conceivable in these hystologies. It is vital to ensure that no endometriotic lesions are left behind in the contralateral ovary during FSS.

Stage IA, non-CCC, G2

FSS is recommended for patients with stage IA non-CCC and G2 disease. When data from nine papers containing sufficient information about patients with stage IA non-CCC and G2 disease (1, 3, 9–12, 16–18) were combined, although the recurrence-free rate was somewhat low, at 87.5% (70/80), the survival rate was high, at 95% (76/80) (Table 3). One patient was alive with cancer, and for one the prognosis was unknown, but even if these two

individuals were to be added to the number of deaths, the survival rate would still exceed 90%, at 92.5%. FSS may therefore be actively recommended to patients in this group, because the prognosis is good.

Although there is a global consensus on the histological types of ovarian cancer, there is as yet no common grading system. The diagnosis of G2 disease may thus vary among institutions or pathologists. In fact, the frequency of G2 disease recorded in studies of FSS differed markedly; 7.1% (1), 8.5% (9), 14.9% (4), 17.3% (11) 25.0% (12), and 28.7% (3). In the case of serous adenocarcinoma (26, 27) and endometrioid adenocarcinoma (28), the pathologists can choose from the several different grading systems that have been so far proposed. When grades are divided into two groups and compared, it is easy to imagine that the evaluation of G2 will differ depending on whether the division is between G1/G2 and G3 (1, 3) or between G1 and G2/3 (4, 12). The former two studies concluded that FSS may be recommended for patients with G2 disease, whereas the latter two found that multivariate analysis identified G2/G3 as an independent factor for significantly poorer prognosis compared with G1.

The diagnostic criteria for G2 disease in mucinous adenocarcinoma may vary with institutions, for which no general grading system has yet been proposed. This difference may underlie the high recurrence rates reported by Schilder *et al.* (11) and Morice *et al.* (10) on the one hand and the lower rates reported by Satoh *et al.* (1) and Fruscio *et al.* (3) on the other hand.

Stage IA, CCC

FSS followed by adjuvant chemotherapy may be considered for patients with stage IA CCC. When data from six papers containing sufficient information about patients with stage IA CCC (1,9–11,15,29) were combined, although the recurrence-free rate was somewhat low,

at 88.9% (24/27), the survival rate exceeded 90%, at 92.6% (25/27) (Table 4). One patient was alive with cancer, and if this individual were to be added to the number of deaths, the survival rate would drop to slightly under 90%. Frucio *et al.* reported that, of 17 patients with CCC, recurrence developed in one stage IA patient and one stage IC patient, although the details of the staging procedures were not described, and they stated that, despite recurrence in the pelvis and abdomen, the stage IA patient was still disease-free 87 months after salvage therapy (3). Kajiyama *et al.* also reported that, of 17 stage I CCC patients, no stage IA patient developed recurrence, *although the numbers of patients of each stage I substage were not given* (4). The fact that no stage IA patient died in either of these studies suggests that the survival rate should exceed 90%, meaning that FSS followed by adjuvant chemotherapy may be considered for patients with stage IA CCC.

In light of the possibility that these numbers include some patients who did not undergo complete surgical staging, particularly those who did not undergo lymph node dissection or biopsies, it is quite possible that mortality will be less than 10% if staging is complete. The only one of these six studies to describe lymphadenectomy as included in the surgical procedures was that of Anchezar (15)**,** with the others listing biopsy, sampling, or lymphadenectomy as options. The rate of lymph node metastasis in retroperitoneal, stage I/II CCC identified by systematic lymphadenectomy has been reported as 29.4% (5/17) (30), and complete staging surgery is essential when performing FSS for CCC.

