Influence of diabetes mellitus and nodal distribution in endometrial cancer and correlation to clinico-pathological prognostic factors

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Summary

Objective: The aim of this study was to describe the relationships between the distribution of nodal disease, clinico-pathological patterns and recurrence and survival in surgically staged cases of endometrial cancer.

Methods: Charts were abstracted from patients with endometrial carcinoma from 1985 to 1995. Data on clinicopathologic variables, adjuvant treatment, site of recurrence and survival were collected. The chi square test was used to test associations between variables. The Kaplan-Meier method was used for survival analysis and Cox's proportional hazards model for multiple regression analysis.

Results: Sixty-nine out of 181 patients underwent lymph node dissection. Twenty-three had pelvic lymph node dissection, 23 underwent pelvic and paraaortic lymph node dissection and 20 patients had lymph node sampling. The median count of removed lymph nodes was 22.4. Fifty-four lymph node dissections showed negative lymph nodes and in 15 cases there was a minimum of one positive lymph node. Overall survival was in correlation to nodal involvement with a p value of 0.0017. Patients with lymph node involvement showed significantly more recurrence than patients with negative lymph nodes ($p = 0.003$). The depth of myometrial invasion correlated with lymph node metastasis ($p = 0.01$) and patients with additional diabetes mellitus showed significantly more nodal involvement ($p = 0.02$).

Conclusion: Endometrial cancer showed pelvic lymph node (PLN) and paraaortic lymph node (PALN) involvement. Under-diagnosis of the disease might result if there was only a PLN, but with or without PALN involvement there was no significant difference in overall survival or recurrence. There was an univariate correlation between lymph node involvement and diabetes.

Key words: Endometrial carcinoma; Nodal distribution; Clinico-pathological; Prognostic factor.

Introduction

Although endometrial cancer is the most common gynecologic malignancy, it is highly curable in most cases. Studies using surgery as the initial step to diagnose disease extention have demonstrated that proven disease beyond the uterine corpus such as lymph node involvement, endocervix and adnexae were strong prognostic parameters. The current approach by radical hysterectomy, pelvic lymphadenoectomy and preoperative radiation to endometrial carcinoma was pointed out by Lewis and Stallworthy in 1970 [1]. Nodal involvement was a strong predictor of recurrence and survival in endometrial cancer in the GOG trial (no. 33) between 1977 and 1983 [2]. In this elderly, frequently obese, patient population, it is of particular interest to the clinician to anticipate the need for node dissection. The breakdown of the GOG trial data allows the clinician to plan surgical management to a certain extent based on FIGO stage and grade [2]. Intraoperatively the evaluation is a risk-benefit ratio between a lymphadenectomy and the surgical risk for each patient. For these patients with a higher perioperative risk it is necessary to collect as much information as possible concerning nodal distribution and clinico-pathological data about nodal involvement to determine the patterns of nodal involvement. In this retrospective study we reviewed our data of surgically staged cases of endometrial cancer to describe the relationships between the distribution of nodal disease, clinico-pathological patterns and recurrence and survival.

Material and Methods

This retrospective study includes 181 patients with histologically proven endometrial carcinoma treated between 1985 and 1995 at the Department of Obstetrics and Gynecology of the University Hospital in Mainz, Germany. Based on information from the hospital records, including surgical notes and pathological reports, a database was generated including tumor type and grading, weight, height and age of the patients, additional internal diseases (e.g. diabetes mellitus), FIGO stage, type of surgery and pathological TNM-classification. FIGO stage followed the surgical staging system for endometrial carcinoma of 1988 [3]. The body mass index (BMI) was calculated (weight/height)^2. All patients were followed up during 1997 and 1998. Time of survival and recurrence-free interval was included in the database. An experienced pathologist reevaluated all histological specimens according to tumor type. The tumor grade was evaluated including architectural and nuclear grade [4]. The depth of myometrial invasion was described as the inner, middle and outer one-third [5]. The standard surgical procedure was total abdominal hysterectomy and bilateral salpingo-oophorectomy. Lymph node dissection was performed in cases where inoperative frozen section showed myometrial infiltration of the outer third of the myometrium and in cases with cervical involvement as far as possible, according to

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factors of the general morbidity of the patient. Statistical analysis was performed using the SPSS (Release 6.1.3) system. Analysis of differences between proportions and survival curves were compared with the chi square test. Recurrence-free interval/survival and overall survival were calculated from the date of surgery, and distributions utilized the product-limit method of Kaplan and Meier. For multivariate regression modeling the Cox proportional hazards regression model was used; p values of less than 0.05 were considered statistically significant.

