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Assessment of Prognostic Factors in Stage IIIA Endometrial Cancer[1]

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Objective. **The objective of this study was the assessment of prognostic factors in stage IIIA endometrial cancer.**

Methods. **Between 1984 and 1993, 51 patients with stage IIIA endometrial cancer received definitive treatment at our institution. Thirty-seven patients had positive peritoneal cytologic findings only (stage IIIA1), and 14 had adnexal or uterine serosal involvement (USI) (stage IIIA2). Median follow-up of surviving patients was 82.5 months.**

Results. **The 5-year disease-related survival (DRS) and recurrence-free survival (RFS) were 88 and 73%, respectively. RFS was 79% in patients with stage IIIA1 disease, compared with 57% in patients with stage IIIA2 disease ($P = 0.04$). However, DRS did not significantly differ between stages IIIA1 and IIIA2. In the 37 patients with stage IIIA1 tumors, histologic grade 3, nonendometrioid histologic subtype, and lymphovascular invasion (LVI) significantly predicted a poor prognosis, with extraabdominal sites of failure ($P < 0.05$). Of the 22 patients who had stage IIIA1 disease with endometrioid histologic subtype and without LVI, none had recurrence [17 had whole abdominal irradiation (WAR) or intraperitoneal injection of ^{32}P, 2 had pelvic external radiotherapy (PRT)]. By contrast, of the 15 patients with either nonendometrioid histologic subtype or LVI, 9 (60%) had recurrence and 7 (47%) died of disease (12 had WAR or ^{32}P). An extraabdominal component was present in 7 of the 9 recurrences observed in this subgroup. Among the 14 patients with stage IIIA2 tumors (6 had WAR, 6 had PRT), those with USI had a 5-year DRS of 83% and a rate of extraabdominal failure of 83%, compared with 100 and 12.5% in patients without USI ($P < 0.05$).**

Conclusion. **Patients with stage IIIA endometrial cancer who have endometrioid tumors, no LVI, and positive peritoneal cytologic findings as the only sign of extrauterine disease have an excellent prognosis. Nonendometrioid histologic subtype, LVI, and USI are strong predictors of distant failures and poor prognosis. Patients with either of these histologic factors should be considered candidates for systemic adjuvant therapy.**

Key Words: **endometrial cancer, stage IIIA; prognosis; distant metastasis; adjuvant therapy; extrauterine disease; peritoneal cytology; uterine serosal invasion; lymphovascular invasion; histologic subtype.**

INTRODUCTION

Adenocarcinoma of the endometrium is the most common malignant lesion of the female genital tract, and the endometrium is the fourth most common cancer site, accounting for 6% of all cancers in women. During 2002, the number of new cases and deaths from endometrial cancer in the United States are estimated to approximate 39,300 and 6600, respectively [1].

Since 1988, patients with cancer cells in peritoneal washings, uterine serosal invasion, or adnexal involvement have been classified as having International Federation of Obstetricians and Gynecologists (FIGO) stage IIIA cancer [2]. However, the prognostic significance of positive results of peritoneal cytology, adnexal spread, and uterine serosal involvement continues to be debated [3]. Furthermore, the use of adjuvant therapy in patients with stage IIIA disease varies widely, from observation only to aggressive management with either pelvic or whole abdominal radiation. Unfortunately, recurrences are not uncommon, including a significant percentage at distant sites [3, 4].

In the present study, we tested the hypothesis that patients with stage IIIA disease and positive peritoneal cytologic findings as the only sign of extrauterine disease (stage IIIA1) have a prognosis that differs significantly from that of patients with adnexal involvement or uterine serosal invasion or both (stage IIIA2). Moreover, we assessed prognostic factors predictive of extraabdominal failures in the different stage IIIA subsets.

PATIENTS AND METHODS

During the period from 1984 to 1993, 612 patients with epithelial endometrial cancer were managed surgically at Mayo

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Clinic (Rochester, MN) and satisfied the following inclusion criteria: (1) treated with hysterectomy and removal of existing adnexal structures and (2) no other malignant disease diagnosed within 5 years before or after the diagnosis of endometrial cancer (with the exception of patients with carcinoma *in situ* or with skin cancer other than melanoma). From the above population, we identified 53 patients (9%) with surgical stage IIIA disease.

