Postoperative Adjuvant Chemotherapy in Surgically Staged Grade 3 Endometrial Cancer

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Abstract. *Background: The effectiveness of postoperative adjuvant chemotherapy for surgically staged grade 3 endometrial cancer was investigated. Patients and Methods: Sixty-three consecutive patients with grade 3 endometrial cancer (49 with surgical stage I-II disease and 14 with stage III disease) were treated surgically. Postoperatively, 40 patients (63.5%) were treated with a chemotherapy regimen consisting of ifosfamide, epiadriamycin, and cisplatin scheduled for 3-5 cycles. No patient underwent radiotherapy. Results: Recurrence developed in 8 out of the 63 patients, all within two years. Six of the 8 recurrences were found to be extrapelvic lesions. Recurrences occurred predominantly at distant sites in the absence of pelvic radiation. Estimated 5-year disease-free survival rates were 89.8% for patients with surgical stage I-II disease, 78.6% for those with surgical stage III disease, and 87.3% overall. Conclusion: The current study suggests the potential role of adjuvant chemotherapy alone in grade 3 endometrial cancer.*

There is little doubt that the grade of endometrial cancer is of prognostic significance (1-3). The 2001 FIGO Annual Report noted 92% 5-year survival of patients with stage I grade 1 cancer compared with 76% of those with stage I grade 3 cancer (4). Since the poor prognosis of patients with grade 3 tumors may be due to the propensity for spread outside of the uterus early in the disease process (5), these patients may be most likely to benefit from lymph node dissection and/or postoperative adjuvant therapy.

Systemic lymphadenectomy has been suggested in several studies to play an important role in the treatment of endometrial cancer (6, 7), and this may be particularly true for patients with grade 3 endometrial cancer because of a higher incidence of nodal disease than in those with grade 1-2 tumors (5). Radiotherapy has long been used as postoperative therapy for high-risk endometrial tumors, but recent studies have cast doubt on its effectiveness (8, 9). Conversely, several studies have suggested the utility of postoperative chemotherapy (10-12), but its effectiveness remains an open question.

Herein, we report treatment outcomes in 63 consecutive cases of grade 3 endometrial cancer for which systemic lymphadenectomy followed by adjunctive chemotherapy was planned.

Patients and Methods

During the period 1995 through 2004, 520 patients with clinical stage I-II endometrial cancer were treated surgically at the Cancer Institute Hospital (Tokyo, Japan). During this period, 63 consecutive patients with clinical stage I-II grade 3 endometrial cancer were identified. Systemic retroperitoneal lymphadenectomy was planned for all patients and adjuvant chemotherapy was planned for all except those with superficial myometrial invasion. Sixty-one patients (96.8%) underwent systemic pelvic lymphadenectomy, while 46 patients (73%) underwent both pelvic and para-aortic lymphadenectomy. Forty patients (63.5%) underwent postoperative chemotherapy. No patient received any treatment before surgery or radiotherapy after surgery.

The lymphadenectomy procedure included complete bilateral pelvic lymphadenectomy and para-aortic lymphadenectomy with the aim of removing all of the external iliac, internal iliac, common iliac, obturator, suprainguinal, presacral and para-aortic lymph nodes. Para-aortic lymphadenectomy was performed to remove all lymph node chains between the renal vein and the bifurcation of the aorta.

A single chemotherapy regimen was used consisting of ifosfamide (1000 mg on days 1-4), epiadriamycin (50 mg/m^2 on day 5), and cisplatin (15 mg/m^2 on days 1-5). Epiadriamycin is a derivative of doxorubicin and is reported to minimize cardiac side effects (13). This regimen was generally scheduled to be repeated every 4 weeks for 3 cycles in surgical stage I-II cases and for 5 cycles in stage III cases.

Treatment outcomes, including toxicity of chemotherapy, were investigated. Median follow-up for surviving patients was 106 (range, 38-155) months. Disease-free survival rates and overall survival rates were calculated by the Kaplan-Meier method and analyzed by log-rank test.

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Results

Patient characteristics are shown in Table I. The median age was 56 (range, 38-77) years. Forty-nine patients (78%) had surgical stage I or II disease, whereas 14 (22%) had surgical stage III disease.

