Safety and efficacy of a splenectomy during debulking surgery for Müllerian carcinoma

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Summary

Purpose: This study was designed to assess the safety and efficacy of a splenectomy and to analyze the prognostic factors of Müllerian carcinoma with spleen metastasis. *Methods:* We reviewed the medical records of 11 patients with Müllerian carcinoma who underwent a splenectomy between 1997 and 2007. The treatment outcome of these patients was examined and the possible prognostic factors were investigated by univariate analysis. *Results:* Four and seven patients underwent a splenectomy for primary and recurrent disease, respectively. A complete resection was achieved in eight patients. A blood transfusion was not required and only two mild postoperative complications were observed. The median and five-year survivals of all patients following treatment were 39 months and 39%, respectively. Older patients (≥ 60 years old) and patients with a poor performance status (PS2) had a poorer prognosis by univariate analysis. *Conclusions:* A splenectomy can be performed safely and effectively during debulking surgery for appropriately selected patients with primary or recurrent Müllerian carcinoma.

Key words: Debulking surgery; Müllerian carcinoma; Prognosis; Spleen metastasis; Splenectomy.

Introduction

More than two-thirds of ovarian cancers are diagnosed in the advanced stages of disease. Even if patients successfully achieve a complete remission, cancer will recur in more than a half of these patients. The prognostic importance of residual disease following primary debulking surgery (PDS) for primary disease is now widely accepted since multiple studies show an inverse correlation between the size of the residual tumor mass and the patient outcome [1]. A similar correlation in the results of secondary debulking surgery (SDS) for recurrent disease has been shown in a smaller number of studies conducted with highly selected patients [2]. The spleen is often involved in either primary or recurrent ovarian cancer. In both PDS and SDS, a splenectomy can be performed safely with an acceptable morbidity [3-10]. We have also performed a splenectomy as a part of debulking surgery for selected patients with primary or recurrent Müllerian carcinomas. This study assessed the safety and the efficacy of a splenectomy and analyzed the factors which influence survival after treatment which includes a splenectomy.

Patients and Methods

Patients

We performed retrospective reviews of the surgical records and pathological reports of patients with Müllerian carcinomas including ovarian, tubal, and peritoneal carcinomas at the National Cancer Center Hospital between January 1997 and December 2007. We found 11 patients with advanced or recurrent Müllerian carcinomas who had undergone a splenectomy for the purpose of debulking during the study period. The detailed medical records of these patients were obtained and the patients were selected for this study. According to the Japanese ethical guidelines for an epidemiologic study, this study was approved by the Institutional Review Board of the National Cancer Center.

In our institution, patients with advanced Müllerian carcinomas generally undergo combined surgery and chemotherapy as the primary treatment. The standard surgical procedures include a total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentectomy (OM) and maximal tumor debulking. A pelvic lymph node biopsy (PLB) and/or paraaortic lymph node biopsy (PALB) are performed if swollen nodes are present. A systematic pelvic lymphadenectomy (PLA) and a paraaortic lymphadenectomy (PALA) are performed when intraperitoneal optimal debulking surgery (maximum residual tumors less than 1cm in diameter) is done and biopsy proven lymph node metastases are present. For patients with spleen metastasis detected by either preoperative or intraoperative findings, a splenectomy is performed when the procedure is expected to effectively reduce the residual tumor mass.

Chemotherapy is usually administered following surgery. For the patients with apparently unresectable tumors or for patients with poor performance status (PS) because of advanced disease or other factors, chemotherapy may precede the debulking surgery. If chemotherapy precedes debulking surgery, then the surgery is performed during the chemotherapy as interval debulking surgery or following the completion of chemotherapy. The timing of surgical debulking depends on the patient's response to chemotherapy and the improvement of PS. Until 1997, the CAP (cyclophosphamide, doxorubicin and cisplatin) was the standard chemotherapeutic regimen for Müllerian carcinoma in our institution. Paclitaxel and docetaxel were introduced into use for ovarian cancer in Japan in 1997 and 2000, respectively. Combination chemotherapy using taxane (paclitaxel or docetaxel) and platinum (cisplatin or carboplatin) have been used as the standard chemotherapy regimen at our institution since the taxane agents were introduced.

