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Original Research Article

The number of metastatic sites for stage IIIA endometrial carcinoma, endometrioid cell type, is a strong negative prognostic factor

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ABSTRACT

The aim of this study was to look at the impact of the number of sites with tumour involvement on outcome for patients with stage IIIA endometrioid-type endometrial carcinoma.

Patients and methods. 141 patients stage IIIA were included. A central histopathological review was performed. Patients staged solely on the presence of a positive peritoneal washing were excluded. Follow-up ranged from 2 to 217 months with a median of 43 months. Endpoints of the study were locoregional recurrence rates, distant metastasis-free survival (DMFS), disease-free survival (DFS) and disease-specific survival (DSS).

Results. In multivariate analyses the number of involved sites showed to be the only independent significant variable for DMFS, DFS, and DSS with a Hazard Ratio of 2.1, 2.2, and 2.2, respectively. The DSS was significantly related to the number of involved sites, with a 5-year DSS of 70.4% for one site, 42.8% for two sites, and 43.9% for three sites, respectively ($p = 0.001$).

Conclusion. The number of involved sites outside the corpus uterine for stage IIIA seems to be a strong negative prognostic factor for stage IIIA endometrial carcinoma.

Introduction

Endometrial carcinoma is the most common malignancy of the female genital tract [1]. In the Netherlands about 1695 cases are yearly diagnosed [2]. The primary treatment for localized clinical stage I endometrial cancer is surgery, which includes total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO), and assessment of the peritoneal fluid, often followed by radiation therapy [3]. In 1988, the International Federation of Gynaecology and Obstetrics (FIGO) mandated the staging of endometrial cancer to be changed from a clinical staging system to a surgical staging system because of the inaccuracies of the former. Staging of the disease is now based on pathological criteria after initial resection and evaluation.

Patients considered at high risk for recurrence of disease and death from cancer includes patients with endometrioid adenocarcinoma stage III and IV and patients with uterine papillary serous and/or clear-cell carcinoma regardless of stage.

Stage IIIA endometrial carcinoma is defined as tumour involvement either as direct extension or metastasis to serosa, adnexa and or cancer cells in peritoneal washings. Due to the definition of stage IIIA the number of sites with tumour involvement differs largely among patients, which might have an impact on outcome.

Approximately 10% of patients with clinically confined endometrial carcinoma are found postoperatively to have involvement of the serosa, adnexa, or peritoneal washings [4].

Most papers regarding stage IIIA are small and focus on the involvement of one specific site, like extension to the adnexa, serosa,

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or peritoneal washings [5–10]. To our knowledge the number of involved sites was mentioned in only one study before [11]. Since several reports have shown that positive peritoneal cytology is not an independent prognostic factor if endometrial cancer is limited to the uterus we excluded those patients from our study [9,10,12–14].

Therefore it was the aim of this study to look at the impact of the number of sites with tumour involvement on outcome for patients with stage IIIA endometrioid-type endometrial carcinoma.

Materials and methods

All patients with FIGO stage IIIA endometrial carcinoma from 1987 through 2005 of six institutes in the Netherlands were identified. Stage IIIA was defined according to the 1997 FIGO. Those with a stage IIIA based solely on cancer cells in ascites or peritoneal washings were excluded from the study.

The clinical data of 184 patients of six radiotherapy institutions were collected from the charts: age at diagnosis, surgical procedure, histology, grade, depth of myometrium invasion, lymph vascular space involvement (LVSI), cervical involvement, adjuvant radiotherapy features, follow-up data (date and site of recurrence), and vital status.

Pathologic sections were received from 160 patients. A central histopathology review was performed at the Laboratory of Pathology Oost Nederland by a single pathologist. All pathologic sections were reviewed on: histology, grade, depth of myometrium invasion, LVSI, extent of cervical involvement, and extension of the tumour outside the uterus. Infiltration of serosa, tube, ovary, parametrium, peritoneum or bowel was also recorded. After the pathology review and restaging, patients with a non-endometrioid type endometrial adenocarcinoma were excluded. Four patients showed papillary serous adenocarcinoma, 8 clear cell carcinoma, 2 carcinosarcoma, and 4 serous adenocarcinoma. From one patient no follow-up was available, leaving 141 patients for further analysis. The analyses were done only on the reviewed patients.

