The current place of radiation therapy in cervical cancer – Focus on image-based brachytherapy

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Introduction

Brachytherapy for the treatment of locally advanced cervical cancer has been used worldwide over the past decades without essential improvements in outcome, although some developments have been introduced, as e.g. afterloading techniques, new dose rates, computerised treatment planning. Significant improvements in outcome could so far only be obtained by the additional simultaneous use of Cis-platinum based chemotherapy during the course of external beam therapy. The best results in regard to local tumour control reported so far [1] have been 45–78% for large tumours, even when interstitial methods were used. High rates of local control were often associated with serious late adverse effects going up to 15% [1].

New perspectives have been opened recently when sectional imaging [MRI (CT)] was systematically implemented into medical-physical brachytherapy treatment planning providing the preconditions for 3D conformal brachytherapy, which will most likely have a significant impact on the improvement of clinical results [2].

MRI has become the method of choice for the assessment of the pre-therapeutic tumour expansion in cervical cancer patients. The crucial role of MRI for cervix cancer brachytherapy is given by the accurate depiction of tumour and pelvic topography at diagnosis and during the whole treatment. The major role of CT is for delineation of organs at risk.

The role of PET imaging in accurate tumour definition is at present questionable due to the limited resolution of PET in general and during the process of radiotherapy in particular. The major role of PET is for staging.

3D-image based brachytherapy

In recent years the use of point A related brachytherapy has been increasingly questioned. The GYN GEC ESTRO group has developed a systematic approach with 3D sectional imaging (MRI (CT)) for the procedure of application and brachytherapy treatment planning. The aim is to enable an individualised adaptation of dose distribution to the target at high or intermediate risk for recurrence (HR CTV/IR CTV) and to the adjacent organs at risk [3,4]. This approach is increasingly replacing the traditional x-ray and point based methods.

Crucial for medical brachytherapy treatment planning is the ability to define the tumour extension in relation to the applicator. The knowledge of tumour extension and topography is required at the time of diagnosis and at brachytherapy.

While with CT the assessment of the dose distribution related to the organs at risk is enabled, with MRI this information can also be accurately provided for the cervix, the tumour and adjacent pathoanatomical structures. T2-weighted images in different orientations are needed. Commercially available CT/MRI compatible applicators are most frequently used: ovoids (Manchester-type) and ring (Stockholm-type). In large tumours with insufficient response and/or unfavourable topography after external beam radiotherapy combined intracavitary/interstitial techniques have been introduced by the Vienna group if adequate coverage of the target is not provided by a pure intracavitary method [2].

The definition of the brachytherapy target volume is based on the tumour extension at brachytherapy and by taking into account its initial extension [3]. The target volume for the high risk area (HR CTV: 80–90+ Gy) consists of the residual tumour at the time of brachytherapy as palpable and visible by clinical examination and as detectable on MRI [3]. Integration of CT or MRI enables also the visualisation of organ walls. The computed dose calculation is done for the most exposed small volumes of these structures [4]: rectum, sigmoid, urinary bladder.

Medical–physical treatment planning, dose–volume–histogram (DVH)-parameters

3D-MRI-assisted medical-physical treatment planning is performed with the applicator in place [2,4]. After applicator reconstruction is performed, a treatment plan is generated as stored for a certain type of applicator. The isodoses are visually checked for the CTV and the organs at risk and adapted. Dose-volume-histograms (DVHs) for the calculation of dose-volume parameters are generated. To achieve an ideal dose distribution, loading times and dwell positions of the source are adapted to the individual needs.

The coverage of the target is described with dose-volume related parameters: e.g. D_{90} and D_{100} (D_{50}, D_{70}) reflecting the dose covering 90% and 100% of the HR-CTV, respectively.

The exposure of the risk structures is described by reporting the dose delivered to defined small volumes of the contoured organs (e.g. $D_{0.1\,cm^3}$, $D_{1\,cm^3}$, $D_{2\,cm^3}$).

Dose prescription, dose volume adaptation, dose escalation

The dose- and fractionation-schedules for the target are based on the application of the linear quadratic model (α/β of 10 for tumour) and on the doses as indicated for DVH-parameters [1,2,4].

Dose prescription is based on dose values from institutional experience and from literature (e.g. point A). A high correlation between doses to point A and HR CTV has been found [2]. Overall doses for definitive radiotherapy in cervix cancer in literature are [1]: 75–80 Gy for small tumours (IB1, IIA, IIB [2–3 cm]) and 85+ Gy for large tumours (IB2, IIB [>3–4 cm], IIIB, IIIA, IVA). Beginning from these values, the overall dose to the HR-CTV can be adapted. Dose can be escalated (large tumours), until dose volume constraints are reached for organs at risk (e.g. 70–75 Gy for 2 cm^3 rectum), or until defined values are reached for CTV, e.g. a D_{90} of 90 Gy for HR CTV. There is some indication of dose levels correlated to outcome (Vienna series): only few local recurrences occurred, even in tumours >5 cm, if a D_{90} of more than 88 Gy could be applied for the HR CTV [2].

Dose-volume tolerance values for organs at risk

The iso-effective dose for organs at risk is likewise calculated using the linear quadratic model (α/β of 3 for late reacting tissues) [2,4].

The dose volume constraint for rectum and sigma was set as 70–75 Gy for the minimum dose in the most exposed tissue (2 cm^3). As there has been no clear evidence for a dose effect in the bladder, a dose volume constraint was 'arbitrarily' determined with 90 Gy for 2 cm^3. Due to the large dose inhomogeneity, doses to smaller volumes are additionally reported for all organs at risk (0.1 cm^3, 1 cm^3). The best validated dose volume constraints seem to be at present for the rectum [2,4].

Clinical results

3D-image based brachytherapy of cervical cancer is being increasingly implemented in clinical institutions. The first mono-institutional experience with systematic exploitation of this comprehensive 3D-radiotherapy in a large consecutive series (145 patients, Vienna 1998–2003) shows that local control in tumours with 2–5 cm and >5 cm can be increased to almost 100% and 90%, respectively [2]. In about one third, a combined intracavitary/interstitial brachytherapy was applied. With growing experience the dose volume constraints could be increasingly respected. The rate of serious late gastrointestinal and urogenital side effects (grade 3–4) could be kept below 5% for each effect, whereas the dose to the HR CTV could be increased from mean 81 Gy to mean 90 Gy.

Conclusion

MRI based brachytherapy in cervix cancer with individualisation and adaptation of treatment planning enables a dose escalation (>10%) resulting in a low local failure rate with <5% for small and ~10% for large tumours. Taking into account the dose volume constraints, a low rate of radiation related G3 and G4 gastrointestinal and urological morbidity (below 5%) can be reached at the same time, indicating a very favourable therapeutic ratio.

Conflict of interest statement

There are no conflicts of interest.

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