Staging was defined according to the FIGO surgical staging system [2]. For patients operated on before 1988, stage was determined retrospectively from postsurgical pathologic assessments. Histologic classification was accomplished according to the World Health Organization classification [5]. Architectural grading was based on the degree of glandular differentiation in accordance with FIGO guidelines [2]. Characteristics of the tumors were abstracted from the original pathology reports. All the hematoxylin-and-eosin-stained slides of the tumor were reviewed retrospectively by one of us (G.L.K.) to confirm the original diagnosis of adenocarcinoma, FIGO grade, histologic subtype, adnexal involvement, and any lymphovascular invasion (LVI). In particular, adnexal metastatic lesions were reviewed for the location and the quantity of tumor involving the tube or ovary. The possibility of a coexistent primary tumor of the ovary instead of an adnexal metastatic lesion was taken into consideration by applying the criteria proposed by Ulbright and Roth [6]. LVI was considered to be present when tumor cells were noted within or attached to the wall of a blood vessel or lymphatic space.

All surgical procedures were performed by a gynecologic oncologist. Frozen sections were available routinely in all cases, providing intraoperatively the cell type, grade of neoplasia, depth of myometrial invasion, and sites of extrauterine spread.

Postoperatively, patients were routinely counseled about the potential benefits of vaginal brachytherapy or intraperitoneal instillation of ^{32}P or external whole pelvic or whole abdominal irradiation (or a combination) on the basis of pathologic risk factors and the patients' physical and medical status. Patients with positive peritoneal cytology (with or without other associated sites of extrauterine disease) were usually counseled to receive adjuvant radiotherapy to include the whole abdomen (i.e., whole abdominal external radiotherapy or intraperitoneal instillation of ^{32}P), whereas patients with isolated uterine serosal involvement (USI) or adnexal spread were counseled to receive external beam pelvic irradiation. The addition of vaginal brachytherapy was generally recommended for patients with invasion of the outer half of the myometrium or with high-grade disease. The technique for administering whole abdominal irradiation has been previously described [7]. Adjuvant radiotherapy was not administered if either the patient or her referring physician elected to forgo adjuvant therapy. Oral megestrol acetate was occasionally used for hormonal therapy.

Follow-up of patients was based on information reported in the clinical histories. When information on survival or recurrence was not sufficiently detailed in the histories, death certificates were obtained and letters or telephone calls to patients and family physicians were used to obtain follow-up information. When death due to disease was the end point, we considered as censored all patients who were alive (with or without disease) at the time of follow-up or who died of a cause not related to the disease; patients who died of disease were considered uncensored. When recurrence or progression of disease was the end point, censoring was at the date of last contact or death in case of no relapse, whereas we considered uncensored all patients who had recurrence of disease.

We defined an intra-abdominal failure as a recurrence diagnosed by physical examination, radiologic imaging, or surgery and localized to the vagina, abdominal and pelvic cavities, pelvic sidewall, and para-aortic area. All other recurrences (including parenchymal liver metastasis) were considered extraabdominal.

For statistical purposes, endometrioid, endometrioid with squamous differentiation, and adenosquamous tumors were considered together. Grades 1 and 2 lesions were combined and compared with grade 3 cases. Statistical analyses were performed with Fisher's exact test for the evaluation of relationships between pairs of categorical variables. The Mann-Whitney U test was used to evaluate differences between groups in the distributions of continuous measures. Survival curves were determined by the Kaplan–Meier product-limit method. Analyses of predictors of disease-related survival (DRS) and recurrence-free survival (RFS) times were performed using the log-rank test and Cox model. Differences between groups were considered statistically significant at $P < 0.05$. SAS System 6.10 statistical software was used for the analysis.