The presence of a positive peritoneal washing was not primarily used as a variable for staging, but as an independent variable in the analysis.

Treatment

All patients were primarily operated on. Standard surgery for clinical stage I endometrial carcinoma was TAH + BSO. In case of a suspected clinical stage II, the surgery was TAH + BSO and staging lymphadenectomy or Wertheim radical hysterectomy. One hundred and twenty-six patients (89,4%) had TAH + BSO, five patients underwent TAH with staging procedure, 5 Wertheim , 3 vaginal hysterectomy, one TAH + BSO with lymphadenectomy, and one supra cervical hysterectomy.

Postoperative imaging to identify occult metastatic disease was not standard procedure. No adjuvant systemic therapy was given.

Pathological stage IIIA 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 tumour and/or the radiotherapy department.

Nearly all patients, 97.2% (137/141) received postoperative pelvic external radiotherapy. The target volume included the upper two third of the vagina and the loco regional nodes. The upper border was defined at the L5-S1 interspaced; the caudal border was defined 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. The external dose ranged from 20.0 to 50.0 Gy in 1.0–2.3 Gy fractions 4–5 times a week. Of the 137 patients the majority (78.8%) received 46.0 Gy in 2.0 Gy fractions 5 times a week. Of the remaining patients 4.4% received 50.0 Gy and 16.8% received a dose ranging between 30.0 and 45.0 Gy. A boost by brachytherapy with a total dose range of 540 to 2000 cGy was received by 30.7%.

Four patients received total abdominal external radiotherapy of 20.0 Gy in 1.0 Gy fractions followed by a boost to the pelvic with doses of 20.0–24.0 Gy in 2.0 Gy fractions.

Statistical methods

Time to recurrence and last date of follow-up were calculated from the time of surgery. To test for between-group differences for categorical data, Chi-square tests were used. The loco-regional free survival (LRFS) is defined as the number of vaginal and/or pelvic recurrences. Abdominal recurrence was regarded as recurrence within the abdomen but outside the pelvic. Distant metastases were regarded as extra pelvic recurrences, e.g. abdomen, para-aortal, liver, lung, and bone. The distant metastasis-free survival (DMFS) is defined as survival without distant metastasis. The endpoint for the survival analysis was disease specific survival (DSS) and overall survival, with censoring at date of last contact or death due to other causes than endometrial carcinoma. Survival statistics were calculated by the method of Kaplan and Meier. For comparison of survival distributions the log rank test was used. Variables that were univariately related to the outcomes of interest ($p<0.05$) were entered in a multivariate Cox regression analysis.

The primary analyses were conducted with the number of sites with tumour involvement ranging from one through three. A secondary analysis was performed with one site versus two or more sites.

All analyses are based on the histopathological reviewed data.

Results

The range of age at diagnosis was 38–87 years, with a median of 67 years. Follow-up ranged from 2 to 217 months with a median of 43 months and a mean of 60 months.

The pathological review demonstrated significant differences between the first and second review (Table 1).

Heterogeneity of stage IIIA

This series showed six possible sites of involvement outside the corpus of the uterus; ovary, uterine serosa, parametria, tube, peritoneum, and bowel, together with a wide diversity in combinations of these sites. We found 29 combinations for stage IIIA in 141

Table 1
Differences in pathologic characteristics for and after pathological review in 141 patients with endometrial carcinoma stage IIIA.

