

# 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).<sup>1-3</sup> 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.<sup>1</sup> 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.<sup>2-3</sup> 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.<sup>4-6</sup> 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.<sup>7,8</sup> 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).<sup>9</sup>

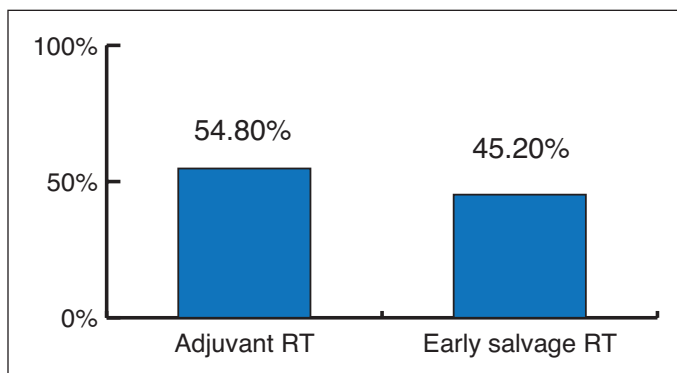
### Statistical analysis

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.<sup>1-6</sup> 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.”<sup>10</sup>

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<sup>11</sup>) 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.<sup>7-8</sup>

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.<sup>12,13</sup>

### 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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# Advanced imaging techniques in prostate cancer

Please complete the survey below. It is 4 pages long and should take approximately 5 minutes to finish.

Thank you very much for your contribution!

Are you actively practicing clinical oncology?

- Yes  No

Is genitourinary oncology your primary focus?

- Yes  No

What is your specialty?

- Radiation oncology  
 Medical oncology/Hematology oncology  
 Urology  
 None of the above

How many years has it been since you completed training (residency/oncology fellowship)?

- 0-4 years  
 5-10 years  
 11-20 years  
 >20 years  
 Still in training

Where did you complete your training?

- Canada
- Alabama
- Alaska
- Arizona
- Arkansas
- California
- Colorado
- Connecticut
- Delaware
- Florida
- Georgia
- Hawaii
- Idaho
- Illinois
- Indiana
- Iowa
- Kansas
- Kentucky
- Louisiana
- Maine
- Maryland
- Massachusetts
- Michigan
- Minnesota
- Mississippi
- Missouri
- Montana
- Nebraska
- Nevada
- New Hampshire
- New Jersey
- New Mexico
- New York
- North Carolina
- North Dakota
- Ohio
- Oklahoma
- Oregon
- Pennsylvania
- Rhode Island
- South Carolina
- South Dakota
- Tennessee
- Texas
- Utah
- Vermont
- Virginia
- Washington
- West Virginia
- Wisconsin
- Wyoming
- Other

Where do you primarily practice?

- Canada
- Alabama
- Alaska
- Arizona
- Arkansas
- California
- Colorado
- Connecticut
- Delaware
- Florida
- Georgia
- Hawaii
- Idaho
- Illinois
- Indiana
- Iowa
- Kansas
- Kentucky
- Louisiana
- Maine
- Maryland
- Massachusetts
- Michigan
- Minnesota
- Mississippi
- Missouri
- Montana
- Nebraska
- Nevada
- New Hampshire
- New Jersey
- New Mexico
- New York
- North Carolina
- North Dakota
- Ohio
- Oklahoma
- Oregon
- Pennsylvania
- Rhode Island
- South Carolina
- South Dakota
- Tennessee
- Texas
- Utah
- Vermont
- Virginia
- Washington
- West Virginia
- Wisconsin
- Wyoming
- Other

How would you best describe your primary practice setting?

- Academic/university
- Hospital-based, no academic/university affiliation
- Free-standing, no academic/university affiliation
- Government employed, such as VA, military, or government-run facility
- Other

How many patients with prostate cancer do you see in consultation per month on average?

- 0-4
- 5-9
- 10-14
- 15-20
- >20

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**Please tell us more about your practice characteristics.**

For this section, check all that apply.

- I often recommend active surveillance for patients with Gleason 6 disease.
- I often recommend active surveillance for patients with Gleason 3+4=7 disease.
- For patients with oligometastatic disease, I would consider offering stereotactic body radiation therapy to the oligometastatic lesion outside of a clinical trial.

Please select one of the following options.

- Most patients I see in clinic present with intact prostate for discussion of definitive treatment.
- Most patients I see in clinic present after prostatectomy for a discussion of adjuvant or salvage radiation.
- I see an even balance of patients with intact prostate and those who are post-prostatectomy.

