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Treatment results in women with clinical stage I and pathologic stage II endometrial carcinoma

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Abstract. Jobsen JJ, Schutter EMJ, Meerwaldt JH, van der Palen J, van der Sijde R, Naudin ten Cate L. Treatment results in women with clinical stage I and pathologic stage II endometrial carcinoma. *Int J Gynecol Cancer* 2001;**11:**49–53.

The aim of this study is to report survival and results of therapy and possible prognostic factors in women with pathologic stage II endometrial carcinoma. Forty-two patients with pathologic stage II endometrial carcinoma were treated at the department of Radiation Oncology of the Medisch Spectrum Twente between 1987 and 1998. All patients received external radiotherapy following standard surgical procedures and no adjuvant systemic therapy was given. From the 42 patients 21 had a pathologic stage IIA and 21 stage IIB. The median follow-up was 62 months. The overall recurrence rate was 21.5% (9/42). Seven patients had distant metastasis, of which three also had locoregional recurrence, vaginal vault and/or pelvic. The presence of myometrial invasion (> ½) and/or lymph-angioinvasion showed a significant relation with distant metastasis ($P = 0.017$). Stage IIB showed more recurrences, 33% (7/21). There was a significant different 5-year disease specific survival for stage IIA and IIB, respectively, 95% and 74% ($P = 0.0311$). Patients with a differentiation grade 3 and stage IIB showed a significantly poorer ($P = 0.003$) 5-year survival of 48.6% ($P = 0.003$). Results obtained in the present series of patients are in accordance with the literature. The present treatment policy seems justified, except for patients with pathologic stage IIB and grade 3, in which a more aggressive treatment should be considered.

KEYWORDS: endometrial carcinoma, pathologic stage II, prognostic factors

Carcinoma of the endometrium is the most common malignant tumor of the female genital tract. The majority of patients (80%), presents as stage I according to the 1997 International Federation of Gynecology and Obstetrics (FIGO), which implies tumor confined to the corpus uteri[1,2]. A minority of women presenting with a clinical stage I in fact appears to have a stage II after pathologic examination of the surgical specimen.

Primary treatment of clinical stage I implies a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO). Those patients becoming a pathological stage II do not have a surgical staging.

Clinical stage II patients are treated primarily by a radical hysterectomy and pelvic lymphadenectomy. With negative lymph nodes patients are not referred for postoperative radiation irrespective of grade and/or infiltration of the myometrium (> ½).

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Although there has been a plethora of reports on results of treatment and survival of women with stage I endometrial cancer, similar reports of women with stage II disease are scarce. Furthermore, most of the reports on stage II have included women with clinical and/or surgical stage II disease, as opposed to pathologic stage II, where the stage determination is done after surgery and pathological examination.

Recommendations on treatment of pathologic stage II are not uniform, and differ from only surgery to surgery with postoperative radiotherapy[3,4]. Series are small and trials concerning treatment do not exist. Therefore, we feel it is important to present the results of our cohort of patients with pathologic stage II endometrial carcinoma, with respect to survival, treatment results, and possible prognostic factors.

Patients and methods

From 1987 to 1998 42 patients with a pathologic stage II endometrial carcinoma were referred to the department of Radiation Oncology of the Medisch Spectrum, Twente. A pathology review was done for all patients according to the 1997 FIGO classification. Patients were primarily clinically staged as having a stage I endometrial carcinoma. Of the 42 patients 41 underwent a TAH + BSO, and one patient had a supra cervical hysterectomy. Peritoneal washings were not obtained in all patients because it was not considered a standard approach.

All patients had postoperative radiotherapy to the small pelvis, which started within 6 weeks from surgery. The target volume of the external beam pelvic radiotherapy included the upper two third of the vagina and locoregional lymph nodes. The upper border was defined at the L5-S1 interspace, the caudal border extended to the inferior margin of the obturator foramen. The lateral borders included the widest opening of the bony pelvis with a 1.5-cm margin. Treatment was given on a daily basis, five times a week at 2.0 Gy per fraction. The total dose ranged from 40.0 to 46.0 Gy. Two patients had a boost irradiation with vaginal brachytherapy of 10.0 Gy. The patient, who underwent a supra cervical hysterectomy, had an external boost of 14.0 Gy. Indications for a boost were histologically positive or dubious margins. No adjuvant systemic therapy was given to any of these patients.

Because of the small number of patients the differentiation grade was divided into grade 1–2 vs. grade 3. The other histologic parameters included infiltration of more than half of the myometrium, and/or lymph-angioinvasion.

The follow-up evaluation included history and gynecological examination. CT scans, chest radiographs or blood tests were done on indication. All patients were evaluated every 3 months during 3 years and thereafter every 6 months.

Recurrences were divided into locoregional 'within the irradiation area, vagina vault and pelvic, and distant metastasis outside the irradiated area.

