

# Survival and prognostic factors of patients treated for Stage I to Stage III endometrial carcinoma in a reference cancer center in Southern Brazil

S.A. Pessini<sup>1</sup>, M.D.; C.G. Zettler<sup>2</sup>, M.D., Ph.D.; M.C.O. Wender<sup>3</sup>, M.C.O., M.D., Ph.D.;  
L.C. Pellanda<sup>4</sup>, M.D., Ph.D.; G.P.G. Silveira<sup>1</sup>, M.D., Ph.D.

<sup>1</sup>Department of Gynecology and Obstetrics, <sup>2</sup>Department of Pathology, Federal Faculty Foundation of Medical Sciences, Santa Casa University Hospital; <sup>3</sup>Department of Gynecology and Obstetrics, Federal University of Rio Grande do Sul; <sup>4</sup>Department of Public Health, Federal Faculty Foundation of Medical Sciences, Porto Alegre (Brazil)

## Summary

**Purpose:** To describe two- and five-year survival of patients with Stage I to III endometrial carcinoma and to identify prognostic factors. Study design: Concurrent cohort study.

**Patients and Methods:** Seventy-two patients were operated on by the same surgeon and followed up for at least two years. All the histopathological examinations were performed by the same pathologist. Survival was analyzed by the Kaplan-Meier method. Age, body mass index, tumor grade, myometrial invasion, histological type and stage were correlated with death.

**Results:** Overall survival at two and five years was 90.2% and 81.4%, respectively. By bivariate analysis, FIGO stage, myometrial invasion, tumor grade, histology, adnexal and/or lymph node metastasis and age were significant predictors of death ( $p < 0.05$ ). Multivariate analysis revealed significant associations with death: FIGO Stage III ( $p = 0.001$ ), histological type other than endometrioid ( $p = 0.027$ ) and age 70 or more ( $p = 0.04$ ).

**Conclusion:** Endometrial carcinoma Stage III patients, histological types other than endometrioid and age 70 years or more are at significant risk for death.

**Key words:** Endometrial carcinoma; Survival; Prognosis; Prognostic factors.

## Introduction

The incidence of uterine corpus cancer in Western Europe is 22.5/100,000 and in Brazil, 4.9/100,000 [1]. At our hospital it is the fourth most frequent female cancer, but corresponds to only 18% of female genital cancers.

Staging is an important risk factor for recurrence and death [2, 3]. Other clinical and histopathological factors affect survival and the main factors are histological. Poor differentiation (G3) and deep myometrial invasion (MI) are risk factors for metastasis, recurrence and survival [2, 4-6]. Serous papillary and clear cell tumors are described as the most aggressive histological types [2, 7, 8]. Older women have more advanced stage, poorer differentiation, deeper myometrial invasion and lower survival [2, 9-11]. The association with body mass index (BMI) is positive: the greater the BMI, the greater the time to recurrence and survival [12-14].

FIGO's Annual Report [2] is one of the most authoritative sources of survival and prognostic factors of gynecological cancer. It is the largest series of cases and, in its 25<sup>th</sup> edition in 2003, our Department is included. Overall survival for endometrial cancer was 88.1% at two years and 77.6% at five years, adjusted to age, stage and country.

The purpose of this study was to determine two- and five-year survival of Stage I to III endometrial cancer

patients, and to correlate death with the following prognostic factors: age, BMI, histological grade (G), myometrial invasion (MI), histological type and stage. The importance of this study stems from the lack of published data concerning survival of women with endometrial cancer in the South of Brazil.

## Materials and Methods

Seventy-nine consecutive patients with a histological diagnosis of cancer of the uterine corpus underwent primary surgical exploration in our department. Exclusion criteria were: non-epithelial tumors (5 patients) and follow-up shorter than two years (2 patients lost to follow-up). Therefore, 72 patients were included in the study.

A concurrent cohort study with patients enrolled at time of diagnosis of endometrial carcinoma (time zero) was conducted from January 1995, when the protocol was established, to December 2004, after a follow-up of at least two years.

