CLINICAL STUDY

Results of Second-Look Laparotomy in Advanced Stage Epithelial Ovarian Cancer and Factors Influencing the Results

Faruk Mehmet **KÖSE**, Taner **TURAN**, Nurettin **BORAN**, Özlem **KARAÇAY**, Gökhan **TULUNAY**, Sevgi **KOÇ**, Burcu **AYKAN**

Etlik Obstetrics and Gynecology Training and Research Hospital, Oncology Department, Ankara, Turkey

Received 11 February 2006; received in revised form 02 May 2006; accepted 12 May 2006

Abstract

Objective: The aim of the study was to determine the results of second-look laparotomy (SLL) in patients with stage III C and IV epithelial ovarian cancer and factors influencing the results.

Materials and Methods: Medical records of seventy-five patients who underwent SLL between January 1998 and March 2003 were reviewed. The outcome of the SLL procedure and recurrence rates in SLL negative patients were evaluated. The effect of patient age, tumor stage, grade, size, and histological type, presence of ascites, volume of ascites, peritoneal cytology and type of chemotherapy on SLL results were also evaluated.

Results: The mean age of the patients was 52 years and mean duration of follow-up was 39 months. In this study, fifty patients received paclitaxel/platinum (six courses) and twenty-five patients received epirubicin/paclitaxel/platinum (six courses) chemotherapy. Of these 75 patients, 47 (62.7%) were SLL negative, 15 (20%) had microscopic residual disease and 13 (17.3%) had gross macroscopic disease. Recurrence occurred in 20 (42.6%) of 47 SLL negative patients. The mean time to recurrence was 14.5 months. The volume of ascites correlated positively with the probability of finding residual tumor at SLL ($p<0.05$). Patient age, clinical stage, histological type and grade, tumor size, presence of ascites and result of peritoneal cytology were found not to influence the outcome of SLL.

Discussion: It is difficult to determine the factors influencing the outcome of SLL because of the insadequacy of the procedure. It is generally considered that SLL doesn't contribute to survival but only gives information about the state of the disease.

Keywords: ovarian cancer, second-look laparotomy, prognostic factor

Özet

İleri Evre Epitelyal Over Kanserlerinde Second-Look Laparotomi ve Bu Sonuçları Etkileyen Faktörler

Amaç: Evre III C-IV epitelyal over kanseri olan hastalarda "second-look laparotomi" (SLL) sonuçlarının ve bunları etkileyen prognostik faktörlerin belirlenmesi amaçlandı.

Materyal ve Metot: Ocak 1998-Mart 2003 tarihleri arasında SLL yapılmış olan 75 hastaya ait medikal kayıtlar gözden geçirildi. SLL prosedürünün sonuçları ve SLL sonucu negatif olanlarda rekürrens oranları incelendi. Hasta yaşının, klinik evrenin, histolojik grad düzeyinin, tümör boyutunun, histolojik tipin, asit varlığının, asit volümünün, peritoneal sitolojinin ve kemoterapi şeklinin SLL sonucu üzerindeki etkisi değerlendirildi.

Sonuçlar: Hastaların yaş ortalaması 52 yıl ve ortalama takip süresi 39 aydı. Çalışmada 50 hasta paklitaksel/platin (altı kür) ve 25 hasta epirubisin/paklitaksel/platin (altı kür) kemoterapisi aldı. Bu 75 hastanın 47'sinde (%62.7) SLL sonucu negatif, 15'inde (%20) mikroskopik, 13'ünde (%17.3) makroskopik olarak pozitifti. SLL sonucu negatif olan 47 hastanın 20'sinde (%42.6) nüks gelişti. Ortalama nüks zamanı 14.5 aydı. Asit volümüyle SLL'de rezidüel tümör saptanma olasılığı arasında pozitif ilişki saptandı ($p<0.05$). Klinik evrenin, histolojik tip ve grad düzeyinin, yaşın, tümör boyutunun, asit varlığının, sitoloji sonucunun SLL sonucu üzerine etkisi olmadığı belirlendi.

Tartışma: SLL sonuçlarını etkileyen faktörleri tanımlayabilmek, SLL prosedürü yetersizliğinden dolayı zordur. SLL'nin genelde sağkalım oranlarını iyileştirmediği kabul edilmektedir. Sadece hastalığın o anki durumu hakkında fikir vermektedir.

Anahtar sözcükler: over kanseri, second-look laparotomi, prognostik faktör

Corresponding Author: Dr. Taner Turan
Ankara Etlik Doğumevi ve Kadın Hastalıkları
Eğitim ve Araştırma Hastanesi, Jinekolojik Onkoloji Bölümü
Etlik Cad. Keçiören, 06010 Ankara, Türkiye
Phone : +90 312 322 01 80
GSM : +90 532 793 33 57
E-mail : turantaner@yahoo.com

Introduction

Second-look laparotomy (SLL) was first introduced by Wangensteen in 1940's to determine the state of intraabdominal malignancy in patients with colorectal cancer (1). Later, this procedure was included in the management of other abdominal malignancies and ovarian cancer.