During the follow-up period, 8 recurrences were identified (Table II). Six of the 8 recurrences were found to be extrapelvic lesions. All recurrences occurred within 2 years. Patients 1 and 2 were encouraged to undergo postoperative chemotherapy because of the pathological findings, but both refused. In one case (Patient 1), lung recurrence was cured by chemotherapy. In another (Patient 8), vaginal recurrence was treated successfully by radiotherapy.

The estimated 5-year disease-free survival rate was 89.8% for patients with surgical stage I-II disease, 78.6% for those with surgical stage III disease and 87.3% overall (Figure 1). No significant difference in the disease-free interval was noted between the first two groups (p=0.2592). Estimated 5-year overall survival rate in all cases were 90.4%.

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (Version 3). Toxicity was generally acceptable and there were no treatment-related deaths. Grade 3 hematologic toxicity was observed in 55% of patients, while grade 4 was observed in 10%. Grade 3 gastrointestinal toxicity was observed in 10% of patients and often necessitated termination of chemotherapy. Grade 2 alopecia was observed in the majority of patients.

Table I. *Patient characteristics (n=63).*

Median age (range)	56 (38-77) years No. of patients
Clinical stage	
Stage 1	61
Stage 2	2
Surgery	
TAH/BSO	2
TAH/BSO/PLA	15
TAH/BSO/PLA/PALA	46
Pathological type	
Endometrioid grade 3	61
Mixed (grade 3 + clear)	1
Mixed (grade 3 + serous)	1
Lymph node metastasis	
No	53
Yes	8
Unknown	2
Post-surgical stage	
Ia	11
Ib	21
Ic	13
IIb	4
IIIa	5
IIIb	1
IIIc	8
Postoperative chemotherapy	
No	23
Yes	40

TAH, total abdominal hysterectomy; BSO, bilateral salpigo-oophorectomy; PLA, pelvic lymphadenectomy; PALA, para-aortic lymphadenectomy.

Discussion

There are two major issues regarding the treatment of grade 3 endometrial cancer: the need for systemic lymphadenectomy and the selection of postoperative adjuvant therapy. The role of lymph node dissection in early-stage endometrial cancer has been debated for many years. Several previous studies (6, 7) have suggested a therapeutic benefit to the performance of lymphadenectomy in cases of endometrial cancer. Trimble *et al.* (14) showed that more extensive lymph node dissection was associated with increased survival among patients with stage I grade 3 disease, but not with grade 1 or grade 2 tumors. Cragun *et al.* (15) showed improved survival of patients with poorly differentiated stage I or stage IIA endometrial cancer who had more than 11 pelvic nodes removed compared with survival of those who had 11 or fewer nodes removed. More recently, Chan *et al.* (16) reported that extensive lymph node resection improves the survival of women with intermediate/high-risk endometrioid uterine cancer. Thus, extensive lymphadenectomy seems to confer a survival benefit in the subsets of patients with a relatively aggressive tumor.

The role of adjuvant therapy in early-stage endometrial cancer has been debated for many years. Traditionally, radiotherapy has been used as postoperative adjuvant treatment to prevent recurrence, but its role has been controversial. In a multicenter randomized trial, Creutzberg *et al.* (8) showed that postoperative radiotherapy in cases of stage 1 endometrial cancer reduces locoregional recurrence but has no effect on overall survival. Another phase III trial (17) showed that adjunctive radiotherapy in cases of endometrial cancer decreases the risk of recurrence, but its effect is limited to patients at high intermediate-risk. More recently, Orton *et al.* (9) showed in their international randomized study that the benefit of postoperative adjuvant radiotherapy alone in endometrial cancer is very limited.

Chemotherapy has been used as postoperative adjuvant treatment for endometrial cancer, and several studies (10-12) have pointed to its value. In a recent Gynecologic Oncology Group study (18), platinum-based chemotherapy (cisplatin and doxorubicin) was found to result in better survival than whole-abdominal radiation in cases of advanced endometrial cancer (stages III and IV). In addition, chemotherapy may

Table II. Recurrence: patients and other clinical details.

