Selected Summaries

Immediate or salvage radiotherapy after radical prostatectomy: Do we finally know?

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SUMMARY

RADICALS-RT

This open-label, multicentre, phase 3 randomized trial compared the efficacy and safety of immediate postoperative adjuvant radiotherapy (RT) against early salvage RT at biochemical progression after radical prostatectomy for localized prostate cancer. Patients had at least one risk factor (Gleason score 7–10, pathological stage T3–4, positive surgical margins or preoperative prostate-specific antigen [PSA] ≥10 ng/ml). A total of 1396 patients were randomized to either adjuvant RT within 26 weeks of surgery (*n*=697) or salvage RT at biochemical progression (PSA ≥0.1 ng/ml, or three consecutive PSA rises) (*n*=699). Prostate bed was treated with RT over 4 to 6 weeks in both arms. Patients were further randomized to 0 or 6 months or 24 months of hormone therapy, the results of which are awaited (RADICALS-HD). The primary outcome measure was freedom from distant metastases (FFDM), whereas the secondary outcome measures were overall survival, disease-specific survival, initiation of non-protocol hormone therapy, toxicity, patient-reported outcomes and biochemical progression-free survival (bPFS).

At a median follow-up of 4.9 years, 33% of the patients in the salvage RT arm received RT for PSA progression. The median PSA at the initiation of salvage RT was 0.2 ng/ml (IQR 0.1–0.3 ng/ml). Although the primary end-point of FFDM has not been reported yet, the 5-year bPFS was 85% with adjuvant RT and 88% with salvage RT

(HR 1.10, 95% confidence interval [CI] 0.81–1.49; p=0.56). Due to a low event rate, data for the primary outcome measure of FFDM and overall survival had not sufficiently matured for comparison between the two groups. Bowel and bladder toxicity were slightly higher in the adjuvant RT arm, with 3% of patients experiencing grade 3–4 haematuria in the adjuvant group versus <1% in the salvage group within the first 2 years of randomization (p<0.0001). Rates of urethral stricture were also higher in patients on the adjuvant RT arm (6% *v*. 4%, p=0.0025). Patient-reported quality of life scores showed no long-term differences between the two arms. The investigators concluded that there was no benefit with adjuvant RT in terms of biochemical control, while further follow-up was required for assessing the effect on long-term outcomes.

ARTISTIC meta-analysis

RADICALS-RT was one of the three ongoing randomized controlled trials globally addressing the question of the timing of RT following radical prostatectomy (immediate postoperative adjuvant RT *v*. salvage RT at biochemical recurrence) in intermediate-to-high risk prostate cancer, the other two being GETUG-AFU 17 and RAVES.[1,2] The ARTISTIC collaborators prospectively planned this meta-analysis to include data from these three trials.[3] RAVES had a non-inferiority design for biochemical progression with salvage RT, while the other two hypothesized the superiority of adjuvant RT over salvage RT. Table I describes the characteristics of the patients included in these three trials. Of the total 2153 patients included in the ARTISTIC meta-analysis, 1075 had been assigned to adjuvant RT and 1078 to salvage RT. The primary outcome measure was event-free survival. The median follow-up ranged from 60 to 78 months.

At the time of analysis, 421 patients (39.1%) randomized to salvage RT had received RT. No difference was observed in the 5-year event-free survival with adjuvant RT as compared to early salvage RT (89% *v*. 88%, HR 0.95, 95% CI 0.75–1.21; p=0.70). On subgroup analysis, the effect of adjuvant RT on event-free survival did not vary according to any of the pre-defined subgroups, namely preoperative PSA, Gleason score, seminal vesicle involvement, surgical margins or cancer of the prostate risk assessment post-surgical score (CAPRA-S) risk group. Based on these findings the authors concluded that early salvage RT following prostatectomy in intermediate-to-high risk prostate cancer does not compromise event-free survival as compared to immediate adjuvant RT, and could potentially avoid postoperative RT in a considerable proportion of men.

TABLE I. Characteristics of patients included in the three trials addressing the timing of postoperative radiotherapy

Characteristic	Name of trial		
	RADICALS-RT (%)	RAVES (%)	GETUG-AFU 17 (%)
Median PSA at diagnosis (ng/ml)	7.9	7.4	NA
Pathological tumour stage			
pT2	24	23	Nil
pT3a	57	58	77
pT3b	18	19	21
pT4	1	0	2
Gleason grade group			
1	7	3	10
2	49	82	52
3	27		28
4–5	17	15	9
Positive surgical margins	63	67	100
Node positive	5	Unknown	Excluded

