Contemporary Issues in Radiotherapy for Clinically Localized Prostate Cancer

Richard Khor, MBBS, FRANZCR*, Scott Williams, MD, FRANZCR

KEYWORDS

• Prostate carcinoma • Radiotherapy • Image-guided radiotherapy • Brachytherapy • Stereotactic body radiotherapy

KEY POINTS

- Radiation is a potent genotoxic agent that induces clonogenic cell death through apoptosis and terminal senescence.
- Increasing radiation dose is associated with improved biochemical outcomes, and is facilitated by improvements in image guidance and better target delineation.
- Neoadjuvant or adjuvant androgen deprivation improves biochemical and survival outcomes in intermediate-risk and high-risk patients, but the benefits must be measured against potential toxicity.
- Prostate cancer may respond to higher doses per fraction than other tumors, which has led to the current interest in brachytherapy and stereotactic body radiotherapy.
- There is level 1 evidence regarding the improved outcomes achieved with adjuvant postprostatectomy radiotherapy, with current trials investigating the role of early salvage postprostatectomy radiotherapy.
- Future improvement in outcomes may be derived from improved adjuvant therapies or technological advancements in radiotherapy delivery techniques.

INTRODUCTION

Radiation therapy remains a valid curative approach to prostate cancer therapy. Significant technological advances over the past 2 decades have facilitated the safe delivery of increasingly higher doses of radiation therapy to the prostate while avoiding relevant adjacent tissues. In turn, short-term and medium-term outcomes have improved, and the addition of endocrine manipulation either before (neoadjuvant) or

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Division of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett Street, Victoria 8006, Australia
* Corresponding author.
E-mail address: richard.khor@petermac.org

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after (adjuvant) curative therapy has shown a substantial impact. Furthermore, radiotherapy in the postprostatectomy setting has gained prominence in recent years.

PRINCIPLES OF RADIATION THERAPY

Therapeutic radiation can be delivered with multiple techniques. For most patients, this involves external beam radiotherapy (EBRT) using a linear accelerator to deliver high-energy photons. Alternatively, brachytherapy uses temporary high-dose-rate (HDR) or permanent low-dose-rate (LDR) radioactive sources to deliver the prescribed dose to the target.

Ionizing radiation is a potent genotoxic agent that predominately interacts with biological matter by inducing double-stranded deoxyribonucleic acid (DNA) breaks. Tumor growth is halted by either induction of tumor cell death by necrosis or loss of cell reproductive integrity; together termed clonogenic cell death. It seems that clonogenic inactivation through instigation of terminal differentiation (senescence) may also be central in the response of prostate cancer to radiation.[1,2]

The aim of traditional fractionated radiation therapy is to exploit potentially defective DNA repair mechanisms through delivery of daily doses, nominally 1.8–2 Gy per day. This allows for normal tissues with ostensibly intact DNA damage repair mechanisms to repair a substantial portion of the DNA damage between fractions. Tumors are usually unable to mount a similar DNA repair response, and thus sustain more damage over multiple fractions than normal tissues.[3] As the total delivered dose accumulates, so does the DNA damage, and more tumor control is achieved.

Different tissues have different patterns of response depending on the dose and dose per fraction given. As a generalization, the model of dose-response shows an initial linear component and subsequent quadratic components to this relationship. In general, normal tissues are more damaged by higher doses of radiation per fraction, whereas most malignancies show a much more linear response to increasing dose per fraction, meaning there is an advantage to delivering high total radiation doses. Recent data suggest that prostate cancer may behave differently, and exhibit a similar fraction size sensitivity to that of normal tissues, suggesting that larger fraction sizes rather than total dose are optimal.[4–7] With approaches such as HDR brachytherapy, impressive biochemical outcomes have been reported with lower doses of radiotherapy delivered in large fractions.[8,9]

PATIENT SELECTION FOR RADIATION THERAPY WITH CURATIVE INTENT

Risk Stratification

There is significant heterogeneity in the biological behavior observed in prostate cancer. The risk of biochemical failure after local therapy has been explored in detail. Increasing stage at presentation, prostate specific antigen (PSA) level, and grade of tumor all predict for PSA recurrence after therapy with curative intent.[10,11]

The National Comprehensive Cancer Network (NCCN) risk stratification (**Table 1**)[11] can be used to stratify patients by risk of biochemical failure after curative therapy

Table 1
NCCN risk stratification and PSA control

NCCN Risk Stratification	AJCC Clinical Stage	Presenting PSA (ng/mL)	Gleason Grade
Low	T1 to T2a, N0	≤10	6 or less
Intermediate	T2b to T2c, N0	>10–20	7
High	T3 or T4, N0–1	>20	8 or greater