

Magnetic resonance imaging of cervical cancer

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SUMMARY



In spite of extensive screening programs for pre-malignancy, cervical cancer is the third most common malignancy among women worldwide. Treatment is generally divided in surgery for early stage cervical cancer and chemoradiation (CRT) for locally advanced cervical cancer. Invasion of the adjacent parametrium is the most important turning point for the assignment to the right treatment. Staging has been traditionally performed by gynecological examination. The addition of MRI to the staging process significantly improves the assessment of the parametrium. However, assessing parametrial invasion on T2W-MRI is prone to false positive results; and still 13-25% of parametrial invasion is missed with conventional MRI. Patients with post-operative parametrial invasion receive additional (C)RT. Guidelines advocate to prevent surgery followed by (C)RT; more accurate staging could reduce triple modality treatment and therefore morbidity with comparable oncological outcome and less costs. Therefore, in **PART I** we addressed the value of new MRI techniques in early stage cervical carcinoma with emphasis on the prediction of parametrial invasion. We focused on the potential of diffusion weighted MRI (DWI). DWI reflects cell density by measuring water diffusion, cervical cancer has a higher cell density compared to normal cervical stroma or parametrium.

Approximately 30% of all cervical cancer patients eventually die due to persistent or recurrent disease. In case of isolated local persistent disease after CRT, salvage surgery is an option with a reasonable 5-year survival of 35-40%; however, both morbidity and mortality (10%) of the intervention are high. Therefore, **PART II** focused on MRI for prediction of local response for locally advanced cervical carcinoma.

PART I. MRI IN EARLY STAGE CERVICAL CARCINOMA, PREDICTION OF PARAMETRIAL INVASION

In **Chapter 2** we aimed to evaluate the diagnostic performance of DWI in addition to regular T2W sequences for the assessment of parametrial invasion. It was shown that the fusion of T2W-MRI with DWI results in an increase in diagnostic performance for the assessment of parametrial invasion in clinical early-stage cervical carcinoma. The positive predictive value for parametrial invasion significantly increased from 23-29% to 50%. Based on these data and the previous literature, DWI as an adjunct to T2W-MRI should be considered as a mandatory work-up tool for the assessment of parametrial invasion.

In addition to a qualitative approach we also aimed to quantitatively evaluate the value of DWI for the pre-operative assessment of parametrial and lymph node involvement (**Chapter 3**). Secondly, we compared different measurement techniques to determine

their reliability for assessing the qualitative derivative of DWI: Apparent diffusion coefficient (ADC). Single two-dimensional region of interest (ROI) ADC measurements were found to be reliable for assessing the mean ADC (ADC_{Mean}) of early stage cervical cancer. Therefore, our study supports meta-analysis of previous literature with different ROI measurement techniques. Second, the use of less time-consuming ADC_{Mean} measurement techniques in future studies is supported. ADC_{Mean} showed to be a more independent predictor of parametrial involvement than tumor diameter and subjective assessment of parametrial invasion on T2W-MRI. In line with other studies, ADC_{Mean} was able to predict lymph node metastases to some extent. Secondly, because we have demonstrated the independent potential of ADC_{Mean} for the assessment of parametrial and lymph node involvement, ADC_{Mean} should be considered as a predictor in future predictive models for these adverse outcomes after surgery.

PART II. MR AND PET IMAGING FOR PREDICTING RESPONSE FOR LOCALLY ADVANCED CERVICAL CARCINOMA

The aims of **chapter 4** were to evaluate the ability of pelvic MRI to detect residual tumor after RT, to identify and validate objective imaging criteria predictive for residual tumor, and to assess their performance. It was shown that the use of objective MRI criteria improved the interobserver agreement and the diagnostic performance of the less experienced reader for assessment of residual disease after RT. The results obtained with the last brachy application were rather poor compared to the evaluation 3 months after RT. We also showed that the evaluation of MRIs obtained during RT could assist in the evaluation after treatment.

We therefore support the use of 'objective' MR criteria for the detection of residual tumor after RT with higher interobserver agreement compared to subjective evaluation; however, taking into account that the use of 'isointensity' on T2W-MRI as a stand-alone criterion performs only moderate-average. The combination of 'isointensity' with 'nodular shape' and 'irregular border' could improve the assessment of residual disease, with the condition that this regression model has to be validated.

Chapter 5 assessed if absolute tumor volume and tumor regression during radiotherapy could discriminate between patients with a complete response and those with a residual tumor after radiotherapy. Absolute volume measurements as well as volume regression at BCT appeared to be promising predictors of local residual disease. If future studies validate our results, volume regression might become an important predictor of response to CRT for locally advanced cervical cancer.

Chapter 6 shares our first experience with the PET-MRI in the evaluation of radiotherapy treatment to discriminate between patients with a complete local response and patients with local residual tumor. The addition of PET to MRI diminished both false positive and false negative MRI findings. Moreover, it was shown that the PET component was able to detect metastatic disease, significantly influencing the policy for these patients. This second finding is important because approximately 50% of patients with local residual disease have remote metastases simultaneously. Future studies will show whether PET-MR proves to be capable of accurately assessing local residual cervical cancer while excluding metastatic disease.

Chapter 7, the general discussion, focused on the contribution of our findings to the existing literature, future perspectives, and directions for future research.