Patient	Age (years)	Surgical stage	Chemotherapy	Time to recurrence	Recurrence site	Survival	Final status
1	53	3c	None	8M	Lung	11Y8M	NED
2	68	1c	None	8M	Lung, liver	10M	DOD
3	60	1b	IEP	8M	Intraabdominal	10M	DOD
4	73	1b	IEP	1Y9M	Lung	3Y7M	DOD
5	65	2b	IEP	1Y3M	Pelvic node	2Y6M	DOD
6	54	3c	IEP	1M	Virhow's node	9M	DOD
7	62	3c	IEP	1Y9M	Lung	4Y1M	AWD
8	54	1b	IEP	3M	Vagina	3Y4M	NED

IEP, ifosfamide, epiadriamycin, and cisplatin; NED, no evidence of disease; DOD, died of disease; AWD, alive with disease; Y, years; M, months.

be advantageous over radiotherapy in terms of treatment-related morbidities, such as small bowel obstruction and leg lymphedema. In relation to cervical cancer, Soisson *et al*. (19) reported that the incidence of lymphedema requiring medical therapy significantly increased from 5.2% in patients treated by surgery alone to 22% in those treated by surgery plus adjuvant pelvic radiotherapy.

Our treatment strategy in the current study was based on the idea that thorough nodal dissection followed by postoperative chemotherapy may eradicate micrometastasis from grade 3 endometrial cancer to improve the prognosis of the disease. The reported 5-year survival of patients with stage I-II grade 3 endometrial cancer ranges from 71% to 89% (20-23). Hamilton *et al*. (24) studied a large patient series and reported a 5-year survival rate of 86% for patients with stage I-II disease and of 53% for patients with stage III-IV disease. In our series, which included 14 patients (22%) with stage III disease, the estimated 5-year disease-free and overall survival rates were 87% and 90%, respectively.

Recurrence of endometrial cancer occurs predominantly outside the pelvis (1). Theoretically, chemotherapy should be the most suitable method for suppressing distant metastasis. However, 6 of the 8 recurrences in our patients were found outside the pelvis. The low incidence of pelvic recurrence in the absence of pelvic radiation supports the use of postoperative chemotherapy, but the relatively high incidence of distant metastasis suggests the limitation of chemotherapy. Susumu *et al*. (25) previously compared the effectiveness of postoperative chemotherapy and radiotherapy for endometrial cancer and concluded that the roles of both therapies were similar, but chemotherapy had a slight advantage for intermediate-risk disease, such as in cases of myometrial invasion deeper than 50%.

In summary, results of our study suggest the potential benefit of adjuvant chemotherapy in cases of endometrial cancer. The role of chemotherapy in the treatment of endometrial cancer will be examined more thoroughly in future prospective trials.

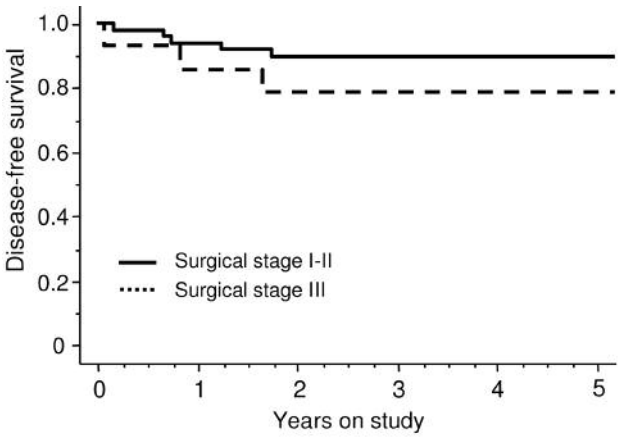

Figure 1. *Relation between disease-free survival and surgical stage. Estimated 5-year disease-free survival rates were 89.8% for patients with surgical stage I-II disease, 78.6% for patients with surgical stage III disease, and 87.3% overall. No significant difference in the disease-free interval between the two groups was noted (p=0.2592).*

References

1 DiSaia PJ, Creasman WT, Boronow RC and Blessing JA: Risk factors and recurrent patterns in Stage I endometrial cancer. Am J Obstet Gynecol *151*: 1009-1015, 1985.

2 Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD and Graham JE: 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 *40*: 55-65, 1991.

3 Zaino RJ, Kurman RJ, Diana KL and Morrow CP: Pathological models to predict outcome for women with endometrial adenocacrcinoma. the impact of the distinction between surgical stage and clinical stage. A Gynecologic Oncology Group study. Cancer *77*: 1115-1121, 1996.

4 Creasman WT, Odicino F, Maisonneuve P, Beller U, Benedet JL, Heintz APM, Ngan HYS, Sideri M and Pecorelli S: Carcinoma of the corpus uteri. J Epidemiol Biostat *6*: 45-86, 2001.

5 Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE and Heller PB: Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group study. Cancer *60*: 2035-2041, 1987.

