Clinical features of 215 Stage I ovarian tumors in Japanese women

S. Kaku[1], N. Takeshima[1], K. Umayahara[1], R. Furuta[2], F. Akiyama[2], K. Takizawa[1]

[1]Department of Gynecology, [2]Department of Pathology, Cancer Institute Hospital, Tokyo (Japan)

Summary

Purpose: Differences of the clinical features of Stage I borderline ovarian tumors and Stage I ovarian cancer need to be clarified. *Methods:* We retrospectively investigated 215 patients with Stage I ovarian tumors (67 with borderline tumors and 148 with ovarian cancer) treated between 1988 and 2001. *Results:* Only one patient with a borderline tumor developed recurrence, while recurrence was found in 20 patients with Stage I ovarian cancer. There was a significant difference in the recurrence rate between patients with Stage Ia or Ib ovarian cancer and those with Stage Ic cancer ($p = 0.007$). Clear cell adenocarcinoma showed a higher recurrence rate. Among our patients with recurrence, only five in whom the recurrent tumor could be surgically resected are currently alive and disease-free. *Conclusions:* This study confirmed the low aggressiveness of Stage I borderline ovarian tumors and high aggressiveness of Stage Ic ovarian cancer or clear cell adenocarcinoma. In patients with recurrence, surgical resection may improve survival.

Key words: Stage I; Borderline ovarian tumors; Ovarian cancer; Recurrence.

Introduction

Borderline ovarian tumors (BOTs) account for approximately 10-15% of malignant epithelial ovarian tumors [1]. These tumors form a separate entity within the category of ovarian tumors, and methods of treatment show a clear difference between BOTs and ovarian cancer [2]. A wide range of recurrence rates has been reported for BOTs [3-8], which may be attributed to the difficulty of distinguishing between these tumors and ovarian cancer by pathological examination [9-11].

We performed a retrospective study that compared the characteristics of Stage I BOTs, which are most commonly encountered, with those of Stage I ovarian cancer in patients treated at the same institution during the same period (to minimize differences of surgical technique or pathological diagnosis).

Materials and Methods

Between 1988 and 2001, 67 patients with Stage I BOTs and 148 patients with Stage I ovarian cancer were treated at the Cancer Institute Hospital in Japan. Clinical features of the patients with Stage I BOTs or Stage I ovarian cancer are shown in Table 1.

Among the 67 patients with Stage I BOTs, 56 had Stage Ia tumors (83.6%) and 11 had Stage Ic disease (16.4%). The tumor was serous in 18 patients (26.9%) and mucinous in 49 patients (73.1%). Among the 148 patients with Stage I ovarian cancer treated at our hospital during the same period, 57 had Stage Ia tumors (38.5%), six had Stage Ib tumors (4.1%), and 85 had Stage Ic disease (57.4%). Tumor histology was serous in 31 patients (20.9%), mucinous in 37 patients (25.0%), endometrioid in 20 patients (13.5%), clear cell in 49 patients (33.1%), and mixed in 11 patients (7.4%) (Table 1).

The pathological diagnosis of all tumors was confirmed after careful histological examination by an experienced gynecologic pathologist according to the World Health Organization (WHO) classification. BOTs were defined as tumors that showed nuclear atypia, stratification of the epithelium, and microscopic papillary projections without any stromal invasion. The 1987 International Federation of Gynecology and Obstetrics (FIGO) classification was used for surgical staging.

The chi-square test or Student's t-test was employed for comparison of the two groups. Survival analysis was done by the Kaplan-Meier method, and the log-rank test was used for comparison of survival times. Survival was calculated from the day of the first operation to the last day of review or to the date of death.

Results

Age

Patients with Stage I BOTs ranged in age from 17 to 72 years (mean age: 46.3 years) and patients with Stage I ovarian cancer ranged in age from 17 to 78 years (mean age: 51.4 years) (Table 1). Comparison of the mean age between the two groups showed that the patients with BOTs were significantly younger than those with ovarian cancer ($p = 0.008$).

Initial surgery

Conservative surgery was defined as preservation of the uterus and at least one ovary. Initial surgery was conservative in 32 out of 67 patients with Stage I BOTs (47.8%). Simple cystectomy was performed in one of these 32 patients, but the residual ovary on the diseased side was resected after a diagnosis of BOT was made. In the remaining 35 patients, non-conservative surgery was performed. Among them, six patients (8.9%) also underwent lymphadenectomy because ovarian cancer was strongly suspected prior to surgery (Table 1).

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Table 1. — *Clinical features of patients with stage I BOTs or Stage I ovarian cancer.*

	BOTs	Cancer
Number of patients	67	148
Age (years)		
Range	17-72	17-78
Average	46.3	51.4
FIGO Stage		
I a	56	57
I b	0	6
I c	11	85
Histology		
Serous	18	31
Mucinous	49	37
Endometrioid	0	20
Clear cell	0	49
Mixed	0	11
Surgical procedure		
Conservative surgery	32	12
Non-conservative surgery without LN	29	33
Non-conservative surgery with PLA	1	14
Non-conservative surgery with PLA+PALA	5	89
Adjuvant chemotherapy		
Yes	1	70
No	66	78

LN: lymphadenectomy, PLA: pelvic lymphadenectomy, PALA: paraaortic lymphadenectomy.