Surgical procedures were laparotomy for 67 (93%) patients, laparoscopic-assisted vaginal surgery for two (2.8%) and vaginal surgery for three (4.2%). The abdominal procedures were: collection of peritoneal cytology, examination of abdominal and pelvic cavity and total extrafascial hysterectomy with bilateral salpingo-oophorectomy. Lymph node sampling or radical pelvic lymphadenectomy alone or combined with para-aortic lymph node sampling was performed in cases with non-endometrioid histology, G3 endometrioid adenocarcinoma, MI > 50%, macroscopic cervical, adnexal or pelvic node involvement, as far as was possible according to the morbidity of the patient. Vaginal surgeries consisted of extrafascial hysterectomy

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with bilateral salpingo-oophorectomy preceded by collection of material for peritoneal washing cytology through a peritoneal opening in the pouch of Douglas. In all cases, a longitudinal incision was performed in the uterus for macroscopic examination of the specimen during surgery. Radiotherapy was performed at the same hospital, in the presence of at least one of the following histopathological findings: G3 tumor, MI greater than 50%, histologic type other than endometrioid, Stage II and III tumors.

On the day of the surgery, the protocol was filled with clinical and surgical data. Other data were later added. A database was generated with clinical (age, menopause, BMI and comorbidities) and cytohistological (peritoneal cytology, histological type, G, MI and stage) data that described the study variables. The outcome under study was death caused by cancer. Histological type was classified according to the International Society of Gynecology Pathologists (ISGP) and the World Health Organization (WHO). Tumor grade of endometrioid carcinomas and surgical staging were defined according to the FIGO classification [2]. Histological type and tumor grade of all cases were reviewed by an experienced pathologist. Follow-up was from date of surgery to at least two years after surgery.

Variables were described as means, standard deviations and range, or percentages for categorical variables. The chi-square test or the Fisher exact test was used to evaluate the association between prognostic factors and death. The Student's *t*-test was used for comparisons between groups of continuous variables. Level of significance was 5%. Survival was analyzed by the Kaplan-Meier method, and deaths by causes other than cancer were censored. Log rank was applied to compare survival curves for each two prognostic factors. Multivariate analysis using the Cox proportional hazard ratios was based on significant or important variables according to the theoretical model.

All patients were informed that data would be used for research and publication and all signed an informed consent. The study was approved by the Ethics in Research Committees of the Federal Faculty of Medical Sciences and Santa Casa University Hospital of Porto Alegre.

## Results

The overall survival at two and five years was 90.1% and 81.4%, respectively. Stage I ( $n = 52$ ) survival was 94.2% and 87.7%; Stage II ( $n = 10$ ), 100% and 83.3%; and Stage III ( $n = 10$ ), 60% and 48%. The two- and five-year survival in patients with endometrioid histology ( $n = 64$ ) was 93.7% and 86.8%, and with the nonendometrioid type ( $n = 8$ ) it was 62.5% and 31.2%.

Patient ages ranged from 44 to 81 years, and mean patient age at diagnosis was 63.3 years ( $SD \pm 9.2$ ). The differences in mean age according to stage were not significant. When the mean age of patients with invasion greater than 50% ( $65.9 \pm 9.3$  years) was compared with the other groups ( $60 \pm 10.3$  years without invasion and  $61.8 \pm 8.7$  years with invasion up to 50%), the difference was significant ( $p = 0.048$ ).

Mean BMI was  $28.7 \pm 5.5$  kg/m<sup>2</sup>. Of the 72 patients, 52 (72.2%) had a BMI equal to or greater than 25, and 29 (40.3%) were obese.

Lymphadenectomy or lymph node sampling was performed in 36 patients (50%). The number of pelvic or aortic lymph nodes ranged from one to 47 (mean = 19.8).

Of the 72 patients, 48 (66.7%) received postoperative adjuvant radiotherapy, not indicated for the other 24 (33.3%) patients.

Mean follow-up time was 4.3 years: minimum follow-up was 5.7 months for patients who died before two years, and 24 months for other patients; maximum follow-up time was 9.6 years. Up to December 2004, 15 patients had died, 11 of them of causes related to endometrial cancer.

