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Multicenter cohort study on treatment results and risk factors in stage II endometrial carcinoma

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Abstract. Jobsen JJ, Lybeert MLM, van der Steen-Banasik EM, Slot A, van der Palen J, ten Cate LN, Scholten A, Coen V, Schutter EMJ, Siesling S. Multicenter cohort study on treatment results and risk factors in stage II endometrial carcinoma. *Int J Gynecol Cancer* 2008;**18:**1071–1078.

The aim of this study was to report outcome data and prognostic factors from a large cohort of pathologic stage II endometrioid type endometrial carcinoma. One hundred forty-two stage IIA–B patients were included. A central histopathologic review was performed. Follow-up ranged from 2 to 217 months with a median of 61 months. End points of the study were local and locoregional recurrence rates, distant metastasis–free survival (DMFS), disease-free survival (DFS), and disease-specific survival (DSS). The local failure rate was 5.1% for stage IIA patients and 10.8% for stage IIB patients. Grade was the only significant prognostic factor for local failure. With respect to DMFS, DFS, and DSS, grade 3 showed to be the most prominent prognostic factor in multivariate analyses. Lymphvascular space involvement combined with grades 3 and 2 and myometrial invasion greater than 0.5 also showed to be significant for DMFS and DFS. Our study showed grade 3 to be the most important single independent predictive factor for locoregional and distant recurrences in endometrial carcinoma stage II.

KEYWORDS: endometrial carcinoma, outcome, prognostic factors, stage II.

Endometrial carcinoma is the most common gynecological cancer, with an annual incidence in Western countries of 15–20 per 100,000 women[1]. The majority of patients present with clinical stage I disease, which has a high cure rate. After pathologic examination of the surgical specimen, a minority of women presenting with a clinical stage I disease are upstaged to a pathologic stage II disease. Stage II disease comprises only 5–15% of cases of endometrial carcinoma. The 1988 FIGO staging for endometrial carcinoma was based on pathologic findings following surgery. Involvement of endocervical mucosa was subclassified as stage IIA and endocervical stromal extension was classified as stage IIB[2].

Resolution of the controversies regarding the optimal management of stage II endometrial carcinoma has been hampered by the relative scarcity of recent data on the outcome of pathologic stage II patients. In time, the management of stage II has evolved from preoperative or radical radiotherapy to surgery and postoperative radiotherapy[3].

Recommendations on treatment of pathologic stage II are not uniform and differ from surgery alone to surgery with postoperative radiotherapy[4–7].

The current standard management in The Netherlands for clinical stage I endometrioid type endometrial carcinoma is a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO) followed by adjuvant radiotherapy depending on generally accepted risk factors.

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The aim of this study was to report treatment outcome data and prognostic factors from a large multicenter cohort study of patients with pathologic stage II endometrioid type endometrial carcinoma after central histopathology review.

Materials and methods

Clinical data from 235 patients with endometrial carcinoma FIGO stage II diagnosed and treated between 1984 and 2000 with surgery followed by adjuvant radiotherapy were collected from seven departments of radiotherapy in The Netherlands.

The patients' charts were reviewed for the following factors: age at diagnosis, operative procedure, histology, grade, depth of myometrium invasion (MI), lymphvascular space involvement (LVSI), cervical involvement, adjuvant radiotherapy features, and follow-up data including date, site of recurrence, and patient status at last follow-up.

A central histopathology review was performed at Laboratory Pathology Oost Nederland by a single pathologist for a total of 161 patients from six departments of radiotherapy, from which the pathologic tissues were received. All pathologic sections were reviewed with special emphasis on histology, grade, depth of MI, LVSI, and extent of cervical involvement.

Stages IIA and IIB were defined according to the 1997 FIGO staging.

After pathology review, five patients were restaged as stage IIIC and one patient as stage IC and were excluded from the study. Ten patients with a nonendometrioid type endometrial carcinoma were excluded and one patient was rediagnosed as having cervical cancer. No follow-up was available on two patients. One hundred forty-two stage IIA–B endometrioid type endometrial carcinoma patients remained in the study.