	Before review $n=141$ (%)	After review $n=141$ (%)	p-value
Differentiation grade			
Grade 1	33 (23.4)	55 (39.0)	
Grade 2	58 (41.1)	46 (32.6)	<0.001
Grade 3	46 (32.6)	40 (28.4)	
Unknown	4 (2.8)	0	
Myometrium invasion			
<1/2	27 (19.1)	30 (21.3)	
>1/2	108 (76.6)	111 (78.7)	<0.001
Unknown	6 (4.3)	0	
LVSI			
Yes	37 (26.2)	59 (41.8)	
None	100 (70.9)	82 (58.2)	<0.001
Unknown	4 (2.8)	0	
Cervical involvement			
Endocervical gland	24 (17.0)	13 (9.2)	
Stroma	39 (27.7)	56 (39.7)	<0.001
None	63 (44.7)	70 (49.6)	
Unknown	15 (10.6)	2 (1.4)	

Table 2
Tumour and treatment characteristics of 141 women with stage IIIA endometrial carcinoma according to the number of involved sites.

Characteristics	One site $n=89$ (%)	Two sites $n=34$ (%)	Three sites $n=18$ (%)	p-value
Age				
<60 years	27 (30.3)	6 (17.6)	6 (33.3)	
≥60 years	62 (69.7)	28 (82.4)	12 (66.7)	ns
Differentiation grade				
Grade 1	44 (49.4)	8 (23.5)	3 (16.7)	
Grade 2	24 (27.0)	15 (44.1)	7 (38.9)	0.018
Grade 3	21 (23.6)	11 (32.4)	8 (44.4)	
Myometrium involvement				
<1/2	23 (25.8)	5 (14.7)	2 (11.1)	
>1/2	66 (74.2)	29 (85.3)	16 (88.9)	ns
Lymph vascular space involvement				
Yes	34 (38.2)	14 (41.2)	11 (61.1)	
None	55 (61.8)	20 (58.8)	7 (38.9)	ns
Cervical involvement				
None	54 (60.7)	11 (32.3)	5 (27.8)	
Endocervical glands	7 (7.9)	3 (8.8)	3 (16.7)	
Stroma	27 (30.3)	19 (55.9)	10 (55.6)	0.037
Unknown	1 (1.1)	1 (2.9)	0	
Peritoneal washings				
Negative	29 (32.6)	8 (23.5)	0	
Positive	13 (14.6)	8 (23.5)	5 (27.8)	0.054
Unknown	47 (52.8)	18 (53.0)	13 (72.2)	
Target volume radiotherapy				
Abdomen + pelvic	2 (2.2)	1 (2.9)	1 (5.6)	
Small pelvic	87 (97.8)	33 (97.1)	17 (97.4)	ns
External dose				
20.0–30.0 Gy	3 (3.4)	2 (5.9)	1 (5.6)	
36.0–45.0 Gy	12 (13.5)	3 (8.8)	6 (33.3)	ns
46.0–50.0 Gy	74 (83.1)	29 (85.3)	11 (61.1)	
Brachytherapy				
Yes	28 (31.5)	14 (41.2)	2 (11.1)	
None	61 (68.5)	20 (58.8)	16 (88.9)	ns

patients. Involvement of one site was found in 63.1% (89/141), two sites in 24.1% (34/141), and three sites in 12.8% (18/141). Involvement of both ovary, or tube, or parametria was regarded as two sites involved. The tumour and treatment characteristics of all 141 patients according to the number of involved sites are shown in Table 2.

A significant relation between number of sites involved on the one hand and grade of differentiation, and cervical involvement on the other hand was observed. Of patients with three sites involved 44.4% showed a grade 3 tumour as compared to 32.3% for patients with two sites, and 23.6% for patients with one site involved ($p=0.018$). No cervical involvement was seen in 60.7% of patients for one site, 32.3% for two, and 27.8% for three sites ($p=0.037$).

Separate analysis for one versus more than one site involved showed significance for grade of differentiation ($p=0.004$), cervical involvement ($p=0.003$), and peritoneal washings ($p=0.019$).

Loco-regional recurrence

The incidence of loco-regional recurrence was 11.4% (16/141), and consisted of 7 vaginal recurrences, 7 pelvic recurrences, and 2 patients with a vaginal and pelvic recurrence (Table 3). The 2-, 5- and 7-year LRFS according to the number of involved sites was 93.0%, 91.6% and 91.6% for one site, 88.7%, 78.2% and 78.2% for two sites, and 77.4%, 77.4% and 77.4% for three sites, respectively. For more than one site this was 85.0%, 77.6% and 77.6%, respectively. The time to loco-regional recurrence ranged from 2 to 85 months with a median of 13.5 months.