Statistical methods

Time to recurrence and follow-up were calculated from the time of surgery. To test for between-group differences for categorical data, chi-square tests and Fischer exact tests were used. Survival statistics were calculated by the method of Kaplan and Meier. The overall survival, due to all causes and the disease specific survival, corrected for intercurrent death, were calculated. For comparing survival distributions the logrank test was used.

Because of the small numbers a multivariate logistic regression and Cox regression were not performed.

Results

From the 42 patients with a pathological stage II, 21 had a pathological stage IIA and 21 stage IIB.

The age of the 42 patients range from 46 to 84 years with a median of 71 years. The follow-up ranged from 9 to 160 months with a median of 62 months. The patient's characteristics concerning histology are presented in Table 1.

The overall recurrence rate was 21.5% (9/42). The vaginal vault recurrence rate was 11.9% (5/42), one patient also had a pelvic recurrence. Seven patients had distant metastasis, of which three also had vaginal

Table 1. Tumor characteristics in 42 patients

Characteristics	*n*	%
Histology		
adenocarcinoma	36	85.7
adenosquamous carcinoma	6	14.3
Differentiation		
grade 1–2	28	66.7
grade 3	13	31
unknown	1	2.3
Hist. parameters		
> ½ myometrial invasion	17	40.5
lymph-angioinvasion	5	11.9
> ½ myometrial + lymph-angioinvasion	3	7.1
none	15	40.5
Peritoneal washing		
positive	1	2.4
negative	19	45.2
unknown	22	52.4

vault recurrences. The recurrence time ranged from 1 to 40 months with a median of 10 months (Table 2).

In univariate analysis we analyzed stage, vaginal vault recurrence and distant metastasis for the pretreatment factors histology, grade and myometrial invasion (> ½) and/or lymph-angioinvasion. Only the presence of myometrial invasion (> ½) and/or lymph-angioinvasion showed a significant relation with distant metastasis ($P = 0.017$). From the 25 patients with myometrial invasion (> ½) and/or lymph-angioinvasion seven (28%) had metastasis and none without these parameters.

We also analyzed stage for recurrences. Overall stage IIB showed more recurrences, 33% (7/21) ($P = 0.06$). Analyzed separately stage IIB showed more metastasis, 23%, and vaginal vault recurrences, 15%, compared to stage IIA, which was 9.5% for both. In relation to the pretreatment factors only for grade there was a trend to more vaginal vault recurrence for stage IIB with grade 3 ($P = 0.076$).

Looking at the follow-up of all 42 patients seven patients died of tumor and 10 patients due to other causes.

The 5-year overall and disease-specific survival for the 42 patients was 63.5% and 84.5%. The difference in 5-year disease specific survival for stage IIA and IIB, respectively, 95% and 74% was significant ($P = 0.031$; Fig. 1).

We also looked at the disease specific survival for stage in conjunction with grade and the presence of myometrial invasion (> ½) and/or lymph-angioinvasion. Only stage IIB in conjunction with grade 3 showed a significantly poorer 5-year survival (48.6%) ($P = 0.003$; Fig. 2). Stage IIB in conjunction with the presence of myometrial invasion (> ½) and/or lymph-angioinvasion showed a trend to a worse survival.

No patients developed severe complications after treatment, such as severe stenosis, vaginal vault necrosis, small bowel obstruction or fistulae.

Table 2. Time of onset in months and site of recurrence for 9 patients

Patient no.	Vaginal vault/pelvis	Metastasis
1		2
2	7	
3		8
4	10	12
5	12	
6	18	19
7	19/19	24
8		28
9		41

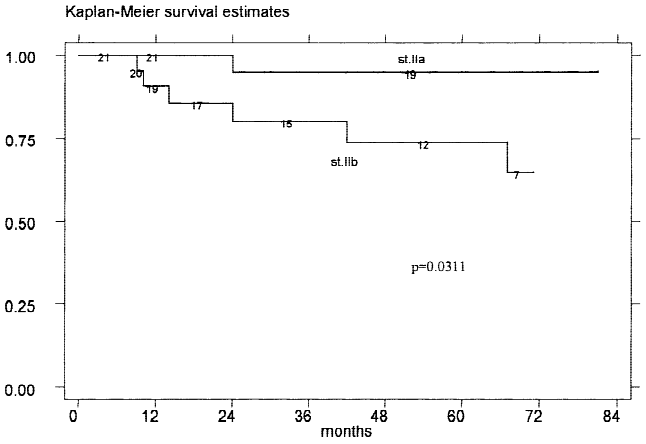

Fig. 1. The disease specific survival of 42 patients with endometrial carcinoma pathological stage IIA and IIB. (the numbers are the patients at risk)

Discussion

Our analysis of 42 pathologic stage II patients, all treated by surgery followed by external radiotherapy, showed a total recurrence rate of 21.5%. Looking at the site and the time of the recurrence (Table 2), we observed that in three of the nine patients vaginal vault recurrence was followed within 5 months by the occurrence of distant metastasis. From the nine patients with recurrences seven died of tumor. Only two patients are still alive, one with a vaginal vault recurrence and distant metastasis and one with vaginal vault recurrence only. Our analysis showed a clear trend for more recurrences in stage IIB, especially in relation to grade and the presence of myometrial invasion (> ½) and/or lymph-angioinvasion.