Some reports have evaluated CCC as a separate entity without grading it (1,4,29), whereas others have included it in G3 disease (3,9–11,15). The proportion of EPITHELIAL OVARIAN CANCER patients with CCC is rising in Japan, and it has recently been found to account for around 25% of all cases (31), whereas in North America and Europe, most ovarian cancer patients suffer from serous adenocarcinoma, with CCC patients accounting for only 1–12% of cases (32). The low number of cases and the generally poor prognosis for

CCC (33,34) suggest that, historically, CCC has probably been included in G3 for the purpose of statistical analysis. If only stage IA is considered, however, the prognosis has been shown to be good (33–35), suggesting that CCC should be handled separately from G3 disease.

Stage IC (unilateral disease), non-CCC, G1

FSS followed by adjuvant chemotherapy can be considered for patients with stage IC non-CCC and G1 disease. When data from six papers containing sufficient information about patients with stage IC non-CCC and G1 disease (1, 3, 9, 10, 15, 36) were combined, although the recurrence-free rate was somewhat low, at 84.8% (134/158), the survival rate was high, at 94.9% (150/158) (Table 5). Two patients were alive with cancer, but even if these individuals were to be added to the number of deaths, the survival rate would still exceed 90%, at 93.7% (148/158). FSS can thus be recommended for patients in this group, because the absolute prognosis is good. Of the patients with recurrence, for the 8 with mucinous adenocarcinoma, the median time to recurrence was 13 months (range 2–43 months), and the pattern of recurrence was in the contralateral ovary alone in 4 patients and elsewhere in 4. For the 10 patients with recurrence of serous or endometrioid adenocarcinoma, the median time to recurrence was 19.5 months (range 3–118 months), and the pattern of recurrence was in the contralateral ovary alone in 6 patients and elsewhere in 4.

Stage IC (unilateral disease), non-CCC, G2

FSS followed by adjuvant chemotherapy can be considered for patients with stage IC non-CCC and G2 disease. When data from five papers containing sufficient information about patients with stage IC non-CCC and G2 disease (1, 3, 9, 11,15) were combined, although the recurrence-free rate was somewhat low, at 86.7% (39/45), the survival rate was high, at 93.3% (42/45) (Table 6). One patient was alive with cancer, but even if this individual

were to be added to the number of deaths, the survival rate would still exceed 90%, at 91.1% (41/45). FSS followed by adjuvant chemotherapy may therefore be considered to patients in this group because the absolute prognosis is good.

Stage IC (unilateral disease), CCC

FSS cannot be recommended for patients with stage IC CCC. When data from seven papers containing sufficient information about patients with stage IC CCC disease (1,9–11,15,29,36) were combined, the recurrence-free rate was low, at 77.4% (24/31), although the survival rate exceeded 90%, at 90.3% (28/31) (Table 7). Three patients were alive with cancer, however, and if these individuals were to be added to the number of deaths, the survival rate would drop below 90%, at 80.6% (25/31). Frucio *et al.* also reported that, of the 17 CCC patients who developed recurrence, 1 individual who was stage IC developed recurrence in the pelvis and died 11 months after salvage therapy (3), and Kajiyama *et al.* reported that, of 17 patients with stage I CCC, 3 stage IC patients died (4). The inclusion of the deaths of stage IC patients from these studies would further decrease the survival rate, and the choice of FSS cannot therefore be recommended for patients with stage IC CCC.

The five-year disease-specific survival rate for patients with stage IC CCC has been reported as 77.3% (34), with a five-year overall survival rate of 60.1% (33) and a three-year OVERALL SURVIVAL rate of 85.9% (35). There are insufficient data to determine whether patients with stage IC CCC belong to a group for which the prognosis would be similar if radical surgery were performed even if the absolute prognosis itself is poor, but the possibility that it may be similar cannot be ruled out. In the seven papers examined, 5 of the 7 patients who developed recurrence were stage IC1. Looking at the two papers that stated that patients were stage IC1 CCC (3, 29), the recurrence-free rate was low, at 75% (12/16), and although the survival rate was 93.8% (15/16), if 2 patients who were alive with cancer

were to be added to the number of deaths, the survival rate would be low, at 81.3% (13/16). Studies have found that the prognosis for patients with stage IC CCC is significantly better for those who are stage IC1 compared with those who are stage IC2/3 (37), and very recently it has been reported that three-year OVERALL SURVIVAL for stage IC1 patients is 96.2%, similar to the 93.5% reported for stage IA patients and significantly better than the 71.9% for patients who are stage IC2/3 (35). Although the prognosis for stage IC1 CCC is generally good, the fact that it is poor for stage IC1 patients who have undergone FSS suggests that FSS cannot be recommended at this point; this is because it has yet to be shown that, even if the prognosis is poor, it is similar to that if radical surgery were performed, although the number of cases reviewed in this study was small.

