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Comment

Treatment de-intensification for low-risk biochemical recurrence after radical prostatectomy: rational or risky?

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Biochemical recurrence, or first detection of measurable serum PSA after radical prostatectomy, occurs in approximately one-third of patients [1] and is often the first indicator of residual or relapsed prostate cancer. Detectable serum PSA in this context may be due to production by malignant cells at the surgical margin, within the periprostatic tissue, and/or within regional or distant sites, with remaining benign cells being a less common cause.

As most potential sources of biochemical recurrence are located in the pelvis, treatment of biochemical recurrence largely relies on salvage radiation therapy (RT), including prostate bed/fossa with or without pelvic lymph node RT, sometimes with androgen deprivation therapy (ADT). Salvage RT is delivered with curative intent, but often at the expense of increased morbidity and reduced quality of life compared to radical prostatectomy alone [2]. Recent salvage RT trials have trended towards treatment intensification, including addition of ADT, alone (GETUG-AFU 16 NCT00423475) as well as with pelvic lymph node RT (SPPORT NCT00567580), and escalation of radiation dose to the prostate bed/fossa (NCT01272050), resulting in increased toxicity.

Clinically appropriate de-intensification of post-prostatectomy RT is an attractive hypothesis, due to potentially reduced toxicity with quality-of-life benefits for equivalent oncological control, as observed in the recently published RAVES (NCT01272050) and RADICALS (NCT00541047) trials. Therefore, further de-intensification is desired; however, suitable predictive factors are lacking. The European Association of Urology (EAU) guidelines [1] suggest use of a stratification framework based on systematic review, where 'low risk' is defined as radical prostatectomy Gleason score < 8 and PSA doubling time ≥ 12 months. These guidelines also suggest that treatment deferral can be considered if adequate life expectancy is questionable.

Almost all data relating to the oncological benefits of salvage RT are based on staging with conventional imaging (CT, bone scan). Prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT has superior sensitivity and accuracy for detection of prostate cancer metastases than conventional imaging (CT, bone scan). Significant clinical management changes occur, although this has yet to be shown to improve oncological outcomes. Up to 15% of patients with biochemical recurrence may have metastases located outside salvage RT fields per PSMA PET/CT [3,4], even at low PSA levels (<0.5 ng/mL) so salvage RT in these patients is likely to be futile, with associated morbidity. Conversely, salvage RT for people with a negative PSMA PET may portend favourable oncological outcomes, including significantly higher event-free survival compared to observation for those with low EAU risk (87% vs 36%; hazard ratio 0.22, $P = 0.02$) [5]. Although the EMPIRE-1 trial recently reported that ^{18}F-fluciclovine-PET/CT-directed salvage RT resulted in better 3-year event-free survival compared to conventional imaging (75.5% vs 63%; $P = 0.03$) [6], PSMA PET is known to be diagnostically superior to ^{18}F-fluciclovine-PET/CT [1]. Unfortunately, high-quality, prospective data are limited.

Less use of early (PSA <0.5 ng/mL) salvage RT has been observed anecdotally within Australian clinical practice,

following similar trends favouring salvage over adjuvant RT prior to publication of RAVES. It is speculated that this trend has been fuelled by the high proportion of negative PSMA PET scans reported at low PSA levels. In one study, 24% of people with negative PSMA PET underwent observation, resulting in 35% event-free survival (mean event-free period 38 ± 7 months) [5]. Therefore, among people with an initial PSMA-avid primary tumour, there may be a subset of people with apparent biochemical recurrence and a negative PSMA-PET scan who may not have potentially significant cancer recurrence, who will not experience progression, and who may be safely monitored and avoid potential side effects from salvage RT.