RESULTS

Demographics and Treatment Variables

Of the 53 patients previously reported to have stage IIIA endometrial cancer, 2 were found to have a coexistent primary tumor of the ovary on histologic review [6] and were excluded from the analysis. Therefore, we analyzed 51 patients with stage IIIA endometrial cancer who had hysterectomy at our institution. Median follow-up of censored patients was 82.5 months (range, 0 to 153 months). The mean age was 62.2 years (range, 32 to 86 years), and mean body mass index was 28.7 kg/m^2 (range, 17.6 to 54.4 kg/m^2). Pelvic lymph nodes were assessed in 36 patients (71%) and para-aortic lymph nodes in 11 (22%). The mean numbers of pelvic and para-aortic lymph nodes evaluated were 14.7 (range, 1 to 48) and 4.5 (range, 2 to 11), respectively.

Adjuvant therapy consisted of irradiation in 43 patients (84%): 34 had external radiotherapy (5 also received vaginal brachytherapy, and 2 hormone therapy) and 9 (18%) had intraperitoneal administration of ^{32}P (1 also received hormone

therapy). All 34 patients who received external beam radiotherapy had the pelvis irradiated (mean, 45.825 Gy; range, 23.7 to 57.6 Gy), but 26 also had whole abdomen radiotherapy (mean, 28.777 Gy). No patient received adjuvant chemotherapy, 1 received only postoperative hormone therapy, and 7 patients received no adjuvant treatment.

Analysis of Prognosis and Sites of Failure

Although the 5-year DRS for the entire group was 88%, the 5-year RFS was 73%, with an extraabdominal failure rate of 24%. Thirty-five patients (69%) were alive with no evidence of disease, 5 (10%) died of a cause not related to the disease and were without evidence of disease at the time of death, 1 patient (2%) died of a cause not related to the disease but had disease at the time of death, and 10 patients (20%) died of disease.

Recurrences were observed in 17 patients (33%). Median time to recurrence or progression was 10 months (range, 1 to 87 months). Of the 17 recurrences, 5 had an intraabdominal and/or vaginal component, whereas 15 (88%) had an extraabdominal, distant component (3 had both). Recurrences in 7 patients had a component in the lymph node bearing areas even though 5 of the patients had previous lymph node dissection (pelvic with or without para-aortic) with negative lymph node status. It is of interest to note that of the 13 patients who had recurrence within 5 years of the diagnosis of endometrial cancer, 6 (46%) were still alive at 5 years.

In the entire population, LVI, grade 3 histologic classification, and nonendometrioid subtype appeared to be significant predictors of poor DRS and RFS ($P < 0.05$). Moreover, USI, myometrial invasion, and cervical invasion were significantly ($P < 0.05$) related to RFS (Table 1). All the significant prognostic indicators as well as the use of postoperative whole abdominal radiation or ^{32}P were entered in a Cox model. Regression analysis demonstrated that nonendometrioid histologic subtype [$P = 0.03$; relative risk (RR), 7.90] and LVI ($P = 0.04$; RR, 4.96) independently predicted poor DRS; grade 3 histologic type ($P = 0.006$; RR, 6.38) and USI ($P = 0.02$; RR, 4.47) were independent predictors of poor RFS. When we addressed the different sites of failure, univariate analysis suggested that grade 3 histology, nonendometrioid subtype, cervical invasion, myometrial invasion >50%, USI, and LVI significantly ($P < 0.05$) predicted extraabdominal recurrences (Table 1). Regression analysis, however, demonstrated that LVI ($P = 0.04$; RR, 4.99) was the only independent predictor of extraabdominal recurrences. Lymphatic failures were found in 5 of 14 patients (36%) with LVI, compared with 1 of 33 (3%) without LVI ($P = 0.006$); moreover, 3 of 4 patients (75%) with cervical invasion had lymphatic failure, compared with 4 of 47 (9%) without cervical involvement ($P = 0.006$).