SLL in ovarian cancer is defined as a systematic surgical re-exploration procedure in patients with complete remission who have no evidence of tumor clinically and by biochemical (CA-125≤35 IU/ml) and imaging techniques following initial cytoreductive surgery and adjuvant chemotherapy (2).

SLL detects tumor in approximately 50% of patients with complete remission, this rate varies depending on stage (3). Today's available non-invasive methods are not capable of diagnosing these tumors. Furthermore the disease recurs in 50% of SLL-negative patients (4,5). Recent studies show that SLL doesn't improve survival rates (6,7).

Today most authors suggest that SLL be used in clinical studies to evaluate the effectiveness of treatment protocols because it is thought only to give information about the disease in patients with complete remission (3,8).

The objective of this study is to evaluate the outcome of SLL in advanced state epithelial ovarian cancer and factors influencing the outcome.

Materials and Methods

The study was carried out in Ankara Etlik Maternity and Women's Health Training and Research Hospital Gynecologic Oncology Department. The medical reports of patients between January 1998 and March 2003 were reviewed.

Eighty-nine patients who were considered in complete remission following 6 courses of adjuvant chemotherapy as evidenced clinically and by biochemical (CA-125≤35 IU/ml) and imaging methods and underwent SLL were evaluated. Among these patients, 14 were excluded from the study because five had undergone suboptimal cytoreductive surgery, five patients were operated in another clinic, two patients had undergone second-look laparoscopy and two patients had received different chemotherapy protocols. So only a total of 75 patients fulfilling the criteria were included.

Operative procedure: Patients were placed in a supine position and a midline incision of sufficient length to allow access to the upper abdomen was performed. Upon entering the abdomen, ascites fluid or peritoneal washings were sampled for cytological examination. Adhesions were removed by dissection and sampled. All peritoneal surfaces were inspected carefully and multiple biopsies were taken from these sites and serosal surfaces. Biopsies from suspicious areas were evaluated for pathological changes on frozen sections. In the absence of a suspicious area in the retroperitoneal space, random tissue samples were collected. In our study, the mean number of samples collected was 30. In cases where a gross tumor was detected, secondary cytoreductive surgery was performed in the same session.

The outcome of the SLL procedure and recurrence rates in SLL negative patients was evaluated. Prognostic factors such as patient age, tumor stage, grade, size, histological type, presence of ascites, volume of ascites, peritoneal cytology and type of chemotherapy were also evaluated.

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) 12.0 version. Anova Table Test was used for mean values and Chi-Square test was used for categorical comparisons of nominal values. P value <0.05 was considered as statistically significant.

Results

The mean age of the patients was 52 years (range 20-71). Ascites was detected in 63 patients (88.7%) at initial operation and the mean ascites volume was 1526 cc (range 0-14 000 cc). The mean tumor size (largest dimension) was 114.7 mm with a range of 40-350 mm. The mean duration of follow-up was 39 months.

Fifty patients received 6 courses of paclitaxel/platinum (PC). Among these patients, 28 received paclitaxel/carboplatin and 22 received paclitaxel/cisplatin. Twenty-five patients received epirubicin/paclitaxel/carboplatin (EPC). In the PC protocol, the treatment started with paclitaxel 175 mg/m^2, continued by a dose of carboplatin calculated by AUC=6 formulation or cisplatin 75 mg/m^2. In EPC protocol, epirubicin 60 mg/m^2 was given initially, followed by paclitaxel (175 mg/m^2) and carboplatin (AUC=6) respectively. Characteristic features were presented in Table 1.

Forty-seven (62.7%) of patients had no evidence of cytopathology (i.e, had negative final pathology), 15 (20%) had microscopic residual disease and 13 (17.3%) had gross macroscopic disease. Gross disease was located in upper abdomen in 6 patients and in pelvis and upper abdomen in 7 patients.

There was not a statistically significant association between results of SLL and other parameters except the volume of ascites (Table 2). However, SLL was positive in 17.3% of patients with negative cytology in initial operation while SLL was positive in 40% of positive cytology (p=0.056). Besides, adding epirubicin to platin plus paclitaxel chemotherapy reduced SLL positivity from 44% to 24% (p=0.091).

Twenty (42.6%) of 47 SLL negative patients developed recurrence during follow-up. The mean time to recurrence was 14.5 months (range 4-35). Four of these 20 patients were lost to follow-up, 8 patients died of disease and 8 patients are still alive.

