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Menopausal status: A possible predictive factor for recurrence in women with cancer of the uterine cervix without pelvic lymph node metastasis☆

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ABSTRACT

Objectives: To evaluate risk factors for recurrence of carcinoma of the uterine cervix among women who had undergone radical hysterectomy without pelvic lymph node metastasis, while taking into consideration not only the classical histopathological factors but also sociodemographic, clinical and treatment-related factors.

Study design: This was an exploratory analysis on 233 women with carcinoma of the uterine cervix (stages IB and IIA) who were treated by means of radical hysterectomy and pelvic lymphadenectomy, with free surgical margins and without lymph node metastases on conventional histopathological examination. Women with histologically normal lymph nodes but with micrometastases in the immunohistochemical analysis (AE1/AE3) were excluded. Disease-free survival for sociodemographic, clinical and histopathological variables was calculated using the Kaplan–Meier method. The Cox proportional hazards model was used to identify the independent risk factors for recurrence.

Results: Twenty-seven recurrences were recorded (11.6%), of which 18 were pelvic, four were distant, four were pelvic + distant and one was of unknown location. The five-year disease-free survival rate among the study population was 88.4%. The independent risk factors for recurrence in the multivariate analysis were: postmenopausal status (HR 14.1; 95% CI: 3.7–53.6; $P < 0.001$), absence of or slight inflammatory reaction (HR 7.9; 95% CI: 1.7–36.5; $P = 0.008$) and invasion of the deepest third of the cervix (HR 6.1; 95% CI: 1.3–29.1; $P = 0.021$). Postoperative radiotherapy was identified as a protective factor against recurrence (HR 0.02; 95% CI: 0.001–0.25; $P = 0.003$).

Conclusion: Postmenopausal status is a possible independent risk factor for recurrence even when adjusted for classical prognostic factors (such as tumour size, depth of tumour invasion, capillary embolisation) and treatment-related factors (period of treatment and postoperative radiotherapy status).

1. Introduction

The treatment for carcinoma of the uterine cervix is dictated by the clinical stage established by the International Federation of Gynaecology and Obstetrics (FIGO) [1,2]. The initial stages (IB and IIA) can be treated by means of class III radical hysterectomy [3] in association with pelvic lymphadenectomy, or by means of radiotherapy. In the more advanced stages (IIB to IVB), radiotherapy presents better results than surgery. When clinical conditions allow, chemotherapy plus radiotherapy is preferred over radiotherapy alone [4].

Many prognostic factors have been described for carcinoma of the uterine cervix. According to the International Union Against Cancer [5], the following are considered to be prognostic factors: clinical stage, tumour size, histological type, presence of pelvic and periaortic lymph node metastases, depth of stromal invasion, capillary invasion, parametrial involvement and performance status. Among all the factors already described, one of the most important for survival is the presence of lymph node metastases [5,6]. However, around half of the cases of recurrence of invasive

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carcinoma of the uterine cervix at initial stages occur in women without metastases in the lymph nodes [7].

There is little information on risk factors for recurrence and death among women without pelvic lymph node metastases who have undergone radical hysterectomy. For this group of women, the results from the few studies already published have varied, and the following risk factors for recurrence have been cited: age less than 35 years, non-squamous histology, tumour size, lymphovascular space involvement, vaginal, parametrial or perineural invasion, histological grade, nuclear grade, depth of tumour invasion and intensity of inflammatory reaction [7–16].

This was an exploratory analysis to evaluate the risk factors for recurrence of carcinoma of the uterine cervix in women who had undergone radical hysterectomy but did not present pelvic lymph node metastases.

2. Materials and methods

This was a retrospective cohort study on women admitted to the Department of Gynaecology of Hospital A. C. Camargo (Brazil) with a diagnosis of carcinoma of the uterine cervix, who had undergone radical surgical treatment between 1980 and 1999. The initial inclusion criteria were: (1) histopathologically confirmed invasive carcinoma; (2) stage IB or IIA (FIGO) [1]; (3) absence of any treatment prior to this surgery; (4) class II or III radical hysterectomy [3] and pelvic lymphadenectomy; (5) free surgical margins; and (6) absence of micro- or macrometastases in the pelvic lymph nodes on conventional histopathological examination (hematoxylin–eosin).

The patients' records were identified from the databases available in the Department of Gynaecology and the Medical Files and Statistics Service. Initially, 240 cases without pelvic lymph node metastases on conventional histopathological examination were selected for this study. Next, immunohistochemical investigation was carried out on the lymph nodes in order to find micrometastases. This investigation was performed using AE1/AE3 primary antibodies (Dako, Carpinteria, USA), in accordance with a technique published previously [17]. Seven cases were excluded because they presented micrometastatic disease in the pelvic lymph nodes.