All patients underwent primary surgery. Standard surgery for clinical stage I endometrial carcinoma was a TAH + BSO. In case of clinical stage II, the surgery is TAH + BSO and staging lymphadenectomy or type Wertheim radical hysterectomy. One hundred thirty patients underwent TAH + BSO, five patients had a TAH + BSO and staging lymphadenectomy, four patients underwent a type Wertheim radical hysterectomy, two patients had a vaginal hysterectomy, and one patient had a subtotal hysterectomy. Peritoneal washings were not obtained in all patients because it was not considered a standard procedure. Postoperative imaging to identify occult metastatic disease was not standard procedure. No adjuvant systemic therapy was given.

Radiotherapy

Pathologic stage II endometrial carcinoma after TAH + BSO was a generally accepted indication in The Netherlands for postoperative external radiotherapy with or without vaginal vault irradiation, depending on the extension of the tumor and/or the department.

One hundred thirty-eight patients received adjuvant postoperative radiotherapy to the pelvis. Four patients received brachytherapy to the vaginal vault alone. The target volume of the external beam pelvic radiotherapy included the upper two thirds of the vagina and the locoregional nodes. The upper border was defined at the L5–S1 interspace; in 24 patients, the field was extended to include the fifth lumbar vertebra, the lower border to the inferior margin of the obturator foramen. The lateral borders included the bony pelvic sidewalls with a 1.5-cm margin. The external dose ranged from 40.0 to 46.0 Gy with 2.0 Gy fractions five times a week or 2.3 Gy fractions four times a week. Two patients did not complete their external radiotherapy course. Four patients received an external boost, instead of brachytherapy to the vaginal vault, ranging from 9.2 to 14 Gy. Brachytherapy to the vaginal vault was not considered to be a standard procedure. For stage IIA, 44.1% (26/59) of patients received brachytherapy compared to 56.6% (47/83) in stage IIB.

Statistical methods

All analyses are based on the results of the histopathologic review. 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 were used. The local failure rate (LFR) is defined as the number of vaginal recurrences during a certain period. The locoregional failure rate (LRFR) is defined as the number of vaginal and/or pelvic recurrences during a certain period. Distant metastases were regarded as extrapelvic recurrences, for instance, abdomen, para-aortal, liver, lung, and bone. Distant metastasis–free survival (DMFS) is defined as survival without distant metastasis in patients. Disease-free survival (DFS) is defined as survival without any recurrence. Survival statistics were calculated by the method of Kaplan and Meier. The disease-specific survival, corrected for intercurrent death, was calculated. This means that data on patients who died of other causes were regarded as censored data. For comparing survival distributions, the log-rank test was used and a multivariate Cox regression was performed. Variables that were univariately related to the outcomes of

interest ($P < 0.10$) were entered in multivariate Cox regression analyses.

To determine possible predictive or prognostic factors, we incorporated two combinations of histologic features; grade + LVSI and MI + LVSI.

Results

Among 142 patients with a pathologic stage II endometrial carcinoma, 59 had a pathologic stage IIA and 83 had stage IIB.

The age at diagnosis ranged from 36 to 86 years with a median of 69 years. Follow-up ranged from 2 to 217 months with a median of 61 months and a mean of 75 months. The patients' clinical, histologic, and radiotherapy characteristics are presented in Table 1. Stage IIB showed significantly more LVSI and deep MI compared to stage IIA.

The pathologic review demonstrated in Table 2 showed significant differences before and after review.

Local and locoregional recurrence

The 5-year LFR was 8.5% (12/142), nine patients isolated in the vaginal vault and three patients in combination with a pelvic recurrence. All vaginal failures were diagnosed within 24 months.

