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Stage IVB endometrial cancer confined to the abdomen: is chemotherapy superior to radiotherapy?

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Summary

Purpose: To determine the impact of clinical variables and adjuvant therapy on survival in patients with Stage IVB endometrial cancer (EC) confined to abdomen. *Methods and Methods:* A total of 65 patients were included. Curative chemotherapy was defined as using only chemotherapy (platin based) or sandwich therapy. Patients receiving only radiotherapy had standard pelvic radiotherapy and extended-field radiotherapy when necessary. *Results:* The optimal cytoreduction was achieved in 89.3% of patients. With a median follow-up of 18 months, two-year progression free survival (PFS) and overall survival (OS) were calculated as 33.4% and 42.2%, respectively. Optimal cytoreduction provided more longer PFS and OS compared to suboptimal cytoreduction. In univariate analysis, curative chemotherapy instead of radiotherapy improved the two-year PFS and two-year OS. Type of adjuvant therapy, tumor grade, and peritoneal cytology were found as the independent prognostic factors for PFS. Peritoneal cytology, adnexal involvement, and adjuvant therapy were independent prognostic factor for OS. *Conclusion:* Curative chemotherapy significantly improved both two-year PFS and OS in patients with Stage IVB endometrial disease confined to abdomen over only radiotherapy.

Key words: Stage IVB endometrial cancer; Adjuvant therapy; Progression free survival; Overall survival.

Introduction

Endometrial cancer (EC) is the most common genital malignancy of women in developed countries, but fortunately only 3-13% are diagnosed with Stage IV disease [1]. However, the incidence of EC was found to be increased by >40% over the age of 60 since the last two decades and more deaths due to this malignancy are expected in the future [2, 3] The estimated five-year survival for women with Stage IVB EC is 15% and aggressive histologic subtypes had also poor prognosis with estimated five-year survival of 0-5% [4]. In addition to poor prognosis, neither surgical treatment nor adjuvant therapies were standardized for the advanced EC. Most oncology centers had limited experience on Stage IVB disease due to relatively small number of patients. Different alternative therapies like combinations of cytoreductive surgery, radiotherapy, chemotherapy and hormonal therapy were still tested for the treatment of disease [5-7].

In a recent meta-analysis, adjuvant chemotherapy was confirmed to provide survival advantage for both OS and PFS in advanced EC (Stage III-IV) [8]. However, whether the survival advantage of adjuvant chemotherapy over radiotherapy continued for Stage IV patients, has not yet been confirmed.

When uterine tumor invades into the intra-abdominal organs or has distant metastasis, patients are staged as IVB and local control is not sufficient. In this study, the authors tested the hypothesis that patients with Stage IVB disease confined to the abdomen might be accepted as having systemic disease like ovarian cancer and might better respond to systemic chemotherapy instead of radiotherapy following surgical cytoreduction.

Materials and Methods

Patients

Patients with International Federation of Gynecology and Obstetrics (FIGO) Stage IVB EC, confined to the abdomen, treated with primary cytoreduction between January 1, 1993 and May 31, 2013 were reviewed. For the preoperative assessment, all patients were routinely had chest X-ray and thorax computerized tomography (CT) when necessary. Negative chest X-ray or when necessary negative thorax CT were required for inclusion. Patients who had histology of uterine sarcoma, extra-abdominal disease (liver parenchyma, lung, and brain metastasis), inguinal LN involvement, and incomplete data were excluded.

A total of 1,602 patients with EC were operated between the study period. Among these patients, 68 (4.2%) were diagnosed as Stage IVB EC. After exclusion criteria were applied, a total of 65 patients were eligible for the study. Clinical and pathologic data were obtained from a computerized database. All pathology specimens were evaluated by experienced gyneco-pathologists. Tumors with histology of serous, clear cell, and undifferentiated carcinoma were classified as FIGO grade III tumor.

