Clinical Analysis of 57 Patients with Ovarian Dysgerminoma

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OBJECTIVE Ovarian dysgerminoma is an uncommon ovarian malignancy. Its clinical features are special and there are many factors affecting its prognosis. If treated properly, the patient can be cured. Otherwise it may endanger the patient's life. The aim of this study is to investigate the clinical features and factors related to prognosis of ovarian dysgerminoma.

METHODS Data from 57 patients with pure ovarian dysgerminoma were analyzed retrospectively. The patients were admitted to the Cancer Center, Sun Yat-sen University from January 1, 1964 to December 31, 2000.

RESULTS The main clinical features were abdominal mass (56.1%), abdominal pain (21.1%), abdominal swelling (17.5%), vaginal bleeding (5.3%) and genital tract abnormalities (5.3%). Twenty-six patients had stage I diseases, 8 stage II, 9 stage III, 1 stage IV and 13 recurrent and persistent diseases. The uterus was involved in 41.2% of patients with stage II-III diseases. Combined modality was given to 52 cases and a single-method treatment to 5 cases. The total overall 5 and 10-year survival rates for stages I-IV was 80.1% and 70.0% respectively. The 5-year survival rate for stage I was 100%, stage II 55.2%, stage III 55.6% and stage IV 0%; for recurrent and persistent diseases, 72.7%. The stage I group of 12 patients received adnexectomy and 14 patients underwent hysterectomy and adnexa removal. There was no significant difference between the 5 and 10-year survival rates (all 100%). Of the 23 patients in the stage I group to whom only chemotherapy was given after operation, 19 cases received 3 or more courses and were well without recurrence; 4 patients received only one course and one of them recurred 21 months after the operation. In the group of stages II and III cases, the 5-year survival rate was 86.7% for those whose chemotherapy courses were ≥4 and 25.0% for patients who received less than 4 courses of chemotherapy ($P<0.05$).

CONCLUSIONS The prognosis of ovarian dysgerminoma is closely related to the disease stage and treatment modality. A fertility-preserving operation can be considered in early-staged patients, but caution needs to be exercised in the middle to late staged cases. Good results can be achieved with an operation-based combined modality in recurrent patients.

KEYWORDS: ovarian cancer, dysgerminoma, chemotherapy, conservative operation.

Ovarian dysgerminoma is a rare ovarian malignancy. The clinical feature of this tumor is unique and occurs predominantly in girls and young women. [1,2] Good results can be expected with proper treatment; otherwise the prognosis could be poor with improper

Received March 20, 2004; accepted May 28, 2004.

treatment.[3,4] This tumor is highly sensitive to both chemotherapy and irradiation. The routine treatment includes surgery and postoperative adjuvant chemotherapy. Because preserving fertility is necessary in most patients who are young, radiotherapy is only administered in some advanced and recurrent cases. The clinical features, treatment method and survival of the patients with ovarian dysgerminoma admitted to our hospital were analyzed retrospectively to investigate the clinical characteristics and prognostic factors.

MATERIALS AND METHODS

General Material

Fifty-seven patients with ovarian dysgerminoma were admitted to our hospital from January 1, 1964 to December 31, 2000, which accounted for 3.3% (57/1781) of all ovarian malignancies and 23.6% (57/242) of malignant ovarian germ cell tumors during the same period. The patients presented as follows: 26 stage I, 8 stage II, 9 stage III, 1 stage IV and 13 patients with recurrent or persistent diseases, who were referred to our hospital from elsewhere. The median follow-up time was 93 months (range, 1-396 months). Two patients were lost to follow-up. Histological review was performed to exclude the mixed malignant ovarian germ-cell tumors with a dysgerminoma component.

Clinical Characteristics

Ages of the patients ranged from 11 to 59 years (median age, 20 years). Major clinical features include an abdominal mass (56.1%), abdominal pain (21.1%), abdominal distention (17.5%), vaginal bleeding (5.3%) and genital tract abnormity (5.3%). Among 3 patients with congenital genital tract abnormity, two cases were with congenital deficiency of uterus and unilateral ovary, and one with uterus deficiency.

