

# Measurement of tumour volume by MRI to evaluate risk of pelvic nodal metastases in early cervical carcinoma patients

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## ABSTRACT

**BACKGROUND:** Apart from the FIGO staging system there are several other factors, including tumour volume and lymph node status, which considerably influence local tumour control and survival of cervical carcinoma patients.

**AIM:** The study aimed to determine the prognostic value of cervical tumour volume measured on the basis of MRI in terms of pelvic nodal metastases prediction in early cervical carcinoma patients.

**METHODS:** The records of 49 early stage cervical carcinoma patients treated with preoperative brachytherapy and radical hysterectomy were analyzed. All patients underwent diagnostic MRI, which was the basis for tumour volume calculations as well as the evaluation of pelvic lymph nodes status and parametrial invasion. In each case the postoperative pathological diagnosis was obtained. The correlation between the occurrence of nodal metastases and such variables as tumour histology, grade and tumour volume, FIGOMRI stage IIB, and patients' age was evaluated. Logistic regression analysis was employed to determine correlations between tumour volume and histological pelvic nodal involvement.

**RESULTS:** A statistically significant correlation between pelvic lymph node involvement and such parameters as tumour volume and parametrial invasion was proven. The probability of lymph node metastasis is 20% for tumour volume of 17 cm<sup>3</sup> and increases up to 50% for tumour volume of 40 cm<sup>3</sup>. An increase of tumour volume by 1 cm<sup>3</sup> increased the risk of lymph node disease by 6.2%.

**CONCLUSIONS:** The study demonstrates that tumour volume may be considered a predicting factor in early cervical carcinoma patients, since it strongly correlates with pelvic lymph node histological status.

**KEY WORDS:** tumour volume, nodal metastases, cervical carcinoma, MRI

## INTRODUCTION

The FIGO staging system is commonly considered to be a convincing predictor of cervical carcinoma treatment outcome. However, there are several other factors, including tumour volume and lymph node status, which are not assessed by this system, still reported to be meaningful predictors as well. A proven indicator influencing the probability of local tumour control and survival is cervical tumour size [1, 2]. In contrast, a definition of early cervical carcinoma (stage IB and IIA)

includes a wide variety of tumour dimensions ranging from the smallest visible tumours with no pathologically involved lymph nodes to bulky tumours with a great probability of invasion to pelvic and periaortic nodes. The limited reliability and objectiveness of physical examination impel us to use different three-dimensional imaging techniques for tumour size estimation [3, 4]. MRI is an especially valuable method for identifying the primary tumour as well as lymph node disease

and distant metastases. However, there are doubts whether the MRI-based estimation of tumour diameter or invasion depth accurately reflects three-dimensional tumour extent. Since tumour volume can vary considerably within one FIGO stage, there is a high probability that it has great value in predicting lymph node involvement, a feature which decreases 5-year survival by 30–40% [1, 5].

### AIM

The present study aimed to estimate the prognostic value of tumour volume in prediction of pelvic nodal metastases in early-stage cervical carcinoma patients.

## MATERIAL AND METHODS

### Selection of patients

Between January 2004 and December 2005 a total of 49 cervical carcinoma patients (clinical stage IB1 and IIA) were treated with preoperative brachytherapy and radical hysterectomy at the Chair and Clinic of Oncology and Brachytherapy and the Chair and Clinic of Obstetrics and Gynaecology. From the total of 108 cervical cancer patients treated with LDR brachytherapy 70 patients (65%) were staged IB and IIA, and 38 (35%) presented more advanced disease. Sixty-four IB1 and IIA patients underwent preoperative brachytherapy and 6 patients were irradiated postoperatively.

Diagnostic MRI was performed in 49 out of 64 patients who underwent preoperative brachytherapy. The mean age of patients was 49 years (range 31–75 years). The clinical staging was based on the recommendations of the International Federation of Gynecology and Obstetrics (FIGO) and comprised the following: general clinical examination, gynaecological examination under general anaesthesia, cervical biopsy, routine blood counts, blood chemistry profile, chest X-ray, cystoscopy and ultrasonography of the abdomen and pelvis. The pathological diagnosis of most patients was squamous cell carcinoma, except in 3 cases, in which adenocarcinoma was proven. Characteristics of patients are given in Table 1.

