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Platinum Opinion

Contemporary Evaluation of Salvage Radiotherapy for Prostate Cancer: Radiotherapy Dose, Field Size, and Use of Hormone Therapy

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1. Introduction

Men who are treated with radical prostatectomy (RP) for prostate cancer may ultimately need salvage radiotherapy (SRT) for biochemical recurrence. In recent years, important studies have provided high-level evidence to inform various aspects of SRT, including radiation field design, radiation dose, and accompanying hormonal therapy regimens.

2. Radiation field design

NRG/RTOG-0534 was a three-arm randomized trial that compared the incremental benefit of adding androgen deprivation therapy (ADT) and whole-pelvis RT to prostate-bed RT in the salvage radiotherapy (SRT) setting [1]. While no improvements in distant metastasis (DM)-free survival or overall survival (OS) were seen with either intervention, the addition of 4–6 mo of ADT and the incremental addition of pelvic nodal RT to prostate-bed radiation significantly improved 5-yr freedom from progression (70.9% vs 81.3% vs 87.4%). Notably, progression was defined using the Phoenix criterion. Significant toxicity was not increased. Although not statistically significant (but not powered), there was mild evidence of greater efficacy for patients with prostate-specific antigen (PSA) >0.35 ng/ml at the time of SRT. Thus, it is reasonable to consider addition of whole pelvis RT in patients who are receiving ADT with SRT and have PSA >0.35 ng/ml. However, the applicability of these results to a population screened with advanced molecular imaging is unclear.

The importance of such imaging on radiation field design was recently demonstrated by the EMPIRE-1 study [2]. The radiation field was rigidly constrained in patients who had ^{18}F-fluciclovine imaging, and fields were changed in 34% of patients. Changes involved the inclusion of pelvic lymph nodes in patients with node-positive findings and exclusion of SRT altogether in patients with radiographic evidence of metastatic disease. Importantly, intensification was not associated with worse toxicity. Given the better sensitivity of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) over fluciclovine PET, results from the PSMA-SRT trial (NCT03582774) are eagerly anticipated.

3. Radiotherapy dose

In the definitive treatment setting, it has been shown that dose escalation improves biochemical control, but not metastasis-free survival (MFS) [3]. SAKK-09/10 compared the conventional SRT dose of 64 Gy against 70 Gy to the prostate bed and found no differences in freedom from biochemical progression (typically PSA $\geq$0.4 ng/ml) at median follow-up of 6.2 yr, although the incidence of grade 2 gastrointestinal toxicity was higher in the dose-escalated arm (20% vs 7.3%) [4]. There also was an increase in acute patient-reported urinary outcomes with higher doses, although no differences were seen at longer follow-up. A smaller, single-center trial from Peking further confirmed no benefit from dose escalation (Table 1). Additionally, an ancillary analysis of the SAKK-09/10 trial found that the Decipher genomic classifier could not identify patients who would benefit from dose escalation [5]. Thus, there is currently no high-level evidence to support dose escalation in the salvage setting, even when considering biochemical

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Table 1 – Key published studies

Trial and phase	C_{arm}	E_{arm}	Patients	Primary endpoint	Outcome (%) C_{arm} vs E_{arm}	mFU
EMPIRE-1 Phase 2/3	CIMG	CIMP plus ^{18}F-fluciclovine PET/CT	165	Event-free survival	75.5 vs 63	3.5 yr
RTOG 0534 Phase 3	Prostate-bed RT	Whole-pelvis RT	1792	FFP	87.4 vs 81.3	8.2 yr
SAKK 09/10 Phase 3	64 Gy in 32 fractions	70 Gy in 35 fractions	350	Freedom from BCP	61 vs 62	6.2 yr
Peking Phase 3	66 Gy in 32 fractions	72 Gy in 36 fractions	144	BCP-free survival	82.6 vs 75.9	48.5 mo
RTOG 9601 (Shipley) Phase 3	RT + placebo	RT + 24 mo Bic (150 mg/d)	760	Overall survival	76.3 vs 71.3	13 yr
GETUG-AFU-16 Phase 3	RT alone	RT + 6 mo goserelin (10.8 mg/90 d)	743	Freedom from BCP or clinical progression	80 vs 62	9.3 yr
RTOG-0534 Phase 3	RT alone	RT + short-term ADT (4–6 mo)	1716	FFP	81.3 vs 70.9	8.2 yr
RADICALS-HD	RT alone	RT + 6 mo ADT	1480	MFS	80 vs 79	9 yr
Phase 3	RT + 6 mo ADT	RT + 24 mo ADT	1523		78 vs 72	
FORMULA-509	RT + GnRH + Bic	RT + GnRH + AAP	345	PSA PFS	67.2 vs 46.8	34 mo
Phase 2				MFS	84.3 vs 66.1	