Discussion

Second-look laparotomy detects tumor in 0-30% of stage I cases who are considered in complete remission as eviden-

Table 1. Tumor characteristics

	n	%
Stage		
III C	71	94.7
IV	4	5.3
Grade		
1	7	9.3
2	41	54.7
3	27	36
Histopathology		
Serous	60	80
Endometrioid	5	6.7
Mucinous	2	2.7
Mixed	3	4
Unidentified	5	6.7
Ascites[1]		
Absent	13	17.3
Present	62	88.7
Ascites Cytology[1]		
Negative	17	22.7
Positive	58	77.3
Chemotherapy[2]		
Paclitaxel/Cisplatin	22	29.3
Paclitaxel/Carboplatin	28	37.4
Epirubicin/Paclitaxel/Carboplatin	25	33.3

[1]before cytoreductive surgery; [2]first-line chemotherapy

ced clinically, biochemically and by imaging techniques (4,9,13). This rate is 30-40% (14,15) in stage II and 50-80% (8,15) in stage III and IV tumors. Most recurrences are overlooked during use of non-invasive methods. Today flourine-18 fluorodeoxyglucose positron emission tomography (FDG PET) is the most important technique which is thought to replace the SLL procedure. In spite of the fact that it hasn't entered routine clinical use, encouraging reports have been published. Kim et al. showed that FDG PET can be used as an alternative to SLL (16).

Besides being an invasive procedure, another disadvantage about SLL is that it doesn't have clearly established surgical steps. It is not clear from where and how many biopsies should be made. Furthermore, there may be microscopic residual or *de novo* tumor in inaccessible sites or in places where it is not possible to take biopsies. These are the question marks about the capability of SLL to determine residual tumor. Besides, the contribution of salvage chemotherapy and secondary cytoreduction to survival in SLL positive patients is not clear.

Recent studies have shown that SLL doesn't improve survival rates (6,7). Recurrence develops in 50% of SLL negative patients with advanced stage epithelial ovarian cancer (4,5). Friedman reported a recurrence rate of 27.9% (8). Podalek detected 46.1% recurrence rate in SLL negative patients during five years of follow-up (17). In our study, recurrence was detected in 42.6% of SLL negative patients during 39 months follow-up.

Table 2. Covariates affecting the outcome of SLL

Covariates	SLL negative n (%)	SLL positive n (%)	Significance
Age			
≤50	20 (66.7)	12 (33.3)	*p*=0.979
>50	27 (62.8)	16 (37.2)	
Stage			
IIIC	45 (63.4)	26 (36.6)	*p*=0.590
IV	2 (50)	2 (50)	
Grade			
1	4 (57.1)	3 (42.9)	*p*=0.950
2	26 (63.4)	15 (36.6)	
3	17 (63)	10 (37)	
Histopathology			
Serous	37 (61.7)	23 (38.3)	*p*=0.720
All others	10 (66.7)	5 (33.3)	
Chemotherapy[1]			
PC	28 (56)	22 (44)	*p*=0.091
EPC	19 (76)	6 (24)	
Ascites[2]			
Absent	10 (76.9)	3 (23.1)	*p*=0.242
Present	37 (59.7)	25 (40.3)	
Volume of Ascites[2]			
≤1000 cc	37 (69.8)	16 (30.2)	*p*=0.047
>1000 cc	10 (45.5)	12 (54.5)	
Ascites Cytology[2]			
Negative	14 (82.4)	3 (17.3)	*p*=0.056
Positive	33 (56.9)	25 (43.1)	
Largest Tumor Size[2]			
≤100 mm	27 (60)	18 (40)	*p*=0.559
>100 mm	20 (66.7)	10 (33.3)	

[1]first-line chemotherapy; [2]before cytoreductive surgery

Factors which are thought to influence the results of SLL are actually the prognostic factors of ovarian cancer. Histological grade is as well an important factor as the stage of the tumor. However there are studies, including the present study, concluding that grade is not a determining factor (4,8,9,18,19). On the other hand, Potter detected a statistically significant association between histological grade and results of SLL (6).

It is known that another important prognostic factor is optimal surgery. Residual tumor size after surgery determines the possibility of detecting macroscopic or microscopic tumor at SLL (4,6,18-20).

Many studies, including our study, have shown that the type of chemotherapy and the number of chemotherapeutic agents do not have prognostic value for SLL positivity (6,8,9).

Smirz has reported that histological type affects SLL results (20), but in most series and in our study a statistically significant association was not found (4,8,9,19).

In this study, SLL positivity was 30.2% when the volume of ascites was ≤1000 cc at initial operation, while it was 54.5% if the

volume of ascites was >1000 cc (p=0.047). Friedman reported similar results (8). In his study, the SLL positivity was 33.3% when volume of ascites was ≤1000 cc and 57.8% if the volume of ascites was >1000 cc. However this difference was not found to be statistically significant (p=0.058).