### Image analysis

Before brachytherapy commencement all patients underwent MRI examination of the

**Table 1.** Characteristics of patients (N=49)

Patients' characteristics	
Factor	Value
Age [years]	
Mean	49
Range	31–74
FIGO <sub>MRI</sub> stage	
I	39 (80%)
II	10 (20%)
Tumor grade	
I	0
II	12
III	8
unknown	29
Tumor volume [cm <sup>3</sup> ]	
Mean	32
Range	1.1–118
pN(-)	30 (61%)
pN(+)	19 (38%)

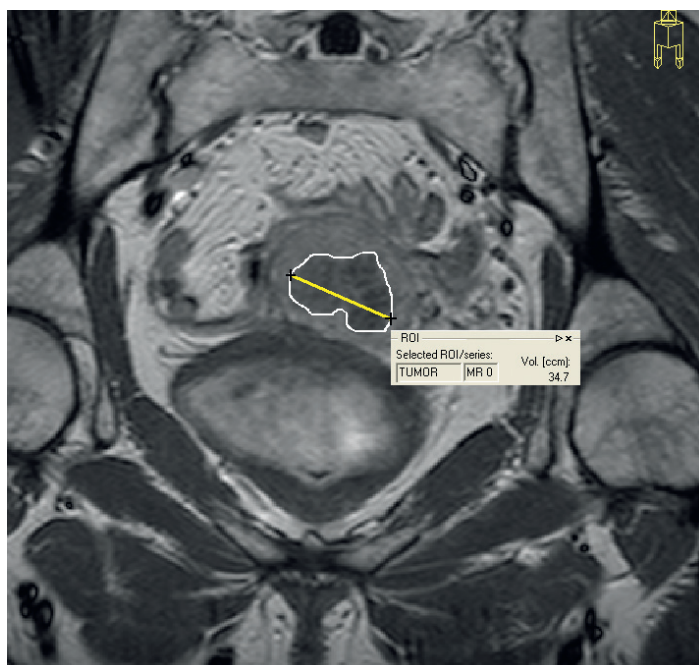
pelvis (1.5T scanner, Siemens, Erlangen, Germany), which served for the evaluation of primary tumour, lymph node enlargement and tumour volume computations. MRI outcomes were revealed to the gynaecologist but the outcomes did not influence the decision regarding surgery, even in the presence of enlarged lymph nodes or infiltration of the proximal parametria.

DICOM formats of T2-weighted pelvis images were sent to the treatment planning system. The tumour area was identified and delineated on each MRI scan by the oncologist with the assistance of a radiologist, who was blind to clinical and pathological findings.

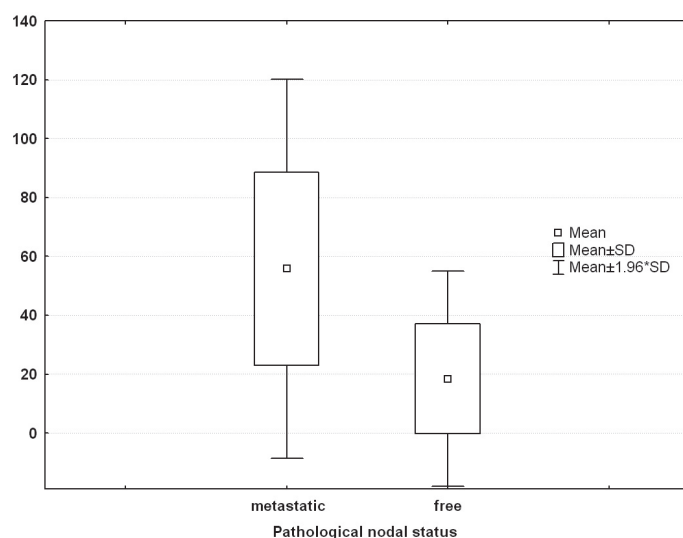
Tumour volumes (TV) were calculated automatically using the Oncentra MasterPlan (Nucletron, Veenendaal, the Netherlands; Figure 1). Lymph nodes greater than 10 mm in the short axis were interpreted as positive ones. Proximal parametrium involvement was classified as FIGO<sub>MRI</sub> stage IIB.

