Lymph-vascular Space Involvement and Outer One-third Myometrial Invasion Are Strong Predictors of Distant Haematogeneous Failures in Patients with Stage I-II Endometrioid-type Endometrial Cancer

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Abstract. *The aim of this retrospective study was to assess the predictive value of different clinicopathological variables (patient age, tumour size, FIGO grade, myometrial invasion, lymph-vascular space involvement [LVSI], invasion margins, peri-tumour phlogistic infiltrate and mitotic activity) for the risk of distant haematogenous recurrences in patients with endometrioid-type stage Ib-II endometrial cancer. Between August 1990 and April 2005, 259 patients had undergone laparotomy, peritoneal washing, total abdominal hysterectomy and bilateral salpingo-oophorectomy, with or without pelvic ± para-aortic lymphadenectomy for endometrioid-type endometrial cancer. Thirty-six (13.9%) patients had developed recurrent disease after a median time of 17 months (range, 2-128 months). The relapse had been locoregional in 9, distant in 21 and both locoregional plus distant in 6 cases. This study assessed 12 patients with FIGO stage Ib-II disease who had developed distant haematogenous recurrences and 20 randomly chosen control patients with FIGO stage Ib-II disease who had remained recurrence-free after a median follow-up of 52 months (range, 37-66 months). Adjuvant therapy had been: no further treatment in 15 patients, external pelvic irradiation in 14 patients, adjuvant external pelvic irradiation plus brachytherapy in 2 patients and platinum-based chemotherapy followed by external pelvic irradiation in 1 patient. The site of distant failure had been the lung in 9 patients, liver in 2 patients and lung plus liver in 1 patient. A concomitant locoregional relapse (vagina or lymph nodes) had occurred in 3 patients. The median interval between surgery and the development of distant failure had been 16.5 months (range, 5-113 months). On univariate analysis, a higher incidence of FIGO grade 3 (50% versus 10%, p=0.0114), outer one-third myometrial invasion (91.7% versus 35.0%, p=0.0051) and LVSI (75.0.% versus 20.0%, p=0.0022) was found in the patients who had developed distant haematogeneous metastases compared to the recurrence-free women. Multivariate analysis showed that LVSI (p=0.0264) and deep myometrial invasion (p=0.0345) were independent predictive variables for the risk of distant haematogeneous failure. Patients with these pathological findings should be enrolled in randomised trials designed to assess the role of adjuvant chemotherapy alone or combined with sequential and /or concomitant external pelvic irradiation.*

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Endometrial cancer is the most common cancer of the female genital tract in western countries. According to the International Federation of Gynaecology and Obstetrics (FIGO) (1), the 5-year overall survival in approximately 8,000 surgically staged patients was 80%, and ranged from 90.8% for stage Ia to 20.1% for stage IVb. Besides tumour stage, histological type, tumour grade, myometrial invasion and lymph-vascular space involvement represent significant prognostic variables for this malignancy (1-9). Total hysterectomy with bilateral salpingo-oophorectomy and surgical staging is the primary treatment for endometrial cancer, whereas adjuvant therapy, mainly represented by external pelvic irradiation, is usually given to moderate or high-risk patients (10-15).

Data from the literature have shown that the rates of relapse in endometrial cancer range from 11 to 19%; 41-90% of recurrences involve distant sites and 70-80% of relapses occurr within 3 years of diagnosis (16-24). Very few data are currently available on the relationship between the common clinicopathological pathological variables and the risk of distant failure (2, 5, 7, 25-27).

In the present retrospective investigation, the predictive value of different clinicopathological variables (patient age, tumour size and grade, myometrial invasion, lymph-vascular space involvement (LVSI), invasion margins, peri-tumour phlogistic infiltrate and mitotic activity) for the risk of distant haematogenous recurrences was assessed in patients with endometrioid-type stage Ib-II endometrial cancer. Non-endometrioid histological subtypes such as serous subtype and clear cell were excluded because they have different biological potentials.

