Surgical Stage III endometrial cancer: analysis of treatment outcomes, prognostic factors and failure patterns

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Summary

Objective: The purpose of this study was to evaluate the survival estimates of stage III endometrial cancer patients, and also to detect the prognostic factors and failure patterns.

Materials and methods: Sixty-eight surgical Stage III endometrial cancer patients treated at Hacettepe University Hospital were included. All patients underwent surgical staging procedures consisting of peritoneal cytology, infracolic omentectomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy and complete pelvic-paraaortic lymphadenectomy. By surgical staging 26 (38%) patients had Stage IIIA and 42 (62%) patients had Stage IIIC disease. The mean resected lymph node number was 26 (median, 25; range, 15-58).

Results: The median age was 60 years (range, 38-77), and the median follow-up period was 62 months (range, 36-90 months). The 5-year disease free survival rate was 58% and the 5-year overall survival rate was 64%. These figures for Stage IIIA were 60% and 68%, respectively; and for Stage IIIC they were 57% and 62%, respectively. No significant survival difference was detected between Stage IIIA and IIIC ($p = 0.60$ for disease-free survival and $p = 0.48$ for overall survival). High grade and positive peritoneal cytology predicted poor survival in both univariate ($p = 0.004$ and $p = 0.006$, respectively) and multivariate ($p = 0.05$ and $p = 0.04$, respectively) analysis. Twenty-eight patients (41%) had recurrence with a median time of 23 months (range, 10-54 months). Nine patients (13%) had only local, 13 patients (19%) had only distant and six patients (9%) had both local and distant relapse.

Conclusion: Surgical staging is important in the management of Stage III endometrial cancer, and the main problem is still distant failure. In multivariate analysis high grade and positive peritoneal cytology predicted poor survival significantly.

Key words: Stage III endometrial cancer; Survival; Prognostic factors; Failure patterns.

Introduction

Endometrial cancer is the most common malignancy of the female genital tract. In approximately 75% of patients with endometrial cancer it is clinically confined to the uterus, and Stage III disease constitutes 10-15% of all endometrial cancer patients [1]. Although the 5-year survival rates for Stage I and II disease have been reported as 90-97% and 75-88%, respectively, the 5-year survival for Stage III endometrial cancer ranges from 46% to 84%, and the therapeutic approach is controversial. Total abdominal hysterectomy and bilateral salpingo-oophorectomy are the cornerstone of surgery, but the indications and the extent of lymphadenectomy varies in the published literature. As an adjuvant treatment radiotherapy and/or chemotherapy or hormonotherapy have been given in many different combinations to these patients after surgery. The purpose of this study was to evaluate the survival rates, prognostic factors and failure patterns in Stage III endometrial cancer patients who underwent initial surgical staging procedure consisting of debulking and complete pelvic-paraaortic lymph node dissection.

Revised manuscript accepted for publication July 5, 2002

Materials and Methods

Surgical Stage III endometrial cancer patients treated at the Hacettepe University Hospital between January 1982 and December 1998 were evaluated. Two patients who had a history of concomitant or previous malignant disease, one patient who received treatment elsewhere, two patients who had incomplete follow-up data, two patients who did not undergo initial surgical intervention including pelvic-paraaortic lymph node dissection were excluded from the study and the remaining 68 patients meeting these criteria were re-evaluated according to the FIGO 1988 definition of Stage III endometrial cancer. Data were obtained from the private oncology files.

The surgical procedure included peritoneal cytology, infracolic omentectomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy and systematic pelvic-paraaortic lymphadenectomy for all patients. By surgical staging 26 (38%) patients had Stage IIIA and 42 (62%) patients had Stage IIIC disease. Of these 26 Stage IIIA patients, 12 had positive cytology, ten had serosal involvement and eight had adnexal metastases. In patients with Stage IIIC disease, 40 had positive pelvic lymph node and 11 had paraaortic lymph node invasion. Only two patients had isolated paraaortic metastases.