In conclusion, determining the factors influencing the results of SLL procedure is difficult because of the insufficiency of the procedure itself. In epithelial ovarian cancer, SLL doesn't contribute to survival but only gives information about the state of disease. There is not a clinically effective, standard non-invasive technique to replace SLL. Today, the use of SLL is limited to studies assessing the efficiency of protocols used in clinical trials.

References

1. Wangensteen OH, Lewis FJ, Tongen LA. The "second-look" in cancer surgery: a patient with colic cancer and involved lymph nodes negative on the "sixth-look". Lancet 1951;71:303-7.
2. Rubin SC, Lewis JJ. Second-look surgery in ovarian carcinoma. Crit Rev Oncol Hematol 1988;8:75-91.
3. Chu CS, Rubin SC. Second-look laparotomy for epithelial ovarian cancer: a reappraisal. Curr Oncol Rep 2001;3(1):11-8.
4. Podratz KC, Malkasian GD Jr, Hilton JF, Harris EA, Gaffey TA. Second-look laparotomy in ovarian cancer: evaluation of pathologic variables. Am J Obstet Gynecol 1985;152(2):230-8.
5. Rubin SC, Hoskins WJ, Hakes TB, Markman M, Cain JM, Lewis JL Jr. Recurrence after negative second-look laparotomy for ovarian cancer: analysis of risk factors. Am J Obstet Gynecol 1988;159(5):1094-8.
6. Potter ME, Hatch KD, Soong SJ, Partridge EE, Austin JM Jr, Shingleton HM. Second-look laparotomy and salvage therapy: a research modality only? Gynecol Oncol 1992;4(1):3-9.
7. Luesley D, Lawton F, Blackledge G, Hilton C, Kelly K, Rollason T et al. Failure of second-look laparotomy to influence survival in epithelial ovarian cancer. Lancet 1988;2(8611):599-603.
8. Friedman RL, Eisenkop SM, Wang HJ. Second-look laparotomy for ovarian cancer provides reliable prognostic information and improves survival. Gynecol Oncol 1997;67(1):88-94.
9. Rubin SC, Jones WB, Curtin JP, Barakat RR, Hakes TB. Second-look laparotomy in stage I ovarian cancer following comprehensive surgical staging. Obstet Gynecol 1993;82(1):139-42.
10. Schwartz PE, Smith JP. Second-look operation in ovarian cancer. Am J Obstet Gynecol 1980;138:1124-30.
11. Webb MJ, Snyder JJ, Williams TJ, Decker DG. Second-look operation in ovarian cancer. Gynecol Oncol 1982;14:285-93.
12. Chambers SK, Chambers JT, Kohorn EI, Lawrence R, Schwartz PE. Evaluation of the role of second-look surgery in ovarian cancer. Obstet Gynecol 1988;72:404-8.
13. Gallup DG, Talledo OE, Dudzinski MR, Brown KW. Another look at the second-assessment procedure for ovarian epithelial carcinoma. Am J Obstet Gynecol 1987;157:590-6.
14. Zhang ZY, Zang RY, Tang MQ, Chen J. Significance of systematic retroperitoneal lymphadenectomy at second-look laparotomy for ovarian cancer (article in Chinese). Zhonghua Fu Chan Ke Za Zhi 2003;38(2):69-71 (abstract) (PMID: 12783690, PubMed-indexed for MEDLINE).
15. Barter JF, Barnes WA. Second-look laparotomy. In: Rubin SC, Sutton GP (eds). Ovarian Cancer. New York: McGraw-Hill, 1993:269-300.
16. Kim S, Chung JK, Kang SB et al. [18F] FDG PET as a substitute for second-look laparotomy in patients with advanced ovarian carcinoma. Eur J Nucl Med Mol Imaging 2004;31(2):196-201.
17. Pudelek J, Kojs Z, Urbanski K et al. Patients with advanced ovarian cancer after negative second-look laparoscopy follow-up study (article in Polish). Ginekol Pol 2004;75(2):85-90 (abstract) (PMID: 15108578, PubMed-indexed for MEDLINE).
18. Wu X, Zhang Z, Tang M. Therapeutic results of second-look laporatomy with extensive dissection of retroperitoneal lymph nodes in ovarian cancer patients (article in Chinese). Zhonghua Zhong Liu Za Zhi 1999;21(4):300-2 (abstract) (PMID: 11776822, PubMed-indexed for MEDLINE).
19. Cain JM, Saigo PE, Pierce VK et al. A review of second look laparotomy for ovarian cancer. Gynecol Oncol 1986;23(1):14-25.
20. Smirz LR, Stehman FB, Ulbright TM, Sutton GP, Ehrlich CE. Second-look laparotomy after chemotherapy in the management of ovarian malignancy. Am J Obstet Gynecol 1985;152(6 Pt 1):661-8.