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COMMENTARY

Hypoxia dose painting in prostate and cervix cancer

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Prostate and cervix cancer are both tumours in which hypoxia has been demonstrated [1–3] and which are treated with radical (chemo)radiotherapy. They are therefore both potential candidates for dose painting to achieve dose escalation within a hypoxic region of tumour to improve the therapeutic benefit. In both cervix cancer and prostate cancer high levels of hypoxia have been associated with a worse prognosis than better oxygenated tumours [4–6].

Hypoxia mapping in the pelvis

Identification of hypoxia in human tumours is undertaken using invasive electrode methods, classically the Eppendorf electrode, extrinsic hypoxic markers, such as pimonidazole and intrinsic markers, which reflect biological responses to hypoxia including HIF1, GLUT1 and CA9 [7–9]. If dose painting is to be employed then it is essential that in the clinical environment accurate definition can be made of the subpopulation of hypoxic cells and translated into the radiotherapy planning software. Computed tomography (CT) is a universal platform for radiotherapy planning enabling incorporation of x-ray absorption characteristics alongside anatomical structural information. It cannot however reliably identify physiological characteristics, such as hypoxia. The two imaging modalities which can be used for this are either magnetic resonance (MR) using dynamic contrast enhancing (DCE) images [10,11] or intrinsic susceptibility [blood oxygen level dependent (BOLD)] sequences based on the paramagnetic properties of deoxyhaemoglobin [12], or positron emission tomography (PET) imaging using a hypoxia seeking ligand, such as fluoro-misonidazole or 5 fluoro-azomycin-arabinoside (AZA) [13,14].

Anatomical imaging of the prostate gland is optimally achieved using multi-parametric MR [15,16] which will include a standard T2 image to give topographic information, a DCE sequence to evaluate blood flow and diffusion weighted imaging (DWI) to locate areas of high cellular density likely to represent significant foci of prostate cancer. In addition it has been shown that combining DCE MR with BOLD MR will give a map of hypoxic regions within the prostate gland using validation against pimonidazole staining [17].

In cervix cancer multi-parametric MR is also widely used for diagnostic purposes [18]. DCE MR of the cervix has been shown to reflect hypoxia, the K trans being a surrogate for hypoxia in three experimental models using pimonidazole as the gold standard for hypoxia [10]. Using a parameter derived from DCE MR based on the transfer rate from tissue to plasma and the rate of clearance from the plasma, correlation with a hypoxia gene sequence has been demonstrated. Using this parameter to reflect a hypoxia score a clear correlation with outcome after chemoradiation in patients with cervical cancer has been shown [19].

It is then possible using coregistered multi-parametric MR and planning CT scans to identify within the radiotherapy planning system biological subvolumes which are hypoxic. What is not known is the relation between such subvolumes at the time of planning and the distribution of hypoxia during a fractionated course of radiotherapy but significant changes with altered tumour blood flow and tumour volume are to be expected [20]. This difficulty for dose painting has yet to be fully resolved.

Delivery of dose-painted radiation treatment

Using functional imaging techniques biological subvolumes reflecting hypoxic cell populations can be identified. There have been a number of initiatives

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using hyperbaric oxygen and chemical radiosensitisers to improve tumour oxygenation during radiotherapy for cervix cancer but no consistent clinical benefit has been shown [21–24]. An alternative approach is to target dose escalation to the hypoxic subvolume. Whilst this strategy has been shown effective in animal models [25] the question arises as to whether this is realistic within the limits of modern radiotherapy technology.

A major technical challenge when treating both prostate and cervix is that of organ movement. It is well recognised that there is considerable day-to-day and even hour-to-hour and minute-to-minute movement of the prostate and cervix resulting from changes in the status of the surrounding bowel and bladder [26,27]. Using modern imaging a hypoxic subvolume will be identified using millimetre precision but several millimetres of organ movement may occur during treatment. This presents a challenge using external beam techniques [28]. Image-guided radiotherapy (IGRT) and four-dimensional (4D)RT techniques may address this in prostate cancer to some degree [29,30] and adaptive techniques have been developed for cervix cancer radiotherapy [31]. Stereotactic radiotherapy techniques (SBRT) are increasingly proposed for both prostate and cervical cancer although currently with limited published clinical data [32,33]. Only one SBRT platform can correct for organ motion using marker-based tracking but in this case the treatments are lengthy often spanning 40 or 50 minutes during which extensive organ movement and physiological changes will occur.

The alternative approach when treating prostate or cervix cancer is to use brachytherapy for the subvolume boost. Brachytherapy can used for both prostate cancer and cervical cancer with either low-dose rate (LDR)/pulsed-dose rate (PDR) (<2 Gy per hour) or high-dose rate (HDR) (>12 Gy/hour) systems. One of the major advantages of brachytherapy is that the source or source carrier is placed directly into the organ to be treated which overcomes the problem of organ movement during treatment. Using HDR brachytherapy (HDRBT), imaging and definition of the clinical target volume (CTV) is undertaken after implant and immediately prior to dose delivery [34] and thus the time between imaging, CTV subvolume definition and actual radiation delivery is minimised. Subvolume boosts to defined CTV subvolumes are technically feasible in prostate brachytherapy [35] and this offers the optimal test bed for hypoxic dose painting in prostate cancer. Brachytherapy for cervical cancer uses the same image-based volume definition [36] and with appropriate modification of applicator insertion using interstitial applicators then similar subvolume boosts can be conceived.

The ultimate goal of dose painting is to achieve dose escalation within the relatively resistant biological subvolume [37]. This will be achieved using an integrated boost and larger dose per fraction within the high dose subvolume. In tissues with a low α/β ratio significant gains can be achieved using large doses per fraction. This is best delivered using HDRBT. In prostate cancer delivery of single doses of 15–20 Gy are well established [38–40]. Using a simple formula for biological effective dose (BED) based on $BED = D\ (1 + f/\alpha\beta))$ where D = total dose and f = dose per fraction and using an α/β of 3 shows that a schedule delivering 15 Gy to the whole prostate and a boost of 20 Gy to a hypoxic region will be delivering 54 Gy EQD2 to the whole gland and 92 Gy EQD2 to the boost, respectively. It is recognised that using such large doses per fraction the linear quadratic equation does not fully describe the dose response, however, the relative effects are likely to be similar; in this case the dose increment represents an increase of 70% to the subvolume. As brachytherapy doses refer to the peripheral dose the dose within the volume will be much greater per fraction and the increment in these regions will be several times this amount, well within the range predicted by experimental oxygen enhancement ratios to overcome hypoxia.

Hypoxia is an established and important entity in the biology of prostate cancer and cervix cancer. It has been identified in both tumour sites and shown to reflect a more aggressive tumour, greater metastatic potential and a worse prognosis. Multiparametric imaging can identify hypoxic elements within the tumour which can be imported into a radiotherapy planning system. Subvolumes within the CTV can be defined reflecting hypoxic tissue which may benefit from higher doses. External beam techniques are limited in their application to dose painting by the problem of organ movement and the need for lengthy fractionated courses of treatment. HDRBT is well established for both prostate and cervix cancer and has enormous potential for dose painting in both prostate and cervix, delivering precise high dose per fraction radiation overcoming the problems of organ motion and with minimal delay between imaging and dose delivery.

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