The mean age was 60 years (range, 38-77; SD=8.8 years). Analysis of the histological cell type of patients revealed that 60 patients had endometrioid, two had mucinous, two had adenosquamous, two had papillary serous, two had clear cell tumors. Endometrioid and mucinous tumors were classified as favorable and the other histologies were grouped as unfavorable. The

mean resected lymph node number was 26 (median, 25; range, 15-58). Characteristics of patients are presented in Table 1.

After surgery, 60% (41/68) of patients received external pelvic radiotherapy. Of these 41 patients, seven patients with paraaortic invasion received concomitant pelvic and paraaortic radiation. Radiotherapy doses were 5040 cGy for pelvic and 4500 cGy for paraaortic portals. Chemotherapy was given to 32 (47%) patients; of whom three had only cisplatin (50mg/m^2), five had cisplatin plus cyclophosphamide (500mg/m^2), five had cyclophosphamide plus doxorubicin (50mg/m^2) and the remaining 20 patients received a combination of all these three agents. All the chemotherapy protocols were given at 4-week intervals for a total of six cycles. Table 2 outlines the administered adjuvant treatment regimens according to the substages. In Stage IIIA, 13 patients received only radiotherapy and six patients received only chemotherapy. The remaining seven patients refused the use of adjuvant therapy. In Stage IIIC, 16 patients had only radiotherapy, 14 patients had only chemotherapy, and 12 patients had both radiotherapy and chemotherapy.

Failure patterns were identified as local if they occurred in the standard radiotherapy field and distant if disease relapsed outside the radiotherapy field including abdominal recurrences. Chi-square and Fisher's exact tests were used to compare categorical data. Overall and disease-free survival estimates were obtained via the Kaplan-Meier method. The Log-rank test was used to assess prognostic importance of therapeutic modalities, demographic and histopathologic characteristics. Cox's regression analysis was used to identify independent prognostic variables.

Table 1. — *Five-year survival rates by demographic and histopathologic variables.*

Prognostic Variables	n (%)	DFS	p	OS	p
Age					
< 60	31 (45)	57%	0.96	64%	0.93
> 60	37 (55)	59%		65%	
Parity					
Nulliparous	12 (18)	50%	0.59	58%	0.73
Parous	56 (82)	60%		66%	
Histology					
Favorable	62 (91)	58%	0.85	64%	0.93
Unfavorable	6 (9)	67%		67%	
Grade					
I	21 (31)	59%	0.02	76%	0.004*
II	26 (38)	73%		77%	
III	21 (31)	38%		38%	
Myometrial invasion					
< 1/2	14 (20)	70%	0.24	86%	0.08
> 1/2	54 (80)	55%		59%	
LVSI					
(–)	5 (8)	80%	0.38	80%	0.48
(+)	63 (92)	57%		63%	
Cervical involvement					
(–)	37 (55)	64%	0.24	73%	0.12
(+)	31 (45)	51%		55%	
Cytology					
(–)	43 (63)	69%	0.007	76%	0.006*
(+)	25 (37)	40%		44%	
Lymph node metastasis					
(–)	26 (38)	60%	0.30	68%	0.16
Only pelvic	31 (46)	61%		68%	
Paraaortic (+)	11 (16)	45%		45%	

* Also significant in multivariate analysis, p = 0.05 for grade, and p = 0.04 for cytology.

Table 2. — *Five-year survival rates by adjuvant therapy.*

	Stage IIIA			Stage IIIC		
Treatment	n	DFS	OS	n	DFS	OS
Only surgery	7	43%	57%	–	–	–
Surgery + only RT[a]	13	67%	75%	16	69%	75%
Surgery + only CT[b]	6	67%	67%	14	29%	36%
Surgery + RT + CT	–	–	–	12	75%	75%

[a]RT, radiotherapy; [b]CT, chemotherapy.