Tumor locations were clearly documented among 53 cases with 24.5% tumors on the left ovary, 60.4% on right ovary and 17.0% bilateral. Among 50 patients with a documented extended tumor, pelvic and abdominal metastases were found in 14.0% and ascites in 24.0% of the patients. Among 17 patients with stage II-III diseases, 41.2% were found to have both gross and microscopic uterus involvement. Retroperitoneal lymphadenectomy was performed in the initial treatment of 7 patients, three of them (with stage I, II, IV disease, one case each) received only pelvic lymphadenectomy, and 4 of them received pelvic plus para-aortic lymphadenectomy (one case with stage II disease, three with stage III). None of the 7 patients were found to have pelvic lymph node metastasis, but 2 of 4 patients had metastatic para-aortic lymph node involvement.

Treatment

Among 57 patients, 50 received surgery and chemotherapy and two received chemotherapy plus irradiation. One patient received only surgery; three patients received chemotherapy only and one received irradiation only. More details are shown in Table 1.

Table 1. Treatment method and case number in each group

		Combined modality				Single treatment		
Stage	n	O+C	O+R	O+C+R	C+R	O	C	R
I	26	23	1	2	–	–	–	–
II	8	6	1	–	–	1	–	–
III	9	5	–	4	–	–	–	–
IV	1	1	–	–	–	–	–	–
R&P	13	3	1	3	2	–	3	1
Total	57	38	3	9	2	1	3	1

R&P: recurrent and persistent diseases; O: operation; C: chemotherapy; R: radiotherapy.

Surgical treatment

Fifty-one of 57 patients received surgical treatment (as primary treatment in 44). The operative procedure consisted of total hysterectomy with bilateral adnexectomy with omentectomy in 23 patients (with stage I, II, III and IV disease in 14, 5, 3 and 1 patients respectively), unilateral adnexectomy in 17 patients (with stage I, II, III disease in 11, 3, 3 patients respectively), bilateral adnexectomy with omentectomy in 2 patients (with stage I, II disease in 1 patient each), palliative tumor excision and tumor biopsy in 1 patient each (with stage III diseases), cytoreduction in 7 referred patients with recurrent or persistent diseases receiving primary surgery elsewhere.

Chemotherapy

The following chemotherapy protocols were used: 1) N-formylsarcolysin 150 mg, administered orally once daily at a total dose of 2.25-4.5 g. 2)VAC regimen: vincristine (VCR) 1 mg/m^2, iv injection on day 1; actinomycin 0.2-0.4 mg/d, iv infusion, on day 1-5; cyclophosphamide (CTX), 400 mg/m^2, iv infusion, on day 1, 2. 3) VBP regimen: VCR was delivered as in the

VAC regimen; bleomycin, 40 mg for each course, im or iv injection, administered once daily over 2-3 days; DDP 70 mg/ m^2 or carboplatin 300-350 mg/ m^2, ip infusion on day 1 or iv infusion, divided over 3 to 5 days. 4) EBP regimen: etoposide 100 mg/d, iv infusion on day 1-5; bleomycin and carboplatin were delivered as in the VBP regimen. 5) Others: CP regimen: CTX plus platinum, CTX was delivered as in VAC regimen and platinum as in VBP regimen; single drug regimen: thiotepa 10 mg/d, ip infusion or im on Day 1-10. In the above-mentioned regimens N-formylsarcolysin and thiotepa were mainly used before 1985 and VAC, VBP, EBP after 1985.

Chemotherapy courses: chemotherapy was administered to 52 of 57 patients including 25 patients with stage I disease, 6 stage II, 9 stage III, 1 stage IV and 11 recurrent or persistent. The median chemotherapy course was 4 in groups with stage I, II-III and recurrent or persistent diseases.

Radiotherapy

Radiotherapy was given to 15 patients including 3 with stage I disease, 2 stage II, 2 stage III and 8 recurrent or persistent. A dose of 46 Gy was delivered to pelvic fields, 36 Gy to abdomen moving strip fields, 46 Gy to para-aortic fields and a boost dose given if necessary.

Statistical method

A SPSS program was used to do the survival analysis and Chi-square test for comparison of recurrent incidence.

RESULTS

Survival rate

The overall 5-year and 10-year survival rates for patients with stages I-IV diseases were 80.1% and 71.0% respectively. The 5-year survival rates for patients with stage I, II, III, IV and recurrent or persistent diseases was 100%, 55.2%, 55.6%, 0% and 72.7% respectively. The 10-year survival rates for cases with stage I, II, III and recurrent or persistent diseases were 100, 55.2%, 0% and 63.3% respectively.