Patients and Methods

Between August 1990 and April 2005, 259 patients had undergone laparotomy, peritoneal washing, total abdominal hysterectomy and bilateral salpingo-oophorectomy, with (n=158) or without (n=101) pelvic ± para-aortic lymphadenectomy for endometrioid-type endometrial cancer at the Division of Gynecology and Obstetrics of the University of Pisa. During laparotomy, an accurate exploration of the whole abdominal pelvic cavity had been performed and any suspicious lesion had been biopsied. Staging had been performed according to the FIGO classification (1). The FIGO stage was Ia in 22 patients, Ib in 110, Ic in 80, IIa in 8, IIb in 11, III in 25 and IV in 3. Adjuvant therapy had been: no further treatment in 136 patients, external pelvic irradiation in 93, external pelvic irradiation plus brachytherapy in 8, brachytherapy in 2, platinum-based chemotherapy in 6, platinum-based chemotherapy plus external irradiation in 14 patients. The patients had been periodically followed until May 2008 or until death. Thirty-six (13.9%) patients had developed recurrent disease after a median time of 17 months (range, 2-128 months). The relapse had been locoregional in 9, distant in 21 and both locoregional and distant in 6 cases.

This retrospective study assessed 12 patients with FIGO stage Ib-II disease who had developed distant haematogenous recurrences, and 20 randomly chosen control patients with FIGO stage Ib-II disease who had remained recurrence-free after a median follow-up of 52 months (37-66 months). The assumption was made that the randomly chosen subgroup of 20 recurrence-free patients was representative of the whole population of stage Ib-II recurrence-free patients.

All the patients satisfied the following inclusion criteria at the time of initial treatment: menopausal; histologically negative pelvic ± para-aortic lymph nodes, or, if not submitted to lymphadenectomy, had negative computed tomography (CT) findings for lymph node involvement; negative peritoneal washing as well no tumour spreading outside the uterus; negative chest X-ray or chest-CT scan and had no other malignancy before or after the diagnosis of endometrial cancer.

All the haematoxylin and eosin-stained slides of the primary tumours were independently reviewed by two pathologists (A.C. and C.DC.) for confirmation of the original diagnosis of endometrioid-type endometrial adenocarcinoma and determination of architectural grade, nuclear grade, FIGO grade, myometrial invasion, LVSI, characteristics of invasion margins, presence or absence of peri-tumour phlogistic infiltrate, mitotic activity (mitoses per 10 high-power fields [10 HPF]), and cervical involvement. At the time of the present analysis, both pathologists worked at the Department of Oncology, Division of Surgical, Molecular and Ultrastructural Pathology of the University of Pisa. The histological classification was performed according to the World Health Organization (WHO) classification (1). The architectural grade was defined: grade 1 (G1), ≤5% of non-squamous or non-morular solid growth pattern; grade 2 (G2), 6-50% of non-squamous or non-morular solid growth pattern and grade 3 (G3), >50% of non-squamous or non-morular solid growth pattern. Notable nuclear atypia, inappropriate for the architectural grade, raised the grade of G1 or G2 tumours by 1. The myometrial invasion was reported as the inner one-third, middle one-third, or outer one-third and the thickness of myometrial invasion was evaluated in millimeters using an automatic image analyzer. Inconsistencies between the two pathologists were solved by a simultaneous review.

LVSI was defined as the presence of tumour cells within or attached to the wall of a blood vessel or lymphatic space using morphological and immunohistochemical analysis (CD34: QBEnd 10, monoclonal; preluted, Ventama Medical System, Inc.).

The development of distant haematogeneous recurrences was related to patient age, tumour size, FIGO grade, myometrial invasion, LVSI, invasion margins, peri-tumour phlogistic infiltrate and mitotic activity.

Statistical methods. The SAS statistical package (release 8.2, SAS Institute, Cary, NC, USA) was used for the computations. The rate of distant haematogeneous recurrences was compared to the explicative variables using Pearson's Chi-square test (or two-tailed Fisher's exact test when appropriate). Multiple logistic regression was carried out to investigate the relationship between the probability of developing distant haematogeneous recurrences and the explanatory variables.

Results

The median age of the 32 patients included in the present study was 63 years (range, 46-81 years). The median mitotic activity of the endometrial cancer was 5 mitoses per 10 HPF (range, 1-28).