Results

The 5-year disease free survival (DFS) rate was 58% and overall survival (OS) rate was 64% for all patients with a median follow-up period of 62 months (range, 36-90 months). The DFS and OS rates for Stage IIIA patients were 60% and 68%, respectively. These figures for Stage IIIC patients were 57% and 62%, respectively. No significant survival difference was detected between Stage IIIA and IIIC (p = 0.60 for DFS and p = 0.48 for OS).

Survival estimates by demographic and histopathologic variables are listed in Table 1. High grade and positive peritoneal cytology predicted poor survival in both univariate (p = 0.004 and p = 0.006, respectively) and multivariate (p = 0.05 and p = 0.04, respectively) analysis (Table 1). Thirty-two patients had at least one of these two prognostic factors. The 5-year DFS and OS rates for these patients were the same (44%). These figures for the remaining 36 patients who did not have any of these two factors were 71% and 81%, respectively. These differences between the two groups were statistically significant (p = 0.009 for DFS and p = 0.0009 for OS).

The applied adjuvant treatment modalities and the corresponding survival estimates are shown in Table 2. As the sample size of each treatment type is small, no comparisons of groups were performed to detect superiority.

Twenty-eight patients (41%) had recurrence with a median time of 23 months (range, 10-54 months). Nine patients (13%) had only local, 13 patients (19%) had only distant and six patients (9%) had both local and distant relapse (Table 3). Seven patients had abdominal recurrence of whom four had concurrent distant failure. No significant relationship was found between the site of

Table 3. — *Site of failures by adjuvant therapy.*

Treatment	n (%)	Recurrence	L[a]	D[b]	L+D[c]	DOD[d]
Only surgery	7 (10)	4	2	1	1	3
Surgery + RT[e]	29 (43)	9	2	5	2	7
Surgery + CT[f]	20 (29)	12	4	5	3	11
Surgery + RT + CT	12 (18)	3	1	2	-	3
Total	68 (100)	28	9	13	6	24

[a]L, only local; [b]D, only distant;
[c]L+D, both local and distant; [d]DOD, died of disease;
[e]RT, radiotherapy; [f]CT, chemotherapy.

recurrence and the type of adjuvant therapy. Although chemotherapy consisting of cisplatin, doxorubicin and cyclophosphamide (19/28) or only doxorubicin (9/28) had been given to recurrent patients, 86% (24/28) of them died within the first year. Median time to death after recurrence was 6.5 months. The time from recurrence to death was not related with failure site or treatment after relapse.

Discussion

Stage III disease constitutes 15% of all endometrial cancer patients. Because of the low incidence of disease, to design a prospective randomized study with a sufficient patient population to extract a definitive treatment regimen in one institution is difficult. Thus, our knowledge is mainly from retrospective series with limited size. As an initial therapeutic approach surgical resection is the cornerstone of treatment with definitively demonstrated survival benefit [2, 3] but there is no consensus on the type of adjuvant therapy applicable to these patients. Many different therapeutic combinations consisting of radiotherapy (teletherapy with or without brachytherapy), chemotherapy and hormonotherapy have been investigated. Greven *et al.* [4] reported a 64% 5-year DFS by treating 105 Stage III patients with surgery plus radiation. Schorge *et al.* [5] evaluated 51 Stage IIIA/B and 35 Stage IIIC endometrial cancer patients with a 5-year OS rate of 54%. They reported adjuvant radiotherapy had a survival advantage in Stage IIIC, while no benefit was found for Stage IIIA patients, and adjuvant chemotherapy did not increase survival in any substage. By giving chemotherapy consisting of cisplatin, doxorubicin and cyclophosphamide after surgery, Burke *et al.* [6] treated 29 patients who had extrauterine involvement (25, Stage III; and 4, Stage IV) and found a 46% 3-year survival rate. Aoki *et al.* [7] used the same protocol for 61 Stage III patients and a showed 78.6% 5-year DFS rate. Onda *et al.* [8] reported an 84% 5-year DFS in 30 Stage IIIC patients by giving radiotherapy plus chemotherapy after surgery. Nelson *et al.* [9] evaluated 17 Stage IIIC patients and found a 72% 5-year OS by adjuvant radiation only. In the study of McMeekin *et al.* [10] 47 Stage IIIC patients were treated with adjuvant radiotherapy (34 patients) or chemotherapy (8 patients) or hormonotherapy (5 patients). Although the survival estimates of each group were not reported, the 5-year OS rate for all patients was 65%. In our study the 5-year DFS and OS rates were 58% and 64%, respectively. These figures for Stage IIIA were 60% and 68%, respectively. In Stage IIIC the 5-year DFS rate was 57% and OS rate was 62%. The 5-year OS rate in 28 Stage IIIC patients treated with radiotherapy with or without chemotherapy was 75%, and in good accordance with the published literature.