Stages IIIA1 and IIIA2: Prognosis and Sites of Failure

Of the 51 patients with stage IIIA cancer, 37 were in stage IIIA1 and 14 were in IIIA2. Comparing patients with stage IIIA1 and stage IIIA2 disease, we observed that the two groups were significantly different in frequency of cervical invasion ($P = 0.004$) and administration of adjuvant radiotherapy ($P = 0.02$) (Table 2). Patients with stage IIIA1 cancer had a 5-year DRS of 86%, RFS of 79%, and extraabdominal failure rate of 15%, whereas patients with stage IIIA2 disease had a 5-year DRS of 93% ($P = 0.74$), RFS of 57% ($P = 0.04$), and extraabdominal failure rate of 43% ($P = 0.01$) (Table 1 and Fig. 1).

When we considered the 37 patients with stage IIIA1 tu-

TABLE 1
Prognostic Factors in 51 Patients with Stage IIIA Endometrial Cancer

	No. patients	5-year DRS %	5-year DRS *P*	5-year RFS %	5-year RFS *P*	5-year EAR %	5-year EAR *P*
Age, years							
≤65	31	93	0.17	73	0.69	25	0.76
>65	20	79		73		22	
BMI, kg/m^2[a]							
<30	30	89	0.37	79	0.63	18	0.68
≥30	20	87		66		31	
Grade							
1–2	35	97	0.01	91	<0.001	9	0.002
3	16	64		29		64	
Histologic subtype							
Endometrioid	38	97	0.002	86	0.003	14	0.03
Nonendometrioid	13	60		28		64	
LVI[b]							
No	33	94	<0.001	84	0.001	14	0.002
Yes	14	70		64		29	
Abdominal RT or ^{32}P							
Yes	35	82	0.43	70	0.63	25	0.84
No	16	93		79		21	
Cervical invasion							
Yes	4	75	0.95	25	0.03	75	0.02
No	47	89		76		20	
USI							
No	45	88	0.07	81	<0.001	15	<0.001
Yes	6	83		17		83	
Myometrial invasion, %							
≤50	39	92	0.16	80	0.005	15	0.001
>50	12	75		50		50	
Peritoneal cytology[a]							
Positive	41	84	0.67	76	0.40	20	0.26
Negative	9	89		67		33	
Adnexa							
Negative	42	85	0.64	71	0.80	25	0.99
Positive	9	89		77		23	
Stage							
IIIA1	37	86	0.74	79	0.04	15	0.01
IIIA2	14	93		57		43	

Note. BMI, body mass index; DRS, disease-related survival; EAR, extraabdominal recurrence; LVI, lymphovascular invasion; ^{32}P, intraperitoneal injection of phosphorus 32; RFS, recurrence-free survival; RT, radiotherapy; USI, uterine serosal involvement.

[a] One patient missing.

[b] Four patients missing.

TABLE 2
Clinical and Pathologic Characteristics of the Two Subgroups of Patients with Stage IIIA Endometrial Cancer

Characteristics	Stage IIIA1 (n = 37)		Stage IIIA2 (n = 14)		P
Median age, years	62.0		66.5		0.49
Median body mass index, kg/m^2 [a]	28.5		27.7		0.22
	No.	%	No.	%	
Grade 3	9/37	24	7/14	50	0.1
Nonendometrioid histologic subtype	8/37	22	5/14	36	0.3
Lymphovascular invasion [b]	9/35	26	5/12	42	0.47
Abdominal radiation, intraperitoneal ^{32}P	29/37	78	6/14	43	0.02
Cervical invasion	0/37	0	4/14	29	0.004

[a] One missing value.
[b] Four missing values.

mors, grade 3 histology, nonendometrioid histologic subtype, and LVI significantly predicted a poor prognosis and extraabdominal sites of failure ($P < 0.05$). In fact, patients with LVI had 5-year DRS, RFS, and rate of extraabdominal failures of 67, 67, and 22%, respectively, compared with 96 ($P = 0.004$), 92 ($P = 0.002$), and 4% ($P = 0.002$) in patients without LVI. Moreover, patients with endometrioid histologic subtype had 5-year DRS, RFS, and rate of extraabdominal failures of 96, 96, and 4%, respectively, compared with 43 ($P < 0.001$), 0 ($P < 0.001$), and 100% ($P = 0.002$) in patients with nonendometrioid histologic subtype. Furthermore, patients with grade 1-2 tumors had 5-year DRS, RFS, and rate of extraabdominal failures of 96, 96, and 4%, respectively, compared with 43 ($P < 0.001$), 14 ($P < 0.001$), and 79% ($P = 0.004$) in patients with grade 3 tumors.

