IMRT and molecular biological approaches in radiotherapy for prostate cancer

Robert G. Bristow

Radiation Medicine Program, Princess Margaret Hospital (University Health Network), Toronto, ON, Canada

Prostate cancer is the most commonly diagnosed cancer in men in the Western hemisphere. Using the prognostic variables of T-category, the serum prostate specific antigen (PSA), and the pathologic Gleason score (GS), men with localised prostate cancer are placed in low, intermediate and high-risk groupings. These risk groupings can also predict for biochemical (PSA) failure-free survival (bFFS) and prostate cancer specific mortality (PCSM) following treatment [1]. In low or intermediate-risk prostate cancer localised to the prostate, treatments such as active surveillance, radical prostatectomy, external beam radiotherapy (using daily doses of 2–3 Gy up to total doses of 60–80 Gy) or brachytherapy are used. The choice of treatment will depend on patient preference and other considerations (e.g. operability and co-morbidities). In other patients, adjuvant or salvage RT to the prostatic fossa is used following a radical prostatectomy for positive surgical margins and/or a rising PSA with curative intent. In patients with high-risk disease, randomised clinical trials support combined modality therapy such as androgen deprivation plus external beam RT due to the increased risk of sub-clinical metastases [1].

External beam radiation therapy (EBRT) has an established role in the management of localised prostate cancer. Prostate cancer is thought to have a steep radiation dose-response curve. A benefit for higher doses has been reported in randomised studies (i.e. the MD Anderson Cancer Center, Massachusetts General Hospital, Dutch Phase III trials) using doses between 78 and 79.2 Gy with improvements in biochemical outcome and possibly prostate-cancer specific survival for particular risk categories [2]. However, dose escalation can lead to increased late gastrointestinal (GI) and genitourinary (GU) toxicity. As such, careful rectal dose constraints and image-guided radiotherapy (IGRT) techniques (e.g. ultrasound or fiducial marker-based methods to track inter-fraction motion) have been utilised along with intensity-modulated radiotherapy (IMRT) in an attempt to improve local control without additional late toxicity [2].

IMRT is a complex treatment planning technique whereby the intensity of radiation across the beam can be modulated and requires increased computing power to achieve multiple beamlets within a field. Proponents of IMRT for prostate cancer speak of the ability to sharpen, shape and conform field edges and steeper dose-gradients between the tumour target volume and surrounding normal tissues when compared to 3D-conformal radiotherapy (3D-CRT) or 2D planning. However, IMRT has not been compared to 3D-CRT in a randomised clinical trial and potential negative aspects of IMRT include possible increases in secondary RT-induced tumours and the potential for marginal miss of cancers due to steep dose gradients [1,2].

The ability to target prostate cancer with increased physical precision using IMRT may open the possibility for further improvement in clinical outcome using biological precision. Fractionated radiotherapy has been a successful therapy for prostate cancer and is thought to maintain the therapeutic ratio (e.g. increased killing in tumour cells relative to normal tissues) by differential cellular repair between malignant and normal tissues. This repair is currently being studied within hypofractionated (e.g. daily doses of >2.5 Gy) radiotherapy protocols [3,4]. By excluding bladder and rectum maximally, this use of larger doses per fraction can potentially attain similar radiocurability without an increase in late injury to GI and GU tissues. Current data support prostate cancer having an α/β repair ratio of 1.5–3.0 and this supports current trials which are studying doses per fraction in the range of 3–6 Gy. The PMH experience of 60 Gy delivered in 3 Gy fractions over 4 weeks utilising both IGRT and IMRT is now being explored in an international randomised trial compared with a 78 Gy in 2 Gy fraction standard arm (PROFIT – Prostate Fractionated Irradiation Trial) [1].

Biologic precision can also be improved by targeting pathways which increase local radioresistance [1]. Individualisation of prostate cancer treatment could be optimised by focusing on the biology of patient-specific tumours and normal tissue genetics. Resistant tumour cell phenotypes may reflect differences in genomic architecture between individual cancers. Altered bFFS and disease-free survival has been associated with differential expression of the p53, $p16^{INK4A}$, MDM2, Ki-67, survivin and BAX/BCL-2 proteins [1,5,6]. Additionally, there is increasing interest in the radiosensitivity of cancer stem cells which constitute 0.1–10% of the tumour and are difficult to quantify using immunohistochemical methods [7]. Finally, single nucleotide polymorphisms (SNPs) in DNA repair or cytokine genes may predict for GI or GU toxicity following radical prostate cancer radiotherapy [8–10]. A molecular-therapeutic ratio for IMRT may therefore come from an understanding of tumour and tissue radiosensitivity at the genetic level.

The tumour microenvironment may also give rise to altered prostate cancer radiocurability. Based on immunohistochemical studies using extrinsic and intrinsic markers, and direct oxygen electrode measurements, clinically-relevant levels of hypoxia are detected in 30–90% of prostate cancers [11–13]. Hypoxia can be a predictor of disease-free survival following radiotherapy or surgery independent of other prognostic factors and may herald androgen-independence [13]. Hypoxic cells may also have differential DNA repair that can be utilised for sensitisation approaches. As such, the use of precision IMRT radiotherapy and non-invasive hypoxia imaging may make it possible to boost or dose-paint certain areas of intratumoural hypoxia with DNA repair inhibitors or hypoxic cell sensitisers or targeting strategies [14].

Conflict of interest statement

None declared.

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