Treatment protocol

According to the present authors' clinical protocols, all patients except patients with FIGO grade 3 tumor or high risk histology in endometrial biopsy routinely undergo hysterectomy and frozen

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section. When the frozen section demonstrated non-endometriod adenocancer, grade 2-3 tumor, ≥½ myometrial invasion or cervical invasion with a tumor > 2 cm; surgical staging was performed. Standard staging consists of hysterectomy, bilateral salpingo-oophorectomy, sampling of cytology and omentectomy, and/or systematic pelvic and para-aortic lymphadenectomy. Cytoreductive surgery was performed in addition to staging surgery in case there was macroscopic disease intraoperatively. Maximal debulking was defined as leaving no gross residual tumor after primary surgery; optimal and suboptimal debulking were used for patients with residual tumor ≤ 1 cm and > 1 cm, respectively. Patients determined to have intra-abdominal metastasis including omentum after pathology report were also staged as IVB and included into the study.

Depending on the surgeon's choice, only radiotherapy, concomitant chemoradiotherapy (with cisplatin), sandwich therapy (three cycles of paclitaxel plus carboplatin followed by radiotherapy and lastly three cycles of paclitaxel plus carboplatin), and only chemotherapy were the alternatives of the adjuvant therapy. Only chemotherapy and sandwich therapy were defined as curative chemotherapy.

Accordingly, the types of clinical response were defined as follows; 'complete clinic response' as clinically disappearance of gross tumor, 'partial clinical response' as 50% or more reduction in tumor size, 'stable disease' as estimated decrease of less than 50% in tumor size or less than 25% increase in tumor size, 'progressive disease' was defined as increase in tumor size more than 25% or appearance of new tumor [9].

Follow-up

Patients were evaluated one month after the adjuvant therapy in order to determine the patients' response to the treatment. The patient with complete clinic response was called for follow-up visits for every three months in the first two years, every six months in the following three years, and annually after the five years.

Recurrences and survival

The recurrences were classified into three groups; within the true pelvis as 'pelvic recurrence', between the diaphragm and true pelvis as 'upper abdominal recurrence' and others as 'extra-abdominal recurrences'. Time between the surgery and the first recurrence, progression or last visit was defined as progression free survival (PFS) and the time between the surgery and the death of any cause or last visit was overall survival (OS). On the other hand patient death within the one month following surgery was excluded from the survival analysis.

Statistics

Statistical analyses were performed using SPSS version 15.0. Prognostic demographic and histopathologic factors were evaluated to determine two-year PFS and two-year OS. The estimates of survival were determined using the Kaplan Meier analysis. Prognostic factors were analyzed with Cox Regression Model. The factors having a p value below 0.25 in the univariate analysis were included in the multivariate analysis. The cut-off for statistical significance was set at $p < 0.05$.

Results

Patients' characteristics

Mean age of the patients at diagnosis was 58.2 years (range, 31-80). There were five (7.7%) patients aged ≤ 40 years and 49 (75.4%) patients aged ≥ 50 years. Most common tumor histology was the endometrioid type in 38 (58.5%) patients. The CA125 level was available in 36 patients preoperatively and detected > 35 IU/ml in 27 (75%) patients. Median CA-125 levels were 64 IU/ml, ranging from 6 to 1,416 IU/ml. Patients with non-endometrioid tumors had significantly higher median preoperative CA125 levels (n=15 median: 168 IU/ml compared to those with endometrioid tumors n=21 median: 42 IU/ml; $p = 0.04$).

During abdominal exploration, ascites was detected in the 21 (32.3%) patients and peritoneal cytology was tumor positive in 40 (61.5%) patients. The demographic and histopathologic data of entire cohort are shown in Table 1.