The 5-year extraabdominal recurrence rate was 13% in patients with myometrial invasion ≤50 and 33% in those with myometrial invasion >50% ($P = 0.04$). Recurrence did not develop in any of the 22 patients who had stage IIIA1 cancer with endometrioid histologic subtype and without LVI [17 had whole abdominal irradiation or intraperitoneal ^{32}P (3 also had subsequent hormonal therapy), 2 had external pelvic radiotherapy, 1 had postoperative hormonal therapy, and 2 received no adjuvant therapy]. By contrast, of the 15 patients with nonendometrioid histologic subtype or LVI or both [12 were treated with whole abdomen irradiation or ^{32}P (3 had associated vaginal brachytherapy), and 3 received no adjuvant therapy], 9 (60%) had recurrence, and 7 (47%) died of disease. An extraabdominal component was present in 7 of the 9 recurrences observed in this subgroup (Table 3).

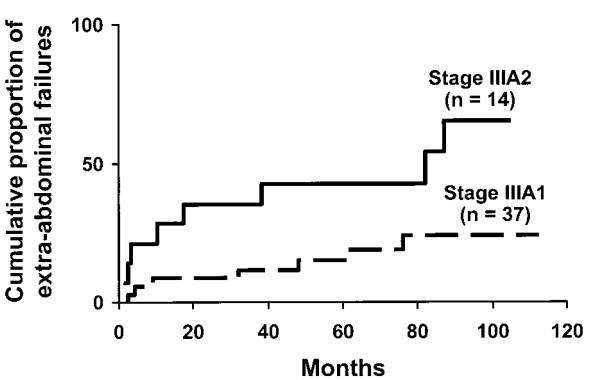

FIG. 1. Cumulative proportion of extraabdominal failures in 51 patients who had stage IIIA endometrial cancer with (stage IIIA2, 14 patients) or without (stage IIIA1, 37 patients) uterine serosal involvement or adnexal metastasis ($P = 0.01$).

Among the 14 patients with stage IIIA2 tumors, 8 were without USI (7 had adnexal involvement only, and 1 had both positive peritoneal cytologic findings and positive adnexae) and 6 had USI (2 also had positive peritoneal cytologic findings, and 1 also had both positive adnexae and positive peritoneal cytologic findings). Treatment consisted of whole abdominal radiotherapy for 6 patients (1 had associated vaginal brachytherapy), external pelvic radiation for 6 (1 had associated vaginal brachytherapy), and no adjuvant therapy for 2. Age, body mass index, LVI, grade, histologic subtype, cervical invasion, positive peritoneal cytologic findings, and treatment with whole abdominal irradiation did not significantly influence prognosis. Patients with USI had 5-year DRS, RFS, and rate of extraabdominal failures of 83, 17, and 83%, respectively, compared with 100 ($P = 0.04$), 87.5 ($P = 0.008$), and 12.5% ($P = 0.008$) in patients without USI. In all 6 patients with USI, an extraabdominal component of failure (4, lung; 1, brain; 1, scalene nodes) developed, and 5 (83%) had recurrence within 5 years of the initial operation. However, only 1 patient died of disease during the initial 5 years of follow-up and another died at 65 months. A third patient died of other causes, but with disease, at 21 months.

