

# Diabetes mellitus is a multivariate independent prognostic factor in endometrial carcinoma: A clinicopathologic study on 313 patients

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## Summary

**Objective:** The aim of this study was to analyse the influence of diabetes mellitus as a prognostic factor for overall survival in endometrial cancer. **Materials and Methods:** Charts were reviewed from patients with endometrial carcinoma from 1985 to 2003. Data on clinicopathologic variables, adjuvant treatment, site of recurrence and survival were collected. The chi-square test was used to examine associations between variables. The Kaplan-Meier method was used for survival analysis and Cox's proportional hazards model for multiple regression analysis. **Results:** Multivariate analysis revealed that diabetes mellitus, FIGO stage and depth of myometrial invasion were significantly associated with overall survival.

**Key words:** Endometrial cancer; Diabetes mellitus; Prognostic factor; Overall survival.

## Introduction

With approximately 10,100 new cases each year in Germany and an incidence rate of 18/100,000, endometrial cancer is the most common gynaecological malignancy (Robert Koch Institute, 2006). In most cases it has a favourable prognosis. A wide variety of prognostic factors (including histological type, stage, grade, depth of myometrial invasion, steroid receptor status, DNA index, peritoneal cytology, p53, and MIB-1) have been described and evaluated in detail. As recently reported, personal and lifestyle characteristics also impact survival [1, 2], but confirmation of this is needed. We therefore studied multivariate independent factors predicting death following a diagnosis of endometrial cancer.

## Materials and Methods

This retrospective study includes 313 patients with histologically proven endometrial carcinoma. Of these 269 were treated between 1985 and 2000 at the Department of Obstetrics and Gynaecology of the University Hospital, Mainz, Germany and data from 44 patients were available who were treated between 1992 and 2003 at the Department of Obstetrics and Gynaecology of the University of Hokkaido, Sapporo, Japan. Based on information from hospital records, including surgical notes and pathologic reports, a database was generated. Histological tumour type and tumour grade, weight, height and age of the patients, comorbidity (such as diabetes mellitus), FIGO stage, type of surgery and pathologic TNM classification were included. The FIGO stage followed the surgical staging system

for endometrial carcinoma of 1988 [3]. The follow-up of all patients was recorded between 2001 and 2002. Data on survival and recurrence-free interval were included in the database. All tumours were classified according to the WHO/ISGYP classification [4]. Tumour grade was evaluated including architectural and nuclear grading [5]. Depth of myometrial invasion was described as the inner, middle, and outer one-third [6]. The standard surgical procedure at Mainz University was abdominal hysterectomy and bilateral salpingo-oophorectomy. Lymph node dissection as far as possible was performed in cases where intraoperative frozen section showed myometrial infiltration of the outer third of the myometrium and in cases of cervical involvement, according to factors of general morbidity of the patient. The standard surgical procedure at Hokkaido University included pelvic and paraaortal lymph node dissection as a standard operative procedure. Postoperative treatment at Mainz University included radiation; at Hokkaido University chemotherapy was also included in selected cases. Statistical analysis was performed using the SPSS (release 6.1.3) system. Analysis of differences between proportions and survival curves was performed with the chi-square test. Recurrence-free survival and overall survival were calculated from the date of surgery, and distributions utilised the product-limit method of Kaplan and Meier. For multivariate regression modelling with Cox's proportional hazards (forward/backward) regression model was used; p values of less than 0.05 were considered statistically significant.

## Results

A total of 313 patients with endometrial carcinoma, 147 (47.7%) with tumour grade 1, 102 (33.1% with tumour grade 2, and 59 (19.2%) with grade 3 tumours were included in the study. The median age at diagnosis was 63.95 years (range 32-91). Two hundred and eleven

Revised manuscript accepted for publication November 27, 2006

patients (67.4%) were initially diagnosed as FIGO Stage I, 35 patients (11.2%) as FIGO Stage II, 50 patients (16.0%) as FIGO Stage III, and 17 patients (5.4%) as FIGO Stage IV. The majority of our patients were obese. Of the tumour patients 27.4% had a body mass index (BMI) of more than 29, 39.5% had a BMI between 25 and 29, and 33.1% of the patients had a BMI between 17 and 24. Sixty-four (23.2%) suffered from diabetes mellitus, 43% were treated by oral medication, 28% were treated with insulin, and 21% did not take any medication. There was no differentiation made between type I and type II diabetes mellitus. The mean follow-up time was 1,353 days (median 1,096 days) and 75 patients died (23.9%). Forty-one patients died from unrelated diseases and were counted as missing cases and not included in the Kaplan-Meier procedure. In 34 patients (12.8%), recurrent disease could be observed and eight patients (3.0%) showed immediate progression of disease without a disease-free interval. Histopathologic tumour type was adenocarcinoma in 265 cases (86.3%), and other tumour types as adenoacanthoma, adenosquamous carcinoma, papillary and clear cell carcinoma occurred in 13.7%. The estimated overall survival was 78.1% for patients with adenocarcinoma. This was significantly higher than in other tumour types (64.3%). The p value was 0.0037 for overall survival and 0.021 for recurrence-free interval. The univariate model revealed diabetes mellitus ( $p < 0.001$ ), FIGO stage ( $p < 0.001$ ) and depth of myometrial invasion ( $p < 0.001$ ) as the strongest prognostic factors (Table 1). These factors were included in a multivariate setting using the forward/backward LR-model. Cox regression analysis was done for 297 cases (94.9%); 16 patients (5.1%) were excluded as missing cases. Multivariate analyses revealed that diabetes mellitus ( $p = 0.049$ ), FIGO stage ( $p < 0.001$ ) and depth of myometrial invasion ( $p = 0.004$ ) as multivariate independent prognostic factors. Hazards ratio was 1.880 for Diabetes mellitus (CI 1.107-3.193) (Table 2). There was no influence between the two different institutions in different countries. The different treatment strategies were also not significantly associated with overall survival.

