African Urology 2021;1(1):17-18
https://doi.org/10.36303/AUJ.2021.1.1.0017

AFRICAN UROLOGY
ISSN 2710-2750 EISSN 2710-2750

ORIGINAL RESEARCH

Indications and timing of radiotherapy after radical prostatectomy: An update

J Lazarus,[1] S Salukazana,[1] G Hart[2]

[1] *Division of Urology, Groote Schuur Hospital, University of Cape Town, South Africa*
[2] *Department of Radiation Oncology, Groote Schuur Hospital, University of Cape Town, South Africa*

Corresponding author, email: may1968.geo@yahoo.com

Keywords: radiotherapy, radical prostatectomy, indications, timing

Introduction

Recently reported trials have shed light on the vexing clinical dilemma of the optimal timing and indications of radiation (RT) following prostatectomy (RP) for carcinoma of the prostate (CaP). The importance of this work can't be overemphasised since recurrence is common, occurring in up to 50% of patients within 10 years, depending on the type of primary therapy and stage of cancer.[1]

The controversy of timing and indications arose following the publication of a landmark 2009 paper by Thompson et al.[2] Their work provided a strong signal in favour of adjuvant RT therapy. This trial randomised patients with high-risk prostate cancer to either immediate adjuvant RT (immediate defined as within four months, 60–64Gy) or observation.

The key finding was a median 1.7-year survival benefit in the adjuvant group. Prior studies had shown reduction in biochemical recurrence, but no improvement in metastasis-free status or survival. At the time, this outcome was practice-changing.

The impact of Thompson's paper

Key to Thompson's paper was the definition of high risk. They included pT3N0M0. Since this definition included positive surgical margins and since roughly a third of men undergoing RP are quoted to have positive margins, this greatly increased the number of men theoretically requiring adjuvant RT.[2]

It is worth now considering the impact of adjuvant radiation on the morbidity associated with RP. The recently reported CEASAR trial aimed to prospectively quantify the impact of RT on functional outcomes. At five years of follow-up, the study showed that RP plus adjuvant RT was associated with a significant decrease in continence, sexual and hormonal function scores and worse urinary and bowel irritation compared with RP alone.[3] The authors concluded that "If it is oncologically safe to avoid RT after RP, or to defer its use until maximum functional recovery from the RP, it seems worthwhile to do so".[4]

The CEASAR trial confirmed what we have long known but gave greater insight into treatment-related toxicity and its impact on quality of life (QOL). Yet there is clearly a trade-off here between QOL and targeting men who have aggressive disease where RT is needed to obtain disease control.

Adjuvant vs salvage RT

Given the toxicity of adjuvant RT and the concern that many patients with an isolated positive surgical margin were being overtreated, the race was on to better define if deferring adjuvant RT to a salvage setting was an option.

Thus, the ongoing aim was to find the balance between oncological safety and treatment-related toxicity. The RAVES, RADICALS and GETUG-17 trials endeavoured to define that balance.

A metanalysis of these three trials concluded that immediate adjuvant RT did not improve event-free survival compared to early salvage RT in men with intermediate, high-risk, or locally advanced CaP undergoing RP.[5]

Seventy-eight per cent of the 1 078 patients included in the metanalysis were Gleason 7. The five-year rate of event-free survival was 89% in the adjuvant vs 88% in the salvage RT group. Most events were biochemical progression. Across the three trials, early salvage radiotherapy was triggered at PSA levels of ≥ 0.2 ng/ml.

Salvage RT: the new gold standard

The EAU–ESMO guidelines have adopted the information from these three trials. The guidelines advise that more than 60% of patients who are treated before the PSA level rises to 0.5 ng/ml (the definition of early salvage) will achieve an undetectable PSA level, providing patients with an 80% chance of being progression-free five years later.[6]

Early salvage holds the promise of avoiding RT in many men with adverse features who may be cured by RP alone. It also appears that salvage impacts functional outcomes to a lesser degree compared to adjuvant RT. In the RADICALS trial, for example, a significant reduction in all radiation-related toxicities (diarrhoea, proctitis, cystitis, haematuria and urethral stricture, all $p \leq 0.02$) was observed in the salvage group. Similar findings were reported in the other two trials.[7]

Limitations and caveats

In contemporary practice, RP is increasingly being offered to men with high-risk disease. Yet in the three trials mentioned above, only 9–17% of men had a Gleason score of 8–10. Do the conclusions – that early salvage is equivalent to adjuvant – hold in this high-risk (Gleason 8–10, seminal vesicle invasion, positive margins and high PSA) subset?

Evidence supports a more cautious approach in these men so as not to miss the opportunity for cure. A 2016 study by Fossati et al. showed that early salvage conferred better cancer control when administered at the very first sign of a PSA rise, as opposed to waiting for the formal definition of a rise above 0.2 ng/ml.[8]

A further consideration addressed only in the GETUG 17 trial is the role of concomitant androgen deprivation (ADT). The study demonstrated that patients receiving RT plus goserelin (six months) were significantly more likely than patients in the RT only group to be free of biochemical progression or clinical progression at five years.[9]

Conclusion

Radiation plays a significant role in managing men who have undergone RP for cure. Salvage RT is the evidence-based modality of choice. The key, however, is *early* salvage RT. Evidence also suggests that ADT may be beneficial when administering RT after RP.

ORCID

J Lazarus https://orcid.org/0000-0003-2417-8332

S Salukazana https://orcid.org/0000-0003-1726-0370

References

1. De Visschere PJL, Standaert C, Fütterer JJ, et al. A systematic review on the role of imaging in early recurrent prostate cancer. Eur Urol Oncol. 2019;2(1):47-76. https://doi.org/10.1016/j.euo.2018.09.010.
2. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009;181:956-62. https://doi.org/10.1016/j.juro.2008.11.032.
3. Huelster HL, Laviana AA, Joyce DD, et al. Radiotherapy after radical prostatectomy: Effect of timing of post prostatectomy radiation on functional outcomes. Urol Oncol. 2020;38(12):930. https://doi.org/10.1016/j.urolonc.2020.06.022.
4. Schieszer J. Radiation therapy after prostate surgery worsens sexual, urinary function. Prostate Cancer Advisor. Available from: https://www.renalandurologynews.com/home/news/urology/prostate-cancer/radiation-prostate-surgery-quality-of-life-erectile-function/. Accessed 11 Jun 2021.
5. Vale CL, Fisher D, Kneebone A, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. Lancet. 2020;396(10260):1422-31. https://doi.org/10.1016/S0140-6736(20)31952-8.
6. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on prostate cancer. Part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol. 2017;71(4):630-42. https://doi.org/10.1016/j.eururo.2016.08.002.
7. Sidaway P. Salvage radiotherapy: a new standard of care. Nat Rev Clin Oncol. 2021;18:5. https://doi.org/10.1038/s41571-020-00443-3.
8. Fossati N, Karnes RJ, Cozzarini C, et al. Assessing the optimal timing for early salvage radiation therapy in patients with prostate-specific antigen rise after radical prostatectomy. Eur Urol. 2016;69(4):728-33. https://doi.org/10.1016/j.eururo.2015.10.009.
9. Carrie C, Hasbini A, De Laroche G, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): A randomized, multicentre, open-label phase 3 trial. Lancet Oncol. 2016;17(6):747-56. https://doi.org/10.1016/S1470-2045(16)00111-X.