Stage IA or IC (unilateral disease), G3 (CCC excluded)

FSS cannot be recommended for patients who are stage I and have G3 disease. As described above, most of the studies from countries other than Japan have counted CCC as G3 disease, but it is possible to identify the number of cases of G3 disease that are not CCC from some carefully written papers from overseas (although for papers that included patients of stage II and above, we assumed that patients with CCC were only stage I). When data from nine papers containing sufficient information about patients with stage I cancer and G3 disease (not including those with CCC) (1,3,9,10,12,16,18,38,39) were combined, the recurrence-free rate was extremely low for stage I, at 54.1% (20/37), and the survival rate was also low, at 67.6% (25/37) (Table 8). One patient was alive with cancer, and if this individual were to be added to the number of deaths, the survival rate would be 64.9% (24/37). FSS cannot be recommended because the absolute prognosis is poor.

Following Frusio *et al.*, we compared this reviewed results with those of the ICON1/ACTION analysis (40). Figure 3 of that paper lists the number of patients with G3

disease, including those with CCC, as well as the individual numbers of patients with CCC and the numbers of events affecting overall survival, making it possible to calculate the survival rate for patients with non-CCC G3 disease by subtracting the number of CCC patients from the number of patients with G3 disease, including those with CCC. Almost 80% of the stage I patients with G3 disease described in the nine papers who underwent FSS and developed recurrence had been treated with chemotherapy, and they may appropriately be compared with the patients who underwent chemotherapy in the ICON1/ACTION analysis. A comparison with the 71 chemotherapy patients in the ICON1/ACTION analysis with G3 disease (non-CCC) showed that 13 events occurred for a survival rate of 81.7%, far higher than the survival rate for the patients with G3 disease who underwent FSS; these cannot be described as similar results. FSS may thus lower the survival rate for patients with stage I non-CCC and G3 disease, and even from the standpoint that it may be possible to perform FSS if the patient belongs to a group for which the prognosis would be similar if radical surgery were performed even if the absolute prognosis itself is poor, FSS cannot be recommended for patients with G3 disease. Among the 79 patients who did not undergo chemotherapy, there were 25 events, for a survival rate of 68.4%.

Stage IB or IC (bilateral disease), G1/2

Very few patients who are stage IB or IC with cancer of both ovaries underwent FSS, and the available data are therefore limited. Satoh *et al.* (1) enrolled two stage IB patients and two who were stage IC with bilateral ovarian disease, but both groups were excluded from their analysis because the follow-up period was less than 60 months; however, at the time of the study, none of those four patients had developed recurrence (unpublished data). Kajiyama *et al.* reported that the only patient in their study who was stage IB/IC developed recurrence of highly differentiated serous adenocarcinoma; although the patient had

undergone adnexectomy of the affected side and wedge resection of the contralateral side followed by platinum-based chemotherapy, the cancer recurred after 138.9 months, and the patient died after 195.7 months (8). At this point, there is no solid evidence that FSS can be selected in patients with stage IB or IC (bilateral disease) irrespective of histologies and grades. And we feel great hesitation about preserving a part of the contralateral ovary in which the cancer has recurred or metastasized.