In a univariate analyses the presence of LVSI was the only variable showing borderline significance ($p=0.064$) in relation to the number of involved sites. All other clinical, histological and treatment-related variables did not show any significance.

Distant metastasis

The incidence rate for distant metastasis- all recurrences outside the pelvic including abdominal recurrences, was 43.9% (62/141). (Table 3) The 2-, 5- and 7-year DMFS was 68.6%, 55.7%, and 51.6%. The time to distant metastasis ranged from 1 to 154 months with a median of 14 months. According to the number of involved sites at 2 , 5 and 7 years the DMFS was 80.0%, 67.8% and 63.3% for one site, 50.1%, 33.4% and 28.6% for two and 44.6%, 38.2% and 38.2% for three sites involved (Fig. 1). For more than one site this was 48.1%, 35.0% and 32.1%, respectively.

In univariate analyses grade of differentiation, cervical involvement, LVSI, myometrium involvement, positive peritoneal washings, and the number of involved sites outside the uterus showed significance. Treatment-related factors did not show any significance.

The multivariate analysis with the above mentioned variables showed significance for endocervical gland involvement compared to no involvement (HR 3.1; 95% CI 1.24–7.95; $p=0.016$), LVSI (HR 1.9; 95% CI 1.03–3.59; $p=0.041$), and involvement of two sites compared to one (HR 2.1; 95% CI 1.17–3.92; $p=0.013$). Involvement of three sites compared to one was not significant (HR 2.0; 95% CI 0.90–4.48; $p=0.088$).

Table 3
Number of involved sites in relation to recurrence for endometrial carcinoma stage IIIA.

Recurrence	One site $n=89$ (%)	Two sites $n=34$ (%)	Three sites $n=18$ (%)	p-value
Vaginal recurrence				
Yes	7 (7.9)	1 (2.9)	1 (5.6)	
None	80 (89.9)	33 (97.1)	17 (94.4)	ns
Unknown	2			
Pelvic recurrence				
Yes	1 (1.1)	5 (14.7)	3 (16.7)	
None	86 (96.6)	29 (85.3)	15 (83.3)	0.004
Unknown	2			
Abdominal recurrence				
Yes	11 (12.4)	17 (50)	2 (11.1)	<0.001
None	76 (85.4)	17 (50)	16 (88.9)	
Unknown	2			
Distant metastasis				
Yes	21 (23.9)	11 (32.3)	9 (50)	
None	67 (76.1)	23 (67.7)	9 (50)	0.077
Unknown	1			

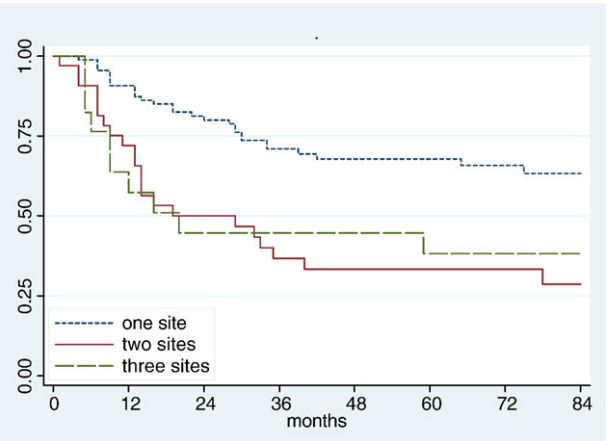

Fig. 1. The distant metastasis-free survival for 141 patients with stage IIIA endometrial carcinoma according to the number of involved sites.

Involvement of more than one site (HR 2.1; 95% CI 1.21–3.66; $p=0.008$) with the above-mentioned variables of endocervical gland involvement and LVSI showed significance.