Only 12 out of 148 patients (8.1%) with Stage I ovarian cancer underwent conservative surgery. Non-conservative surgery without lymphadenectomy was performed in 33 out of 148 patients (22.3%), while procedures that included lymphadenectomy were done in 103 patients (69.6%) (Table 1). In the patients with clear cell adenocarcinoma, lymphadenectomy was performed in the majority of them (46/49, 93.9%).

Adjuvant chemotherapy

Only one of the 67 patients (1.5%) with BOTs received adjuvant chemotherapy, while it was performed in 70 out of 148 ovarian cancer patients (47.3%). An average of three courses of platinum-based chemotherapy was given as adjuvant therapy, with a range of one to eight courses (Table 1).

Recurrence of Stage I BOTs

Among patients with Stage I BOTs, the mean follow-up period was 101.8 months (range: 12-183 months). Recurrence was only discovered in one patient with a Stage Ia mucinous tumor that was treated by left salpingo-oophorectomy. In this patient, pulmonary metastasis was found at 14 months after initial surgery, and metastatic BOT was verified by pathological examination of a biopsy specimen obtained from the lung tumor at bronchoscopy. CT scans did not reveal any signs of recurrence in the lymph nodes or other organs.

Recurrence of Stage I ovarian cancer

Among patients with Stage I ovarian cancer, the mean follow-up period was 91.9 months (range: 2 to 185 months), and recurrence was found in 20 patients (Table 2). A significant difference in the recurrence rate was observed between patients with stage Ia or Ib tumors and patients with Stage Ic tumors ($p = 0.007$).

Table 2. — *Tumor histology and recurrence rate of Stage I ovarian cancer.*

	Stage Ia	Stage Ib	Stage Ic	Total
Serous	0/10	0/5	2/16	2/31 (6.5%)
Mucinous	2/22	–	3/15	5/37 (13.5%)
Endometrioid	0/12	–	0/8	0/20 (0%)
Clear cell	1/12	–	9/37	10/49 (20.4%)
Mixed	0/1	0/1	3/9	3/11 (27.3%)
Total	3/57 (5.3%)	0/6 (0%)	17/85 (20.0%)	

With respect to tumor histology, patients who had clear cell carcinoma showed a high recurrence rate (10/49, 20.4%), despite lymphadenectomy being performed in almost all cases. There was a higher recurrence rate for clear cell carcinoma than the average rate for other types of tumors, but the difference was not significant.

Disease-free survival and overall survival

Disease-free survival and overall survival five years after the initial operation were compared between the patients with BOTs and those with ovarian cancer. The 5-year disease-free survival rate for all patients with Stage I BOTs was 98.2% and their overall survival rate was 98.5%. On the other hand, the 5-year disease-free survival rate for all patients with Stage I ovarian cancer was 85.9% and their 5-year overall survival rate was 89.6%. A significant difference was observed with respect to both 5-year disease-free survival ($p = 0.008$) (Figure 1) and 5-year overall survival ($p = 0.025$) (Figure 2) when patients with Stage I BOTs were compared to patients with stage I ovarian cancer.

Treatment of recurrence

The only BOT patient with metastasis (to the lung) received chemotherapy, but she died approximately 11 months after the detection of recurrence. Twenty ovarian cancer patients developed recurrence; all 20 patients received chemotherapy and eight of them underwent further surgical treatment. Five patients in whom the recurrent tumor could be completely resected are currently alive without further recurrence, but the patients whose lesions could not be removed surgically and the patients who only received chemotherapy all died. A significant difference in the survival rate was observed between patients who had surgery as well as chemotherapy and patients who received chemotherapy alone ($p = 0.009$) (Figure 3).

Discussion

BOTs form a separate entity within the category of ovarian tumors. Because BOTs occur in younger women and are usually diagnosed at an early stage, the prognosis is excellent [12]. However, a wide range of recurrence