Table 1. — *Univariate analysis.*

Variable	Likelihood ratio (p value)
Diabetes mellitus	0.049
FIGO stage	0.000
Myometrial invasion	0.004

## Discussion

The major new result from this retrospective clinical study – based on two different institutions in two different countries – was that women with diabetes as a comorbidity had a significantly higher risk of death from endometrial cancer than nondiabetic women. The association between diabetes and shorter survival was not explained by other important prognostic variables, such

Table 2. — *Cox's proportional hazards regression (backward/forward LR-model).*

Variable	Hazard ratio	CI	CI
Diabetes mellitus	1,880	1,107	3,193
FIGO stage			
Stage I			
Stage II	1,425	0,681	2,983
Stage III	1,705	0,826	3,518
Stage IV	9,347	4,067	21,483
Invasion			
Only endometrium			
inner 1/3	0,904	0,346	2,361
middle 1/3	1,632	0,610	4,364
outer 1/3	2,784	1,148	6,751

as the extent or grade of endometrial cancer at time of diagnosis or by differences in initial course of treatment, different institutions or nations.

The variability in overall survival and recurrence-free survival of patients with endometrial cancer has prompted numerous studies examining several clinical and pathologic factors as prognostic factors. There are various clinical and pathologic variables which are reported to be of prognostic significance in univariate or multivariate analysis. Up to now, we have identified six studies with multivariate analyses of more than one or two prognostic factors concerning all four FIGO stages [7-14]. As recently reported, personal and lifestyle characteristics also impact survival [1, 2]. We have already published a study with multivariate analyses in a group of 189 patients [2]. These patients were included in the present study. Knowing the limitation of biases and confounding factors it is worth while analysing epidemiological results [1] in a clinical series of patients. In the present study we analysed multivariate independent prognostic factors in a total of 313 patients with endometrial cancer. Our study represents a large group of patients with endometrial cancer who were treated under comparable conditions. In our univariate analysis we identified diabetes mellitus, FIGO stage and depth of myometrial invasion as the strongest factors. This is comparable to our data from the 189 patients in the previous study. The prognostic evidence for FIGO stage and depth of myometrial invasion is no doubt beyond dispute and has been previously published by different authors [7-14]. Multivariate analysis using the forward/backward LR Cox regression model revealed now in a total of 313 patients that diabetes mellitus, FIGO stage and depth of myometrial invasion are independent prognostic factors for overall survival. The hazards ratio was 1.880 for diabetes mellitus (CI 1.107-3.193) and endometrial cancer mortality. There was no influence of nation, institution or treatment strategy. Currently there is now only one epidemiological study, which evaluates mortality risk for patients with endometrial cancer in association with diabetes mellitus. Folsom *et al.* [1] reported in an epidemiological setting a comparable hazard ratio of 2.38 (CI 1.05-5.37) for endometrial cancer mortality. In the literature,

between 6% [15] and 19% [16] of patients affected with endometrial cancer suffered from diabetes mellitus; in an unaffected population 4.3% would be affected [17]. In the present study 23.2% of patients suffered from diabetes mellitus. Unfortunately diabetes type I and type II were mixed, thus a differentiation was not possible retrospectively and HbA1c levels were not available. As is known cancer-stromal interactions initiate endometrial cancer invasion, therefore depth of myometrial invasion is one of the multivariate independent prognostic factors. Since these results are independent of age, extent of cancer at diagnosis, tumour grade, and initial treatment, it might be possible that diabetes, hyperglycemia, or hyperinsulinemia could contribute directly to late effects of endometrial cancer. This could be a reasonable explanation because recent studies have demonstrated diabetes [18] and greater glucose concentrations [19] to be risk factors for endometrial cancer. Additionally laboratory results showed that endometrial cancer cells in vitro have high-affinity binding sites for insulin and proliferate in response to insulin exposure [20].

In summary, we have described diabetes mellitus as a multivariate independent prognostic factor for overall survival of patients with endometrial cancer in a retrospective analysis of 313 patients. The significant hazard ratio in endometrial cancer mortality suggests an influence of endocrine disorders, e.g., diabetes mellitus, on the aggressiveness of endometrial cancer. Examination of endometrial cancer molecular biology under the influence of endocrine disorders like diabetes mellitus and/or under the influence of steroid hormones could offer a better understanding of this association and its possible mechanism.

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