Conclusion

FSS with optimal staging followed by adjuvant chemotherapy can be considered for patients with stage IC non-CCC and G1/2 disease and patients with stage IA CCC, though FSS with optimal staging not followed by adjuvant chemotherapy is recommended for stage IA non-CCC and G1/2 disease. FSS cannot be recommended for patients with stage IC CCC because the absolute prognosis is poor. FSS is not recommended for patients with stage IA/C non-CCC and G3 disease because it may result in a poorer prognosis in comparison with that of patients who undergo radical treatment. Since there is insufficient information to reach a judgment in the case of patients with stage IB/IC (bilateral ovarian involvement), we cannot recommend FSS for these patients.

All of the studies of FSS for epithelial ovarian cancer patients that were evaluated in the present review were retrospective investigations. The quality of the data is therefore limited. This point must be fully borne in mind when dealing with individual patients.

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Conflict of interest statement

None declared.

References

1. Satoh T, Hatae M, Watanabe Y, et al. Outcomes of Fertility-Sparing Surgery for Stage I Epithelial Ovarian Cancer: A Proposal for Patient Selection. J Clin Oncol 2010;28:1727-32.
2. Hu J, Zhu LR, Liang ZQ, et al. Clinical outcomes of fertility-sparing treatments in young patients with epithelial ovarian carcinoma. J Zhejiang Univ Sci B 2011;12:787-95.
3. Fruscio R, Corso S, Ceppi L, et al. Conservative management of early-stage epithelial ovarian cancer: results of a large retrospective series. Ann Oncol 2013:24;138-44.
4. Kajiyama H, Mizuno M, Shibata K, et al. Recurrence-predicting prognostic factors for patients with early-stage epithelial ovarian cancer undergoing fertility-sparing surgery: a multi-institutional study. Eur J Obstet Gynecol Reprod Biol 2014;175:97-102. (with personal communication)
5. Nam JH, Park JY. Fertility-sparing surgery for young women with early-stage epithelial ovarian cancer. Gynecol Obstet Invest 2013;76:14-24.
6. Zapardiel I, Diestro MD, Aletti G. Conservative treatment of early stage ovarian cancer: oncological and fertility outcomes. Eur J Surg Oncol 2015;l40:387-93.
7. Satoh T, Tsuda H, Kanato K, et al. A non-randomized confirmatory study regarding selection of fertility-sparing surgery for patients with epithelial ovarian cancer: Japan Clinical Oncology Group Study (JCOG1203). Jpn J Clin Oncol 2015;45:595-9.
8. Kajiyama H, Shibata K, Suzuki S, et al. Fertility-sparing surgery in young women with invasive epithelial ovarian cancer. Eur J Surg Oncol 2010;36:404-8.

9. Park JY, Kim DY, Suh DS, et al. Outcomes of fertility-sparing surgery for invasive epithelial ovarian cancer: Oncologic safety and reproductive outcomes. Gynecol Oncol 2008;110:345-53.

10. Morice P, Leblanc E, Rey A, et al. Conservative treatment in epithelial ovarian cancer: results of a multicentre study of the GCCLCC (Groupe des Chirurgiens de Lutte Contre le Cancer) and SFOG (Societe Francaise d'Oncologie Gynecologique). Hum Reprod 2005;20:1379-85.

11. Schilder LM, Thompson AM, DePriest PD, et al. Outcome of reproductive age women with stage Ia or Ic invasive epithelial ovarian cancer treated with fertility-sparing therapy. Gynecol Oncol 2002;87:1-7.

12. Zanetta G, Chiari S, Rota S, et al. Conservative surgery for stage I ovarian carcinoma in women of childbearing age. Br J Obstet Gynecol 1997;104: 1030-5.

13. Marpeau O, Schilder J, Zafrani Y, et al. Prognosis of patients who relapse after fertility-sparing surgery in epithelial ovarian cancer. Ann Surg Oncol 2008;15:478-83.

14. Bentivegna E, Fruscio R, Roussin S, et al. 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. Fertil Steril 2015;104:1319-24.

15. Anchezar JP, Sardi J, Soderini A. Long-term follow-up results of fertility sparing surgery in patients with epithelial ovarian cancer. J Surg Oncol 2009;100:55-8.