Relationship between stage, treatment method and survival rate

Stage and survival rate

The 5 and 10-year survival rates of patients with stage I disease were significantly higher than that of patients with stage II, III, IV and recurrent or persistent diseases ($P<0.01$). There were no significant differences among the 5 and 10-year survival rates of patients with stage II, III and recurrent or persistent diseases ($P>0.05$).

Treatment method and survival rate

Among patients with stage I disease, twelve patients received adnexectomy; fourteen patients received hysterectomy with adnexectomy. The median chemotherapy course was 4 in both of the two groups with one and two cases in each group receiving postoperative radiotherapy respectively. The 5 and 10-year survival rates were both 100% in the two groups ($P>0.05$). In patients with stage II or III disease , seven patients received a surgical procedure with hysterectomy and eight patients without hysteredtomy. The median chemotherapy course was 4 in both of the two groups. Two patients received postoperative radiotherapy in the group with hysterectomy and one patient in the group without hysterectomy. The 5-year survival rates were 85.7% and 42.9% respectively ($P>0.05$).

For 26 patients with stage I disease , three received postoperative radiotherapy and all of them survived at least 10 years. Twenty-three patients received postoperative chemotherapy. Four of 23 patients received only one course of treatment and one of the 4 patients hand recurrence 21 months after operation (the median follow-up time was 318 months). Three or more courses of chemotherapy were given to 19 patients and all of them remained free of the disease (the median follow-up time was 88 months). The recurrent rates were 25.0% and 0% respectively ($P>0.05$). Eight of 17 patients with stage II or III diseases received less than 4 courses of chemotherapy and 9 patients 4 or more courses. The 5-year survival rate was 25.0% and 86.7% respectively ($P<0.05$).

Recurrent or persistent disease and death

The location of recurrences

The location of recurrences was determined through physical examination, radiologic examination or intraoperative exploration. Four of 11 recurrent cases occurring from the primary treatment group of this study had a clear recurrent position. Thirteen cases with recurrent or persistent diseases were transferred from elsewhere. Therefore the location of recurrences could be analyzed in 17 patients, which consisted of pelvic recurrences in 88.2% patients (15/17), abdominal metastases in 23.5% (4/17), pelvic lymph node metastases in 17.6% (3/17), para-aortic lymph

node metastases in 35.3% (6/17), and 0.6% (1/17) for liver, lung, and mediastinum metastases respectively. Pelvic and para-aortic lymph nodes were a common position for recurrences in this study.

The time of recurrence

The median time for the first-time recurrence was 17 months (range, 6-60 months). Three patients had recurred disease again at 75, 113 and 288 months respectively after clinical relief of their first-time recurrence and then died of the disease.

Treatment results for recurrent or persistent cases

Three of 11 patients with recurrent or persistent diseases, who received their primary treatment in our hospital, recurred again at 75, 113 and 288 months respectively after their first-time recurrences and then died of their disease. The remaining 8 cases gave up treatment and died of their disease. The 5 and 10-year survival rates were 72.7% and 63.3% respectively for 13 referred cases with recurrent or persistent diseases.

Fifteen patients in this study died from their disease, among whom 1 case was at stage I, 3 cases at stage II, 6 cases at stage III , and 1 case at stage IV , plus 4 cases with recurrent or persistent diseases.

DISCUSSION

The clinical and behavioral characteristics of ovarian dysgerminoma

Ovarian dysgerminoma is rare and patients with this disease are usually young. The main clinical features are abdominal mass, abdominal pain, distension and genital developmental abnormalities.[1,2] The disease is more common on the right ovary. The involvement of bilateral ovaries accounts for 5% ~ 15% of all cases. The results of our study are consistent with the literature.

The metastases of ovarian dysgerminoma occur mainly through lymphatic vessels. It has been reported that lymph node metastases were found by lymphangiography in 37% of patients with stage I; only para-aortic lymph nodes disease involvement was found in 60% of patients , and both para-aortic and pelvic lymph node metastases in the remaining 40%. Seven cases in this study received retroperitoneal lymphadenectomy as part of their primary treatment; pelvic lymph node metastases and para-aortic involvement were found in 0/7 and 2/4 patients respectively. In cases with recurrent or persistent diseases para-aortic lymph node involvement and pelvic lymph node metastases were found in 35.3% and 17.6% respectively. These data show that lymph node, especially para-aortic lymph node involvement is likely to occur in dysgerminoma.

