Adjuvant vs. salvage radiation therapy in men with high-risk features after radical prostatectomy: Survey of North American genitourinary expert radiation oncologists

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Abstract

Introduction: The management of patients with high-risk features after radical prostatectomy (RP) is controversial. Level 1 evidence demonstrates that adjuvant radiation therapy (RT) improves survival compared to no treatment; however, it may overtreat up to 30% of patients, as randomized clinical trials (RCTs) using salvage RT on observation arms failed to reveal a survival advantage of adjuvant RT. We, therefore, sought to determine the current view of adjuvant vs. salvage RT among North American genitourinary (GU) radiation oncology experts.

Methods: A survey was distributed to 88 practicing North American GU physicians serving on decision-making committees of cooperative group research organizations. Questions pertained to opinions regarding adjuvant vs. salvage RT for this patient population. Treatment recommendations were correlated with practice patterns using Fisher's exact test.

Results: Forty-two of 88 radiation oncologists completed the survey; 23 (54.8%) recommended adjuvant RT and 19 (45.2%) recommended salvage RT. Recommendation of active surveillance for Gleason 3+4 disease was a significant predictor of salvage RT recommendation (p=0.034), and monthly patient volume approached significance for recommendation of adjuvant over salvage RT; those seeing <15 patients/month trended towards recommending adjuvant over salvage RT (p=0.062). No other demographic factors approached significance.

Conclusions: There is dramatic polarization among North American GU experts regarding optimal management of patients with high-risk features after RP. Ongoing RCTs will determine whether adjuvant RT improves survival over salvage RT. Until then, the almost 50/50 division seen from this analysis should encourage practicing clinicians to discuss the ambiguity with their patients.

Introduction

Three randomized clinical trials (RCTs) have established the role of adjuvant radiation therapy (RT).[1-3] SWOG 8794 revealed a survival advantage when patients who received adjuvant RT were compared to patients who were followed clinically with no salvage RT option even in the setting of prostate-specific antigen (PSA) failure.[1] The other two trials — EORTC 22911 and ARO 96/02 —failed to reveal an overall survival advantage, likely due to the protocol stipulation of allowed or recommended salvage RT in men randomized to observation in case of biochemical failure.[2-3] Moreover, all three trials have shown a 10-year biochemical progression-free survival rate of 26–41% in the observation arm, arguing that a third of patients with high-risk features after radical prostatectomy (RP) will never develop biochemical failure and, therefore, would receive unnecessary overtreatment with pelvic radiotherapy.[4-6] Two large, modern randomized trials (RAVES, RADICALS) are underway to help physicians determine if adjuvant RT has any advantage over initial observation and early salvage RT, but until results are published, this topic remains highly controversial.[7,8] We sought to determine the current view of adjuvant vs. salvage RT among North American genitourinary (GU) radiation oncology experts due to their influence in shaping clinical trials and national guidelines.

Methods

Survey design and deployment

The survey was designed to assess the opinion of GU experts on the preferred management of a hypothetical patient with a high-risk feature (extracapsular extension) following RP for prostate cancer — adjuvant RT or observation with early salvage RT only if PSA rises. A copy of the survey is shown in Appendix 1. The study was approved by the institutional

review board and electronically sent in November 2016 to 88 North American GU oncology physicians, who serve on cooperative group research organizations such as NRG Oncology. The survey was designed and hosted by Research Electronic Data Capture (REDCap).[9]

Statistical analysis

Based on responses, participants were categorized as supporters of either adjuvant RT or salvage RT for men with high-risk features following RP. Treatment recommendations were correlated with practice patterns using Fisher's exact test.

Results

Forty-two of the 88 radiation oncologists completed the survey, of whom 23 (54.8%) recommended adjuvant RT after RP; the remaining 19 (45.2%) recommended observation with early salvage RT if PSA rises (Fig. 1).

No demographic factors (years in practice, geographic location of residency, geographic location of practice, monthly patient volume, practice type) were found to correlate with treatment recommendation. When we analyzed for association with other treatment recommendations for men with prostate cancer, only recommendation of active surveillance for Gleason 3+4 disease was a significant predictor of recommending salvage RT following RP for disease with high-risk features (p=0.034) (Table 1). No other treatment recommendations (active surveillance recommendation for Gleason 6 disease, first choice treatment preference for low-risk prostate cancer, brachytherapy boost for high-risk disease, consideration of stereotactic body RT for oligometastatic disease, elective pelvic lymph node coverage, support for incorporation of advanced imaging modalities in standard practice) were significant. Monthly patient volume approached significance for recommendation of adjuvant RT over salvage RT; respondents who see fewer than 15 patients per month were more likely to endorse adjuvant RT over salvage RT (p=0.062).