Surgery is the treatment of choice for recurrent Müllerian car-

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Table 1. — *The characteristics of patients who underwent a splenectomy due to metastatic Müllerian cancer.*

No.	Age	PS	Primary site	FIGO stage	Timing of SPL	Chemotherapy (preop-postop)	Additional procedures	Parenchymal involvement	Residual tumor	Postop-morbidity	Operative time	Blood loss	Hospital stay	Outcome[b]
1	60	2	Ovary	IIIc	Recurrence	None/None	None	Yes	< 1 cm	Fever	90 min	280 ml	18 days	9M DOD
2	57	2	Ovary	IIIc	Primary	Yes/None	TAH+BSO+OM	No	None	No	197 min	192 ml	20 days	38M DOD
3	57	2	Ovary	IIIc	Recurrence	None/Yes	Pancreas tail and Ing Tumor Res	Yes	5 mm	SBO	113 min	85 ml	13 days	39M DOD
4	47	1	Ovary	Ib	Recurrence	Yes/None	Ing Tumor Res	Yes	None	No	156 min	142 ml	13 days	83M AWD
5	47	1	Tube	IV	Primary	Yes/Yes	TAH+BSO+OM+ pHPT+PLB	Yes	None	No	270 min	342 ml	13 days	81M NED
6	63	1	Peritoneum	IV	Recurrence	None/Yes	None	No	None	No	153 min	224 ml	14 days	29M DOD
7	48	1	Ovary	IIIc	Recurrence	None/Yes	None	No	None	No	85 min	130 ml	14 days	31M NED
8	27	1	Ovary	IIIa	Recurrence	None/Yes	OM+Peritoneal Tumor Res	Yes	5 mm	No	275 min	322 ml	13 days	31M AWD
9	52	1	Peritoneum	IIIc	Primary	Yes/Yes	LSO+OM	No	None	No	255 min	132 ml	14 days	26M AWD
10	61	0	Ovary	IV	Primary	Yes/Yes	TAH+BSO+OM+ PALB	No	None	No	430 min	703 ml	15 days	17M NED
11	73	0	Ovary	IV	Recurrence	None/None	None	No	None	No	109 min	107 ml	7 days	13M NED

PS: performance status, Preop: preoperative, Postop: postoperative, min: minutes, TAH: total abdominal hysterectomy, BSO: bilateral salpingo-oophorectomy, OM: omentectomy, Res: resection, Ing: inguinal, pHPT: partial hepatectomy, PLB: pelvic lymph node biopsy, LSO: left salpingo-oophorectomy, PALB: paraaortic lymph node biopsy, SBO: small bowel obstruction, DOD: died of disease, AWD: alive with disease, NED: no evidence of disease, M: months.

cinoma only when the disease is not persistent and when the recurrent tumors seem resectable based on preoperative evaluations by CT scan and/or MRI plus physical examination. Chemotherapy is usually provided following surgery irrespective of the presence or the absence of residual tumors. Although there is no standard chemotherapy regimen, platinum- and taxane-based regimens are commonly used postoperatively.

We obtained informed consent of the patients for each treatment.

Statistical methods

Survival was measured from the first day of treatment for primary disease and for recurrent disease. The survival curves were determined by the Kaplan-Meier product limit method. Factors influencing survival were analyzed using the log-rank test (univariate analysis); $p < 0.05$ was considered to indicate statistical significance. All analyses were performed using the JMP software program (SAS Institute Inc., USA).

Results

Patients characteristics

The relevant characteristics of the 11 patients who underwent a splenectomy are shown in Table 1. Eight patients had ovarian cancer, one patient had tubal cancer and two patients had peritoneal cancer. Histologic types of all 11 patients were serous adenocarcinoma. Five patients had a parenchymal metastasis and six patients had only capsular involvement of the spleen. The performance status at diagnosis of primary or recurrent disease was PS 0 in two patients, PS 1 in six patients and PS 2 in three patients. The median age of the patients was 52 years (range, 27 to 73 years). The median follow-up duration after treatment, including a splenectomy, was 31 months (range, 13 to 83 months), excluding the patients who died.

Four patients underwent a splenectomy during primary treatment. Three patients underwent a splenectomy as interval debulking surgery after three to four cycles of neoadjuvant chemotherapy and one patient underwent debulking surgery after completion of six cycles of primary chemotherapy. The debulking procedure was the first debulking intent surgery for all four patients. Two patients were FIGO Stage IIIc and two patients were FIGO Stage IV.