### Treatment

Prior to surgery all patients received intracavitary caesium treatment in two sessions



**Fig. 1.** T2-weighted MRI scan – delineated tumour (white line) is visible as a low-signal mass comprising the central part of the uterine cervix. The calculated tumour volume is shown



**Fig. 2.** Tumour volume parameters categorized into two groups according to the status of pelvic lymph nodes, pN(+) – positive (metastatic) lymph nodes, pN(-) – negative lymph nodes

with a two-week interval in between. The low dose rate afterloading technique was used and a total dose of 45 Gy to point A was given. Five to six weeks after completion of radiotherapy

radical hysterectomy with vaginal resection limited to the upper one-third was performed. Periaortic lymphadenectomy was not routinely performed.

### Statistical analysis

Pathologically confirmed pelvic lymph node involvement was the endpoint of the study. Correlations between different variables and lymph node involvement were assessed using univariate logistic regression. Multivariate logistic regression analysis was employed to determine correlations between statistically significant variables, identified in univariate logistic regression, and nodal involvement. The second step was to eliminate irrelevant statistics from multivariate logistic regression variables. Odds ratio (OR) and its 95% confidential interval (CI) were calculated.

Additionally, a sigmoid risk curve was drawn and its coefficient was obtained. The maximum likelihood method enabled the best adjusted risk curve to be drawn and the statistical significance of the adjustment to be assessed. A value of  $p=0.05$  was accepted as statistically significant. Tumour volumes were computed for both distinguished patient groups, with and without lymph node disease, and compared with Student's t-test.

### RESULTS

Pelvic nodal metastases (pN+) were found in 18 (38%) out of 48 operated patients. Additionally, one patient who did not undergo surgery due to confirmed skin metastasis was also attached to this group. Thus 30 (61%) out of 49 patients represented negative lymph node status. In the whole group of patients approximately 13 lymph nodes (SD 7.2; range 3–38) were removed. In groups pN(+) and pN(-) approximately 11 (SD 2.5; range 3–38) and 14 (SD 5.5; range 4–25) lymph nodes were removed, respectively. In group pN(+) were observed a vessel embolism of neoplasm cells in five patients and an extracapsular infiltration in three others. The mean tumour volume was  $32 \text{ cm}^3$  (SD  $30 \text{ cm}^3$ ). In patients with nodal metastases tumour volumes were significantly higher compared to those in patients with no nodal involvement:  $55.8 \text{ cm}^3$  (SD  $32.8 \text{ cm}^3$ ) vs.  $18.4 \text{ cm}^3$  (SD  $26 \text{ cm}^3$ ; t test,  $p=0.008$ ; Figure 2). The correlation between nodal metastasis

occurrence (pathologically confirmed) and such parameters as tumour volume, FIGO<sub>MRI</sub> stage IIB (unexpected findings in 10 patients), lymph node > than 10 mm in MRI (1 pt), tumour pathological type and grade as well as patient's age was determined.

In the univariate logistic regression, statistical significance was found for 2 parameters only, tumour volume (p=0.00001) and FIGO<sub>MRI</sub> stage IIB (p<0.03).

The multivariate logistic regression, in which the variables tumour volume and FIGO<sub>MRI</sub> stage IIB were used, revealed a mutual association between them. This association resulted in loss of statistical significance of FIGOMRI stage IIB. This was the reason for its exclusion in further analysis. Spearman's correlation coefficient between TV and FIGO<sub>MRI</sub> stage IIB was R=0.64.