In univariate analysis, we analyzed the clinical, histologic, treatment factors, and the two combinations for LFR. Only grade showed significance in the log-rank test ($P = 0.004$). Concerning the two combinations, grade + LVSI also showed significance ($P = 0.002$).

We also looked at the incidence of vaginal recurrence by stage and noticed 10.8% (9/83) for stage IIB and 5.1% (3/59) for stage IIA. With respect to vaginal vault brachytherapy as a boost after external irradiation, all stage IIA recurrences were grade 2, two had not received brachytherapy and one had. For stage IIB, seven patients were grade 3, four patients without brachytherapy and three with. Two patients had grade 2, one with and one without brachytherapy. In stage IIB, grade 3 did not show significance for LFR in relation to brachytherapy.

On top of the nine vaginal recurrences, three had vaginal and pelvic and three isolated pelvic recurrences, making 15 patients with locoregional recurrences. The 5-year LRFR was 9.9%, 5.1% for stage IIA and 13.3% for stage IIB. In univariate analysis, we analyzed the clinical, histologic, and treatment factors for LRFR. Only differentiation grade showed a significant relation with LRFR ($P = 0.002$). For the two combinations, only grade + LVSI showed significance ($P = 0.006$).

Table 1. Patient and histologic characteristics in 142 patients according to stage

Characteristics	Stage IIA 59 (%)	Stage IIB 83 (%)	*P*
Age (years)			
<60	12 (20.3)	18 (21.7)	NS
≥60	47 (79.7)	65 (78.3)	
Grade			
1	26 (44.1)	28 (33.8)	
2	22 (37.3)	27 (32.5)	NS
3	10 (16.9)	27 (32.5)	
Unknown	1 (1.7)	1 (1.2)	
MI			
>0.5	29 (49.2)	67 (80.7)	<0.001
<0.5	29 (49.2)	16 (19.3)	
Unknown	1 (1.6)	0	
LVSI			
Yes	7 (11.9)	32 (38.6)	<0.001
None	52 (88.1)	51 (61.4)	
MI ± LVSI			
<0.5	28 (47.5)	12 (14.5)	
<0.5 + LVSI	1 (1.7)	4 (4.8)	<0.001
>0.5	23 (38.9)	39 (47)	
>0.5 + LVSI	6 (10.2)	28 (33.7)	
Unknown	1 (1.7)	0	
Grade ± LVSI			
Grade 1	26 (44.1)	23 (27.7)	
Grade 1 + LVSI	0	5 (6.0)	
Grade 2	17 (28.8)	16 (19.3)	
Grade 2 + LVSI	5 (8.5)	11 (13.3)	
Grade 3	8 (13.6)	12 (14.5)	0.024
Grade 3 + LVSI	2 (3.4)	15 (18.1)	
Unknown	1 (1.7)	1 (1.2)	
External radiotherapy			
Small pelvis	45 (76.3)	69 (83.1)	
Pelvis + L5	12 (20.3)	12 (14.5)	NS
None	2 (3.4)	2 (2.4)	
Total dose (Gy)			
28.0/36.8	1 (1.7)	1 (1.2)	
40–42	19 (32.2)	32 (38.6)	
46	37 (62.7)	48 (57.8)	NS
None	2 (3.4)	2 (2.4)	
Fraction dose (Gy)			
2.0	52 (88.1)	70 (84.3)	
2.3	5 (8.5)	11 (13.2)	NS
Brachytherapy			
Yes	26 (44.1)	47 (56.6)	
None	33 (55.9)	36 (43.4)	NS
Dose brachytherapy (Gy)			
8–10	3 (5.1)	10 (12.1)	
14–15	10 (16.9)	21 (25.3)	
20.0	11 (18.6)	14 (16.9)	NS
33.6–40.0	2 (3.4)	2 (2.4)	
None	33 (55.9)	36 (43.4)	

NS, not significant.

