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**ORIGINAL ARTICLE**

# Magnetic resonance imaging for assessment of parametrial tumour spread and regression patterns in adaptive cervix cancer radiotherapy

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**Abstract**

*Purpose*. To investigate the impact of magnetic resonance imaging (MRI)-morphologic differences in parametrial infiltration on tumour response during primary radiochemotherapy in cervical cancer. *Material and methods.* Eighty-five consecutive cervical cancer patients with FIGO stages IIB (n = 59) and IIIB (n = 26), treated by external beam radiotherapy (± chemotherapy) and image-guided adaptive brachytherapy, underwent T2-weighted MRI at the time of diagnosis and at the time of brachytherapy. MRI patterns of parametrial tumour infiltration at the time of diagnosis were assessed with regard to predominant morphology and maximum extent of parametrial tumour infiltration and were stratified into five tumour groups (TG): 1) expansive with spiculae; 2) expansive with spiculae and infiltrating parts; 3) infiltrative into the inner third of the parametrial space (PM); 4) infiltrative into the middle third of the PM; and 5) infiltrative into the outer third of the PM. MRI at the time of brachytherapy was used for identifying presence (residual vs. no residual disease) and signal intensity (high vs. intermediate) of residual disease within the PM. Left and right PM of each patient were evaluated separately at both time points. The impact of the TG on tumour remission status within the PM was analysed using $\chi^2$-test and logistic regression analysis. *Results.* In total, 170 PM were analysed. The TG 1, 2, 3, 4, 5 were present in 12%, 11%, 35%, 25% and 12% of the cases, respectively. Five percent of the PM were tumour-free. Residual tumour in the PM was identified in 19%, 68%, 88%, 90% and 85% of the PM for the TG 1, 2, 3, 4, and 5, respectively. The TG 3–5 had significantly higher rates of residual tumour in the PM in comparison to TG 1 + 2 (88% vs. 43%, $p < 0.01$). *Conclusion.* MRI-morphologic features of PM infiltration appear to allow for prediction of tumour response during external beam radiotherapy and chemotherapy. A predominantly infiltrative tumour spread at the time of diagnosis resulted in a significantly higher rate of residual tumour in the PM at the time of brachytherapy in comparison to a predominantly expansive tumour spread.

Currently, magnetic resonance imaging (MRI) appears to be the modality of choice for morphologic imaging of cervical cancer [1,2] and allows for assessment of local tumour extension by differentiating between normal soft tissue and tumour. In primary radiochemotherapy consisting of external beam radiotherapy (EBRT), concomitant chemotherapy and brachytherapy, the gross tumour volume at diagnosis ($GTV_{init}$) can be accurately depicted as high signal intensity mass on T2-weighted images [3]. The $GTV_{init}$ presents a wide variety of morphologic features and may be exophytic, infiltrating or endocervical, etc. [4]. During radiochemotherapy, the signal intensity of the $GTV_{init}$ changes, leading to high-intermediate signal intensity areas [5].

Tumour regression during EBRT and concomitant chemotherapy, visualised by repetitive MRI, accounts for approximately 80% shrinkage [6]. Several authors investigated the prognostic impact of quantitative tumour regression on outcome showing

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that poor tumour regression leads to higher risk of local failure [7,8]. Beside other prognostic factors, the width of the tumour reflecting somehow parametrial infiltration as well as the extent of parametrial infiltration (medial vs. lateral parametrium involved and unilateral vs. bilateral involvement) were shown to be of relevance – especially in regard of the performance of brachytherapy [9–11].

The aim of this study was to analyse the topography of parametrial tumour infiltration and to investigate the impact of MRI-morphologic differences in parametrial infiltration on tumour response during primary radiochemotherapy in cervical cancer.

## Material and methods

### *Patients and treatment*

All patients with squamous cell cervical cancer FIGO stage IIB and IIIB, treated between 1998 and 2005 at the Department of Radiotherapy of the Medical University of Vienna with primary radiochemotherapy including image-guided adaptive brachytherapy (IGABT), were considered for this study. All patients were staged clinically. Inclusion criterion was the availability of complete MRI data sets at the time of diagnosis and at the time of first brachytherapy. Complete MRI datasets at both time points were available in 85 patients.