TABLE 3
Distribution of Intraabdominal (IAR) and Extraabdominal (EAR) Recurrences According to Risk Factors in Stage IIIA Subsets

	Stage IIIA1 (n = 37)				Stage IIIA2 (n = 14)			
	Endometrioid, no LVI (n = 22)[a]		Nonendometrioid or LVI (n = 15)[b]		USI (n = 6)[c]		No USI (n = 8)[d]	
	No.	%	No.	%	No.	%	No.	%
Failure sites								
IAR	0	0	2	13	0	0	0	0
EAR	0	0	7[e]	47	6[e]	100	2[e]	25
Total	0	0	9	60	6	100	2	25

Note. LVI, lymphovascular invasion; USI, uterine serosal involvement.

[a] Whole abdomen radiotherapy or intraperitoneal injection of phosphorus 32, 17 (3 received associated hormone therapy); pelvic radiotherapy only, 2; hormone therapy only, 1.

[b] Whole abdomen radiotherapy, 12 (3 received associated vaginal brachytherapy).

[c] Whole abdomen radiotherapy, 4 (1 received associated vaginal brachytherapy); pelvic radiotherapy, 2.

[d] Whole abdomen radiotherapy, 2; pelvic radiotherapy, 4 (1 received associated vaginal brachytherapy).

[e] One patient had an associated IAR.

DISCUSSION

Stage IIIA endometrial cancer is a rather heterogeneous substage because it includes one or more of the following conditions: adnexal involvement, uterine serosal invasion, and positive results of peritoneal cytology. However, from the literature it is sometimes difficult to ascertain the prognosis of patients with stage IIIA disease in detail because they are generally combined with patients who have other stage III disease [8], the reports have analyzed clinical stages [9–13], or various studies have analyzed collectively patients with stage III/IV tumors and positive peritoneal cytology [9, 11, 12, 14, 15] or positive adnexae [16, 17].

Isolated adnexal involvement has been reported to be a favorable occurrence of extrauterine disease [3]. Patients with isolated adnexal spread have a reported 5-year disease-free survival ranging from 71 to 86% [10, 16–18]. By contrast, serosal invasion portends a poor prognosis, with a high percentage of distant failures [19, 20]. However, the prognostic significance of positive peritoneal cytologic findings in endometrial cancer is a controversial issue [3, 21]. Positive peritoneal cytologic findings have been reported to be associated with other extrauterine sites of disease [12, 15], and although numerous investigators recognize the prognostic value of these findings [7, 11, 12, 14, 15], others do not [9, 22, 23]. We recently demonstrated that positive peritoneal cytology in patients with lymph node invasion (stage IIIC) is a significant unfavorable prognostic factor [24]. By contrast, when positive peritoneal cytologic findings are the only sign of extrauterine disease, the prognostic significance is less clear and appears to depend more on other histopathologic variables [9, 13, 25]. If positive peritoneal cytology is considered the only evidence of extrauterine disease, recurrence rates vary considerably in the literature [7–9, 15, 22]. This variation may be a reflection of incomplete surgical staging, the small number of patients analyzed, and different treatments used [3]. Risk factors in patients with isolated positive peritoneal cytologic findings have not yet been clearly established [3, 4, 21, 26]. In particular, it has not been established whether a positive peritoneal cytologic result by itself is a sign of systemic disease, with a high probability that distant hematogenous or lymphatic extraabdominal failures will develop, or whether it is a predictor of subsequent intraabdominal spread [3, 9, 15, 21, 27, 28]. The answers to these questions have important therapeutic implications. In fact, in many series (including the present) positive peritoneal cytologic disease has been treated with locoregional therapy limited to the whole abdomen and pelvis [3, 7, 8, 15, 22, 25, 26]. However, whole abdomen radiation may possibly constitute overtreatment in some low-risk patients with isolated positive peritoneal cytology [13, 25, 29], whereas it may be inadequate therapy in other patients with stage IIIA disease at high risk for distant extraabdominal failures [3, 4, 8] (Table 3). At present, the literature does not differentiate low risk from high risk in patients with stage IIIA cancer [3, 4, 21, 26]. Therefore, in the present study we analyzed patients with positive peritoneal cytologic findings as the only indication of extrauterine disease (i.e., stage IIIA1), attempting to identify a subgroup at low risk for recurrence and death, separately from patients with other sites of pelvic involvement (i.e., stage IIIA2), searching for risk factors predictive of distant extraabdominal recurrences.