Deep myometrial invasion [7, 10], lymphovascular space involvement [5, 7], clear cell or papillary serous histologies [4], high grade [3-5, 11], positive peritoneal cytology [4, 9, 12] have been reported as significantly related to poor survival. In this study, high grade and positive peritoneal cytology predicted poor survival independently. The survival rates of patients who had at least one of these two prognostic factors were worse than the remainder ($p = 0.009$ for DFS and $p = 0.0009$ for OS). The 5-year survival rates of patients with paraaortic invasion was approximately 20% lower than the patients with only pelvic involvement, but did not reach a significant value. Hirahatake *et al.* [12] and Morrow *et al.* [13] observed a significant difference between these two groups contrary to McMeekin *et al.* [10] and Katz *et al.* [14] who reported that while the survival was better without paraaortic disease, the difference was not significant. In our study, seven of 11 patients with paraaortic involvement received extended-field radiation and two of them had recurrence, but all the remaining four patients who received only chemotherapy had a relapse. Rose *et al.* [15] and Hicks *et al.* [16] evaluated the efficiency of extended-field radiotherapy and showed a significant survival benefit in patients with paraaortic involvement.

Recurrences were seen in 28 patients. Of whom, nine had only local, 13 had only distant and six had both local and distant failure. These values are in accordance with the literature consisting of predominantly distant relapse [5, 6, 8-10]. As in some other studies, we did not find any significant relationship between the site of recurrence and the type of adjuvant therapy [5, 10]. Twelve percent of the patients who had been treated with radiotherapy (5/41) relapsed in the radiotherapy area. Greven *et al.* [4] showed a 21% local recurrence rate following adjuvant radiation therapy. In our study, the abdominal recurrence rate was 10% (7 patients) but four of them had concurrent distant failure. Application of whole abdominal radiation might have a preventive role for an abdominal failure, but the low rate of isolated abdominal relapse and approximately 25% in-field failure rate [17] questions its use. In fact, the main problem is still distant failure even in patients treated with adjuvant chemotherapy. We found a 31% distant recurrence rate in patients who received chemotherapy. Burke *et al.* [6] reported 18 of 22 recurrences were extrapelvic, and also Aoki *et al.* [7] observed eight of 13 failures at distant sites after adjuvant chemotherapy. The results of a GOG's prospective study (Protocol 122) comparing whole abdominal radiation to chemotherapy will clarify the many controversies about the efficiency and failure patterns of both adjuvant treatment modalities.

Conclusion

Surgical staging remains important in the management of Stage III endometrial cancer. Distant failure is still the main problem. In multivariate analysis high grade and positive peritoneal cytology significantly predicted poor survival. Prospective randomized studies are needed to evaluate the role of different adjuvant therapies, and also to prescribe a definitive management plan for Stage III endometrial cancer.

References

[1] Creasman W., Odicino F., Maisonneuve P., Benedet J., Shepherd J., Sideri M.: "Carcinoma of the corpus uteri. Annual report on the results of treatment in gynecological cancer". *J. Epidemiol. Biostat.*, 1998, *3*, 35.

[2] Aalders J. G., Abeler V., Kolstad P.: "Clinical (stage III) as compared to subclinical intrapelvic tumor spread in endometrial carcinoma: a clinical and histopathologic study of 175 patients". *Gynecol. Oncol.*, 1984, *17*, 64.