Table 1. — *Demographic and histopathologic features of the study population.*

Parameters	Mean, range	n.	%
Age (years)	58.2	31-80	
Tumor size (mm)	50.9	5-110	
Tumor type	Endometrioid	38	58.5
	Serous	14	21,5
	Clear cell	6	9.2
	Undifferentiated	5	7.7
	Mixed	2	3.1
Grade	1-2	28	43.1
	3	37	56.9
Depth of myometrial invasion	<1/2	16	25.4
	≥1/2 [1]	49	74.6
Peritoneal cytology	Negative	17	26.2
	Positive	40	61.5
Lymphovascular space invasion	Negative	9	13.8
	Positive	32	49.2
	Not reported	24	36.9
Cervical invasion	Negative	35	53.8
	Positive	30	46.2
Adnexal metastases	Negative	23	35.4
	Positive	42	64.6
Omental metastasis*	Negative	5	8.1
	Positive	57	91.9
Other intra-abdominal metastasis	Negative	31	47.7
	Positive	34	52.3

[1] Uterine serosal invasion included.
* Omentectomy was performed in 62 patients.

Surgico-pathologic factors

a) Status of the pelvic and para-aortic LNs: Although most of the patients (n=55) underwent both para-aortic and pelvic LN dissection, one patient underwent only para-aortic lymphadenectomy without pelvic lymphadenectomy. Nine patients did not undergo lymphadenectomy due to the poor performance status and surgeon's preferences. Median number of total LNs removed was 46 (range: 8-99). The median number of removed pelvic and para-aortic LNs were 31.2 (range: 2-70) and 16.3 (range: 2-45), respectively. LN metastasis was detected in 32 (57.1 %), isolated pelvic metastasis and isolated para-aortic metastasis were detected in nine (16.1%) and in six (10.7%) patients, re-

Table 2. — *Recurrence patterns of the patients with Stage IVB endometrial cancer.*

Recurrence site	n	%	Median (range)
Only pelvic	6	21.4	9 months (5-25)
Only upper abdominal	6	21.4	14.5 months (6-84)
Only extra abdominal	4	14.3	13.5 months (5-18)
Pelvic + extra abdominal	12	42.9	15 months (4-50)
Total	28	100	11 months (4-84)

Table 3. — *Factors determining two-year disease free survival and two-year overall survival in univariate analysis.*

Parameters		Two-year PFS [3]		Two-year OS [4]	
		%	*p*	%	*p*
Age [1] (years)	≤ 58	34.1	0.655	44.2	0.572
	> 59	31.3		40.0	
Tumor type	Endometrioid	42.0	0.121	45.1	0.105
	Nonendometrioid	22.6		38.0	
Grade	1 and 2	56.7	0.005	56.9	0.020
	3	17.9		32.5	
Depth of myometrial invasion	< 1/2	40.0	0.673	43.8	0.885
	≥ 1/2 [2]	28.3		40.2	
Uterine serosal invasion	Negative	41.3	0.060	49.1	0.037
	Positive	14.0		23.9	
Lymphovascular space invasion	Negative	42.9	0.995	62.5	0.843
	Positive	33.4		42.6	
Cervical invasion	Negative	34.4	0.851	49.2	0.495
	Positive	28.9		30.3	
Peritoneal cytology	Negative	48.7	0.039	59.3	0.121
	Positive	22.2		29.8	
Adnexal metastasis	Negative	37.8	0.255	55.4	0.101
	Positive	29.4		34.4	
Lymphadenectomy	No	14.3	0.361	33.3	0.926
	Yes	36.4		43.3	
Number of removed LNs [1]	≤ 46	33.6	0.369	43.8	0.812
	> 46	42.5		42.3	
Presence of pelvic LN metastasis	Negative	48.3	0.212	47.7	0.319
	Positive	13.1		32.9	
Presence of para-aortic LN metastasis	Negative	41.2	0.611	51.7	0.158
	Positive	27.8		30.3	
Primary cytoreduction	Suboptimal	16.7	0.217	33.3	0.209
	Maximal&optimal	34.2		41.9	
Adjuvant therapy	Curative CT [5]	34.9	0.043	44.5	0.022
	Radiotherapy	11.1		11.0	

[1] Median value; [2] uterine serosal invasion included;
[3] progression free survival; [4] overall survival; [5] chemotherapy.