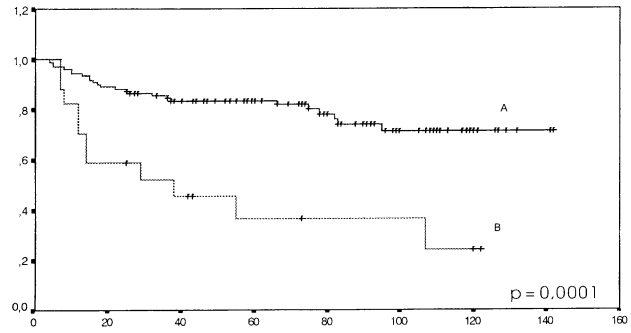
Results

A total of 181 patients with endometrial carcinoma, 89 (49.2%) with grade 1, 57 (31.5%) nine with grade 2 and 35 (12.2%) with grade 3 tumors were included in the study. The median age at diagnosis was 65 years (range 38-81); 125 patients (69.1%) were initially diagnosed in FIGO Stage I, 17 (9.4%) in FIGO Stage II, 28 patients (15.5%) in FIGO Stage III and 11 patients (6.1%) in FIGO Stage IV. A great majority of our patients were obese. A BMI of more than 29 showed 27.4%, while 39.5% had a BMI between 25 and 29 and 33.1% of our patients had a BMI between 17 and 24. In addition 39 patients (21.8%) had diabetes mellitus; 43% were treated by oral medication, 28% were treated using insulin and 21% did not need any medication. There was no differentiation made between type 1 and type 2 diabetes mellitus. Patient characteristics are described in Table 1. The mean follow-up time was 72 months (range 36-156 months). Forty-four patients died (24.3%), nine patients died of unrelated diseases and were counted as missing cases, and not included in the Kaplan-Meier procedure. Complete follow-up was available for 135 patients

Table 1. — *Patient characteristics and p value (univariate χ^2 test).*

FIGO stage	p = 0.0001 (overall survival and recurrence-free interval)
I	69.1% (n = 125)
II	9.4% (n = 17)
III	15.5% (n = 28)
IV	6.1% (n = 11)
Age	p = 0.0446 (overall survival)
< 60	30.9% (n = 56)
> 60	69.1% (n = 125)
Myometrial invasion	p = 0.0001 (overall survival and 0.0002 for recurrence-free interval)
Only endometrium	10.4% (n = 19)
Inner 1/3	44.5% (n = 77)
Middle 1/3	16.8% (n = 29)
Deep 1/3	27.8% (n = 48)
Unknown	4.4 % (n = 8)
Treatment	
Hysterectomy and BSO	59.1% (n = 107) n.s.
Wertheim and Te Linde	22.1% (n = 40) n.s.
Hysterectomy without BSO	5.5% (n = 10) n.s.
Radiation	3.9% (n = 5) n.s.
Diabetes in addition	21.8% (n = 39) p = 0.0009 (overall survival)
BMI	
17-24	33.1% (n = 61) n.s.
25-29	39.5% (n = 67) n.s.
over 29	27.4% (n = 48) n.s.

n.s. = non significant.



A: Adenocarcinoma; B: other type of tumor.

Figure 1. — Overall survival and type of tumor.

(75%). Altogether 20 (15.6%) of the patients developed recurrent disease and seven (5.2%) showed progression of the disease without a disease-free interval. The histopathological tumor type was adenocarcinoma in 143 cases (79%), adenoacanthoma in 15 cases (8.3%), and adenosquamous carcinoma in nine cases (5%). Other differentiations were papillary in eight cases (4.4%), clear cell carcinoma in four cases (2.2%) and others in two cases (1.1%). The estimated overall survival was 78.4% for patients with adenocarcinoma and 80% for patients with adenoacanthoma which was significantly higher in comparison to other tumor types (35.3%). The p value was 0.0001 for overall survival (Figure 1) and 0.0018 for recurrence-free interval. Sixty-nine (38.1%) out of 181 patients underwent lymph node dissection. Twenty-three patients had pelvic lymph node (PLN) dissection, 23 underwent PLN and paraaortic lymph node (PALN) dissection and 20 patients had lymph node sampling (Table 2). The median count of removed lymph nodes was 22.4 (median 18, range 1-84). Fifty-four (78.3%) lymph node dissections showed negative lymph nodes and in 15 (21.7%) cases there was a minimum of one positive lymph node. In nine cases we found positive PLNs, in two cases positive PALNs and in four cases positive