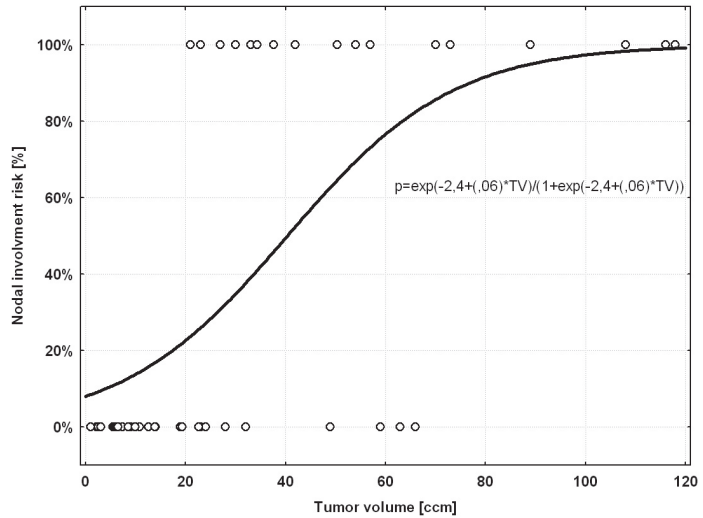
Figure 3 represents the risk of pelvic lymph node involvement as a function of tumour volume defined on the basis of MRI images. The probability of lymph node metastasis is 20% for tumour volume of 17 cm<sup>3</sup> and increases up to 50% for tumour volume of 40 cm<sup>3</sup>. The logistic regression analysis showed that each 1 cm<sup>3</sup> of tumour volume increases the risk of pelvic lymph node involvement by 6.2% (odds ratio 1.062; 95% CI 1.023-1.1). The model predicts an 8% risk for the "0" cm<sup>3</sup> tumour volume (invisible tumour).

The sensitivity and specificity of MRI in the assessment of pathologically affected lymph nodes were 5.5% (1/18) and 100% (30/30), respectively.

**DISCUSSION**

In patients with cervical carcinoma MRI has been extensively evaluated and reported to be currently the most accurate imaging modality for tumour measurement and delineation [7, 8, 9, 10]. The role of MRI cannot be overestimated when allowing for the fact that tumour size is a strong predictor of local control in radically treated patients, including those who are irradiated. According to Ito and co-workers tumour mass has a statistically significant influence on both tumour response rate after 2 months and survival [11].

Mitchell reported an odds ratio of 4.1 (1.5–11.5, 95% CI) for detection of histological lymph node involvement for average tumour



**Fig. 3.** Relationship between the risk of pelvic nodal involvement and tumour volume, the logistic regression equation

size using a threshold of > 3cm versus =< 3 cm [12]. Sahadev demonstrated an increase in the incidence of nodal metastasis with tumour size. Rate of nodal infiltration varied from 1.6% when no residual primary tumour was present, 11.5% when the primary tumour was < 2 cm, 33% in tumours between 2 and 4 cm, to 37.5% in tumours greater than 4 cm [13].

Some documented facts contradict the assumption that the risk of pelvic nodal involvement depends on tumour volume. Miller and Grisgby showed that in advanced cervical carcinoma both tumour volume and lymph node status strongly predict survival but do not correlate with each other [6]. The authors explain the phenomenon with diversified biological characteristics of different tumours independently of their size.

Their conclusions were based on an analysis of the relationship between tumour volume and macroscopic lymph node disease visualized with PET-CT. In our study pelvic node involvement was in each case confirmed by pathological examination. Our principal finding is the correlation between tumour volume and lymph node status. The frequency of lymph node metastases was significantly higher in patients with larger tumour volumes compared with those with smaller ones. An increase of tumour volume by 1 cm<sup>3</sup> increased the risk of nodal involvement by 6.2%. In the current



FIGO system nodal involvement is not taken into account when assessing disease stage. It is well known, however, that positive lymph nodes are the most significant, apart from distant metastases, prognostic factor for recurrence and death in cervical cancer patients.

We realize that the relatively small group of patients that might have influenced the statistical power of the analysis is a major limitation of our results. However, the important fact is that our model allowed us to distinguish a group of patients whose risk of lymph node disease is low, for example less than 10% or 15% (predicted for the volume of 4 cm<sup>3</sup> and 11 cm<sup>3</sup>, respectively). A more pronounced risk, for example higher than 50% (predicted in our model for 41 cm<sup>3</sup>) could suggest a change in the treatment strategy, such as excluding surgery. Unquestionably, further studies, with a higher number of patients, are required to confirm the presented preliminary results. So far our retrospective research, restricted to one hospital, does not allow us to give any strong recommendations on treatment protocol changing depending on tumour volume and thus the risk of pelvic node metastasis, and is only a monograph to discuss that topic.

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