16. Borgfeldt C1, Iosif C, Måsbäck A. Fertility-sparing surgery and outcome in fertile

women with ovarian borderline tumors and epithelial invasive ovarian cancer. Eur J Obstet Gynecol Reprod Biol 2007;134:110-4.

17. Colombo N, Parma G, Lapresa MT, Maggi F, Piantanida P, Maggioni A. Role of conservative surgery in ovarian cancer: the European experience. Int J Gynecol Cancer 2005;15:206-11.
18. Colombo N, Chiari S, Maggioni A, Bocciolone L, Torri V, Mangioni C. Controversial issues in the management of early epithelial ovarian cancer: conservative surgery and role of adjuvant therapy. Gynecol Oncol 1994;55:S47-51.
19. Provenza C, Young RH, Prat J. Anaplastic carcinoma in mucinous ovarian tumors: a clinicopathologic study of 34 cases emphasizing the crucial impact of stage on prognosis, their histologic spectrum, and overlap with sarcomalike mural nodules. Am J Surg Pathol 2008;32:383–9.
20. Bague S, Rodriguez IM, Prat J. Sarcoma-like mural nodules in mucinous cystic tumors of the ovary revisited: a clinicopathologic analysis of 10 additional cases. Am J Surg Pathol 2002;26:1467–76.
21. Khunamornpong S, Suprasert P, Pojchamarnwiputh S, et al. Primary and metastatic mucinous adenocarcinomas of the ovary: Evaluation of the diagnostic approach using tumor size and laterality. Gynecol Oncol 2006;101:152 – 7.
22. Seidman JD, Kurman RJ, Ronnett BM. Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. Am J Surg Pathol 2003;27:985-93.

23. Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A 2011;108:18032–7.

24. Vercellini P, Scarfone G, Bolis G, Carinelli S, Crosiqnani PG. Site of origin of epithelial ovarian cancer: the endometriosis connection. Br J Obstet Gynaecol 2000;107:1155–7.

25. Ogawa S, Kaku T, Amada S, et al. Ovarian endometriosis associated with ovarian carcinoma: a clinicopathological and immunohistochemical study. Gynecol Oncol 2000;77:298–304.

26. Scully RE. World Health Organization International Histological Classification of Tumours. Histological typing of ovarian tumours. 2nd ed. Berlin: Springer 1999:45-53.

27. Silverberg SG. Histopathologic grading of ovarian carcinoma: a review and proposal. Int J Gynecol Pathol 2000;19:7-15.

28. Zaino RJ, Kurman RJ, Diana KL, Morrow CP. The utility of the revised International Federation of Gynecology and Obstetrics histologic grading of endometrial adenocarcinoma using a defined nuclear grading system. A Gynecologic Oncology Group study. Cancer 1995;75:81-6.

29. Kajiyama H, Shibata K, Suzuki S, et al. Is there any possibility of fertility-sparing surgery in patients with clear-cell carcinoma of the ovary? Gynecol Oncol 2008;111:523-6.

30. Onda T, Yoshikawa H, Yasugi T, et al. Patients with ovarian carcinoma upstaged to stage III after systematic lymphadenectomy have similar survival to Stage I/II patients and

superior survival to other Stage III patients. Cancer 1998;83:1555-60.

31. Yamagami W, Aoki D. Annual report of the Committee on Gynecologic Oncology, the Japan Society of Obstetrics and Gynecology. J Obstet Gynaecol Res 2015; Epub ahead of print.
32. del Carmen MG, Birrer M, Schorge JO. Clear cell carcinoma of the ovary: a review of the literature. Gynecol Oncol 2012;126:481-90.
33. Sugiyama T, Kamura T, Kigawa J, et al. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. Cancer 2000;88:2584-9.
34. Chan JK, Teoh D, Hu JM, Shin JY, Osann K, Kapp DS. Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. Gynecol Oncol 2008;109:370-6.
35. Shu CA, Zhou Q, Jotwani AR, et al. Ovarian clear cell carcinoma, outcomes by stage: The MSK experience. Gynecol Oncol 2015;139:236-41.
36. Kashima K, Yahata T, Fujita K, Tanaka K. Outcomes of fertility-sparing surgery for women of reproductive age with FIGO stage IC epithelial ovarian cancer. Int J Gynaecol Obstet 2013;121:53-5.
37. Takano M, Kikuchi Y, Yaegashi N, et al. Clear cell carcinoma of the ovary: a retrospective multicentre experience of 254 patients with complete surgical staging. Br J Cancer 2006;94:1369-74.
38. Kajiyama H, Shibata K, Mizuno M, et al. Long-term survival of young women receiving

