

*Clinical Observations***RESULTS OF SECOND-LOOK LAPAROTOMY WITH EXTENSIVE DISSECTION OF RETROPERITONEAL LYMPH NODE IN OVARIAN CANCER PATIENTS**

WU Xiao-hua 吴小华, ZHANG Zhi-yi 张志毅, TANG Mei-qing 唐美琴, CHEN Jie 陈洁

*Department of Gynecologic Oncology, Cancer Hospital, Shanghai Medical University, Shanghai 200032, China***ABSTRACT**

Objective: To evaluate retrospectively the results of extensive lymphadenectomy during second-look laparotomy on patients with ovarian cancer. **Methods:** A total of 63 patients with ovarian malignancies received second-look laparotomy (SLL). Retroperitoneal lymph nodes, including pelvic and para-aortic lymph nodes below the level of left renal vein, were extensively dissected. **Results:** Of the 63 patients, residual tumor was found in 24 (38.0%) on SLL. The frequency of residual tumor was positively correlated with the clinical stage and with the amount of tumor left after initial debulking but not with degree of differentiation of tumor cells. Lymph node metastasis(LNM) was pathologically confirmed in 19 cases (30.2%), of which no residual tumor was found in 8 patients. Tumor recurred in only 4 of the 39 patients (10.3%) with negative SLL. The overall 3- and 5-year survival rate were 75.0% and 68.0%, respectively. **Conclusion:** Extensive retroperitoneal lymph node dissection was recommended during SLL. It favored a decrease in recurrence rate in ovarian cancer patients negative on SLL.

Key words: Ovarian cancer, Lymphadenectomy, Second-look laparotomy, Recurrence

Second-look laparotomy (SLL) has been introduced to the treatment procedure for ovarian cancer over three decades, whose original intention

was to evaluate the disease statuses of patients with ovarian cancer after primary cytoreduction and planned chemotherapy, and to determine further management. However, the results for the clinical applications of SLL have revealed that about 20%-71% of patients with negative SLL would relapse in 2 years,^[1] so that the disputation about clinical significance of SLL remains. In all the literatures available about SLL, selected sampling of pelvic and paraaortic lymph nodes is routinely performed.^[2] Now, it is known that retroperitoneal lymph node metastasis in patients with ovarian cancer is a common spread way. But for some advanced stage patients, it is difficult performing the systematic lymphadenectomy during primary cytoreductive surgery. Since the middle of 1980s, we have performed the systematic lymphadenectomy instead of selected sampling of lymph node during SLL.^[3]

MATERIALS AND METHODS**Patients**

The study included 63 patients with primary ovarian cancer, treated in our hospital from January 1987 to October 1995. The means age of all patients was 49 years (range 16-61-years). According to the staging criterion of the International Federation of Gynecology and Obstetrics (FIGO, 1985) without considering the status of lymph nodes, 15 patients were categorized as stage I ovarian cancer, 12 as stage II, 35 as stage III, and one as stage IV. There were 46 patients with epithelial carcinoma, including 26 serous, 8 mucinous, 6 undifferentiated, and 6 other subtype carcinoma. In other 17 patients, 7 patients were dysgerminoma, 5 immature teratoma, and 5 endodermal sinuse tumor. The means time of follow-up was 56.5 months (range 6-104 months).

Received December 26, 1999; accepted March 15, 2000

Correspondence to: Wu Xiao-hua, Department of Gynecologic Oncology, Cancer Hospital, Shanghai Medical University, No.399 Ling-ling Road, Shanghai 200032, China; Phone: (0086-21)-64175590; Fax: (0086-21)-64174774; E-mail: wuxzhou@public7.sta.net.cn

Surgical Procedure

In this study, all patients underwent staging laparotomy. According to the findings of the laparotomy and pathological examination, a stage of disease for each patient was identified. Abdominal total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, or appendectomy were performed, but without lymphadenectomy during primary cytoreductive operation. Complete resection of primary and intraperitoneal metastasis disease was attempted. Then those patients were subjected to combination chemotherapy with platinum-based regimen, including intraperitoneal chemotherapy with the mean courses of 4.2 (range 1–5), and intravenous chemotherapy with the mean courses of 4.8 (range 1–8). After completing the planned chemotherapy, these patients were considered as the candidates for SLL if they were tallied with following conditions: no evidence of tumor by physic and imaging examination such as ultrasound, CT and MRI scan; a normal level of CA125 or AFP in blood; and informed consent. The mean interval between primary cytoreduction and SLL was 11.2 months (range 4–16 months).