[3] Mackillop W. J., Pringle J. F.: "Stage III endometrial carcinoma". *Cancer*, 1985, *56*, 2519.

[4] Greven K. M., Lanciano R. M., Corn B., Case D., Randall M. E.: "Pathologic stage III endometrial carcinoma". *Cancer*, 1993, *71*, 3697.

[5] Schorge J. O., Molpus K. L., Goodman A., Nikrui N., Fuller A. F.: "The effect of postsurgical therapy on stage III endometrial carcinoma". *Gynecol. Oncol.*, 1996, *63*, 34.

[6] Burke T. W., Gershenson D. M., Morris M., Stringer C. A., Levenback C., Totolero-Luna G., Baker V. V.: "Postoperative adjuvant cisplatin, doxorubicin, and cyclophosphamide (PAC) chemotherapy in women with high-risk endometrial carcinoma". *Gynecol. Oncol.*, 1994, *55*, 47.

[7] Aoki Y., Kase H., Watanabe M., Sato T., Kurata H., Tanaka K.: "Stage III endometrial cancer: Analysis of prognostic factors and failure patterns after adjuvant chemotherapy". *Gynecol. Oncol.*, 2001, *83 (1)*, 1.

[8] Onda T., Yoshikawa H., Mizutani K., Mishima M., Yokota H., Nagano H., *et al.*: "Treatment of node-positive endometrial cancer with complete node dissection, chemotherapy and radiation therapy". *Br. J. Cancer*, 1997, *75 (12)*, 1836.

[9] Nelson G., Randall M., Sutton G., Moore D., Hurteau J., Look K.: "FIGO stage IIIC endometrial carcinoma with metastases confined to pelvic lymph nodes: Analysis of treatment outcomes, prognostic variables, and failure patterns following adjuvant radiation therapy". *Gynecol. Oncol.*, 1999, *75*, 211.

[10] McMeekin D. S., Lashbrook D., Gold M., Johnson G., Walker J. L., Mannel R.: "Analysis of FIGO stage IIIC endometrial cancer patients". *Gynecol. Oncol.*, 2001, *81*, 273.

[11] Grigsby P. W., Perez C. A., Kuske R. R., Kao M. S., Galakatos A. E.: "Results of therapy, analysis of failures, and prognostic factors for clinical and pathologic stage III adenocarcinoma of the endometrium". *Gynecol. Oncol.*, 1987, *27*, 44.

[12] Hirahatake K., Hareyama H., Sakuragi N., Nishiya M., Makinoda S., Fujimoto S.: "A clinical and pathologic study on para-aortic lymph node metastasis in endometrial carcinoma". *J. Surg. Oncol.*, 1997, *65 (2)*, 82.

[13] Morrow C. P., Bundy B. N., Kurman R. J., Creasman W. T., Heller P., Homesley H. D., Graham J. E.: "Relationship between surgical pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group Study". *Gynecol. Oncol.*, 1991, *40*, 55.

[14] Katz L. A., Andrews S. J., Fanning J.: "Survival after multimodality treatment for stage IIIC endometrial cancer". *Am. J. Obstet. Gynecol.*, 2001, *184*, 1071.

[15] Rose P. G., Cha S. D., Tak W. K., Fitzgerald T., Reale F., Hunter R. E.: "Radiation therapy for surgically proven para-aortic node metastasis in endometrial carcinoma". *Int. J. Radiat. Oncol. Biol. Phys.*, 1992, *24*, 229.

[16] Hicks M. L., Piver M. S., Puretz J. L., Hempling R. E., Baker T. R., Mcauley M., Walsh D. L.: "Survival in patients with paraaortic lymph node metastases from endometrial adenocarcinoma clinically limited to the uterus". *Int. J. Radiat. Oncol. Biol. Phys.*, 1993, *26*, 607.

[17] Potish R. A.: "Abdominal radiotherapy for cancer of the uterine cervix and endometrium". *Int. J. Radiat. Oncol. Biol. Phys.*, 1989, *16*, 1453.

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