The population for this study comprised 233 women of mean age 44.3 years (S.D. 10.2; range 18–72) who were mostly white (73.8%), married (76.9%) and of low schooling level (16.3% were illiterate). Most of these women were classified clinically as IB (90.1%). The radical hysterectomy most commonly used was type III (97.9%). The number of lymph nodes dissected per operation ranged from 4 to 60, with a mean of 19.6 (S.D. 8.6; median 19.0). Postoperative radiotherapy was performed on 77 women (33.1%), and consisted of applying brachytherapy alone for 19, pelvic radiotherapy alone for three, and brachytherapy + pelvic radiotherapy for 55. In accordance with the hospital's protocol, pelvic radiotherapy associated with vaginal brachytherapy is formally offered to women with the following risk factors: blood and/or lymphatic capillary embolisation, presence of pelvic lymph node metastases, close or involved surgical margins, parametrial infiltration, tumour size greater than 4 cm, grade 2 or 3, and deep stromal infiltration. When the indication for postoperative radiotherapy results from only one of the last three parameters, pelvic radiotherapy is dispensed with and only vaginal brachytherapy is given.

Sociodemographic, clinical and treatment-related variables were collected from medical files. The histopathological variables were obtained from two sources: either from the medical files (tumour size and invasion of the parametrium, vagina and body of the uterus) or from reviewing the slides containing the histopathological sections from the uterine cervix. This review was carried out by a single pathologist (FAS), by means of observations using a Labophot-2 (Nikon) optical microscope. In 37 cases, the histopathological sections from the uterine cervix could not be reviewed because of poor slide quality or because they could not be located in the files. In two additional cases, the uterine cervix sections were insufficiently representative for determining the depth of invasion, and in one further case, for evaluating the extent of capillary embolisation and perineural invasion. These cases were not excluded from the analyses.

All the information collected was stored in a computerised database and analysed using SPSS 15.0. The disease-free period was taken to be the time elapsed between the surgery and recurrence of the disease. Five-year disease-free survival (DFS) rates were calculated using the Kaplan–Meier method, and the curves were compared using the log-rank test. Sociodemographic, clinical and histopathological variables with descriptive levels of up to 0.20 were selected for the Cox proportional hazards model. In the multivariate analysis, the stepwise selection technique was used and a significance level of 5% was stipulated. The model was adjusted for classical prognostic factors (tumour size, depth of tumour invasion and capillary embolisation) and treatment-related factors (period of treatment and postoperative radiotherapy status). The relative risk of recurrence was estimated by means of the hazards ratio.

This work formed part of a larger study linked to the postgraduate program of the Antônio Prudente Foundation, Hospital A. C. Camargo (São Paulo, Brazil), with funding from the research support foundation of the State of São Paulo (FAPESP; *Fundação de Amparo à Pesquisa do Estado de São Paulo*). This study had been submitted to and granted prior approval by the hospital's research ethics committee.

3. Results

The women were followed up for a mean of 108.3 months (S.D. 64.3; range 0.2–259.5; median 106.4). Twenty-seven recurrences were recorded (11.6%), of which 18 were pelvic, four were distant, four were pelvic and distant simultaneously and one was of unknown location. The disease-free interval ranged from 2.4 to 78.1 months (mean 21.9; S.D. 16.2; median 17.5) and the five-year DFS rate for the population studied was 88.4%. It was not possible to calculate the disease-free interval in one case because of a lack of information on recurrence in the medical file. Over the five-year periods, 35 women were lost from follow-up (15.0%). The mean follow-up for these women was 25.2 months (S.D. 19.8; median 23.8), ranging from 0.5 to 58.8 months.

The cases for which information on the variables was not available in the medical files did not present any statistically significant differences in five-year DFS, in relation to the cases for which this information was available (Table 1).

Table 2 (univariate analysis) shows the five-year DFS rates relating to the sociodemographic, clinical, histopathological and treatment-related variables. The independent risk factors for recurrence in the multivariate analysis were: postmenopausal status (HR 14.1; 95% CI: 3.7–53.6; $P < 0.001$), absent or slight inflammatory reaction (HR 7.9; 95% CI: 1.7–36.5; $P = 0.008$) and deep stromal invasion (HR 6.1; 95% CI: 1.3–29.1; $P = 0.021$). Postoperative radiotherapy was identified as a protective factor against recurrence (HR 0.02; 95% CI: 0.001–0.25; $P = 0.003$). This model was adjusted for tumour size, capillary embolisation and period of treatment (Table 3).

4. Discussion

This was a retrospective cohort study covering a long period, with a mean follow-up of nine years. It was conducted among