Cytologic washings, random peritoneal biopsies, and secondary cytoreduction were performed during SLL. In addition, a systematic lymphadenectomy was done, including removal of both pelvic and paraaortic lymph nodes up to the level of left renal vein. The procedure of the systematic lymphadenectomy was the followings: the posterior peritoneum was incised along the right paracolic gutter nearly up to the hepatocolic ligament, along the base of the mesentery from the caecum to Treitz's ligament, and finally along the bilateral common and external iliac artery to the groin. The ascending colon and small bowel were mobilized, wrapped with a wet pad and placed on the chest. The retroperitoneum included the field between the right and left ureter, inferior the level of the left renal vein and the region of pelvic lymph nodes. The surgical specimen included the en bloc lymphatic tissue overlying the aorta, vena cava, bilateral external and internal iliac arteries nerve.

For those patients with negative finding at SLL, only immunotherapy or the consolidate chemotherapy of 1–2 courses was used. But for those patients with positive SLL, the residual tumor was removed and second-line' chemotherapy was given.

RESULTS

Factor associated with Positive SLL

The results of SLL were confirmed by surgical

and pathological examination in all 63 patients studied. 24 (38.0%) patients were found residual tumor deposit, including 15 patients with gross tumor and 9 patients with microscopic tumor. A positive result of SLL was defined as having gross or microscopic residual tumor, and a negative result of SLL as no residual tumor found in intraperitoneal cavity or retroperitoneal space.

All 15 patients with stage I disease were negative SLL. Of 12 patients with stage II, 4 (33.0%) patients were positive SLL, including 2 patients with LNM which was the only residual tumor. Of 35 patients with stage III, 19 (54.0%) patients were positive SLL, including 6 patients with LNM which was the only residual. In one patient with stage IV who previously had tumor cell found in the thorax, both intraperitoneal residual tumor and retroperitoneal LNM were still observed. So comparing the rate (15.0%) of positive SLL in stage I and II patients with that (56.0%) in stage III and IV patients, it was manifest that the positive result was associated with advanced clinical stage ($P < 0.01$).

Of 19 (19/63, 30.0%) patients having LNM, 8 patients had only LNM without intraperitoneal residual tumor. The diameter of each metastatic lymph node was not more than 2 cm. The rate of LNM in stage II patients (2/12, 16.0%) was lower than that in stage III patients (16/35, 45.7%, $P = 0.07$). There was 10 patients with stage III who had both LNM and intraperitoneal residual tumor.

In 31 patients without gross residual tumor after primary cytoreductive surgery, no residual tumor was found during SLL. But of 19 patients with the residual tumor of less than or equal 2 cm diameter, 8 patients (42.0%) were positive SLL. And 85.0% (11 cases) of 13 patients with residual tumor of more than 2 cm diameter were positive SLL. So that the other factor associated with positive result of SLL was the size of residual tumor after primary cytoreductive operation ($P < 0.05$).

However, there was no significant difference ($P > 0.05$) on the positive rate of SLL result between epithelial carcinoma patients (41.0%, 19/46) and noepithelial tumor patients (29.0%, 5/17). In 46 patients with epithelial carcinoma in this study, the positive rates of SLL in the patients with grad 1,2 and 3 patients were 30.0% (3/10), 45.0% (11/24) and 42.0% (5/12), respectively. Obviously, the result of SLL was not related to the grade of tumor differentiation ($P > 0.05$).

SLL Results and Prognosis

The follow-up in all 63 patients were followed-up end until January 1996. The mean time of follow-

up was 56.5 months. Of 39 patients with negative SLL, only 4 patients with stage III relapsed, including recurrence intraperitoneal in 3 patients and metastasis up clavicle in one patient. Of 19 patients who had LNM found, 16 patients died of recurrence, 8 patients with LNM which was the only residual tumor. Of the 8 cases, 5 patients died of relapsed, including metastasis to up clavicle in 2 patients and intraperitoneal recurrence in 3 patients.