Distant metastasis–free survival

The 5-year DMFS was 80.7%, with no difference between stage IIA and IIB. None of the clinical- or treatment-related factors had influence on DMFS in

Table 2. Differences in pathologic characteristics for and after pathologic review in 161 patients with endometrial cancer stage II

	Before review, $n = 161$ (%)	After review, $n = 161$ (%)	P
Cervical involvement			
Endocervical gland	88 (54.7)	65 (40.4)	
Stroma	73 (45.3)	90 (55.9)	<0.001
None		6 (3.7)	
Grade			
1	32 (19.9)	56 (34.8)	
2	77 (47.8)	54 (33.5)	<0.001
3	42 (26.1)	45 (27.9)	
Unknown	10 (6.4)	6 (3.7)	
Myometrial invasion			
<0.5	41 (25.5)	48 (29.8)	
>0.5	110 (68.3)	107 (66.5)	<0.001
Unknown	10 (6.2)	6 (3.7)	
LVSI			
Yes	35 (21.7)	46 (28.6)	
None	126 (78.3)	115 (71.4)	<0.001

univariate analyses and were not taken into the multivariate analyses. Only the histologic variables (grade 3, MI >50% and LVSI) showed significance in univariate analyses. In multivariate analyses, grade 3 showed to be the most important prognostic factor (Table 3). LVSI was only significant in combination to MI greater than 0.5 and grade 3.

Disease-free survival

The 5-year DFS was 77.4%, 80.9% for stage IIA and 75% for stage IIB (Fig. 1).

None of the clinical- or treatment-related factors had influence on DFS in univariate analyses and were not taken into the multivariate analyses. Only the histologic variables showed significance in univariate analyses (Table 4). In multivariate analyses, grade 3 showed to be the most prominent prognostic factor, even in combination with LVSI. LVSI was only significant in combination with grade and borderline significant with MI greater than 0.5.

The 5-year DFS by grade is shown in Figure 2 and was 90.1% grade 1, 77.9% grade 2, and 56.2% grade 3, respectively ($P = 0.0012$).

Disease-specific survival

The 5-year disease-specific survival was 79.7%, with 84.4% for stage IIA and 76.6% for stage IIB. In the multivariate Cox regression analyses, grade 3 (HR 9.32; 95% CI 2.46–35.28; $P = 0.001$), grade 3 + LVSI (HR 6.17; 95% CI 1.57–24.31; $P = 0.009$), and grade 2 + LVSI (HR 5.94; 95% CI 1.41–24.95; $P = 0.015$) were prognostic factors. MI greater than 0.5 (HR 2.94; 95% CI 0.98–8.85; $P = 0.054$) tended to be relevant for the prognosis.

Discussion

This study of a large series of patients with pathologic stage II endometrioid type endometrial carcinoma demonstrated a 5-year DFS of 77.4%, 80.9% for stage IIA and 75% for stage IIB. Overall grade turned out to be the major prognostic factor with regard to loco (-regional) failure, DMFS, and DFS. LVSI was not an independent prognostic factor, only in combination with grade or MI.

Several limitations of this study should be noted. First, it is a retrospective analysis encompassing a 15-year period; second, it is a multicenter study, with the possibility of patient selection. The indications for adjuvant postoperative radiotherapy in The Netherlands for FIGO stage II endometrial carcinoma following TAH + BSO were uniform, but the indication for vaginal brachytherapy boost differed between the institutions. Grade, MI, and/or LVSI in stage II did not have any implication for adjuvant therapy. So the selection will not be a major bias.

The central pathologic review revealed significant differences with the original report on all pathologic features concerned, emphasizing the value of pathologic reviews in retrospective and prospective studies in endometrial carcinoma. The importance of central pathologic review is paramount, the key strong point of this study.