The characteristics of the 12 patients who developed distant haematogeneous metastases were: tumour size >2 cm in all 12 patients; FIGO stage Ib in 1 patient, Ic in 8 patients and IIa/b in 3; FIGO grade G1 in 1 patient, G2 in 5 patients and G3 in 6; invasion of middle one-third of myometrium in 1 patient and of outer one-third of myometrium in 11 patients; LVSI in 9 patients; infiltrative invasion margins in 11 patients; peri-tumour phlogistic infiltrate in 10 patients; mitotic activity was >5 mitoses per 10 HPF in 4 patients. Five patients had undergone pelvic and/or para-aortic node lymphadenectomy, with a median number of removed nodes of 31 (range, 5-38) and had histologically proven negative nodes, whereas the other 7 patients had negative CT findings for lymph node involvement. Two patients had received no

postoperative treatment, 9 patients had received adjuvant external pelvic irradiation (followed by brachytherapy in 2 cases), and one patient had received platinum-based chemotherapy followed by external pelvic irradiation.

The site of distant failure was the lung in 9, liver in 2 and lung plus liver in 1. A concomitant locoregional relapse (vagina or lymph nodes) occurred in 3 patients. The median interval between surgery and the development of distant failure was 16.5 months (range, 5-113 months).

The characteristics of the 20 recurrence-free patients were: tumour size ≥2 cm in 15 patients; FIGO stage Ib in 12 patients, Ic in 6, and IIa/b in 2; FIGO grade G1 in 3 patients, G2 in 15, and G3 in 2; invasion was of the inner or middle one-third of the myometrium in 13 patients and of the outer one-third in 7; LVSI in 4 patients; infiltrative invasion margins in 14 patients; peri-tumour phlogistic infiltrate in 13 patients; mitotic activity was >5 mitoses per 10 HPF in 8 patients. Fourteen patients had undergone pelvic and/or para-aortic node lymphadenectomy, with a median number of removed nodes of 19 (range, 8-52), and had histologically proven negative nodes, whereas the other 6 patients had negative CT findings for lymph node involvement. Thirteen patients had received no postoperative treatment and 7 patients had received adjuvant external pelvic irradiation.

FIGO grade 3 (p=0.0114), outer one-third myometrial invasion (p=0.0051) and LVSI (p=0.0022) significantly predicted haematogeneous distant recurrence on univariate analysis (Table I), and outer one-third myometrial invasion (p=0.0345) and LVSI (p=0.0264) retained significant value on logistic regression (Table II).

The median follow-up of the 7 recurrence-free patients with deep myometrial invasion was 60 months (range, 37-66 months). The median follow-up of the 4 recurrence-free patients with LVSI was 45 months (range, 38-52 months).

Table I. *Distribution of pathological variables in patients who developed distant haematogeneous recurrences and in recurrence-free patients.*

	Patients with distant failure		Recurrence-free patients		
	n	(%)	n	(%)	p-Value
Age (years)					
<63	5	(41.6%)	11	(55.0%)	0.462
≥63	7	(58.3%)	9	(45.0%)	
Tumour diameter (cm)					
<2	0		5		
≥2	12	(100%)	15	(75%)	0.059
FIGO grade					
G1	1		3		
G2	5		15		0.0114
G3	6	(50%)	2	(10%)	
Myometrial invasion					
<33%	-		10		
33- 66%	1		3		0.0051
≥66%	11	(91.7%)	7	(35.0%)	
LVSI					
No	3		16		0.0022
Yes	9	(75%)	4	(20.0%)	
Invasion margins					
Pushing	1		6		
Infiltrative	11	(91.7%)	14	(20%)	0.151
Peri-tumour phlogistic infiltrate					
No	2		7		
Yes	10	(83.3%)	13	(65%)	0.2641
Mitotic activity (mitoses/10 HPF)					
≤5	8		12		
>5	4	(33.3%)	8	(40.0%)	0.706

LVSI, lymph vascular space involvement; HPF, high power fields.