Detailed treatment characteristics are described in a previous publication [12]. In short, treatment consisted of whole pelvis EBRT with or without concomitant chemotherapy and (MRI-based) IGABT. EBRT was performed using a four-field box technique after individual computed tomography (CT)-based treatment planning with a single dose of 1.8–2 Gy per fraction up to a total dose of 45–46 Gy. Concomitantly, up to five cycles of cisplatin-based chemotherapy (40 mg/m$^2$ body surface) were administered. If chemotherapy was not delivered, the total EBRT dose was increased to 50–50.4 Gy. Additionally, 3–6 fractions of MRI-based high-dose rate brachytherapy were performed with the aim of delivering in total $>85$ Gy $EQD2_{10\ Gy}$ (biologically equieffective dose; reference dose per fraction = 2 Gy, linear-quadratic model, $\alpha/\beta = 10$) to the high-risk clinical target volume (HR CTV). IGABT was performed in the end of or directly after EBRT.

### *MRI examination*

All 85 patients underwent MRI prior to EBRT and at the time of the first brachytherapy fraction. MRI examinations were performed using a 0.2-Tesla low field system (Siemens Magnetom Open-Viva®). Details on MRI technique have been previously described by Dimopoulos et al. [3].

### *Image analysis*

MR images were independently interpreted by two radiation oncologists, experienced in (MRI-based) IGABT. T-2 weighted images were used for analyses. Ambiguities in results were a subject of joint discussion with a consensus decision thereafter. A DICOM viewer (E-Film version1.5.3) was used for the evaluation of all imaging findings. Each parametrial side of each patient was evaluated separately at the time of diagnosis and at the time of brachytherapy. At the time of diagnosis morphologic features of the tumour spread were assessed with regard to the predominant tumour growth pattern (expansive with spiculae, expansive with spiculae and infiltrative parts, infiltrative). In case of an infiltrative tumour growth pattern, the maximum extent of parametrial infiltration (inner, middle and outer third) and the direction of infiltration (based on sectors: axial view: ventrolateral, lateral, dorsolateral sector; coronal view: craniolateral, mesolateral, caudolateral sector) were registered, in addition. An example of the extent of parametrial infiltration and the various sectors is given in Supplementary Figures 1a–d and 2a+b (available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.818251). Based on the tumour growth pattern and the extent of infiltration, five different types of tumours were defined:

Tumour group 1: Initially predominantly expansive tumours with spiculae;
Tumour group 2: Initially predominantly expansive tumours with spiculae and infiltrating parts;
Tumour group 3: Initially predominantly infiltrative tumours with the extension into the inner third of the parametrial space (PM);
Tumour group 4: Initially predominantly infiltrative tumours with the extension into the middle third of the PM;
Tumour group 5: Initially predominantly infiltrative growing tumours with the extension into the outer third of the PM.

MRI at the time of brachytherapy was used for identifying presence of residual disease (residual versus vs. no residual disease) and subjective evaluation of signal intensity (bright versus vs. grey zone) of residual disease within the PM, differentiating between the five defined tumour groups.

### *Tumour characteristics at diagnosis: Predominant growth pattern*

Classical MRI criteria of cervical cancer staging [13] were used for evaluation of parametrial infiltration. PM was assumed to be involved if the cervical stroma

was disrupted or if irregular linear and nodular structures in the PM were present [1]. In case of expansive tumours with spiculae a continuous low-signal-intensity stromal rim of the cervix with short interruptions and/or with linear radiate structures going into the PM was observed. Expansive tumours with spiculae and infiltrating part additionally featured an infiltrating part, representing less than 10% of the entire tumour mass. If more than 10% of the tumour appeared to be infiltrative, it was defined as an infiltrative tumour. The extent and direction of infiltration were assessed as shown in Supplementary Figure 2 available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.818251. If more than one sector was involved, each sector was counted separately.

### *Tumour characteristics at brachytherapy*

Cases with a restored low signal intensity cervical rim and no signs of residual disease in the PM, were designated as: *no remnants*. Suspicious residual tumour in the PM was classified as the *remnants*. These cases were further subdivided in accordance to the GEC ESTRO target volume concept to: 1) *bright zones* in case of high signal intensity area corresponding to the GTV at brachytherapy ($GTV_{res}$); and/or 2) *grey zones* in case of intermediate signal intensity area in the area of initial tumour extension, as included in the HR CTV. If *bright zones* and *grey zones* were present within one PM, both were registered.