spectively. On the other hand, 17 (30.4%) patients had both pelvic and para-aortic LN metastasis. Median number of metastatic pelvic and para-aortic LNs were 5.5 (1-25) and 5.0 (range 1-28), respectively.

b) Cytoreductive surgery: Among all patients, 54 (83.1%) underwent maximal debulking, four (6.2%) had optimal and seven (10.8%) underwent suboptimal debulking. Omentectomy was done in 62 patients and tumor was positive in 57 (91.9%). Appendectomy was done in 25 patients and of these 14 (56%) had positive tumor in the appendix. In order to decrease the tumor load, resection of tumor with a segment of small intestine or bowel was done in five (7.7%) patients and diaphragm stripping in four (6.2%) patients. Totally four (6.2%) patients underwent splenectomy, tumor was positive in these three patients and one was due to the surgical trauma.

Survival analysis of 62 patients with Stage IVB disease

Because three patients refused the adjuvant therapy and lost from follow-up, 62 patients were included into the survival analysis. Median follow-up was 18 months (range:2-180 months). Among these patients, 28 (45.2%) had recurrence. The mean time from surgery to recurrence was 11 months (range: 4-84). Recurrence was outside the pelvis in 22 (78.5%) and was extra-abdominal in 16 (56.1%) patients (Table 2). In the entire cohort, two-year PFS and two-year OS were calculated as 33.4% and 42.2%, respectively.

Four patients having optimal cytoreduction were analyzed within the same group of patients with maximal cytoreduction. Although median two-year PFS for patients with optimal and maximal cytoreduction were higher than those with suboptimal cytoreduction, it did not reach statistical significance (16.7% and 34.2%, respectively; p = 0.217). The two-year OS for patients who underwent suboptimal and maximal and optimal cytoreduction were also estimated as 33.3% and 41.9% respectively (p = 0.209).

The rate of maximal and optimal cytoreductive surgery did not differ in patients with endometrioid and non-endometrioid tumors (88.9% *vs.* 88.5%; p = 1.0). In endometrioid tumor; two-year PFS and two-year OS were 58.2% and 39.8%, respectively, for 32 patients who underwent maximal and optimal cytoreduction. In the non-endometrioid tumor; two-year PFS and two-year OS were 39.8% and 39.7%, respectively, for 23 patients with maximal and optimal cytoreduction. There were only seven patients who had suboptimal cytoreduction; four with endometrioid and three with non-endometrioid tumor. Except one all experienced recurrence. Two of three patients with non-endometrioid tumor had mortality at 10th and 37th months after surgery. On the other hand, three of six had mortality at 9th, 18th, and 24th months after surgery.

In the entire cohort, 31 patients received only chemotherapy and it was the most commonly used adjuvant therapy. Of these, 24 (77.4%) patients received platin and taxane, six (19.4%) received cisplatin in combination with adriamycine, and one (3.2%) received cyclophosphamide and cisplatin. Only radiotherapy was the second prefered adjuvant therapy received by 16 patients. Only radiotherapy was given to 12 patients with endometrioid tumor and four patients with non-endometrioid tumor and all patients were operated between 1992 and 2003. Whole pelvic radiotherapy was the

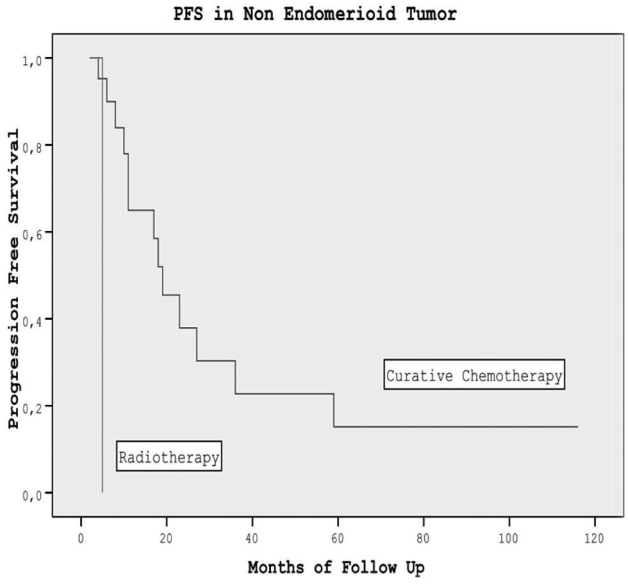

Figure 1. — Progression-free survival stratified by type of adjuvant therapy.