Table 2. — . *Univariate analysis for possible prognostic factors after splenectomy.*

Possible prognostic factors		Number of patients	Median survival	Five-year survival	*p* velue (Log-rank)
Age at surgery	< 60	7	39M	50%	
	≥ 60	4	29M	0%	0.012
PS (0, 1 vs 2)	0, 1	8	NR	80%	
	2	3	38M	0%	0.086
Disease origin	ovary/tube	9	39M	44%	
	peritoneum	2	29M	0%	0.195
History of distant metastasis	absent	7	39M	29%	
	present	4	29M	50%	0.800
Disease status	primary	4	38M	50%	
	recurrent	7	39M	34%	0.612
Preoperative chemotherapy	none	6	39M	0%	
	any	5	NR	67%	0.171
Postoperative chemotherapy	none	4	38M	38%	
	any	7	39M	40%	0.587
Residual disease	absent	8	NR	53%	
	present	3	39M	0%	0.341
Metastatic status of spleen	capsular	6	38M	0%	
	parenchymal	5	NR	53%	0.347

PS: performance status, NR: not reached.

Seven patients underwent a splenectomy for recurrent disease, six patients for first recurrence and one patient for a second recurrence. The surgery, including a splenectomy, was a second debulking surgery for five patients and a third debulking surgery in two patients. The median interval from initial treatment to recurrence was 33 months (range, 23 to 174 months). The median treatment-

Table 3. — *Review of the literature regarding prognosis and complications of splenectomy in the treatment of ovarian and Müllerian cancer.*

Authors	Number of patients Total (Pri/Rec)	Survival		Surgery					
		Median Total (Pri/Rec)	Rate Total (Pri/Rec)	Completeness NoRT	Completeness RT < 1 cm	Transfusion	Operative Time	Complications (Events/Patients)	Postoperative Mortality
Uehara *et al*.	11 [4/7]	39M [38M/39M]	39% [50%/34%] (5Y)	73% (8/11)	100% (11/11)	0%	156 min *	18% (2/11)	0%
Magtibay *et al*. [9]	112 [66/46]	NA [22M/20M]	NA [46%/42%] (2Y)	22% (12/55) b	76% (42/55) b	4 units *	NA	23% (26/112)	5% (6/112)
Eisenkop *et al*. [8]	49 [49/0]	56M [56M/NA]	48% [48%/NA] (5Y)	100% (49/49)	100% (49/49)	5 units *	245 min *	41% (20/49)	2% (1/49)
Manci et al. [10]	24 [0/24]	56M [NA/56M]	91% [NA/91%] (3Y) a	67% (16/24)	100% (24/24)	21% (5/24)	155 min *	13% (3/24)	NA
Bilgin *et al*. [7]	13 [7/6]	18M [NA/NA]	NA [NA/NA]	NA	77% (10/13)	NA	NA	0% (0/13)	8% (1/13)
Ayhan *et al*. [6]	34 [34/0]	37M [37M/NA]**	37% [37%/NA] (5Y)	NA	100% (34/34)	NA	NA	44% (15/34)	9% (3/34)
Chen *et al*. [5]	35 [13/22]	NA [NR/41M]	NA [NA/NA]	54% (19/35)	91% (32/35)	3 units **	227 min **	165% (56/34) c	3% (1/35)
Scarabelli *et al*. [4]	34 [12/22]	NA [37M/27M] a	NA [83%/78%] (2Y) a	44% (15/34)	NA	3 units *	330 min *	45% (18/40) d	NA
Nicklin *et al*. [3]	18 [11/7]	NA [NA/NA]	NA [NA/NA]	17% (3/18)	89% (16/18)	NA	368 min **	100% (18/18)	NA

Pri: primary disease, Rec: recurrent disease, M: months, Y: year, NA: not available, NR: not reached, RT: residual tumor, min: minutes.
*: median, **: mean, a: survival for the patients who underwent complete resection, b: excluding patients whose residual tumor size were unknown.
c: excluding a patient who died postoperatively, d: including patients who had splenectomy for iatrogenic injury

free interval from any previous treatment was 21 months (range, 11 to 135 months). At primary treatment, one patient was FIGO Stage Ib, one patient was FIGO Stage IIIa, three patients were FIGO Stage IIIc and two patients were FIGO Stage IV.

Safety of the splenectomy

For patients with primary disease, a splenectomy was performed following standard procedures such as TAH, BSO and OM. One patient had already undergone TAH during treatment for myoma earlier. One patient underwent PALB, and one patient underwent a partial hepatectomy and PLB. The median operative time was 263 minutes (range, 197 to 430 minutes) and median blood loss was 267 ml (range, 132 to 703 ml). A blood transfusion was not required for these four patients. There were no postoperative complications reported in any of the patients with primary disease. The median postoperative hospital stay was 15 days (range, 13 to 20 days).