Disease-free survival

The 2-, 5- and 7-year disease-free survival (DFS) according to the number of involved sites were 80.1%, 67.9% and 65.3% for one site, 50.1%, 34.4% and 28.6% for two sites, and 38.2%, 38.2% and 38.2% for three sites, respectively ($p<0.001$). For more than one site this was 46.1%, 35.1% and 32.2%, respectively. Table 3 gives an overview of the different recurrences according to the number of involved sites. The median time to recurrence was 14 months.

Univariate analyses showed significance for grade of differentiation, cervical involvement, LVSI, myometrium involvement, peritoneal washings, and the number of involved sites outside the uterus.

The multivariate analysis with the above mentioned variables showed significance for endocervical gland involvement (HR 3.2; 95% CI 1.27–8.12; $p=0.014$), LVSI (HR 1.9; 95% CI 1.04–3.75; $p=0.038$), and two sites involved compared to one (HR 2.2; 95% CI 1.20–4.07; $p=0.011$). Involvement of three sites compared to one was not significant (HR 2.1; 95% CI 0.93–4.72; $p=0.073$).

Involvement of more than one site (HR 2.2; 95% CI 1.24–3.82; $p=0.007$) with the above mentioned variables of endocervical gland involvement and LVSI showed significance.

Disease-specific survival and overall survival

The 2-, 5- and 7-year disease-specific survival (DSS) according to the number of involved sites was 88.1%, 70.4% and 68.3% for one site, 68.7%, 42.8% and 34.0% for two sites, and 50.2%, 43.9% and 43.9% for three sites respectively ($p=0.001$), (Fig. 2). For more than one site this was 62.6%, 43.3% and 37.9%, respectively.

Univariate analyses showed significance for grade of differentiation, cervical involvement, LVSI, myometrium involvement, peritoneal washings, and the number of involved sites outside the uterus.

The multivariate analysis showed significance for grade 3 (HR 2.5; 95% CI 1.02–5.98; $p=0.045$) compared to grade 1, and two sites involved compared to one (HR 2.2; 95% CI 1.18–4.26; $p=0.013$). Involvement of three sites compared to one was not significant (HR 1.9; 95% CI 0.79–4.68; $p=0.145$).

Involvement of more than one site (HR 2.2; 95% CI 1.18–3.92; $p=0.012$) with the above-mentioned variable differentiation grade 3 showed significance.

The 2-, 5- and 7-year overall survival according to the number of involved sites was 84.1%, 60.2% and 52.4% for one site, 64.7%, 36.9% and 29.4% for two sites, and 44.4%, 38.9% and 33.3% for three sites respectively ($p=0.042$). For more than one site this was 57.7%, 37.8% and 31.2%, respectively.

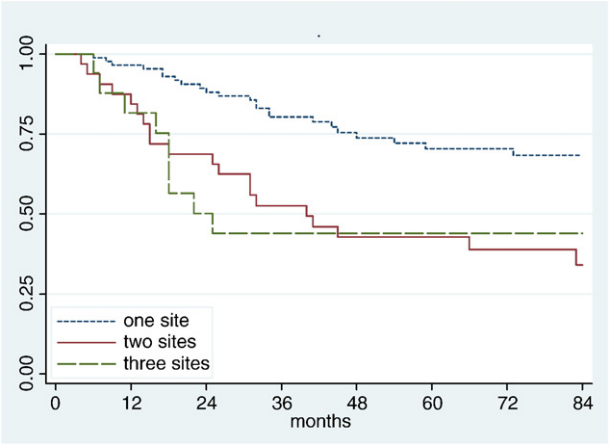

Fig. 2. The disease-specific survival for 141 patients with stage IIIA endometrial carcinoma according to the number of involved sites.

Discussion

This study demonstrated the impact of the number of involved sites outside the corpus uterine for stage IIIA endometrial carcinoma on distant metastasis-free survival, disease-free survival and disease-specific survival.