The authors assessed clinician opinions regarding treatment de-intensification for biochemical recurrence after radical prostatectomy using an online survey tool, which was distributed through Australian urology and radiation oncology email networks. The survey received institutional ethical approval (UQ 2020/HE002695) and participant consent was implied by completion of the survey. Low risk patient criteria were outlined, including early biochemical recurrence (PSA 0.1–0.5 ng/mL) and low EAU risk (radical prostatectomy Gleason score <8; PSA doubling time ≥ 12 months), and willingness for randomization according to two scenarios was assessed:

A. Negative PSMA PET/CT, randomize to:
   a. Surveillance OR
   b. Prostate bed/fossa RT only (no ADT)

B. Positive PSMA PET/CT at prostate bed/fossa only, randomize to:
   a. Prostate bed/fossa RT only OR
   b. Prostate bed/fossa RT +/− additional regional lymph node RT +/− ADT

Fifty-three clinicians completed the survey (59% urologists, 40% radiation oncologists). Clinical experience was diverse (median [interquartile range] 15 [6–23] years). Overall, 81% of respondents (78% urologists, 93% radiation oncologists) supported the concept of de-intensification. Scenario A was supported by 85% of respondents (88% urologists, 80% radiation oncologists) and Scenario B was supported by 87% of respondents (94% urologists, 73% radiation oncologists). Among clinicians who did not support de-intensification in patients with negative PSMA PET/CT patients, urologists indicated that both microscopic systemic disease or local relapse could be present and other information (e.g., seminal vesicle invasion) aided decision making, while radiation oncologists preferred to irradiate at lower PSA levels due to concern for worse oncological outcomes if treatment is given at higher PSA levels, and a wish to use ADT if salvage RT is to be used. For patients with positive PSMA PET/CT, a urologist commented that 'most men won't agree to ADT without clear evidence of benefit', while radiation oncologists were mixed in their preference for ADT, with some preferring a focal boost as 'ADT is overkill in this setting', while others felt ADT was mandatory in PET-positive disease.

The high willingness to enrol low-risk patients in a risk-adjusted trial indicates uncertainty regarding the optimal management of low-risk biochemical recurrence after radical prostatectomy. Currently, patients in this uncertain situation face pros and cons of salvage RT and surveillance, as outlined in Table 1. These competing oncological and quality-of-life factors require comprehensive, multi-faceted assessment within prospective trials. Ultimately, individualization for each patient, supported by high-quality evidence for decision making, is the pipedream but not yet possible until current and future trials, such as the DIPPER Trial (ACTRN12622001478707), are completed.

Table 1 Comparison of salvage radiation treatment and surveillance as management strategies for low-risk biochemical recurrence with negative prostate-specific membrane antigen positron emission tomography/CT.

	Salvage radiation treatment	Surveillance
Pros	1. High chance of disease remission (>80% event-free survival) 2. Higher-level evidence 3. Treat at lower disease volume ➔ better oncological outcomes 4. Weight of evidence favours treatment for local control 5. Technology advancements (CT guidance, hypofractionation) may reduce morbidity and inconvenience 6. Limit follow-up intensity 7. Accepted clinical practice	1. Low risk of prostate cancer-specific mortality 2. Low-volume disease/benign tissue 3. Limit local morbidity/side effects (similar to active surveillance for localized disease) 4. Option for alternative/targeted treatment for radiologically proven disease (often outside standard radiotherapy fields) 5. Avoid treatment and side effects if competing morbidity or other cause of mortality 6. Accepted clinical practice
Cons	1. Higher local side effects (bladder, bowel) 2. Supportive evidence based on conventional imaging 3. Inconsistent outcomes/effect on metastasis-free and overall survival 4. Treatment-related burden (travel, accommodation, cost)	1. Worse biochemical control overall (higher PSA progression) 2. Delayed treatment at higher PSA levels may have worse oncological outcomes 3. Higher-risk strategy in some patients (no fixed address) or health system (wait list, service availability) circumstances

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Disclosure of Interests

MJR and LE are co-Principal Investigators of the DIPPER (Dedicated Imaging Post-Prostatectomy for Enhanced Radiotherapy outcomes) trial (ACTRN12622001478707) sponsored by the ANZUP Cancer Trials Group. All authors confirm no relevant conflict of interest.

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Abbreviations: ADT, androgen deprivation therapy; EAU, European Association of Urology; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RT, radiation therapy.