Tumor grade and MI are well-known risk factors for subsequent recurrence in endometrial carcinoma[4,8–12]. LVSI is related to the depth of MI in endometrial carcinoma and has both prognostic and therapeutic significance. Prognostically it correlates with extrauterine spread, lymph node metastasis, recurrence, and tumor-related death[13–15]. Therapeutically, its presence is interpreted as a potential for undetected extrauterine disease and an indication for adjuvant therapy[13,16–18]. Some have considered cervical stromal involvement to be a separate risk factor, but it is unclear whether this is an independent risk factor as it is usually associated with other risk factors[9]. Finally, randomized trials have shown age to be an independent risk factor, which we could not confirm[4].

The study of Honore and Hanson[18] in 2006 showed that the depth of MI is a significant risk factor for LVSI. This study included 314 cases of endometrial carcinoma reviewed by a single pathologist. In our study, we revealed that MI greater than 0.5 in combination with LVSI was an even stronger prognostic risk factor than the two factors separately. Also the risk of

Table 3. The univariate and multivariate analyses by Cox regression analysis for DMFS with 142 patients with a pathologic stage II endometrial carcinoma

Age + pathologic variables	Univariate *P* value	HR (95% CI)	Multivariate *P* value	HR (95% CI)
Age (years)				
>59	—	1.00		
<60	0.731	0.8 (0.32–2.244)		
Stage				
IIA	—	1.00		
IIB	0.802	1.1 (0.49–2.47)		
Grade				
1	—	1.00	—	1.00
2	0.292	1.8 (0.59–5.57)	0.445	1.6 (0.49–4.87)
3	**0.006**	4.3 (1.52–12.31)	**0.048**	3.1 (1.01–9.64)
Depth of MI (%)				
<50	—	1.00	—	1.00
>50	**0.017**	5.8 (1.37–24.62)	**0.046**	4.5 (1.02–19.56)
LVSI				
None	—	1.00	—	1.00
Present	**0.014**	2.7 (1.2–5.9)	0.390	1.5 (0.62–3.47)
MI ± LVSI				
<0.5	—	1.00	—	1.00
<0.5 + LVSI	1.000	1.00	1.00	1.00
>0.5	0.097	3.6 (0.79–16.17)	0.088	3.7 (0.82–16.79)
>0.5 + LVSI	**0.006**	8.2 (1.84–36.74)	**0.025**	5.8 (1.25–26.66)
Grade ± LVSI				
Grade 1	—	1.00		1.00
Grade 1 +LVSI	**0.024**	7.9 (1.32–47.51)	0.070	5.3 (0.87–32.09)
Grade 2	0.344	2.1 (0.46–9.21)	0.409	1.9 (0.42–8.41)
Grade 2 + LVSI	0.053	4.4 (0.98–19.61)	0.079	3.8 (0.86–17.19)
Grade 3	**0.010**	6.2 (1.54–24.72)	**0.009**	6.4 (1.61–25.81)
Grade 3 + LVSI	**0.005**	7.2 (1.81–28.98)	**0.027**	4.8 (1.19–19.65)

Statistically significant values are bolded.
MI, myometrial invasion; LVSI, lymph vascular space involvement.

LVSI increases significantly with increasing grade, which might lead to higher relative risk in the combination of the two, which was indeed confirmed by our study.

Many studies trying to identify prognostic factors for distant metastasis include stage I and/or II patients. Grade, age, and MI are the most important factors found[4,19,20].