6 Kilgore LC, Partridge EE, Alvarez RD, Austin JM, Shingleton HM, Noojin F 3rd and Conner W: Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol *56*: 29-33, 1995.

7 Mohan DS, Samuels MA, Selim MA, Shalodi AD, Ellis RJ, Samuels JR and Yun HJ: Long-term outcomes of therapeutic pelvic lymphadenectomy for stage I endometrial adenocarcinoma. Gynecol Oncol *70*: 165-171, 1998.

8 Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhius CC, Winter KA, Lutgens LC, van den Bergh AC, van de Steen-Banasik E, Beerman H and van Lent M: Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomized trial. Lancet *355*: 1404-1411, 2000.

9 Orton J and Blake P: Adjuvant external beam radiotherapy (EBRT) in the treatment of endometrial cancer: results of the randomized MRC ASTEC and NCIC CTG EN.5 trial. Proc Am Soc Clin Oncol *25*: 18S (suppl; abstr 5504), 2007.

10 Aoki Y, Kase H, Watanabe M, Sato T, Kurata H and Tanaka K: Stage III endometrial cancer: analysis of prognostic factors and failure patterns after adjuvant chemotherapy. Gynecol Oncol *83*: 1-5, 2001.

11 Aoki Y, Watanabe M, Amikura T, Obata H, Sekine M, Yahata T, Fujita K and Tanaka K: Adjuvant chemotherapy as treatment of high-risk stage I and II endometrial cancer. Gynecol Oncol *94*: 333-339, 2004.

12 Takeshima N, Umayahara K, Fujiwara K, Hirai Y, Takizawa K and Hasumi K: Effectiveness of postoperative chemotherapy for para-aortic lymph node metastasis of endometrial cancer. Gynecol Oncol *102*: 214-217, 2006.

13 Launchbury AP and Habboubi N: Epirubicin and doxorubicin: a comparison of their characteristics, therapeutic activity and toxicity. Cancer Treat Rev *19*: 197-228, 1993.

14 Trimble EL, Kosary C and Park RC: Lymph node sampling and survival in endometrial cancer. Gynecol Oncol *71*: 340-343, 1998.

15 Cragun JM, Havrilesky LJ, Calingaert B, Synan I, Secord AA, Soper JT, Clarke-Pearson DL and Berchuck A: Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. J Clin Oncol *23*: 3668-3675, 2005.

16 Chan JK, Cheung MK, Huh WK, Osann K, Husain A, Teng NN and Kapp DS: Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. Cancer *107*: 1823-1830, 2006.

17 Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, Pearlman A, Maiman MA and Bell JG: A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol *92*: 744-751, 2004.

18 Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, Thigpen JT and Benda JAl: Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: Gynecologic Oncologic Group study. J Clin Oncol *24*: 36-44, 2006.

19 Soisson AP, Soper JT, Clarke-Pearson DL Berchuk A, Montana G and Creasman WT: Adjuvant radiotherapy following radical hysterectomy for patients with stage IB and IIA cervical cancer. Gynecol Oncol *37*: 390-395, 1990.

20 Cirisano FD, Robboy SJ, Dodge RK, Bentley RC, Krigman HR, Synan IS, Soper JT and Clarke-Pearson DL: The outcome of stage I-II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with endometrioid carcinoma. Gynecol Oncol *77*: 55-65, 2000.

21 Alektiar KM, McKee A, Lin O, Venkatraman E, Zelefsky MJ, McKee B, Hoskins WJ and Barakat RRl: Is there difference in outcome between stage I-II endometrial cancer of papillary serous/clear cell and endometrioid FIGO Grade 3 cancer? Int J Radiat Oncol Biol Phys *54*: 79-85, 2002.

22 Boruta 2nd DM, Gehrig PA, Groben PA, Bae-Jump V, Boggess JF, Fowler WC Jr and van Le L: Uterine serous and grade 3 endometrioid carcinoma: is there a survival difference? Cancer *101*: 2214-2221, 2004.

23 Creasman WT, Kohler MF, Odicino F, Maisonneuve P and Boyle P: Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium. Gynecol Oncol *95*: 593-596, 2004.

24 Hamilton CA, Cheung MK, Osann K, Chen L, Teng NN, Longacre TA, Powell MA, Hendrickson MR, Kapp DS and Chan JK: Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer 94 :642-646 ,2006.

25 Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, Satoh S and Kudo R: Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer. Gynecol Oncol *108*: 226-133, 2008.

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