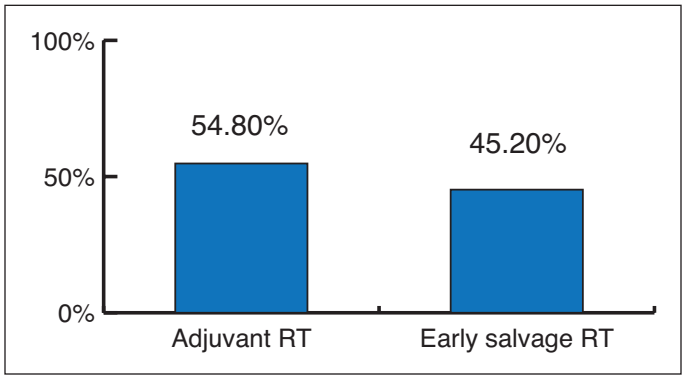

Fig. 1. Default recommendation for men with high-risk features after radical prostatectomy for prostate cancer among North American genitourinary oncology expert radiation oncologists. RT: radiation therapy.

Discussion

Although biochemical control of prostate cancer with high-risk features following RP (extracapsular extension, seminal vesicle invasion, and/or positive surgical margins) has indisputably been shown to be improved by adjuvant RT in three RCTs, only one of these trials has shown an improvement in overall survival — when patients randomized to observation were not offered salvage RT in case of biochemical progression.[1-6] The other two trials recommended and stipulated salvage RT on observation arm and failed to show a survival advantage to upfront intervention with adjuvant pelvic RT. Moreover, in all three trials, a third of patients on observation arm never experienced biochemical failure on observation arms, despite having high-risk features after RP. The 2017 National Comprehensive Cancer Network (NCCN) guidelines delineate indications for adjuvant RT as "pT3 disease, positive margin(s), Gleason score 8–10, or seminal vesicle involvement" and that "evidence supports offering adjuvant/salvage RT in most men with adverse pathological features or detectable PSA and no evidence of disseminated disease."[10]

The results of our study indicate that for men with high-risk features after RP, North American GU experts who are more likely to recommend salvage RT are also those who are more likely to recommend active surveillance for Gleason 3+4 disease. This intuitively makes sense, as physicians who are more comfortable with initiation observation of patients with intermediate-risk prostate cancer (established by the recently published ProtecT randomized trial[11]) should also feel as comfortable with initial observation of men with high-risk features after RP. Although no other demographic factor proved significant, the trend of experts seeing fewer than 15 patients/month being more likely to recommend adjuvant RT over salvage RT is interesting and deserves further investigation; perhaps high-volume experts are more likely to believe in salvage RT than their low-volume counterparts. It is our hope that ongoing phase 3 RCTs in this arena, such as the Radiotherapy – Adjuvant vs. Early Salvage (RAVES) and RADICALS trials, will shed more light on adjuvant vs. early salvage RT.[7-8]

Our study shares the limitations of the survey from which it is derived: a relatively small sample size, inability to capture a full range of options due to multiple-choice format, and a lack of granularity in addressing the socioeconomic and racial demographic of patients, the latter of which may impact the applicability of RCTs comprised of inadequately low non-White patient participation.[12,13]

Conclusion

There is currently a nearly even split between radiation oncology experts in North America recommending adjuvant vs. salvage RT for patients with high-risk features after RP

Table 1: Association between clinical practice recommendations and choice of adjuvant RT vs. observation with salvage RT for high-risk prostate adenocarcinoma following radical prostatectomy

Clinical demographic	Clinical practice variable	Adjuvant RT after radical prostatectomy	Observation with early salvage RT	p
Monthly patient volume	Fewer than 15	11 (47.8%)	3 (15.8%)	0.062
	15 or more patients	12 (52.2%)	16 (84.2%)	
Active surveillance recommendation for Gleason 6 disease	Yes	21 (52.5%)	19 (47.5%)	0.493
	No	2 (100%)	0 (0%)	
Active surveillance recommendation for Gleason 3+4 disease	**Yes**	**1 (14.3%)**	**6 (85.7%)**	**0.034**
	No	**22 (62.9%)**	**13 (37.1%)**	
SBRT for oligometastatic lesions	Yes	16 (50%)	16 (50%)	0.305
	No	7 (70%)	3 (30%)	
Treatment of pelvic lymph nodes in localized high-risk prostate cancer	Rarely	8 (61.5%)	5 (38.5%)	0.739
	Often	15 (51.7%)	14 (48.3%)	
Treatment of high-risk prostate cancer	EBRT+ADT	13 (56.5%)	10 (43.5%)	1.0
	EBRT+ADT+ brachytherapy boost	10 (52.6%)	9 (47.4%)	
Believer in advanced-imaging (Novel ligand-based PET imaging)	Yes	14 (46.7%)	16 (53.3%)	0.173
	No	9 (72.7%)	3 (27.3%)	
First choice for treatment of Gleason 6 disease who desires intervention	Brachytherapy	11 (52.4%)	10 (47.6%)	1.0
	EBRT	4 (57.1%)	3 (42.9%)	
	No preference	8 (57.1%)	6 (42.9%)	

EBRT: external beam radiation therapy; PET: positron emission tomography; RT: radiation therapy; SBRT: stereotactic body radiation therapy.

for prostate cancer. Ongoing, large, randomized trials will determine whether adjuvant therapy offers a survival advantage over salvage RT. Until then, the almost 50/50 division seen among leading GU experts, according to this analysis, should help practicing clinicians discuss the ambiguity with their patients. National care and reimbursement policies may also influence the accepted standard of care.

Competing interests: The authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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