Bivariate analysis revealed that Stage III ( $p = 0.004$ ), MI greater than 50% ( $p = 0.023$ ), G3 ( $p = 0.007$ ), histological types other than endometrioid ( $p = 0.016$ ), adnexal and/or lymph node metastasis ( $p = 0.006$ ), and age ( $p = 0.047$ ) were associated significantly with death.

Multivariate analysis revealed that age greater than 70 years, Stage III and histological types other than endometrioid were associated significantly and independently with death. Patients aged 70 or older had a four-fold risk of death in comparison with patients younger than 70 years (CI, 1.06 - 15.13,  $p = 0.04$ ). Patients with stage III cancer had a 11.97 times greater risk of death than patients with Stage I tumors (CI, 2.86 - 50.16,  $p = 0.001$ ). Histological types other than endometrioid carried a risk 4.37 times greater than endometrioid type (CI, 1.18 - 16.23,  $p = 0.027$ ).

## Discussion

In this study overall survival at two and five years was slightly greater than the literature rates (88.1% and 77-77.6%) [2, 15]. In Stage I it was similar to the literature [2, 15] and in Stage II it was slightly greater than other series (88.8% and 74.8%-79%) [2, 15, 16], but lower than that reported by Feltmate *et al.* [17] (93% at 5 years). The better two-year survival in Stage II vs Stage I may be a result of the small number of patients in Stage II and of the fact that all Stage II patients had endometrioid tumors. In Stage III, survival was lower than that reported by some authors (72.9% and 55%-58%) [2, 15], but greater than that reported by Connel *et al.* [18] (37.1%). It is important to point out that 20.1% surgical Stage III patients evaluated in the annual report received adjuvant chemotherapy, a procedure not used in our department up to December 2002. A recent meta-analysis [19] about chemotherapy in advanced stages showed a significant improvement in disease-free survival and a trend to longer survival when it is used. Survival at two and five years for the endometrioid type was 93.7% and 86.8%, slightly greater than in other series [2, 3]. For nonendometrioid histology, we found 62.5% and 31.2% at two and five years, rates that are lower than those reported by other groups [2, 3, 20, 21].

Depth of myometrial invasion and tumor grade are associated with survival and lymph node metastases. The greatest difference in survival is observed in the comparison of Stage Ia and Ic and G1 and G3 [2, 4]. Creutzberg *et al.* [6] compared IaG2-3 patients and IbG1-2 patients with IcG3 patients, and found that the most important adverse prognostic factor for recurrence

and death was G3 (HR 5.4 and 5.5;  $p < 0.0001$ ). In our study, grade and death were significantly associated ( $p = 0.007$ ). The number of deaths was not significantly different between the three groups according to invasion, but the comparison of the group of patients with invasion greater than 50% with the other two groups revealed a significant difference ( $p = 0.023$ ). In the group without invasion, there was one case of clear cell tumor, and the patient died, a fact in agreement with reports that have demonstrated that histological types other than endometrioid have the worst prognosis regardless of invasion or stage [7, 22].

Multivariate analysis showed that being 70 years or older increased risk of death by fourfold. The literature reported more advanced stages, higher grade, deeper MI and lower survival rates for patients older than 60 [23], 65 [9] and 70 years [11].

In this series, 52 (72.2%) patients were overweight or obese, but no survival difference was found between obese and normal weight patients, different from other authors [12-14] that have reported better prognosis in obese patients.

This study was the first to evaluate survival and prognostic factors of endometrial carcinoma in Brazilian women. Results are likely to be representative of the population in Southern Brazil because the sample was homogeneous (all patients were treated by one surgeon, at a single radiotherapy department, and followed-up at the same department) and because it was conducted in a reference center for pelvic cancer with a follow-up of at least two years. However, it is an observational study and additional studies are warranted to confirm clinical and pathologic characteristics as well as their associations with survival for women with endometrial carcinoma in Brazil.

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Address reprint requests to:  
S. A. PESSINI, M.D.  
Vinte e Quatro de Outubro 80  
Porto Alegre 90510-000  
(Brazil)