fertility-sparing surgery for ovarian cancer in comparison with those undergoing radical surgery. Br J Cancer 2011;105:1288-94.

39. Raspagliesi F, Fontanelli R, Paladini D, di Re EM. Conservative surgery in high-risk epithelial ovarian carcinoma. J Am Coll Surg 1997;185:457-60.

40. Trimbos JB, Parmar M, Vergote I, et al. International Collaborative Ovarian Neoplasm Trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. J Natl Cancer Inst 2003;95:105-12.

Table 1. Oncologic outcomes of stage I patients with isolated ovary recurrence or with extraovarian recurrence

Author (year)	n	Recurrence n	isolated ovarian recurrence			extraovarian recurrence		
			Status					
			NED	AWD	DOD	NED	AWD	DOD
Fruscio (2013)	237	27	12	1	0	3	0	11
Kajiyama (2010)	60	8	0	1	1	1	0	5
Satoh (2010)	211	18	5	0	0	3	5	5
Park (2008)	59	9	1	0	0	1	3	4
Morice (2005)	33	9	2	0	2	2	2	1
Schilder (2002)	52	5	3	0	0	0	0	2
Zanetta (1997)	56	5	1	0	0	0	1	3
Rate of disease free survival after salvage			82.1% (23/28)			19.2% (10/52)		

n, number; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease.

Table 2. Oncologic outcomes after fertility-sparing surgery in patients with stage IA non-clear cell carcinoma grade 1

Author (year)	n	Recurrence n	Histology	Recurrence sites	TTR (months)	Status	FAR (months)
Fruscio (2013)	84	7	Endometrioid	contralateral ovary alone	172	NED	46
			Mucinous	contralateral ovary alone	19	NED	106
			Serous	contralateral ovary alone	77	NED	56
			Serous	homolateral ovary alone	23	NED	46
			Serous	homolateral ovary alone	61	NED	136
			Mucinous	pelvis	11	DOD	43
			Mucinous	pelvis-abdomen	38	DOD	5
Satoh (2010)	95	5	Mucinous	contralateral ovary alone	83	NED	119
			Serous	contralateral ovary alone	52	NED	164
			Mucinous	peritoneum	70	NED	149
			Mucinous	abdominal wall	14	AWD	39
			Mucinous	lung	73	DOD	34
Anchezar (2009)	11	2	Endometrioid	peritoneal carcinomatosis	63	NED	15
			Mucinous	lung, liver, abdomen	7	DOD	9
Park (2008)	29	1	Mucinous	contralateral ovary alone	33	NED	20
Borgfeldt (2007)	9	0					
Morice (2005)	13	2	Mucinous	contralateral ovary alone	16	NED	12
			Mucinous	bone, subcutaneous	7	DOD	40
Colombo (2005)	4	0					
Schilder(2002)	33	2	Serous	contralateral ovary alone	69	NED	14
			Mucinous	pelvis-abdomen	9	DOD	4
Zanetta (1997) Colombo (1994)	24	1	Serous	contralateral ovary alone	44	NED	NR
Total	302	20		ovary alone: 11, others: 9	NED: 13, AWD: 1, DOD: 6		

n, number; TTR, time to recurrence; FAR, follow-up after recurrence; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; NR, not reported.