Table 2. — *Types of lymph node dissection.*

Type of operation	No.
Pelvic lymph node dissection	23
Pelvic and paraaortic lymph node	26
Lymph node sampling	20

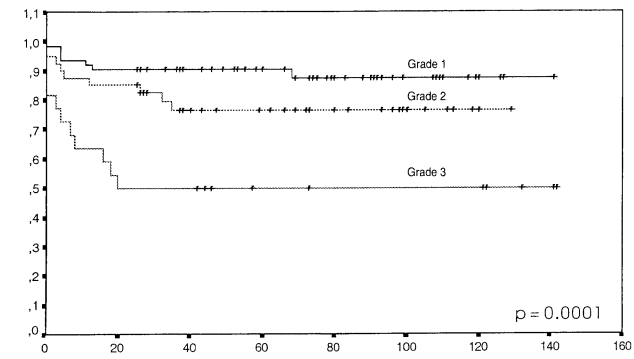


Figure 2. — Recurrence-free survival and tumor grade.

PALNs and positive PLNs. The overall survival was in correlation to nodal involvement with p value of 0.0017 (Figure 2). The calculation between only positive and negative nodal involvement showed a p value of 0.0005. There was no correlation between extension of lymph node dissection and survival or recurrence. The p value was 0.1603 for survival and 0.1685 for recurrence-free interval. Forty percent of patients with lymph node involvement developed recurrent disease, 13% of patients without lymph node involvement and 24% of the patients without lymph node surgery. Patients with lymph node involvement showed significantly more recurrence than patients with negative lymph nodes p value 0.003. We found a correlation between depth of myometrial invasion and lymph node metastasis (p = 0.01), and there was no lymph node metastasis if there was no myometrial invasion (Table 3). Patients with diabetes mellitus showed significantly more nodal involvement (Table 4). The p value was 0.02. There was no correlation between type of tumor, age, menopausal status or BMI and nodal involvement. The univariate model revealed that FIGO Stage (p = 0.0001), tumor grade (p = 0.0001), depth of myometrial invasion (p = 0.0001), age (p = 0.0446), lymph node metastasis (p = 0.0017), diabetes mellitus (p = 0.0009) and type of tumor (p = 0.0001) were significantly associated with the overall survival (Table 5). For the disease-free interval FIGO stage (p = 0.0001), tumor grade (p = 0.0001, 49.2% vs 31.5% vs 12.2%, Figure 3), depth of myometrial invasion (p = 0.0002), lymph node metastasis (p = 0.0290) and type of tumor (p = 0.0018) were significantly associated (Table 6). Moreover multivariate analyses revealed that FIGO stage (p = 0.0001), tumor grading (p = 0.0108) tumor type (p = 0.0019) and depth of myometrial invasion (p = 0.0347) were significantly associated with overall survival (Table 7). We found a strong correlation between FIGO stage and tumor grade (p = 0.0005) and tumor type (p = 0.0003). There was no significant correlation of FIGO stage with age, diabetes mellitus or BMI, but tumor grade was correlated with tumor type (p = 0.00001). There was also a correlation between tumor grade and age (p = 0.005) but no correlation for BMI or diabetes mellitus. We found a strong correlation between depth of myometrial invasion and FIGO stage (p = 0.00001), tumor grade (p = 0.00001), tumor type (0.04) and age (p = 0.02). A correlation between depth of myometrial invasion and diabetes mellitus was found (p = 0.004) but there was no correlation between myometrial invasion and BMI or age. As independent prognostic factors a significant correlation was also seen in multivariate analyses for recurrence-free interval and FIGO stage (p = 0.0060) and tumor grade (p = 0.0186) (Table 8). BMI and type of treatment were not significantly associated with overall survival or recurrence-free interval.