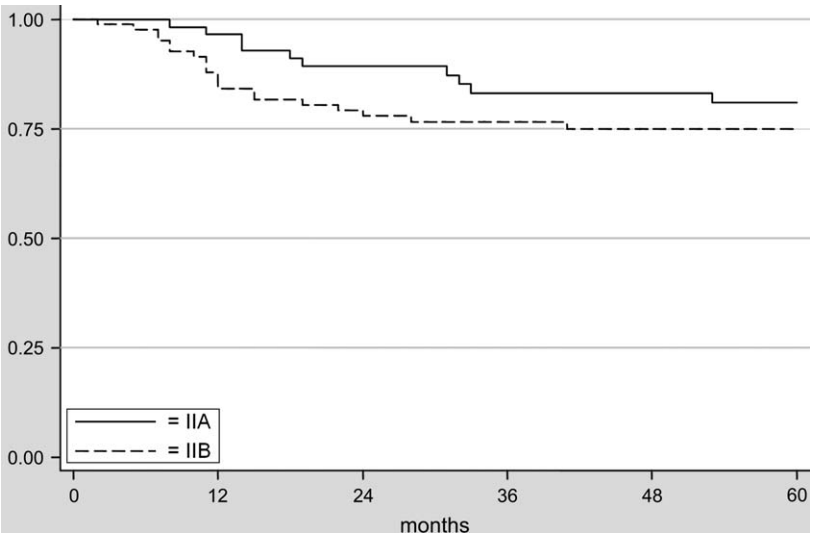

Figure 1. DFS for 142 stage II endometrioid type endometrial carcinoma patients according to stage.

Table 4. Univariate and multivariate analyses by Cox regression analysis for DFS with 142 patients with a pathologic stage II endometrial carcinoma

Age + pathologic variables	Univariate *P* value	HR (95% CI)	Multivariate *P* value	HR (95% CI)
Age (years)				
>59	—	1.00		
<60	0.428	0.7 (0.26–1.77)		
Stage				
IIA	—	1.00		
IIB	0.281	1.5 (0.71–3.24)		
Grade				
1	—	1.00	—	1.00
2	0.125	2.3 (0.79–6.78)	0.195	2.1 (0.69–6.15)
3	**0.001**	5.6 (2.05–15.57)	**0.007**	4.4 (1.49–12.97)
Depth of MI (%)				
<50	—	1.00	—	1.00
>50	**0.025**	3.3 (1.16–9.52)	0.095	2.5 (0.85–7.51)
LVSI				
None	—	1.00	—	1.00
Yes	**0.011**	2.5 (1.24–5.22)	0.428	1.4 (0.63–3.03)
Grade ± LVSI				
Grade 1	—	1.00	—	1.00
Grade 1 + LVSI	**0.026**	7.7 (1.28–45.99)	0.058	5.9 (0.94–37.27)
Grade 2	0.188	2.6 (0.62–10.94)	0.216	2.5 (0.59–10.34)
Grade 2 + LVSI	**0.019**	5.5 (1.33–23.25)	**0.027**	5.1 (1.21–21.55)
Grade 3	**0.001**	8.6 (2.28–32.49)	**0.001**	8.9 (2.36–33.81)
Grade 3 + LVSI	**0.002**	8.7 (2.26–33.88)	**0.008**	6.6 (1.64–26.49)
MI + LVSI				
<0.5	—	1.00	—	1.00
<0.5 + LVSI	1.00	0	1.00	0
>0.5	0.236	2.0 (0.64–6.15)	0.217	2.0 (0.66–6.35)
>0.5 + LVSI	**0.005**	4.8 (1.59–14.76)	0.051	3.1 (0.99–9.79)

Statistically significant values are bolded.
HR, hazard ratio; MI, myometrial invasion; LVSI, lymph vascular space involvement.

Pitson analyzed 170 patients with surgicopathologic stage II[6]. The prognostic factors identified were similar to those known to predict outcome in stage I. Factors significant for relapse were age, grade, and LVSI. Factors significant for DFS were age, LVSI, and stage.

In our analysis, we noticed a difference in predictive factors for recurrence between local and distant