Table 3. Oncologic outcomes after fertility-sparing surgery in patients with stage IA non-clear cell carcinoma grade 2

Author (year)	n	Recurrence n	Histology	Recurrence sites	TTR (months)	Status	FAR (months)
Fruscio (2013)	31	2	Endometrioid	pelvis	50	NED	77
			Mucinous	pelvis-abdomen	20	DOD	21
Satoh (2010)	13	0					
Park (2008)	3	0					
Borgfeldt (2007)	1	0					
Morice (2005)	14	4	Mixed	contralateral ovary alone	12	NED	120
			Endometrioid	contralateral ovary, peritoneum	14	NED	44
			Mucinous	contralateral ovary alone	24	Unknown	-
			Mucinous	contralateral ovary alone	2	DOD	54
Colombo (2005)	4	0					
Schilder(2002)	6	2	Endometrioid	contralateral ovary alone	13	NED	40
			Mucinous	lung	78	DOD	19
Zanetta (1997)	8	2	Endometrioid	spleen	20	AWD	NR
Colombo (1994)			Endometrioid	brain	8	DOD	NR
Total	80	10		ovary alone: 4, others: 6	NED: 4, AWD: 1, DOD: 4		

n, number; TTR, time to recurrence; FAR, follow-up after recurrence; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; NR, not reported.

Table 4. Oncologic outcomes after fertility-sparing surgery in patients with stage IA clear cell carcinoma

Author (year)	n	Recurrence n	Recurrence sites	TTR (months)	Status	FAR (months)
Satoh (2010)	15	0				
Anchezar (2009)	1	0				
Kajiyama (2008)	4	0				
Park (2008)	2	2	pelvic peritoneum	11	DOD	23
			contralateral ovary, liver	9	DOD	20
Morice (2005)	2	1	para-aortic LNs, liver	16	AWD	12
Schilder(2002)	3	0				
Total	27	3	ovary alone: 0, others: 3		AWD: 1, DOD: 2	

n, number; TTR, time to recurrence; FAR, follow-up after recurrence; AWD, alive with disease; DOD, dead of disease; LNs, lymph nodes.

Table 5. Oncologic outcomes after fertility-sparing surgery in patients with stage IC non-clear cell carcinoma grade 1

Author (year)	n	Recurrence n	Histology	Recurrence sites	TTR (months)	Status	FAR (months)
Fruscio (2013)	54	6	Endometrioid	homolateral ovary alone	14	NED	14
			Mucinous	contralateral ovary alone	25	NED	86
			Serous	contralateral ovary alone	118	NED	76
			Serous	contralateral ovary alone	44	NED	193
			Serous	contralateral ovary alone	19	AWD	5
			Serous	homolateral ovary alone	45	DOD	56
Kashima (2013)	14	4	Mucinous	contralateral ovary alone	14	NED	114
			Mucinous	pelvis lymph nodes	23	DOD	43
			Mucinous	contralateral ovary, pelvis	7	DOD	10
			Serous	brain	19	DOD	30
Satoh (2010)	65	5	Endometrioid	contralateral ovary alone	7	NED	45
			Mucinous	contralateral ovary alone	43	NED	16
			Mucinous	peritoneum	8	AWD	18
			Endometrioid	liver	20	DOD	6
			Serous	peritoneum	3	DOD	22
Anchezar (2009)	3	0					
Park (2008)	15	1	Mucinous	peritoneum, lung	12	DOD	19
Morice (2005)	2	2	Serous	contralateral ovary, peritoneum	44	NED	NR
			Mucinous	contralateral ovary alone	2	DOD	52
Total	158	18		ovary alone: 10, others: 8	NED: 8, AWD: 2, DOD:8		

n, number; TTR, time to recurrence; FAR, follow-up after recurrence; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; NR, not reported.