PSA prostate-specific antigen NA not available

COMMENT

Radical prostatectomy is one of the treatment options for localized prostate cancer. Based on the stage at diagnosis and postoperative histopathological features, 30%–70% of patients will experience a recurrence.[3] The American Urological Association defines biochemical recurrence as a PSA value of ≥0.2 ng/ml after surgery, with a second confirmatory level ≥0.2 ng/ml.[4] Immediate adjuvant RT post-prostatectomy reduces the risk of biochemical recurrence but adds to the morbidity. Since about half of the patients following surgery remain free of biochemical recurrence, they could potentially be spared the added toxicity by adopting the approach of early salvage RT at the time of PSA progression. Thus, it has been long debated whether to follow surgery with immediate postoperative adjuvant RT at the cost of increased toxicity and overtreatment or to reserve RT for patients who have a biochemical failure with risk of delay in treatment or metastatic progression. While previous randomized trials have suggested improvement in outcomes with adjuvant RT, multiple lacunae in their design and conduct failed to provide a conclusive answer.[5–8] Less than half the patients who developed progression received salvage RT in these trials, with initiation of RT delayed till PSA increased to 0.75–1.0 ng/ml. Given the control arms of observation and underutilization of salvage RT, the results from these trials do not define current practice.

Currently available ultrasensitive PSA assays allow early detection of biochemical recurrence and timely initiation of salvage RT. Phase 3 randomized trials of RADICALS-RT, GETUG-AFU 17, and RAVES have addressed the question of timing of postoperative RT by taking a low cut-off for post-surgery PSA of 0.1–0.2 ng/ml to trigger initiation of salvage RT. Each trial was powered for a different primary outcome, namely FFDM (RADICALS-RT), event-free survival (GETUG-AFU17) and freedom from biochemical progression (RAVES). To provide a more reliable and systematic evidence, ARTISTIC collaboration prospectively pooled the randomized data and analysed the collective clinical outcomes (not individual patient data) for the harmonized end-point of event-free survival. None of the trials showed any significant difference between adjuvant and salvage RT for their respective end-points, and the meta-analysis also reported similar 5-year event-free survival for the two arms.

These results suggest that early salvage RT should now become the standard of care following radical prostatectomy. It would avoid overtreatment for patients who either do not develop recurrence or recur late in the course of their disease, thus avoiding the additional morbidity of RT. Although encouraging, this approach needs to be implemented carefully in the context of Indian practice. To be equivalent to adjuvant RT, the timing of salvage RT is critical and should be instituted early, at PSA levels of around 0.2 ng/ml. Patients with lower pre-RT PSA levels have higher long-term biochemical control compared to patients with higher pre-RT PSA levels.[9] Thus, this approach should only be adopted in highly compliant patients and healthcare systems where serial PSA monitoring is possible and biochemical relapse can be detected early.

Patients undergoing radical prostatectomy for locally advanced prostate cancer, as increasingly seen in India, show a high likelihood of multiple adverse histopathological features, with a higher risk of disease recurrence.[10] Not surprisingly, the majority of radiation oncologists in India prefer adjuvant RT for patients with high-risk factors (preoperative PSA >20 ng/ml, Gleason score ≥8, positive surgical margins, extraprostatic

extension or lymph nodal involvement) after the surgery.[11] These patients who are at the highest risk of biochemical failure were under-represented in the three trials included in the ARTISTIC meta-analysis. For instance, RADICALS-RT included 17% of patients with Gleason score ≥8, lymph nodal involvement was seen in only 5% of patients, and 37% of patients had a CAPRA-S score of ≥6 (CAPRA-S is a predictive score from 0 to 12 for biochemical recurrence, with a score of ≥6 being at high risk of recurrence). With increasing adoption of robotic-assisted prostatectomy in India even for locally advanced prostate cancer as a part of multimodality treatment, increase in proportion of patients with multiple adverse pathological factors is inevitable.

The concerns regarding tolerance of postoperative RT have been allayed by the low absolute rates of toxicity reported in both the arms of RADICALS-RT, though the relative rate was higher with adjuvant RT. Of note, these trials did not mandate the use of modern RT such as intensity-modulated RT which a large majority of radiation oncologists in India use for prostate RT. These techniques help reduce the toxicity with adjuvant RT further.[12,13]

Based on the results of these landmark studies, early salvage RT can be recommended as the preferred approach for most patients in whom close monitoring can be undertaken. However, for patients with multiple high-risk factors of relapse in locally advanced prostate cancer, adjuvant RT will still continue to have an important role after surgery.

Conflicts of interest. None declared

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SHASHANK SRINIVASAN

SHREYA KUNDER

PRIYAMVADA MAITRE

VEDANG MURTHY

Department of Radiation Oncology
ACTREC and TMH, Tata Memorial Centre
Homi Bhabha National Institute
Mumbai
Maharashtra
India
vmurthy@actrec.gov.in; vedangmurthy@gmail.com

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