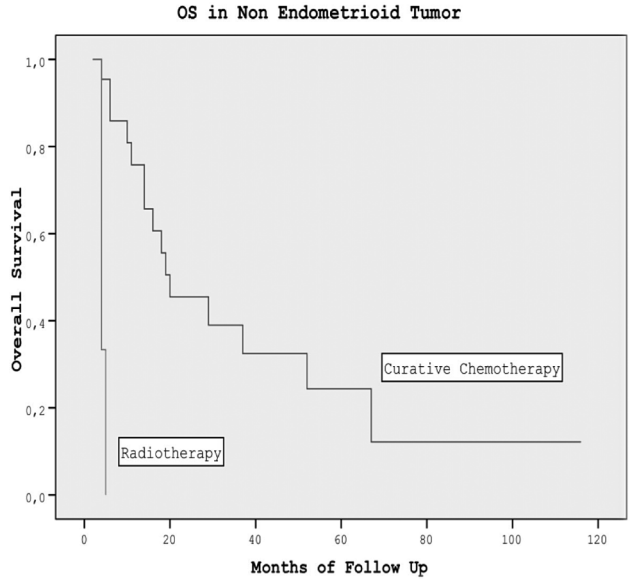

Figure 2. — Overall survival stratified by type of adjuvant therapy.

Table 4. — *Multivariant analysis of selected clinico-pathological variables regarding progression-free survival and overall survival.*

		p value	Hazard ratio	95% Confidence interval
Progression free survival	Tumor type *(endometrioid vs. non-endometrioid)*	0.581	1.334	0.478−3.721
	FIGO grade *(grade 1 and 2 vs. grade 3)*	0.038	3.514	1.072−11.517
	Serosal invasion *(negative vs. positive)*	0.520	1.298	0.586−2.875
	Peritoneal cytology *(negative vs. positive)*	0.029	2.345	1.090−5.045
	Pelvic LN metastasis (*negative vs. positive*)	0.565	1.249	0.586−2.666
	Cytoreduction (*optimal and maximal vs. suboptimal*)	0.861	1.150	0.242−5.456
	Adj[1] therapy *(curative chemotherapy vs. radiotherapy)*	0.004	4.204	1.580−11.187
Overall survival	Tumor type *(endometrioid vs. non-endometrioid)*	0.275	2.043	0.566−7.370
	FIGO grade *(grade 1 and 2 vs. grade 3)*	0.599	1.413	0.389−5.128
	Serosal invasion *(negative vs. positive)*	0.539	1.309	0.555−3.087
	Peritoneal cytology *(negative vs. positive)*	0.018	2.799	1.190−6.583
	Para-aortic nodal involvement *(negative vs positive)*	0.211	1.756	0.727−4.242
	Cytoreduction *(suboptimal vs. optimal and maximal)*	0.112	4.003	0.724−22.136
	Adj[1] therapy *(curative chemotherapy vs. radiotherapy)*	0.036	3.210	1.078−9.562
	Adnexal invasion *(negative vs. positive)*	0.023	3.478	1.184−10.219

[1]Adjuvant therapy.

standard treatment modality and extended-field radiotherapy was used when extra-pelvic metastasis was present. Four (6.5%) patients who had concomitant chemoradiotherapy were excluded when the impact of adjuvant therapy on survival was analyzed. The median survival for these four patients were 66 months, one experienced a distant lung metastasis in the 18th month of surgery and died at 21st month of surgery. Other three patients were living without disease at their last follow-up visit and also one was a long term survivor with 180 months OS.