Fig. 1

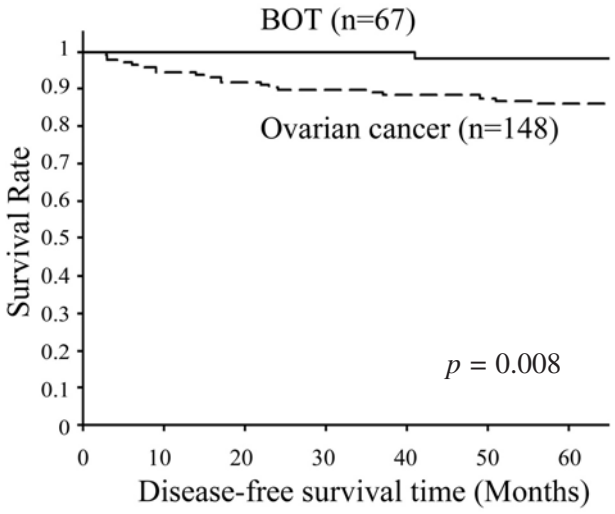

Fig. 2

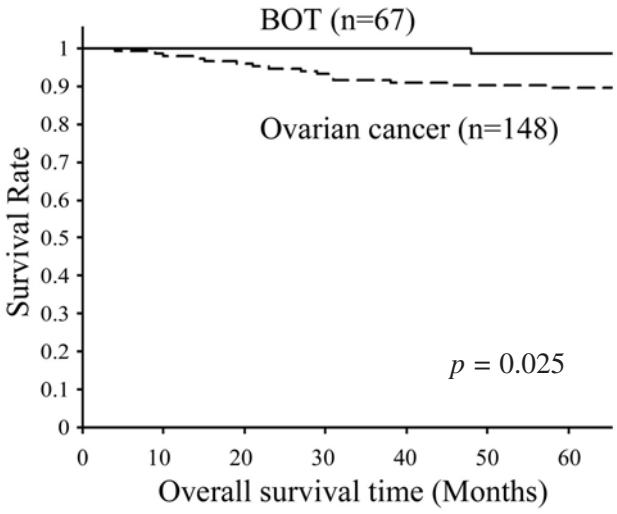

Figure 1, 2 — Comparison of 5-year disease-free survival and overall survival between patients with Stage I borderline ovarian tumors (BOTs) and patients with Stage I ovarian cancer.
Figure 1 — Disease-free survival.
Figure 2 — Overall survival. There was a significant difference between the BOTs and cancer groups with respect to both 5-year disease-free survival ($p = 0.008$) and 5-year overall survival ($p = 0.025$).

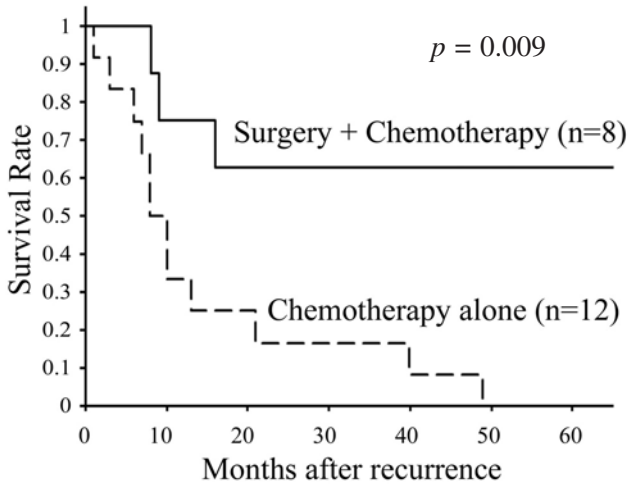

Figure 3 — Influence of therapy on the survival of patients with recurrent Stage I ovarian cancer. Patients who had surgery as well as chemotherapy showed significantly better survival than patients who received chemotherapy alone ($p = 0.009$).

rates have been reported [3-8]. This may be attributable to the fact that it can be difficult to differentiate between BOTs and ovarian cancer by pathological examination [9-11]. In the present study, we compared patients with BOTs to patients who had ovarian cancer. Both groups were treated during the same period at the same institution, thus minimizing any differences related to surgical technique or pathological diagnosis.

Only one patient developed recurrence in our group with BOTs tumors, so there were no differences of the recurrence rate between Stage Ia, Ib, and Ic BOTs, or between the histological types. On the other hand, there was a significant difference of the recurrence rate between patients with Stage Ia or Ib ovarian cancer and patients with Stage Ic cancer ($p = 0.007$). We also found a higher recurrence rate of clear cell carcinoma compared with the average rate for the other types of ovarian cancer ($p = 0.081$), although the difference was not statistically significant. Several authors have reported that clear cell tumors have a higher recurrence rate than other histological types of ovarian cancer [13-16]. Indeed, our patients with clear cell carcinoma had a very high recurrence rate (20.4%) even though the majority of them underwent non-conservative surgery with lymphadenectomy. Accordingly, we feel that it is necessary to not only perform surgery but also intensive adjuvant chemotherapy for Stage Ic ovarian cancer or clear cell adenocarcinoma.

Among our patients with recurrence, only five in whom the recurrent tumor could be surgically resected are currently alive and disease-free. There was a significant difference in the survival rate between patients who underwent additional surgery as well as chemotherapy and patients who received chemotherapy alone, suggesting the value of aggressive resection for managing intraperitoneal recurrence of ovarian cancer.

Conclusion

This study confirmed the low aggressiveness of Stage I borderline ovarian tumors and high aggressiveness of Stage Ic ovarian cancer or clear cell adenocarcinoma. Accordingly, we feel that it is necessary to not only perform surgery but also intensive adjuvant chemotherapy for the latter tumors. In patients with recurrence, surgical resection may improve survival.

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Address reprint requests to:
S. KAKU, M.D.
Department of Obstetrics and Gynecology
Shiga University of Medical Science
Tsukinowa-cho, Seta, Otsu
Shiga 520-2192 (Japan)
e-mail: kaku@belle.shiga-med.ac.jp