The majority of the literature on stage II endometrial carcinoma is limited to clinical and/or surgical stage

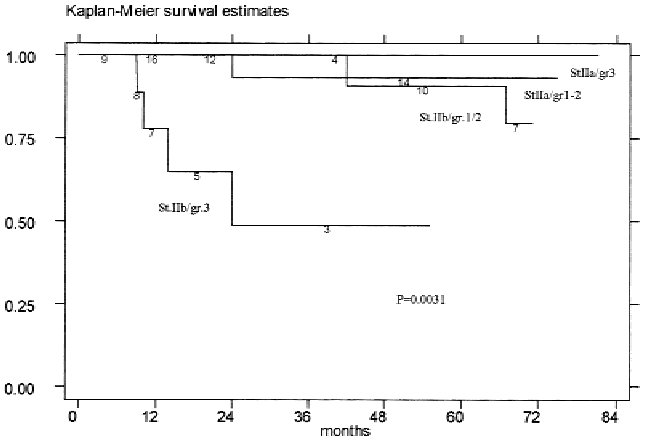

Fig. 2. The disease specific survival of 42 patients with endometrial carcinoma according to pathologic stage II and differentiation grade. (the numbers are the patients at risk)

II. With the first the tumor presents as a clinical stage II endometrial carcinoma. Surgical staging is mostly defined as exploratory laparotomy, extrafascial total abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal washings, and bilateral pelvic and periaortic lymphadenectomy or sampling.

Patients with a pathologic stage II are primarily operated upon as having a clinical stage I disease. Histological examination of the uterus reveals infiltration of the cervix, which makes it a pathologic stage IIA or IIB. These patients might have a different prognosis compared to those with clinical or surgical stage II disease. Also the treatment may have to be adjusted according to pathologic stage IIA or IIB. Whether this treatment should be a second operation with a lymphadenectomy or postoperative radiotherapy, external with or without brachytherapy, or no adjuvant therapy at all, remains the question. No prospective randomized trials are available.

In a retrospective review of 156 patients, Wolfsen demonstrated that surgical plus pathological staging is indicated to accurately determine the initial extent of the disease, and in addition, surgical staging is the strongest predictor of survival[5,]. The literature is scarce about data on pathologic stage II only.

The role of radiotherapy as an adjuvant to surgery is not clear. Data are restricted to small retrospective series and no phase III studies are available[6–10]. Poulsen looked retrospectively at the treatment of 1214 newly diagnosed carcinoma of the endometrium over a period of 2 years[8]. The primary treatment was TAH + BSO followed by external radiation. He found 105 patients with pathologic stage II. With a follow-up of more than 5 years a recurrence rate of 29% was observed. Eltabbakh showed only one recurrence (7.7%) in 13 patients treated with TAH + BSO, followed by external radiotherapy[11]. Calvin noted in a retrospective study of 44 pathologic stage II patients, treated with surgery followed by radiotherapy, a 30% recurrence rate[10]. He also showed that most of these recurrences were distant metastasis.

Weiss, in a recent analysis of 33 patient with stage II, did not see any locoregional recurrence after adjuvant external irradiation and vaginal brachytherapy[12]. He had a 9% recurrence rate, all outside the treatment area. Also Eltabbakh did not observe locoregional recurrence in 13 patients treated with TAH + BSO and external radiotherapy[11].

The 5-year survival of stage II, clinically or pathologically staged, ranges from 45 to 90%[5–7,11–17]. Our analysis of 42 pathologic stage II patients showed a 5-year disease specific survival of 84.5%.

Reisinger and Boothby found that grade was the most important predictor of survival, and infiltration of the myometrium was less significant[6,7,9,13,15].

Our results showed, in a univariate analysis, a significant relationship between stage and survival and stage with grade and survival (Figs 1 and 2). With respect to stage with myometrial invasion (> ½) and/or lymph-angioinvasion there was a clear trend (P = 0.093) for a worse survival of stage IIb in combination with this histological parameter. The latter would be in agreement with Leminen[15].

The question arises whether a more aggressive local treatment in particular for stage IIB/grade 3, external radiotherapy with vaginal brachytherapy or surgical lymphadenectomy, would result in a better prognosis for these patients. One can argue that less loco-regional recurrence also decreases the probability of distant metastasis. Looking at the short interval between the incidence of loco-regional recurrence and metastasis this hypothesis seems doubtful.

Conclusion

Looking at our results and comparing these with data of the literature it seems that the treatment policy of TAH + BSO followed by external radiotherapy to the small pelvis is still the treatment of choice for pathological stage II endometrial carcinoma. Only for stage IIB in combination with grade 3 and possibly also in the presence of myometrial invasion (> ½) and/or lymph-angioinvasion, a more aggressive treatment should be the treatment of choice. Whether this should be a more aggressive local treatment or a combination with adjuvant systemic treatment can only be answered in a randomized trial.

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