The desirability of evidence based medicine tailored on the individual patient is widely championed, but often unavailable for clinical guidance. Often only limited clinical results are available. Most published series are small, but by collecting all stage IIIA from different centres we were able to present one of the largest series published. Because of the multi centric character of the study the pathology slides of all patients were reviewed by a single centre, which turned out to be indispensible to get a uniform scoring of data (Table 1).

The aim of staging patients is to have an insight in the relative prognosis. Stage IIIA according to the FIGO-staging system is a very heterogeneous group of patients. Patients with a positive peritoneal washing and/or any extensions outside the corpus uterine within the pelvis are incorporated in this stage, resulting in a heterogeneous population of patients. Due to this diversity, outcome might vary greatly, and the prognostic value of stage IIIA endometrial carcinoma might be questioned.

Limiting ourselves to those with an extension outside the corpus uterine with or without a positive peritoneal washing, we were confronted with 29 combinations ultimately. Therefore we looked at the number of involved sites outside the uterus as a reliable and reproducible parameter. Three categories were formed one, two, and three sites involved.

With regard to the loco-regional recurrence rate this study shows a higher recurrence rate related to the number of involved sites. It also shows that although the median time to a loco-regional recurrence is 13.5 months, no plateau was reached after 5 years in contrast to stage I and II endometrial carcinoma, although we could not show statistically more recurrences at 7 years [15,16]. It only shows us that even after 5 years patients with endometrial carcinoma stage IIIA still recur.

This study also shows a clear correlation between the distant metastasis rate, abdominal as well as metastasis elsewhere, and the number of involved sites for stage IIIA. A significant difference was noticed between those patients with one involved site as compared to those with more sites involved. It confirms an earlier study by Greven et al. [11]. Given the high rate of metastasis for those with more than one site involved the impact of locoregional adjuvant radiotherapy should be considered and looking for a more systemic adjuvant therapy seems necessary. Particularly for the latter local adjuvant therapy seems not sufficient, looking at the timing of metastasis within 12 months of primary treatment.

The DFS in the literature for one involved site ranged from 34% to 80% [6–8,10,17–20]. Particularly patients with isolated adnexal involvement do better as compared to other involved sites [8,18]. In some small series it was shown that the DFS for patients with isolated adnexal involvement was superior to survival of those with adnexal involvement plus additional extra uterine disease sites [6–8,18]. In our study we confirmed this with an overall recurrence rate of 44.0% at 5 years. This was highly significant for the number of involved sites.

Adjuvant therapy for patients with stage IIIA disease varies widely from observation to chemotherapy with or without radiotherapy. There is no consensus regarding the best treatment strategy for these patients. Morrow et al. [18] and Ashman et al. [17] showed a benefit from adjuvant pelvic radiotherapy for patients with isolated serosa or adnexa involvement. Others showed that the majority of relapses were outside the true pelvis and therefore outside the treated field of

external pelvic radiotherapy [20,21]. Schorge et al. [20] did not show any benefit of external pelvic radiotherapy for stage IIIA.

Several limitations of this study should be noted. Firstly, it is a retrospective analysis encompassing a 15-year period; secondly it is a multi-centre study, with the possibility of patient selection. Indications for adjuvant postoperative radiotherapy in The Netherlands for FIGO stage IIIA endometrial carcinoma following TAH+BSO were uniform, but the indication for vaginal brachytherapy boost differed between the institutions. So the selection will not be a major bias.

On the basis of this study it might be possible to tailor treatment for those patients with only one site involved and those with more than one site involved. The benefit of adjuvant pelvic radiotherapy is highly questionable particularly for those with more than one involved site. A systemic adjuvant therapy seems more reasonable for this subset of patients. A difference between two and three sites involved could not be demonstrated in this study, this might be due to the small number of those with three sites, although one can argue that two or three sites is already a sign of multiple metastatic sites.

Given the small number of those with three sites involved, and the fact that the DMFS and DFS of three sites compared to one site showed significance in univariate analysis, we might conclude that patients with more than one site involved do have a worse prognosis.

Conclusion

The number of involved sites outside the corpus uterine for stage IIIA seems to be a strong prognostic factor for stage IIIA endometrial carcinoma.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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