Table 3. — *Comparison between lymph node involvement and depth of myometrial invasion.*

	Negative nodes	Positive nodes
Only endometrium	9	0
Inner 1/3	21	4
Middle/3	11	3
Deeper 1/3	13	8

Table 4. — *Comparison between lymph node involvement in addition to diabetes mellitus.*

	No diabetes	Diabetes	Total
Negative	51 (80.2%)	3 (42.7%)	54
Positive	11 (18.0%)	4 (57.1%)	15
Total	62	7	69

Table 5. — *Univariate analysis of prognostic factors for overall survival.*

FIGO Stage	p = 0.0001
Tumor grade	p = 0.0009
Depth of myometrial invasion	p = 0.0001
Age	p = 0.0446
Diabetes mellitus	p = 0.0009
Lymph node metastasis	p = 0.0017
Type of tumor	p = 0.0001

Table 6. — *Univariate analysis of prognostic factors for recurrence-free interval.*

FIGO Stage	p = 0.0001
Tumor grade	p = 0.0001
Depth of myometrial invasion	p = 0.0002
Lymph node metastasis	p = 0.03
Type of tumor	p = 0.0018

Table 7. — *Multivariate analysis of prognostic factors for overall survival.*

FIGO Stage	p = 0.0001
Tumor grade	p = 0.0186
Depth of myometrial invasion	p = 0.0347
Type of tumor	p = 0.0019

Table 8. — *Multivariate analysis of prognostic factors for recurrence-free survival.*

FIGO Stage	p = 0.0060
Tumor grade	p = 0.0186

Discussion

Surgical staging is important in the management of endometrial cancer. Contemporary studies of Stage IIIc endometrial cancer indicate that the identification of nodal metastasis can lead to the use of appropriate adjuvant therapies with a 77% 3-year survival [6]. Mariani et al. previously demonstrated the prognostic significance of the maximal diameter of nodal metastasis as a multivariate independent prognostic factor [7]. The strength of the host immune response and the intrinsic characteristics of the disease itself balance the ability of a tumor to produce metastasis [8]. The reflection of the interaction between these two factors leads to the suggestion that lymph node metastases are a strong reflector of the aggressiveness of the tumor. The endocrinological envi-

ronment of cancerogenesis in endometrial cancer might be an important risk factor for overall patient survival and recurrence-free survival as well. Kauppila and colleagues reported that diabetes mellitus had a significant influence on overall survival [9]. Wagenius *et al.* [10] were not able to show any influence of diabetes mellitus in endometrial cancer. Diabetes mellitus was in this study an univariate significant prognostic factor. Up to now there have been no studies concerning diabetes mellitus and nodal distribution in endometrial cancer. Well knowing the limitations of the methodology, diabetes mellitus was correlated to the depth of myometrial invasion and to the incidence of lymph node metastasis. Therefore the strong influence of lymph node metastases and depth of myometrial invasion clarify why diabetes mellitus was not a multivariate independent prognostic marker. In the literature between 6% [11] and 19% [12] of patients affected with endometrial cancer suffer from diabetes mellitus, in an unaffected population 4.3% would be expected [13]. In the present study 21.8% of patients suffered from diabetes mellitus. This is much more than in the study group of Kauppila and colleagues (11%) [10] but it is comparable to the study group published by Tabernero and colleagues in 1995 [12]. These univariate results suggest an influence of endocrine disorders, e.g., diabetes mellitus in the aggressiveness of endometrial cancer. Limited data exist on endometrial cancer patients with positive paraaortic lymph nodes. The GOG reported PALN involvement in 49% of cases [14]. In this study nodal involvement was 21.7% (PLN and PALN) but in this group there was selective lymph node dissection in 38.1%. This might be why, in contrast to Vavra *et al.* (for overall survival) [15] and Lurain *et al.* (for disease free interval) [16], we found no multivariate independence. This is the first study reporting an univariate correlation between lymph node involvement and diabetes mellitus in endometrial cancer. The reflection of the interaction between these two factors leads us to suggest that if there is in addition diabetes mellitus a systematic lymph node dissection should be required. However since our data do not answer the question of who should have what kind of lymph node dissection, to prevent overtreatment, this should be included in the conception of a randomized trial.

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