Overall survival rates of 63 patients in this study at 2, 3 and 5-year were 84.0%, 75.0% and 68.0% respectively. Of them, there were 39 patients with negative SLL, their 2, 3 and 5-year survival rates were 97.0%, 90.0% and 83.0%. But in the other 24 patients with positive SLL, the survival rates at 2, 3 and 5-year were 54.0%, 33.0% and 21.0%, respectively. By log-rank analysis, the patients with negative SLL had a superior survival than these patients with positive SLL ($P < 0.05$).

Operative Complications

In the 63 patients who underwent systematic lymphadenectomy during SLL, the mean blood loss was 500 ml (range 400-800ml), and the operative mean time was 165 minutes (range 120-210minutes). There was no trauma of vena cava inferior or aorta. Eight (13.0%) of 63 patients were found having pelvic lymphocysts by ultrasound examination postoperatively, whose clinical evidence included a lower abdominal pain, a fever and a pelvic mass. We observed obvious adhesion in pelvic and abdominal cavities of most patients during SLL, because those patients had subjected to multicycles of intraperitoneal and systemic chemotherapy. There were 4 patients appearing serious intestinal obstruction, of which 2 patients need to surgical treatment for obstruction.

DISCUSSION

Generally, a negative second-look laparotomy (SLL) is termed as no evidence founding at the time of second-look surgery and by pathological confirmation, namely complete pathological remission. It is believed that those patients with negative SLL would have a good prognosis. But according to these reports available to date, about 20%-71% patients with negative SLL would relapsed in 2 years after the operation,^[1] and the median survival time of these recurrent patients is only from 11 months to 32 months.

In addition to a recurrence in pelvic and peritoneal cavity, the recurrence in retroperitoneal

lymph nodes is the other important space. A study of Podrtz, et al.^[4] shows that the relapsed rate of lymph nodes in the patients with negative SLL is as much as 27.0%, following that in intraperitoneal cavity. Rubin, et al.^[5] found 9.5% of recurrent patients having metastasis up to clavicle. Gadducci and his colleagues^[1] observed that 48.9% of advanced patients with negative SLL would relapsed 18 months after SLL, including 13.8% recurrence in retroperitoneal lymph nodes. According to describing SLL procedure in those literatures available, the status of retroperitoneal lymph nodes is determined by lymph node sampling and pathological examination. However, we performed systematic lymphadenectomy instead of lymph node sampling during SLL in this study, so only one patient relapsed in the lymph node up to clavicle in our follow-up period.

Additionally, Camino, et al.^[6] studied the significance of pelvic and paraortic lymph node sampling in threatment for ovarian cancer patients. The study showed that the rates of lymph node metastasis in patients with stage I, II, III and IV of disease are 4.2%, 35.7%, 41.3% and 87.5% respectively. And the study confirmed the positive correlation between the metastasis rate and the number of lymph node. So they concluded that lymph node sampling is not creditable way to identify the lymph node status. The report from Gadducci, et al.^[1] also provided information about relationship between a process of second-look surgery and a relapsed rate after negative exploration. Compared with a second-look laparoscopy, a second-laparotomy facilitates more lymph node sampling and adhesion separation so that more harbor residual tumor are found. In the present study, 30.2% of patients had lymph node metastasis found. Specially, there were 8 patients in whom the retroperitoneal lymph node metastasis was only residual tumor. If a lymph node sampling instead of a systematic lymphadenectomy was done during SLL process it will determine the SLL results, and a diagnosis of 'negative SLL' without a systematic lymphadenectomy was not believable.

Only 4 (10.3%) patients with negative SLL in the present study relapsed, but as much as 20%-71% patients with negative SLL reported from the literature would relapsed.^[1] So we suggested that performing systematic lymphadenectomy during SLL can reduced the recurrence after a negative SLL.

Addition to SLL process, the risk factors associated with recurrence after a negative SLL also include the extension of tumor at primary laparotomy (clinical stage), the size of residual tumor after primary cytoreduction, the grade of tumor, and the number and sensitivity of chemotherapy before SLL.