AAP = abiratrone + apalutamide + prednisone; ADT = androgen deprivation therapy; BCP = biochemical progression; Bic = bicalutamide; C_{arm} = control arm; CIMG = conventional imaging; CT = computed tomography; E_{arm} = experimental arm; FFP = freedom from progression; GnRH = gonadotropin-releasing hormone; MFS = metastasis-free survival; mFU = median follow-up; PET = positron emission tomography; PFS = progression-free survival; PSA = prostate-specific antigen; RT = radiation therapy.

recurrence–based endpoints. Once again, the manner in which advanced molecular imaging might impact the benefit of dose escalation remains unclear. The recent SPIDER multicenter analysis suggests that dose escalation may have a role for patients with macroscopic local recurrences [6], who were excluded from the SAKK 09/10 trial.

4. Addition of hormone therapy

In the definitive treatment setting, robust data support a survival benefit from addition of hormonal therapy to RT (Table 1). While not all patients will require hormonal therapy in the salvage setting, several key studies have identified the population that may experience a benefit from treatment intensification with ADT. NRG/RTOG-9601 randomized patients undergoing SRT to either placebo or 150 mg bicalutamide daily for 2 yr. At long-term follow-up, the study (which was effectively a study of late SRT given the median pre-SRT PSA of 0.6 ng/ml) found that hormonal therapy improved 12-yr OS (76.3% vs 71.3%) and 12-yr DM (14.5% vs. 23%). However, patients with entry PSA <0.7 ng/ml did not derive a DM, prostate cancer–specific mortality, or OS benefit from addition of hormone therapy. Importantly, there was a two to threefold increase in high-grade cardiac and neurologic events in the bicalutamide arm. This translated to a nearly twofold increase in death from other causes among patients with entry PSA <0.7 ng/ml. An ancillary analysis demonstrated that that the Decipher genomic classifier might serve as a predictive biomarker, as men with a Decipher score of $\geq$0.45 derived a benefit from hormonal therapy even if they had PSA <0.7 ng/ml at the time of SRT [7].

The GETUG-16 randomized trial evaluated a more contemporary hormonal therapy regimen (6 mo of goserelin) and was functionally a study of early SRT given the median pre-SRT PSA of 0.3 ng/ml [8]. The results showed that hormonal therapy improved 10-yr progression-free survival (PFS; 64% vs. 49%). MFS, which was retrospectively determined, was also improved (75% vs 69%). No analyses have yet identified whether certain subgroups in particular would benefit. These results are consistent with the freedom-from-progression benefit seen in RTOG 0534 with the addition of hormonal therapy.

Results from several as-yet unpublished studies are eagerly anticipated in this space. Early results from the RADICALS-HD trial, which randomized men receiving SRT or adjuvant RT to 0, 6, or 24 mo of hormonal therapy, suggested no significant improvement in MFS or OS with 6 mo in comparison to 0 mo of ADT. However, 24 mo of ADT did improve 10-yr MFS in comparison to 6 mo of ADT (78% vs 72%) [9]. Moreover, preliminary results from the DADSPORT study-level meta-analysis suggest an absolute MFS benefit of 2% with the addition of 6 mo of ADT in comparison to SRT alone (hazard ratio 0.82) [10].

Finally, the FORMULA-509 study compared 6 mo of a gonadotropin-releasing hormone agonist plus either bicalutamide or the combination of abiraterone acetate, prednisone, and apalutamide in patients with high-risk features. Early results suggest that intensification of hormonal therapy improved 3-yr PFS (67.2% vs 46.8%) and MFS (84.3% vs 66.1%), but only for patients with PSA >0.5 ng/ml.

5. Conclusions

Multiple aspects of SRT, including field design, radiation dose, and the integration of hormonal therapies have been interrogated in rigorous randomized trials. PSA remains an important prognostic and predictive biomarker for treatment intensification. Mounting evidence suggests that for patients with higher PSA at the time of SRT, addition of hormonal therapy and pelvic nodal radiation will improve

PSA-based endpoints; conversely, dose escalation is not supported by level 1 evidence in this setting. Additional biomarkers in the form of genomic classifiers and molecular imaging will continue to refine the selection of ideal candidates for treatment intensification in the salvage setting.

Conflicts of interest: The authors have nothing to disclose.

Appendix A. Peer Review Summary

Peer Review Summary to this article can be found online at https://doi.org/10.1016/j.eururo.2023.05.012.

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