### *Statistics*

Descriptive statistics were performed using Excel software (Microsoft) and SPSS version 15 (SPSS, Chicago, IL, USA). To analyse the overall difference in remnants between predominantly infiltrative and expansive growth pattern, a $\chi^2$-test was performed. To analyse the difference in the (PM-) remission status between the various tumour groups, a logistic regression analysis was performed with the remission status as dependent outcome and the tumour groups as independent predictors. The odds ratio describes the probability for (PM-) remission for each group in comparison to tumour group 1 as a reference group.

## Results

### *Patient and tumour characteristics*

Patient and tumour characteristics are given in Table I. The FIGO stage distribution was as follows: IIB n = 59, IIIB n = 26. Hence, a total of 170 parametrial sides were analysed. All patients had the histology of squamous cell carcinoma. Sixty-one patients received concomitant chemotherapy with cisplatin.

Table I. Patient and tumour characteristics.

| Characteristic | Patients n = 85 |
|---|---|
| Histology, n (%) | |
| – Squamous cell carcinoma | 85 (100%) |
| FIGO stage, n (%) | |
| – IIB | 59 (69%) |
| – IIIB | 26 (31%) |
| Tumour grade, n (%) | |
| – G1 | 5 (6%) |
| – G2 | 51 (60%) |
| – G3 | 17 (20%) |
| – unknown | 12 (14%) |
| Lymph node involvement, n (%) | |
| – positive | 41 (48%) |
| – negative | 44 (52%) |
| Chemotherapy, n (%) | |
| – concomitant | 61 (72%) |
| – neoadjuvant | 2 (2%) |
| – none | 22 (26%) |
| – GTVinit | 49.2 (6.3–380.4) |
| – GTVres | 9.3 (1.5–111.3) |
| – GTVres + grey zones | 20.4 (2.8–206.1) |

### *MRI analysis at the time of diagnosis*

At the time of diagnosis, a predominantly infiltrative tumour was found in 122 (72%) of the PM: infiltration into the inner, middle and outer third of the PM was present in 59 (35%), 43 (25%) and 20 (12%) PM, respectively. In 40 (23%) PM, a predominantly expansive tumour was found: An expansive tumour with spiculae was found in 21 (12%) PM and an expansive tumour with spiculae and infiltrating parts was detected in 19 (11%) PM. Eight (5%) PM appeared disease-free (due to the separate evaluation of the left and right PM).

Details of the topography of infiltrative tumours are provided in Supplementary Table I (available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.818251). In coronal view, infiltration of the craniolateral, mesolateral and caudolateral sectors was present in 12%, 59% and 22% of the PM, respectively. In axial view, infiltration of the ventrolateral, lateral and dorsolateral sectors was present in 4%, 59% and 35% of the PM, respectively.

### *MRI analysis at the time of brachytherapy*

All results on tumour groups and remission patterns are provided in Table II. At the time of brachytherapy, no parametrial remnants were observed in 37 (23%) PM. Bright and grey zones were found in 29

Table II. Tumour groups and remission patterns.

| At diagnosis Tumour groups 1–5 n = 162* | Total number n | At brachytherapy | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Remnants n (%) | Odds ratio n | p-value | Bright zone n (%) | Odds ratio n | p-value | Grey zone n (%) | Odds ratio n | p-value |
| 1) expansive with spiculae | 21 | 4 (19%) | – | – | 1 (5%) | – | – | 4 (19%) | – | – |
| 2) expansive with spiculae and infiltrating parts | 19 | 13 (68%) | 8.9 | 0.003 | 1 (5%) | 0 | 0.9 | 13 (68%) | 8.9 | 0.003 |
| 3) infiltrative inner third | 59 | 52 (88%) | 25.3 | $<0.001$ | 4 (7%) | 0.1 | 0.7 | 52 (88%) | 25.2 | $<0.001$ |
| 4) infiltrative middle third | 43 | 39 (90%) | 23.7 | $<0.001$ | 14 (33%) | 4.4 | 0.035 | 37 (86%) | 21.2 | $<0.001$ |
| 5) infiltrative outer third | 20 | 17 (85%) | 14.4 | $<0.001$ | 9 (45%) | 6.2 | 0.012 | 17 (85%) | 14.4 | $<0.001$ |

*8 PM appeared disease-free (due to separate evaluation of right and left PM.