Prognosis-related factors in ovarian dysgerminoma

The prognosis of ovarian dysgerminoma patients is related to their disease stage. It has been reported that the 5-year survival rate is 96.9% for stage I-II patients and only 53.9% for stage III-IV patients.[4] In this study the 5-year survival rates for patients with stage I, II, III and IV diseases were 100%, 55.2% ,55.6% and 0% respectively. The 5-year survival rate in stage I patients was significantly higher than that of patients with stage II, III or IV disease showing the importance of early diagnosis. Ovarian dysgerminoma is highly sensitive to both chemotherapy and radiotherapy.[5,6] Combined treatment modality consisting of surgical treatment, postoperative adjuvant chemotherapy and radiotherapy should be used if necessary. However in adolescent patients irradiation should be administered with care. Unilateral adnexectomy and postoperative chemo-therapy can be considered for patients with early diseases who desire future fertility.

The course of postoperative chemotherapy was closely related to treatment efficacy. In our study the median number of courses was 4 in patients with stage I disease with both the 5 and 10-year survival rates of 100% . Nineteen patients who received 3 or more courses of chemotherapy were alive and disease-free ; in 4 cases who received only one course of chemotherapy, recurrence developed in one patient. Among cases with stage II or III disease the 5-year survival rate of patients who received 4 or more courses of chemotherapy was higher than that of patients whose chemotherapy courses was less than 4. The data of this study show that patients with stage I diseases must receive 3-4 courses of postoperative chemotherapy , and patients with stage II or III disease more than 4 courses.

The likelihood and safety of preserving fertility

As dysgerminoma is more common in young women, preserving fertility is of great importance. Generally the conservative surgery of preserving fertility is recommeded if the uterus and contralateral ovary are normal, but adequate courses of postoperative chemotherapy must be administered. In this study both the 5 and 10-year survival rates were 100% in 11 stage I patients with their uterus preserved, and 15 stage I

patients with the uterus removed, showing that conservative surgery in stage I patients does not affect prognosis. Among 23 stage I patients only chemotherapy was delivered as postoperative adjuvant treatment, the 5 and 10-year survival rates reached 100%, showing that it is feasible for stage I patients to receive just chemotherapy as postoperative adjuvant therapy.

For early-stage patients: most authors agree with the preservation of fertility in stage I patients. But attention must be paid to the point that the bilateral incidence of the disease is high, (17% in this group). The contralateral ovary must be examined carefully and biopsy should be performed if unilateral adnexectomy is performed. For middle and advanced-stage patients: conservative surgery is controversial in patients with stage II-III diseases. Generally hysterectomy is considered, but some authors suggest that a normal uterus can be preserved. In stage II-III of this study patients there is no difference in the 5-year survival rate for patients whose uterus was preserved versus those whose uterus was removed ($P>0.05$), suggesting that preserving a normal uterus does not necessarily reduce survival time. As uterus involvement was found in 43.8%(7/17) patients with stage II-III disease, it is evident that the uterus metastasis incidence is high in middle and advanced stage patients, so preserving the uterus must be considered with care while planning the operation style.

Diagnosis and treatment of recurrent and persistent diseases

Recurrence of the tumors developed more frequently in the pelvis and para-aortic lymph nodes[1,2]. In our study pelvic recurrences and para-aortic lymph node involvement were found in 88.2% and 35.3% of the patients, while involvement of organs such as liver and lung where epithelial ovarian carcinoma recurrence often occur,[7] was rare in our study . Liver or lung metastases were found in 0.6% cases of this group. So special attention must be paid to possible pelvis and para-aortic lymph node involvement during follow-up for dysgerrminoma .

The mean recurrent time for dysgerminoma was reported to be 23 months.[8] In our study the median recurrent time was 17 months. Therefore close follow-up is important especially during the first two years after surgery. Some late recurrence may ensue in dysgerminoma patients with the recurrent time being as long as 240 months.[9] One tumor in our study recurred again at 288 months after relief from the first recurrence. So follow-up must be carried out for a long time.

Treatment of recurrent or persistent diseases: long-time survival can be expected if an active combined treatment modality is administered [3]. Three of 11 patients who each had a recurrence after primary treatment in our hospital lived for as long as 288, 75 and 11 months when finishing a second round of treatment; the 5 and 10-year survival rates were 72.7% and 63.8% respectively for 13 referred patients with recurrent or persistent diseases, These results show that cure can be expected in patients with recurrent or persistent diseases. Surgery-based combined modality is the usual therapy.

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