In the present study, we distinguished distant extraabdominal recurrences from intraabdominal failures. Recognizing that the vagina, pelvis, and para-aortic area as well as the whole abdomen are potentially amenable to treatment with radiother-

apy, we elected to group the vagina and retroperitoneum together with intraabdominal failures. This was done to identify those patients at risk for extraabdominal spread in which radiotherapy is not sufficient treatment for the prevention of recurrent disease.

Reflecting institutional preference for managing stage III disease, most patients in this study were treated with abdominal or pelvic irradiation (or both); none were treated with systemic chemotherapy. Consequently, most identified treatment failures were extraabdominal (Table 3). The most important prognostic indicators of extraabdominal sites of failure in patients with stage IIIA1 cancer (i.e., positive peritoneal cytology only) were LVI, nonendometrioid histologic subtype, and grade 3 disease. In fact, patients who had stage IIIA1 disease with endometrioid histologic type and without LVI had an excellent prognosis (100% RFS) after locoregional abdominal therapy (Table 3). Therefore, systemic therapy with its potential associated morbidity may represent excessive treatment in patients with endometrioid stage IIIA1 disease without LVI. By contrast, patients who had stage IIIA1 disease with nonendometrioid histologic type or LVI (or both) had a significant frequency of extraabdominal failures, suggesting the need for new trials investigating adjuvant systemic therapies (Table 3). Similarly, patients with stage IIIA2 disease, especially those with USI, have an extremely high rate of extraabdominal recurrences (Tables 1 and 3). Specifically, extraabdominal failure developed in all 6 patients with USI (in 5 within 5 years), and 3 died either of (5 and 65 months) or with (21 months) disease. Therefore, new trials investigating adjuvant systemic therapy appear to be indicated in these patients as well. The prognostic significance of histologic subtype and grade in patients with extrauterine disease has been demonstrated [3, 4, 7, 30], but unfortunately, most reports did not consider the possible influence of LVI on prognosis [4, 8–12, 14, 15, 22, 23, 26].

During the study interval, we favored adjuvant therapy including the whole abdomen (i.e., whole abdominal external radiotherapy or intraperitoneal administration of ^{32}P) for patients who had positive peritoneal cytology, whereas the majority of patients with isolated spread to the adnexa or with USI received external pelvic radiotherapy (Table 3). However, as our postoperative management was not uniform during the 10-year interval, we cannot draw any definitive conclusion about the role and type of adjuvant locoregional therapy in the management of stage IIIA endometrial cancer.

In our study, 29% of patients did not have surgical assessment of the retroperitoneum. This may be a potential weakness of our data, owing to the fact that some patients who subsequently had recurrence might have had stage IIIC disease. However, we observed that most (5 of 7) nodal failures occurred in women with previous lymph node dissection and negative nodes. Consistent with our previous findings [28], both LVI and cervical invasion were predictive of nodal recurrence in the present analysis.

An interesting observation of our study is the favorable 5-year survival of stage IIIA2 patients, when considering their relatively high rate of extraabdominal failures (Table 1). This is especially evident when analyzing the subgroup of stage IIIA2 patients with USI. These findings possibly suggest a favorable prognosis for distant failures in stage IIIA endometrial cancer. However, this is not consistent with the literature [20], and our cases are too few to make a definitive statement regarding these observations.

In conclusion, we observed no significant difference in DRS in patients with stage IIIA cancer between those with positive peritoneal cytologic findings as the only indication of extrauterine disease (stage IIIA1) and those with USI or adnexal spread (stage IIIA2). However, patients with stage IIIA2 disease had a significantly lower RFS. Patients who had stage IIIA1 disease with endometrioid tumors and without LVI had an excellent prognosis (100% RFS) when given adjuvant therapy limited to the abdominal cavity. Nonendometrioid histologic subtype, LVI, and USI are strong predictors of poor prognosis and distant sites of failure. Patients with any of these factors should be considered candidates for trials testing new systemic adjuvant therapies.

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