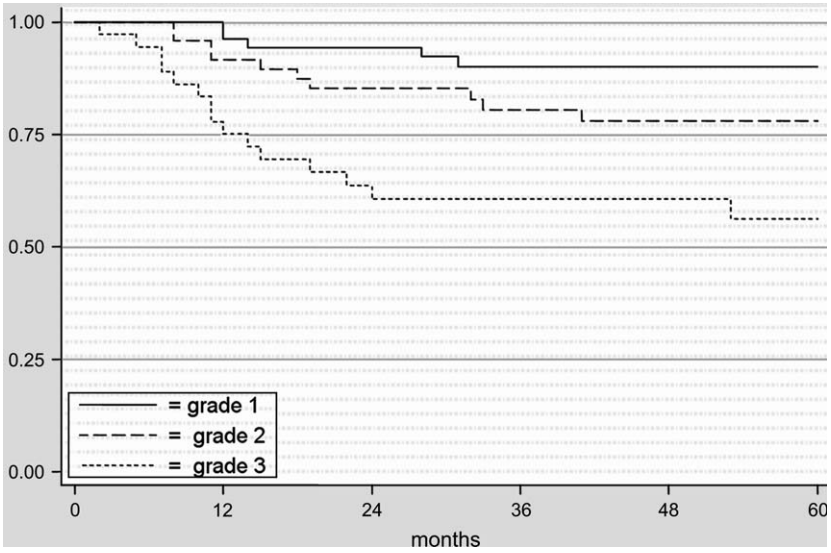

Figure 2. DFS for 142 stage II endometrioid type endometrial carcinoma patients according to grade.

failures. For local control, the only factor seems to be grade. Other factors including MI, LVSI, and age were not significant. Only the combination of LVSI + grade showed significance. With regard to distant metastasis, we demonstrated the impact of grade, LVSI, and MI on the outcome. The impact of the combination of LVSI + MI greater than 0.5 and LVSI + grade 3 was even greater than for MI greater than 0.5 and grade 3 separately. In addition, grade 3 showed a hazard ratio of 6.4 compared to a hazard ratio of 4.8 for grade 3 + LVSI, emphasizing the importance of grade 3 as a predictive factor for distant metastasis. Age did not have an effect on distant relapse.

Due to the low prevalence of stage II endometrial carcinoma, previous studies are mainly retrospective and small.

Eltabbakh and Moore[21] showed no recurrences in 20 stage II patients treated with TAH + BSO external radiotherapy and vaginal vault brachytherapy. Thirteen patients were treated with TAH + BSO and external radiotherapy, one of those showed recurrence. Weiss *et al*.[22] published their results on 33 stage II patients treated with TAH + BSO external radiotherapy and vaginal vault brachytherapy. They showed a 79% DFS, three relapses all grade 3.

Calvin *et al*.[23] analyzed 44 stage II patients all treated with TAH + BSO and postoperative radiotherapy. They had a 72.4% DFS. The predominant site of recurrence was extrapelvic (27%), with only 4.5% pelvic recurrence. MI was the only significant prognostic factor in this series.

With regard to the use of vaginal vault irradiation as a boost after external irradiation, the small number of events makes it hard to draw any definitive conclusions. It seems that the value for stage IIA is limited and can even be regarded as overtreatment. A limitation of this series is the number of patients and the small number of events in particular with regard to MI and age.

Most studies focus on DFS and overall survival with regard to prognostic factors. Our study showed a 5-year incidence rate for all recurrences of 21.9% (30/137) resulting in a 76.5% DFS. In multivariate analysis, grade 3 was shown to be the only single significant prognostic factor. In combination with grade and MI, LVSI was also shown to be an independent prognostic factor.

In conclusion, the current treatment, surgery followed by adjuvant radiotherapy for stage II endometrial carcinoma, showed a 5-year LFR of 5.4%. In contrast, the distant recurrence rate was 19.7%, which emphasizes the need for an effective adjuvant systemic treatment. Further studies should be focused on the aspect of distant recurrences. Our study showed grade 3 to be the most important single independent predictive factor for locoregional and distant recurrences in endometrial carcinoma stage II. The value of MI as an independent factor seems to be limited to distant recurrences in combination with LVSI. LVSI did not show to be an independent predictive factor for recurrence. In combining risk factors, LVSI in combination with grade 3 or MI greater than 0.5 seems to be highly predictive for distant recurrences.

Addendum

The contribution of the different departments was 45, 29, 25, 25, 8, and 7 patients, respectively.

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