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Distant metastasis in patients with cervical cancer after primary radiotherapy with or without chemotherapy and image guided adaptive brachytherapy

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HIGHLIGHTS

- FIGO stage and lymph node status are significant predictors for distant metastasis in cervical cancer patients.
- 5 year distant metastasis free survival of 91% and 60% in low and high risk patients
- Significant impact of number of chemotherapy cycles on the occurrence of distant metastasis in high risk patients

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ABSTRACT

Objective. The aim of this study is to investigate patterns of distant relapse after primary radiochemotherapy in cervical cancer patients.

Methods. All patients with cervical cancer treated in curative intent with external beam radiotherapy +/− chemotherapy and image-guided adaptive brachytherapy between January 1998 and June 2009 at the Medical University of Vienna were included in this retrospective analysis. Patients with locoregional recurrences were excluded from this study. Presence, site of and time to distant metastases were recorded. For identifying prognostic factors, uni- and multivariate analyses using Cox regression analysis were performed. Based on the result from the multivariate analysis, patients were stratified into a high and a low risk group. The Kaplan–Meier method was used to estimate distant-metastasis-free-survival in the overall cohort, in the risk groups and for analysing the impact of chemotherapy within the risk groups.

Results. A total number of 189 patients were included in this study. After a median follow-up of 54 months, 49 patients developed distant metastases. Overall, distant-metastasis-free-survival 5 years after treatment was 73%. FIGO stage, lymph node status and the extent of tumour regression during treatment were significant predictors for distant metastasis. Distant-metastasis-free-survival 5 years after treatment was 91% and 60% in the low and high risk groups, respectively. The number of the cycles of chemotherapy had a significant impact on the occurrence of distant metastasis in high risk patients, but not in low risk patients.

Conclusion. Patients with high risk factors have a 40% probability of developing distant metastasis within 5 years. In these patients, decreasing the number of cycles of cisplatin may increase their probability of developing distant metastasis.

Introduction

Cervix cancer is one of the most common malignancies in women worldwide and still remains a prominent cause of female cancer death [1,2]. Radiotherapy has been the mainstay of treatment for locally advanced cervix cancer for decades. Since the late nineties chemotherapy is added to standard radiotherapy as this addition improves overall and disease free survival by about 6% at 10 years [3]. Besides improving the effectiveness of radiotherapy in terms of improvement of local tumour control, the addition of chemotherapy also decreases the rate of distant metastases, but to a lesser extent [3,4]. In spite of the clear benefits of adding chemotherapy to radiotherapy for cervix cancer patients, many questions still remain regarding the optimal agent and timing, as well as the added benefit for the higher stages [3,4].

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More recently, technological advances in radiotherapy have led to significant improvements in local tumour control. With image guided adaptive brachytherapy (IGABT) a local control rate of >90–95% appears to be achievable for all tumour stages. These promising findings in several single institution series are currently the subject of a multicenter verification in the EMBRACE study (European study on MRI guided BRAchytherapy in locally advanced CErvix cancer) [5–11]. However, it still needs to be clarified to which extent this improvement in local control translates into an improvement in overall or distant metastases-free survival [3,5,12,13].

Hence, in the setting of an excellent local control resulting from IGABT for locally advanced cervical cancer, distant failure emerges as the predominant type of failure for these patients.

We performed a retrospective analysis of patients with locally advanced cervix cancer treated with definitive radiotherapy including IGABT to (1) investigate time to occurrence of distant metastases and patterns of spread, (2) determine the impact of prognostic factors on the occurrence of distant metastases, (3) analyse the impact of chemotherapy on the occurrence of distant metastases.

Methods and materials

Patients

All patients with cervix cancer FIGO Ib to IVa treated with definitive radiotherapy between January 1998 and June 2009 at the Department of Radiation Oncology of the Medical University of Vienna were included in this retrospective analysis. Patients were excluded from this analysis in case of local/regional recurrence, delivery of neoadjuvant chemotherapy or a contraindication for chemotherapy due to patient age.

Pre-treatment evaluation included patient history, complete physical and gynaecological exam, routine laboratory studies, abdomino/pelvic CT or whole body (FDG-) PET-CT and MRI-scan of the pelvis.

Follow up investigations were performed every 3 months in the first two years after treatment, every 6 months in the next two years and then yearly thereafter. These included gynaecological examination and regular MRI-scans of the pelvis and thoraco/abdominal CT scans.