Discussion

The majority of relapses in endometrial cancer patients involve distant sites (16-22, 24). The risk of distant failure ranges from 4-12% (11, 17, 19, 24, 25, 28-30) with the risk of isolated distant failure at 4-6% (28, 29). Although Corn *et al*. (31) suggested that locoregional control might prevent subsequent distant failure, a recent meta-analysis of four randomised trials (11-13, 32) showed that the addition of external pelvic irradiation to surgery reduced the locoregional recurrence rate, with a relative risk (RR) of 0.28 (95% CI, 0.17- 0.44, p<0.00001), but did not reduce the risk of distant recurrence or endometrial cancer death or death from all causes (14). A subgroup analysis showed that there was a trend towards a survival benefit following adjuvant external irradiation in the patients with stage Ic and grade 3 disease. A similar meta-analysis of five trials (11-13, 32, 33) showed that adjuvant external irradiation was detrimental for low-risk patients (stage Ia-Ib and grade 1 disease), being associated with a decreased odds ratio (OR) for overall survival (0.71; 95% CI 0.52-0.96), did not alter survival for intermediate-risk patients (stage Ic and grade 1-2 disease or stage Ib grade 3 disease) (OR, 0.97; 95% CI, 0.69-1.35), and offered a survival advantage for high-risk patients (stage Ic and grade 3 disease (OR, 1.76; 95% CI, 1.07-2.89) (15). This study confirmed that the risk of distant metastasis was not reduced by this adjuvant external irradiation (OR, 1.58; 95% CI 1.07-2.35). The role of adjuvant chemotherapy (34, 35) as well as sequential and concurrent adjuvant chemo-radiation in high-risk endometrial cancer is still controversial (36, 37). The identification of surgical or pathological variables predictive of a high risk of distant recurrence could allow the selection of a group of patients suitable for randomised trials of adjuvant chemotherapy with or without external irradiation.

Table II. *Variables predictive of distant haematogenous recurrence by logistic regression.*

Variable	Parameter estimate	Standard error	Wald Chi-square	*p*-Value	OR	95% CI
Intercept	–4.8590	1.9796	6.0247	0.0141	-	-
Myometrial invasion	2.1085	0.9971	4.4717	0.0345	8.236	1.167-58.134
LVSI	2.3397	1.0537	4.9306	0.0264	10.378	1.316-81.850

OR, Odds ratio; 95% CI, 95% confidence interval; LVSI, lymph-vascular space involvement.

Some authors have reported that deep myometrial invasion is a strong predictor of distant failure (2, 5, 7, 25, 26). Mariani *et al*. (7) reviewed the medical records of 229 patients with surgical stage I endometrial cancer of any subtypes who had total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic and para-aortic lymphadenectomy, with histologically proven negative lymph nodes. After a median follow-up of 83 months, 22 (10%) patients had developed a recurrence that was vaginal in 7, distant in 14 and both pelvic and distant in 1. Haematogenous failure was observed in 12 patients. It is noteworthy that none of the 10 patients with non-haematogenous recurrence had myometrial invasion ≥66% compared with 10 (83%) of the 12 patients with haematogeneous recurrence ($p<0.001$). By univariate analysis, the 5-year distant recurrence rate was significantly related to myometrial invasion, LVSI and primary tumour diameter, but Cox analysis showed that myometrial invasion ≥66% was the only independent predictor of distant recurrence.

The frequency of LVSI in endometrial cancer ranges from 4 to 36% (3, 6, 7, 8, 38-45) and is associated with an increased risk of lymph node metastases and unfavourable clinical outcome (3, 5, 6, 8, 38-44, 46, 47). Few data are currently available in the literature on the relationship between LVSI and risk of distant failure (7).

In the present study, FIGO grade 3, outer one-third myometrial invasion and LSVI were all significant predictive variables for distant haematogeneous recurrence at univariate analysis. These factors display strong interrelationships, since G1-2 tumours tend to be less invasive and to have less LVSI, while G3 tumours are more often deeply invasive and have a greater frequency of LVSI (41). In fact, multiple logistic regression showed that only deep myometrial invasion and LVSI were independent predictive variables for distant haematogeneous failure. In most studies, the depth of myometrial invasion was reported as < or ≥50% in agreement with the FIGO staging system (1, 12, 16, 22, 24-26, 29, 30, 32, 35, 36, 39, 44, 46, 48). However, the present data, in agreement with those of Mariani *et al*. (7), would advise classifying myometrial invasion as inner one-third, middle one-third and outer one-third. Patients with early-stage endometrioid-type endometrial cancer with outer one-third myometrial invasion and/or LSVI should be enrolled in randomized trials designed to assess the role of adjuvant chemotherapy alone or combined with sequential and /or concomitant external pelvic irradiation.

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