There were five long-term survivor patients (8.1%, n: 5/62) in the present study and median survival was 116 months ranging from 84 to 180 months. All had maximal cytoreduction. Of these, three received platinum and paclitaxel chemotherapy and two received sandwich chemotherapy as an adjuvant therapy.

In the univariate analysis; FIGO grade (*grade 1-2 vs. 3*) and peritoneal cytology (*negative vs. positive*) was the only predictor of two-year PFS ($p = 0.005$ and $p = 0.039$, respectively). On the other hand; tumor grade (grade 1-2 *vs.* 3), serosal tumor involvement (negative *vs.* positive) and type of adjuvant therapy (curative *vs.* radiotherapy) were statistically significant predictors for two-year OS ($p = 0.020$, $p = 0.037$, $p = 0.022$, respectively) (Table 3). Patients with endometrioid

and non-endometrioid tumors received similar rates of curative chemotherapy ($p = 0.086$). In patients with endometrioid tumors, although receiving curative chemotherapy suggest higher PFS and OS compared to receiving only radiotherapy, it did not reach statistical significance (46.1% *vs.* 14.1%; $p = 0.16$ for PFS and 49.4% *vs*. 13.8%; $p = 0.09$ for OS, respectively). However, in patients with non-endometrioid tumors, receiving curative chemotherapy earned significant survival advantage for both two-year PFS and two-year OS compared with those who received only radiotherapy ($p < 0.001$ and $p < 0.001$, respectively) (Figures 1 and 2).

On the multivariate analysis; FIGO grade 1 and 2 tumor, negative peritoneal cytology and receiving curative chemotherapy independent predicted higher PFS ($p = 0.038$, $p = 0.029$, and $p = 0.004$, respectively) Peritoneal cytology, absence of adnexal involvement, and curative chemotherapy were associated with improved rates of OS ($p = 0.018$, $p = 0.23$, and $p = 0.36$, respectively) (Table 4). When compared to only radiotherapy, curative chemotherapy was associated with less risk for mortality (HR: 3.210, CI: 1.078-9.562; $p = 0.036$).

Discussion

In the analysis of 62 patients with Stage IVB intra-abdominal disease, two-year PFS and OS were calculated as 33.4% and 44.2%, respectively. While independent prognostic factors were peritoneal cytology, FIGO grade, and systemic adjuvant therapy for PFS, they were peritoneal cytology, adnexal involvement, and systemic chemotherapy for OS in the present study. These results were consistent with the other studies [10, 11].

Due to rarity of the disease, many studies had small and heterogenous group of patients, like Stages IIIA-IVB EC. In a GOG study, patients with advanced EC (Stages III-IV), receiving combination chemotherapy was confirmed to have significant survival advantage over only radiotherapy [12]. In that study, the patients with Stage IVB disease either received chemotherapy regimen with the doxorubicin plus cisplatin or the whole abdominal radiation, and chemotherapy regimen significantly improved survival compared to radiotherapy. In the current study, most common chemotherapy regimen was taxane plus cisplatin and survival advantage of curative chemotherapy was specifically confirmed in Stage IVB EC confined to the abdomen. In a recent meta-analysis, adjuvant chemotherapy was also confirmed to provide survival advantage for both OS and PFS in advanced EC (Stages III-IV) [8]. However, whether the survival advantage of adjuvant chemotherapy over radiotherapy still continued for Stage IV patients, was not confirmed. In a high risk group of Stages I-III EC, Hogberg *et al.* evaluated the sequential radiation and chemotherapy compared to only radiotherapy, superior survival advantage was obtained in sequential therapy [13]. Recently, Huang *et al.*, suggested that complete cytoreduction with combination of radiation and chemotherapy had the survival advantage for Stages III-IV UPSC patients [14]. In the current study, almost all (95.4%) patients received adjuvant therapy and curative chemotherapy was found superior to only radiotherapy in terms of both two-year DFS and OS ($p = 0.043$ and $p = 0.022$, respectively). The survival advantage of curative chemotherapy in terms of both OS and PFS were also true for non-endometrioid tumors ($p < 0.001$ and $p < 0.001$). Although patients with endometrioid tumors who had also higher PFS and OS with curative chemotherapy compared to only radiotherapy, statistical significance could no be achieved (49.4% *vs*. 13.8%; $p = 0.092$ for OS and 46.1% *vs*. 14.1%; $p = 0.16$ for PFS).