Radiotherapy

Detailed treatment characteristics are described in previous publications [14–20]. In brief, treatment consisted of whole pelvis EBRT with or without concomitant chemotherapy and IGABT. Before initiation of radiochemotherapy, laparoscopic lymph node staging and debulking of suspicious lymph nodes were performed in the majority of cases. If not, lymph node involvement was assessed by CT or PET-CT. EBRT was performed using a four-field box technique, with the gradual implementation of intensity modulated radiotherapy (IMRT) towards the end of the study period, after individual CT-based treatment planning with 1.8 Gy per fraction up to a total dose of 45 Gy. In case of suspicious lymph nodes (loss of oval shape, size >1 cm, significant FDG uptake), an additional boost up to ~15 Gy was considered. Concomitantly, 5–6 cycles of cisplatin-based chemotherapy (40 mg/m^2 body surface) were administered. If chemotherapy was not delivered, then the total EBRT dose was increased to 50.4 Gy. Additionally three to six (mainly four) fractions of MRI based high dose rate IGABT were performed in the end or after EBRT with the aim of delivering in total (EBRT + IGABT) >85 Gy EQD2 (biologically equieffective dose; reference dose per fraction = 2 Gy, linear quadratic model, $\alpha/\beta = 10$ Gy) to the D90 of the high risk clinical target volume (HRCTV). The performance of brachytherapy (including the number of brachytherapy fractions) varied during the learning period of IGABT. Since 2001, a systematic approach was used. Details on the concept of IGABT, the learning period and the systematic period are given in previous publications [5,14,15].

Chemotherapy

Concomitant weekly cisplatin-based chemotherapy (5–6 × 40 mg/m^2) was administered to patients who had a Karnofsky performance score of at least 60, age <80 years, neutrophil count >3.0 × 10^9 per litre, platelet count >100 × 10^9 per litre and creatinine clearance >70 ml/min. Chemotherapy was withheld if patients had a neutrophil count <2.0 × 10^9 per litre or a platelet count <100 × 10^9 per litre and if creatinine clearance was <50 ml/min. Patients with creatinine clearance in the range 50–70 ml/min received a reduced chemotherapy dose.

Methodology and statistics

Time to occurrence of distant metastases and patterns of spread/location

The probability of distant metastasis free survival (DMFS) at three and five years was estimated with the Kaplan–Meier method, with the date of initial biopsy as a starting point. Distant metastasis was defined as any first site of distant recurrence in the absence of loco-regional failure. Results are given with 95% confidence intervals (CI). The median time to occurrence of distant metastases and the median time from occurrence of distant metastases to death were calculated. Location of distant metastases is described.

Impact of prognostic factors on the occurrence of distant metastases

Exploratory univariate analyses were performed to assess the impact of known prognostic factors on the development of distant metastasis: FIGO stage, tumour size (grouped as <5 cm and ≥5 cm), lymph node status (positive or negative), histology, grade, patient age, overall treatment time, HRCTV size at the time of first brachytherapy, tumour regression during EBRT, D90 (EBRT + IGABT) of HRCTV and the number of cycles of cisplatin received by the patient. The extent of tumour regression was calculated from the gross tumour volume (GTV) on the T2-weighted pelvic MRI-scan at diagnosis and the residual GTV on the T2-weighted pelvic MRI-scan at the time of first brachytherapy, excluding the greyzones. Details on the methodology of the tumour regression analysis are described elsewhere [21]. Two-sided *p*-values below 0.05 were considered significant. Univariate significant factors were included in a multivariate Cox regression model on DMFS. Based on the hazard ratios of multivariate significant prognostic factors and the sub-analysis within these significant prognostic factors (Figs. 1 and 2), high and low risk groups of patients were defined and compared with a log rank test regarding DMFS.

Impact of chemotherapy on the occurrence of distant metastases

The dose of concomitant chemotherapy applied was defined as no chemotherapy (0 cycles), reduced number of cycles (1–4 cycles) and full number of cycles (5–6 cycles). The impact of chemotherapy on the occurrence of distant metastases was analysed with log rank tests in both the high risk and the low risk groups.

For all calculations, the IBM Statistical Package for Social Sciences (SPSS), version 17.0 was used (IBM Corp., Chicago, Illinois).

Results

Patient and treatment characteristics

A total number of 253 patients with primary locally advanced cervix cancer were treated with definitive radiotherapy with or without chemotherapy between January 1998 and June 2009.

Of these 253, 189 met the inclusion criteria for this analysis. The reasons for excluding the 64 patients were loco-regional failure ($n = 30$) or failure to achieve a complete response ($n = 8$), no chemotherapy administered due to age ($n = 23$) or neoadjuvant chemotherapy administered ($n = 3$). Patient- and tumour characteristics of these 189 patients are summarised in Table 1. Treatment characteristics are