(17%) and 123 (72%) PM, respectively. Overall, PM with predominantly infiltrative tumours (tumour group 3–5) had significantly higher rates of remnants in the PM compared to predominantly expansive tumours (tumour group 1 + 2) (88% vs. 43%, $p < 0.01$). In detail, the tumour groups 1, 2, 3, 4 and 5 had in 19%, 68%, 88%, 90% and 85% remnants within in the PM. The tumour groups 2–5 had significantly higher rates of any remnants than tumour group 1, but only tumour group 4 and 5 showed a significantly higher rate of bright zones in the PM.

Details of the frequency of bright and grey zones within the various sectors of parametrial infiltration are given in Supplementary Table I available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.818251. Remnants were present in the craniocaudal, mesolateral, caudolateral, ventrolateral, lateral, dorsolateral sector in 45%, 80%, 75%, 71%, 77%, 63%, respectively. The proportion of bright zones in the craniocaudal, mesolateral, caudolateral, ventrolateral, lateral, dorsolateral sector was 5%, 16%, 24%, 43%, 18%, 17%, respectively. The proportion of grey zones in these sectors was 45%, 78%, 70%, 71%, 75%, 62%, respectively.

## Discussion

Parametrial infiltration is a major prognostic parameter in cervix cancer [9]. The fact that the extent of parametrial infiltration is reflected in the FIGO staging system shows its outstanding importance. Differentiation between FIGO stage IIB and IIIB is mainly based on the extent of parametrial infiltration (and the occurrence of hydronephrosis) leading to a difference of approximately 10–30% in local control, cancer-specific survival and overall survival [11]. Further, clinical experience indicates also differences in local outcome within the large group of patients with IIB cancers [9], as well as within the group of IIIB cancers [14]. Reasons for the differences in local outcome may partly be attributed to differences in the extent and topography of parametrial tumour spread (uterosacral space involvement, e.g. was reported as poor prognostic factor [14]), to differences in tumour regression during EBRT and concomitant chemotherapy and subsequently to differences in brachytherapy dose coverage. It was shown (without using IGABT) that in case of tumour regression during EBRT > 20% of the initial tumour volume local recurrences occurred in 9.5% whereas in case of tumour regression during EBRT < 20% local recurrences occurred in 76.9% [7]. The primary aim of this study was to link different morphological aspects of parametrial tumour spread to response to EBRT and concomitant chemotherapy.

Attempts to morphologically classify cervical tumours started in the beginning of the last century. Kundrat in 1903 and Brunet in 1905 described different types of parametrial invasion based on findings from histological specimens [15,16]. In 1962, in order to facilitate the understanding of tumour growth and spread, Ober and Huhn introduced the term "boundary zone" which describes the border between cervix and parametria, and contains branches of the uterine vessels [17]. Years later, in the MRI era, the "boundary zone" was also identified on MR images [13].

Due to the high contrast resolution, MRI allows for discrimination between normal soft tissue and tumour in the pelvis and therefore has the capability of assessing parametrial infiltration [3]. On T2-weighted images various morphologic aspects of the tumour (exophytic, infiltrating etc.) can be differentiated [4,18]. During radiochemotherapy, the occurrence of grey zones – tissue with intermediate signal intensity in the area of primary hyperintense tumour extension – can be observed [6].

In this study, consisting of 85 patients with FIGO IIB and IIIB squamous cell carcinoma, a total number of 170 PM were analysed. Parametrial sides were analysed separately due to the typically asymmetrical tumour spread in cervical cancer. In our study, five tumour groups were defined based on the amount of infiltrative parts, ranging from predominantly expansive tumours with spiculae to predominantly infiltrative tumours with extension into the outer third of the PM. Differentiation between predominantly expansive and predominantly infiltrative tumours was based solely on morphological aspects; it was not related to tumour size or volume. Overall, it could be shown that predominately infiltrative tumours had significantly higher rates of remnants in the PM than predominantly expansive tumours. PM with predominantly expansive tumours (TG 1 + 2) showed frequencies of remnants in the PM ranging from 19% to 68% in comparison to PM with predominantly infiltrative tumours (TG 3–5) showing frequencies of $>85\%$. As far as the morphological appearance of the remnants in the PM is concerned, bright and grey zones, were distinguished in our study. Based on the literature on correlations between MRI and histopathologic findings after preoperative radiotherapy in cervical cancer, bright zones are considered as macroscopic residual tumour whereas the histologic composition of grey zones is unclear and may consist of fibrosis, oedema as well as residual (microscopic) tumour cells [19]. Whereas grey zones were almost always present in case of remnants in the PM in this study, statistically significantly higher rate of bright zones in the PM at time of brachytherapy was only found in case of a predominantly infiltrative growth pattern into the middle/outer third.