Among the patients with recurrent disease, four patients had only inspection of the peritoneal cavity plus splenectomy. One patient had a pancreas tail and inguinal tumor resection, one patient had a peritoneal tumor resection and one patient had a superficial inguinal tumor resection. The median operative time for patients with recurrent disease was 113 minutes (range, 85 to 275 minutes) and the median blood loss was 142 ml (range, 85 to 322 ml). There were no blood transfusions needed for these seven patients. Two patients exhibited mild postoperative morbidity, one had a fever and one had bowel obstruction. The median postoperative hospital stay was 13 days (range, 7 to 18 days). Although postoperative complications were observed in patients who underwent a third debulking surgery, there were no correlations between the number of debulking surgeries and the operative time, blood loss or postoperative hospital stay.

Outcome of the treatment including splenectomy

A complete resection of all visible tumors was accomplished in all four patients with primary disease. One patient died 38 months after initial treatment, one patient remained alive with disease at 26 months, and two patients remained alive with no evidence of disease at 17 months and 81 months. The median survival of patients with primary disease was 38 months and five-year survival rate was 50%.

Among the patients with recurrent disease, three patients had residual tumor less than 1 cm in diameter and four patients had complete resection of all visible tumors. Among the four patients without residual disease after a splenectomy, one patient died 29 months after treatment of recurrent disease, one patient remained alive with disease at 83 months and two patients remained alive with no evidence of disease at 13 months and 31 months. Among the three patients with residual tumor after a splenectomy, two patients died at nine months and 39 months and one patient remained alive with disease at 31 months. While there were no five-year survivors among this group of patients, the median survivals of the patients without residual tumor and with minimal residual tumor were not reached and 39 months, respectively. The median survival of all patients with recurrent Müllerian cancer was 39 months.

The median survival for all patients was 39 months and the five-year survival rate was 39% (Figure 1).

Factors influencing survival

Possible prognostic factors after splenectomy were analyzed by univariate analysis. Table 2 shows the results of the analyses. Age (< 60 or ≥ 60), PS (0-1 or 2), disease origin (ovary/tube or peritoneum), history of distant metastasis (absent or present), disease status (primary or recurrent), preoperative chemotherapy (none or any), postoperative chemotherapy (none or any), residual dis-

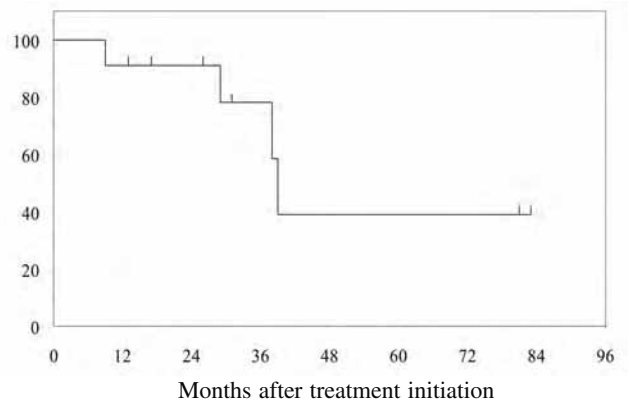

Figure 1. — Survival curves of all 11 patients who underwent splenectomy. The median survival for all patients was 39 months and the five-year survival rate was 39%.

ease (absent or present) and metastatic status of spleen (parenchymal or capsular) were all assessed. Age ≥ 60 years old emerged as a significantly poor prognostic factor ($p = 0.012$) and PS 2 was revealed to be marginally significant ($p = 0.086$).

Discussion

In the present study, we evaluated the safety and efficacy of splenectomy in a group of selected patients with Müllerian cancer and evaluated the prognostic factors influencing survival after treatment.

Several studies have reported the safety of splenectomy in the treatment of ovarian cancer. We reviewed previous studies of splenectomy for patients with ovarian cancer which included more than ten patients (Table 3) [3-10]. Magtibay *et al*. reported the largest study of patients with ovarian cancer who underwent a splenectomy [9]. Of 112 patients included in their study, 66 patients had primary disease and 46 patients had recurrent disease. The authors reported a total of 26 complications (23%), an overall perioperative mortality rate of 5% and a median of four units of transfused packed red blood cells (PRBCs). The next largest study, by Eisenkop *et al*., reported the results of treatment for 49 patients with primary ovarian cancer requiring a splenectomy [8]. They reported a total of 20 complications (41%), a median total blood loss of 1500 ml and a median five units of transfused PRBCs. The studies with smaller numbers of patients reported a higher incidence of complications (44%-165%) [3-6] and postoperative mortality rates (8%-9%) [6, 7]. From the results of these studies, it may be concluded that splenectomy is an invasive procedure which frequently requires a blood transfusion. Magtibay *et al*. stated that splenectomy as part of debulking surgery is associated with modest morbidity and mortality [9]. Complications reported to be associated with splenectomy are injury of the pancreas tail or stomach, infection, thrombocytosis, thromboembolism, atelectasis, pneumonia and so on [6, 9, 11]. However, the parameters of surgical invasiveness depend on the extent of disease and the procedures performed in addition to a splenectomy. Many authors [3, 4, 7, 8, 10] concluded that a splenectomy could be performed safely during debulking surgery for either primary or recurrent ovarian cancer. Although the number of patients is small and the patients were only selected patients, our experience with 11 splenectomies showed this procedure to be associated with a low incidence of morbidity and blood transfusion. Our data suggest that splenectomy as part of the debulking procedure for primary or recurrent Müllerian cancer can be performed safely.