Although survival advantage of optimal cytoreduction was confirmed for advanced ovarian cancer, there is limited high quality data about the impact of cytoreductive surgery on survival for advanced EC [15]. In a recent meta-analysis, Barlin *et al.* reported superior overall survival with optimal cytoreduction (residue ≤ 2cm) in advanced (both Stages III-IV) and recurrent EC, such that each 10% increase in cytoreduction to no gross residual disease was associated with a 9.3-month increase in survival [16]. Previously, Ayhan *et al.* treated 37 patients with Stage IVB disease and confirmed the advantage of optimal cytoreduction, with a median survival of 25 months for patients with optimal cytoreduction (residue tumor ≤ 1 cm) compared to ten months for suboptimal cytoreduction [1]. Lee *et al.* evaluated the clinical outcomes of 48 patients who had tumor confined to abdomen with Stage IVB uterine papillary serous cancer (UPSC); majority of patients received platinum based chemotherapy and reported median survival was also superior for optimal compared to suboptimal cytoreduction (26.5 *vs.* 12.6 months) [17]. Bristow *et al.* reported that patients with no gross residual tumor had significantly longer median survival time compared to patients with optimal (residue tumor ≤ 1 cm) but macroscopic residual disease (41 *vs.* 15 months; $p = 0.0001$) in patients with Stage IV UPSC [18]. In the former studies, optimal cytoreduction was usually defined as presence of 1 cm, and only 52% of patients with Stage IVB EC were optimally cytoreduced [19]. Probably with advances in surgical techniques and the cumulative data regarding the importance of optimal cytoreduction with minimal tumor burden on survival, recent studies reported higher percentages (75%) for performing optimal cytoreduction in Stage IVB disease [16]. In accordance with the literature, the present authors achieved maximal and optimal cytoreduction in most patients (89.3%) and OS for patients with maximal and optimal cytoreduction was comparable with the literature [4, 20, 21]. Although, patients with maximal and optimal cytoreduction was higher two-year PFS and OS than those with suboptimal cytoreduction, it did not reach statistical significance. Statistical significance might not be demonstrated due to the few number of (only seven) patients in the suboptimal cytoreduction group.

The strength of this study was that all of the patients were treated by gynecologic oncologists in a single institution and optimal cytoreduction with no gross disease was achieved in most of them, with one of the highest ratios in the literature. According to the present authors' knowledge, it is one of the largest studies evaluating the effect of cytoreduction and adjuvant therapy for Stage IVB disease. Although most studies evaluated both recurrent and advanced (Stages III and IV) disease together, they did not accurately determine the efficacy of adjuvant therapies and cytoreduction on survival in Stage IVB EC. Therefore, the present authors evaluated the impact of cytoreduction and adjuvant therapy in a specific group with only Stage IVB disease, confined to the abdomen.

The limitation of the study was the retrospective nature and the 20-year time period. Significant changes in both surgical techniques and adjuvant therapies were took place in previous two decades. Due to the rarity of disease and relatively small number of patients, especially seven cases within the suboptimal cytoreduction group, caused inability to detect the difference between variables in statistical analysis. However, the authors believe that the present findings gave additional information on the management of Stage IVB cancer.

Conclusion

In the current study, significant decrease in both recurrence and mortality by using systemic chemotherapy instead of only radiotherapy was shown in Stage IVB patients with intra-abdominal disease. Patients having optimal cytoreduction had higher PFS and OS for Stage IVB disease compared to those having suboptimal cytoreduction, but it did not reach statistical significance. Randomized trials investigating the influence of the alternative adjuvant therapies specifically for patients with Stage IVB EC are also required.

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