Those risk factors above referred also influence the positive rate of finding residual tumor at SLL.^[7] Walton and his colleague^[8] compared the outcome in 112 patients with stage I and II ovarian cancer who underwent SLL with in 105 patients with same stage disease but did not undergo SLL. The results showed the death rates for recurrence of the two are 13% and 12% respectively. In the present study, all patients with stage I disease were negative SLL and didn't relapse postoperatively. So it indicated the patients with early stage disease who had underwent the laparotomy were not the candidate for SLL. We have only considered the patients with advanced stage disease or residual tumor as the candidates for SLL.

It is difficult that the primary tumor with a lot of metastatic intraperitoneal tumor is removed to the optimal extent during primary cytoreduction for most ovarian cancer patients with advanced stage disease; and if a systematic lymphadenectomy is performed at the same time, it is more difficult. So we believed it was practicable that performing lymphadenectomy during SLL. In our preliminary study of 63 patients who underwent systematic lymphadenectomy during SLL, the complication was receivable.

It is rational that second cytoreductive surgery including lymphadenectomy would be performed during SLL, but whether SLL can improve the survival rate remains disputation. Bolis, et al.^[9] reported the results of survival rate in 140 ovarian cancer patients with stage III and IV disease. Their the all survival rates in patients with negative SLL at 3, 5 and 8-year are 76%, 66% and 51% respectively. They suggested that the 5-year survival rate in the patient whose residual tumor is less than a diameter of 2 cm was superior, and the status of lymph node indicated the prognosis. Though the present study showed the survival rate in patient with negative SLL was better than that with positive SLL, we couldn't conclude that SLL with systematic lymphadenectomy can improve survival from the retrospective analysis.

Clinical significance of SLL in ovarian cancer patients remains a controversy, but we thought it is important in understanding the clinical value of the negative or positive results of SLL. For a patient having a negative finding at SLL, it indicated the ovarian tumor was sensitive to chemotherapy or of relative benignant biologic behaviour; the patient would be an ideal candidate for consolidate treatment selected according to the risk factors of recurrence. For a patient having a positive finding at SLL, a

secondary recytoreductive surgery should performed to the optimal, then second-line chemotherapy such as paclitaxel and topotecan should be chosen. We agree with Podratz's opinion for SLL.^[10] At present, whether continuing to apply SLL or not is not necessary to discuss, and it is important to perform thorough SLL by experience and trained surgeons, and to make each patient undergone SLL benefit from the operation.

REFERENCES

- [1] Gadducci A, Sartori E, Maggino T, et al. Analysis of failures after negative second-look in patients with advanced ovarian cancer: an Italian multicenter study. *Gynecol Oncol* 1998; 68: 150.
- [2] Morrow CP, Curtin JP, Townsend DE. Tumor of the ovary. In: Morrow CP, Curtin JP, eds. *Synopsis of Gynecologic Oncology*. 4th Ed. New York: Churchill Livingstone, 1994; 262-276.
- [3] Wu XH, Zhang ZHY, Tang MQ, et al. A clinical study on the incidence of retroperitoneal lymph node metastasis and its risk factors. *Chin J Obstet Gynecol* 1996; 31:9, 543.
- [4] Podratz KC, Malkasin GD, Wieand HS, et al. Recurrent disease after negative second-look laparotomy in stage III and IV ovarian. *Gynecol Oncol* 1988; 29: 274.
- [5] Rubin SC, Hoskins WJ, Hakes TB, et al. Recurrence after negative second-look laparotomy for ovarian cancer: analysis of risk factors. *Am J Obstet Gynecol* 1988; 159: 1094.
- [6] Camino F, Fuda G, Ciccone G, et al. Significance of lymph node sampling in epithelial carcinoma of the ovary. *Gynecol Oncol* 1997; 65: 467.
- [7] Muder spach L, Maggia FM, Cont PS. Second-look laparotomy for stage III epithelial ovarian cancer: rationale and current issues. *Cancer Treat Rev* 1995; 21: 499.
- [8] Walton L, Elenberg SS, Major Jr F, et al. Result of second-look laparotomy in patients with early-stage ovarian carcinoma. *Obstet Gynecol* 1987; 70:770.
- [9] Bolis G, Villa A, Guarneio P, et al. Survival of woman with advanced ovarian cancer and complete pathologic response at second-look laparotomy. *Cancer* 1996; 77: 128.
- [10] Podratz KC, Cliby WA. Second-look surgery in the management of epithelial ovarian carcinoma. *Gynecol Oncol* 1994; 55: 128.