The median survivals of the patients with primary or recurrent disease in our study were 38 months and 39 months, respectively. Magtibay *et al*. reported a median survival in patients with primary disease of 22 months and a two-year survival of 46%. Patients with recurrent disease had a median survival of 20 months and a two-year survival of 42% [9]. Our results may therefore be better. For patients with primary Stage IIIc ovarian cancer, Eisenkop *et al*. [8] reported a median survival of 56 months and a five-year survival of 48%. For surgical patients with recurrent disease, Manci *et al*. reported a median survival of 56 months [10]. One of the reasons these results vary so widely may be differences in patient selection. Eisenkop *et al*. included only patients who underwent complete resection of all visible tumors [8] while Magtibay *et al*. included more than 50% of patients who had gross residual disease (residual tumor larger than 1 cm in diameter) or unknown residual tumor size at the time of debulking surgery [9]. In addition, the studies by Magtibay *et al*., Manci *et al*. and our group included patients with primarily Stage IV disease [9, 10], while the study by Eisenkop *et al*. was limited to patients with Stage IIIc disease [8]. Although the patient selection criteria were not the same, the results of Eisenkop *et al*. and Manci *et al*. [8, 10] are comparable with the results of the Gynecologic Oncology Group (GOG) study for optimally debulked Stage III ovarian cancer, including patients without spleen metastasis [12], and the results of several studies of SDS including patients without spleen metastasis [13, 14]. These favorable results are not consistent with poor outcome of patients with liver metastases. The reasons for the difference is not obvious, the differences of both vital importance and possibility of total organ resection between liver and spleen may be related. Nonetheless, we conclude that patients with spleen metastasis from either primary disease or recurrent disease may show an improved outcome following adequate debulking surgery that includes splenectomy, based on the results of these studies and our research. We also conclude that the improved outcome is comparable to outcomes in patients without spleen metastasis.

In the previous studies, some factors, such as splenic parenchymal involvement [3], residual tumor [10], histologic type of tumor [6] and PS [6], have been reported to correlate with patient prognosis. We also investigated the prognostic factors that influence survival by a univariate analysis. Histologic type was not included in the analysis

because all 11 patients in our study had serous adenocarcinoma. We did not detect any prognostic impact of disease status ($p = 0.612$), residual disease ($p = 0.341$) or metastatic status of spleen ($p = 0.347$), possibly due to the small sample size in this study. However, we determined that an age ≥ 60 years old was a significantly poor prognostic factor ($p = 0.012$) and PS 2 was a poor prognostic factor with marginal significance ($p = 0.086$). These two factors are both common prognostic factors of ovarian cancer. Thus, poor prognosis of older patients or patients with poor PS may not be specific to the procedure of splenectomy. Possibly, these factors affect survival through affecting surgical completeness, time to initiation of postoperative chemotherapy, interval of chemotherapy, dose of chemotherapy and so on. We can suggest that for older patients or patients with poor PS, the risks and benefits of surgery should be taken into consideration before performing a splenectomy.

Our study has several important limitations, such as small number of patients, data from a single institution, retrospective nature of the study, long study period allowing change of chemotherapeutic regimen, diverse disease origin or disease status and so on. However, we can say that splenectomy can be performed safely during debulking surgery for primary or recurrent Müllerian cancer and that the prognosis of patients with spleen metastasis can be improved when debulking surgery, that includes splenectomy, is performed on appropriately selected patients. Age and PS of the patients should be one of the important factors in the selection of patients.

Conclusion

A splenectomy can be performed safely during debulking surgery for primary or recurrent Müllerian cancer, and the prognosis of patients with spleen metastasis can be improved when debulking surgery including a splenectomy, is performed on appropriately selected patients. Age and PS of the patients should be one of the important factors in the selection of patients.

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