Topographic analysis revealed that at the time of diagnosis the PM were most frequently infiltrated in the lateral and mesolateral sector in the axial and coronal view, respectively. In these sectors, infiltration, reaching up to the inner third only, was present in 50%. In contrast, infiltration of all other parametrial sectors combined, accounted for approximately 40%. However, in these sectors, infiltration of the middle and outer third was observed more frequently (65–86%). The proportion of remnants at the time of brachytherapy (~70–80%) was – apart from the dorsolateral and craniolateral sector – similar in the various sectors according to the initial tumour spread.

The findings of our study may be useful in adaptive radiotherapy for prediction of tumour regression. It seems that the assessment of the initial tumour growth pattern by MRI allows for an estimation of tumour response to EBRT and chemotherapy. Based on the results of the study, it can be assumed that areas with a predominantly infiltrative tumour growth harbour biologically more aggressive/resistant tumour cells in comparison to areas with a predominantly expansive tumour growth. Tumour hypoxia, e.g. was shown to be an important biological factor for the development of radioresistance in cervical cancer and could be one of the underlying factors for the observed difference in tumour response [20]. Therefore – as indicated in the GYN GEC-ESTRO recommendations – adaptation of dose according to tumour response is needed for brachytherapy treatment planning. The patterns of PM infiltration of the middle to outer third especially in the craniolateral, caudolateral, ventrolateral and dorsolateral sectors have to be judged as topographically unfavourable situations, which are difficult to reach by intracavitary brachytherapy. A previous analysis of local recurrences consisting mainly of FIGO stage IIB and IIIB patients revealed low-dose regions at the border of the HR CTV in 85% of all local recurrences because of poor target coverage [21]. With IGABT the dose can be adapted – and if necessary and feasible escalated – according to the individual topography by dwell point optimisation and eventual interstitial needle implantation [22]. The local tumour control rate at three years with IGABT with application of the adaptive approach including interstitial needle insertion (mean D90 to HR CTV: 93 Gy) for the FIGO stages IIB and IIIB was recently reported as 96% and 86%, respectively [11].

Similar investigations on morphological tumour spread and response to radiotherapy were already performed for other tumour entities such as glioblastoma, lymphoma and small cell lung cancer [23–25]. Diehn et al., e.g. demonstrated that an infiltrative imaging phenotype in patients with glioblastoma multiforme was related to specific gene expression programs as well as to significantly shorter survival compared to patients with an oedematous growth pattern [25]. Such studies may become increasingly important for the currently ongoing research and development of adaptive radiotherapy strategies. Investigations in other tumour entities, e.g. head and neck cancer, may be worthwhile.

Functional imaging may provide new information in this field [26,27]. For example, the use of FAZA-PET in order to identify tumour hypoxia in cervical cancer patients was recently described as feasible [28]. Diffusion-weighted MRI and the use of the apparent diffusion coefficient (ADC) are currently being discussed for monitoring tumour response. Haack et al. found a significant difference of ADC-values for the different target volumes (GTV, HRCTV, IRCTV) in IGABT of cervical cancer [29]. Dynamic contrast-enhanced (DCE) MRI was reported to detect prognostically unfavourable subvolumes within the target. It was shown that

DCE-MRI improves prediction of (long-term) treatment outcome compared to quantitative morphology-based tumour regression rates [30–32].

## Conclusion

MRI-morphologic features of PM infiltration appear to allow for prediction of tumour response during external beam radiotherapy and chemotherapy. A predominantly infiltrative tumour spread at the time of diagnosis resulted in a significantly higher rate of residual tumour in the PM at the time of brachytherapy in comparison to a predominantly expansive tumour spread.

***Declaration of interest:*** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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## Supplementary material available online

Supplementary Figures 1, 2, and Supplementary Table I.