Table 6. Oncologic outcomes after fertility-sparing surgery in patients with stage IC non-clear cell carcinoma grade 2

Author (year)	n	Recurrence n	Histology	Recurrence sites	TTR (months)	Status	FAR (months)
Fruscio (2013)	37	4	Endometrioid	homolateral ovary alone	169	NED	2
			Mucinous	pelvis-abdomen	25	DOD	13
			Serous	pelvis-abdomen	10	DOD	13
			Serous	skin	48	DOD	9
Satoh (2010)	2	0					
Anchezar (2009)	1	0					
Park (2008)	2	1	Mucinous	contralateral ovary, pelvis-abdomen, LNs	11	AWD	16
Schilder(2002)	3	1	Mixed*	contralateral ovary alone	8	NED	10
Total	45	6		ovary alone: 2, others: 4	NED: 2, AWD: 1, DOD: 3		

n, number; TTR, time to recurrence; FAR, follow-up after recurrence; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; AWD, alive with disease. * serous and endometrioid

Table 7. Oncologic outcomes after fertility-sparing surgery in patients with stage IC clear cell carcinoma

Author (year)	n	Recurrence n	Recurrence sites	TTR (months)	Status	FAR (months)
Kashima (2013)	4	1	pelviic LNs	15	DOD	93
Satoh (2010)	15	5	contralateral ovary alone	21	NED	124
			para-aortic LNs	15	AWD	86
			contralateral ovary, ascites, peritoneum	11	DOD	19
			liver	46	AWD	8
			contralateral ovary, pelvic LNs, peritoneum	21	AWD	29
Anchezar (2009)	1	0				
Kajiyama (2008)	6	1	brain, abdominal wall	20	DOD	17
Park (2008)	2	0				
Morice (2005)	1	0				
Schilder (2002)	2	0				
Total	31	7	ovary alone: 1, others: 6		NED: 1, AWD:3, DOD: 3	

n, number; TTR, time to recurrence; FAR, follow-up after recurrence; LNs, lynph nodes; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; AWD, alive with disease.

Table 8. Oncologic outcomes after fertility-sparing surgery in patients with stage I non-clear cell carcinoma grade 3

Author (year)	n	IA/IC	Recurrence n	IA/IC	Histology	CT	Recurrence sites	TTR (months)	Status	FAR (months)
Fruscio (2013)	12	NR	5	IC	Serous	yes	LNs	65	NED	143
				IA	Endometrioid	yes	pelvis-abdomen	40	DOD	13
				IA	Mucinous	no	pelvis-abdomen	7	DOD	8
				IA	Mucinous	yes	lung	9	DOD	4
				IA	Endometrioid	yes	brain	7	DOD	2
Kajiyama (2011)	4	NR	2	NR	NR	NR	NR	NR	DOD	NR
				NR	NR	NR	NR	NR	DOD	NR
Satoh (2010)	6	IA:3 IC:3	3	IA	Serous	no	contralateral ovary, ascites	25	NED	231
				IA	Endometrioid	no	para-aortic LNs	31	NED	34
				IC	Mucinous	yes	NR	1	DOD	5
Park (2008)	4	IA:2 IC:2	4	IC	Endometrioid	yes	contralateral ovary, uterus, pelvic peritoneum	34	NED	79
				IA	Mixed	yes	peritoneum	6	AWD	5
				IA	Mucinous	yes	LNs	54	DOD	60
				IC	Mucinous	yes	Omentum, mesentery, incisional scar	6	DOD	8
Borgfeldt (2007)	1	IC:1	1	IC	Mucinous	NR	pelvis-abdomen	NR	DOD	<12
Morice (2005)	1	IA:1 IC:1	1	IC	Serous	yes	contralateral ovary, peritoneum, liver	6	DOD	3
Raspagliesi (1997)	2	IA:2	0							
Zanetta (1997) Colombo (1994)	7	NR	1	IA	Mucinous	yes	lung, para-aaortic LNs	12	DOD	NR
Total	37	IA:8, IC:7	17	IA:9 IC:6			ovary alone: 0, others: 15	NED: 4, AWD: 1, DOD: 12		

n, number; CT, chemothepapy during primary treatment; TTR, time to recurrence; FAR, follow-up after recurrence; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; NR, not reported; LNs, lymph nodes.