Dynamic Response of Carcinoma of the Uterine Cervix Using Serial Magnetic Resonance Imaging

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Background

3D-conformal and intensity-modulated radiotherapy (IMRT) techniques are able to shape the high dose treatment volume to the known tumor and regions at risk of tumor spread while minimizing the dose to adjacent normal tissues (organs at risk - OAR). This enables the delivery of higher doses of radiotherapy to the tumor while sparing critical normal structures. Each technique requires accurate identification of both the tumor and OAR. It is hindered by uncertainties such as the reduction in tumor volume during treatment. Tumor involution may lead to the entry of adjacent OAR into the high dose region previously occupied by the regressing tumor mass. The steep dose gradients, which would normally spare adjacent OAR, may now unnecessarily over dose these structures. Knowledge of the rate and manner of tumor response during radiotherapy treatment is necessary.

Tumor hypoxia and interstitial fluid pressure are important microenvironmental factors which can be used as biomarkers to predict treatment outcome. Tumor hypoxia has been shown to correlate with a poor response to radiotherapy and an increased risk of relapse and death in multiple human tumors. Similarly, high tumor interstitial fluid pressure predicts for an increased probability of tumor recurrence and death from progressive disease independent of tumor hypoxia in patients with cervix cancer. The relationship between the rate of tumor regression during radiotherapy and these important biologic parameters is unknown. An ability to predict treatment response early in the course of treatment would help to identify those patients who may be failed by standard therapy and enable the earlier introduction of more aggressive treatments.

Purpose

Assessment of the temporal-spatial response of cervix cancer during a course of radiotherapy using serial magnetic resonance imaging (MRI) scans was undertaken during this study. The relationship between tumor oxygen pressure (pO2) and interstitial fluid pressure (IFP) on disease regression as measured by MRI was also evaluated.

Methods and Materials

Patients with histopatholigcally proven carcinoma of the uterine cervix, eligible for radical chemo-radiotherapy, were approached for this study. IFP was measured using a wick-in-needle apparatus and oxygen tension was measured using a polarographic needle electrode system (Eppendorf-Netheler-Hinz, Hamburg, Germany) at the time of initial staging examination under anaesthetia. Treatment consisted of external beam radiotherapy (EBRT) 45 to 50 Gy in 1.8 to 2 Gy daily fractions delivered over 5 weeks using a 4-field technique and 18-to-25 MV photons. Cisplatin was administered weekly at a dose of 40 mg/m2. Upon completion of EBRT, patients received intra-uterine brachytherapy with a line source to a dose of 40 Gy at 2 cm from the centre of the stem. An initial pre-treatment MRI scan and weekly serial MRI scans were performed during EBRT. T2-weighted axial images (4-mm FSE, TR/TE 5800/106, ETL 12, NEX 3, matrix 256 x 256) were acquired at each time point using a 1.5 Tesla scanner with a pelvic coil (GE Medical Systems, Milwaukee, WI). The Pinnacle treatment planning system was used to delineate gross tumor in each image set, defined as the region of high signal intensity in the cervix and adjacent tissues (Philips Medical Systems, Bothell, WA). The slope of the linear regression line relating tumor volume to cumulative radiation dose was used to determine the volume regression rate for each patient.

Results

15 patients with cervix cancer participated in this prospective study between July 2003 and September 2004. The median age at treatment was 46.0 years (range 34 – 70 years) and their International Federation of Gynecologic Oncology (FIGO) stages were: 4 with IB; 4 with IIB; 6 with IIIB; and 1 with IVA disease. SIx patients had squamous carcinomas, 5 had adenosquamous carcinomas, and 4 had adenocarcinomas. The MRI determined median pre-treatment tumor volume was 41.7 cm^3 (range 18.8–176.4 cm^3). Tumor regression began early after the start of EBRT and was linearly related to cumulative dose. The Spearman correlation coefficients between tumor volume and dose in the 15 patients (4 to 6 data points for each case) ranged from -0.954 to -0.988 ($p<0.002$ to $p<0.024$). The regression rate varied between 0.37 and 1.77 cm^3/Gy, with a median value of 0.90 cm^3/Gy. The dose to achieve a 50% reduction in initial tumor volume was between 18.8 and 47.1 Gy (median 26.2 Gy). A more rapid rate of regression was observed in tumors with larger initial volumes (Spearman $r=0.65$, $p=0.022$). There was no apparent relationship between the initial tumor volume and the residual volume at the completion of EBRT. Pre-treatment tumor oxygenation did not affect regression rate. However, tumors with high initial IFP regressed significantly more slowly than those with lower IFP (Spearman $r=0.618$, $p=0.043$).

Conclusion

Cervix cancer regression can be assessed using MRI during EBRT. The visible tumor regression begins early and is linearly related to cumulative dose. Significant changes in tumor size and configuration may occur during EBRT. MRI has the potential to facilitate adaptive planning during treatment. This would enable changes in the radiotherapy treatment plan to parallel the regression of the tumor while avoiding surrounding critical structures. Adapting the treatment, in response to the MRI demonstrated anatomic changes in the irradiated area, should reduce organ-specific toxicities and enable a more aggressive use of concurrent systemic therapies. In addition, the rate of regression determined in this manner may provide an important early indication of overall response to radiotherapy. Tumors with high IFP appear to regress more slowly in keeping with the results of our previous study that showed reduced local control and patient survival. Future work will build on these observations to better understand the role of serial MR imaging in the management of patients with cervix cancer and may help to individualize therapy selections with the early identification of those women who are unlikely to respond to the current management approach.