Please select one of the following options.

- As a general rule for patients with high risk features, I recommend adjuvant radiation after surgery.
- As a general rule for patients with high risk features, I recommend observation and early salvage radiation if PSA rises.

Please select one of the following options.

- For localized high risk prostate cancer, I treat pelvic lymph nodes rarely.
- For localized high risk prostate cancer, I treat pelvic lymph nodes often.

Do you consider yourself an expert brachytherapist?

- Yes
- No

For patients with Gleason 6 disease who desire treatment, with no baseline urinary symptoms and a 40cc prostate, which would you consider your first choice for treatment?

- External beam radiation
- Brachytherapy
- Either external beam or brachy (no preference)

For patients with localized high risk disease, with no baseline urinary symptoms and a 40cc prostate, which would you consider your first choice for treatment?

- External beam radiation with ADT (androgen deprivation therapy)
- External beam radiation with ADT and brachytherapy boost

What is your current practice with regard to digital rectal examinations (DRE)? (Check all that apply)

- I routinely perform DRE before treatment
- I routinely perform DRE at follow-up visits
- I never perform DRE
- I believe DRE will change management
- I do not believe DRE will change management

What do you consider the default EBRT dose and fractionation for Gleason 3+4 prostate adenocarcinoma?

- Conventional fractionation: 78 Gy in 2 Gy fractions, 79.2 Gy in 1.8, or equivalent
- Moderate hypofractionation: 70 Gy in 2.5 Gy fractions or equivalent
- SBRT/Radical hypofractionation: 5-12 fractions or equivalent



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Are you aware that the NCCN recommends consideration of C-11 choline PET, but not PSMA PET for patients with prostate cancer?

- Yes  
 No

The NCCN recommends considering C-11 PET in the following scenarios:

- In the setting of detectable PSA after prostatectomy
- Biochemical failure after definitive radiation
- In M0 patients on androgen deprivation therapy with a rising PSA.

What are your thoughts on these recommendations?

- I agree with the NCCN recommendations.  
 The NCCN should recommend the use of C-11 PET in more scenarios than those listed above (specify)  
 The NCCN should recommend considering C-11 PET in some, but not all of the above scenarios (specify)  
 The NCCN should not recommend considering C-11 PET at all because there is not enough evidence to support its use in routine practice.

Please specify

\_\_\_\_\_

Do you think that the NCCN should recommend consideration of PSMA PET?

- The NCCN should recommend consideration of PSMA PET in the same scenarios as C-11 PET.  
 The NCCN should recommend consideration of PSMA PET in more scenarios than C-11 PET (specify).  
 The NCCN should recommend consideration of PSMA PET in some, but not all of the same scenarios as C-11 PET (specify).  
 The NCCN should not recommend consideration of PSMA PET because there is not enough evidence to support its use in routine practice.

Please specify

\_\_\_\_\_

Regarding the comparison of C-11 PET to PSMA PET, select the answer which best describes your opinion.

- C-11 PET has better efficacy than PSMA PET.  
 PSMA PET has better efficacy than C-11 PET.  
 C-11 PET and PSMA PET have the same level of efficacy.  
 There is not enough data to know whether C-11 PET or PSMA PET is more effective.

Which of the following imaging studies are available at your practice (or at an affiliated facility)?

- C-11 PET  
 PSMA PET  
 Both  
 Neither

What is your current practice with regard to the new imaging modalities PSMA PET and C-11 PET?

- I routinely order them for my patients and use the results to guide treatment decision-making.  
 I have ordered them on rare occasion for my patients and used the results to guide treatment decision-making.  
 I do not order them, but if a patient already has results at the time I see them, I will use the results to guide treatment decision-making.  
 I do not order them and do not use the results to guide treatment decision-making.

What is your current practice with regard to the new imaging modalities PSMA PET and C-11 PET?

- I often refer patients to centers capable of performing one of these tests.
- On rare occasions I have referred my patients to centers capable of performing one of these tests.
- I do not refer them, but if a patient already has results at the time I see them, I will use the results to guide treatment decision-making.
- I do not refer them and do not use the results to guide treatment decision-making.

What is the primary reason you do not use results from PSMA PET or C-11 PET to guide treatment decision-making?

- There is not enough data to guide usage of these tests.
- I do not believe these tests are effective.
- I lack personal experience using these tests.
- Other (specify)

Please specify

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**For each of the following patient scenarios, please enter the lowest PSA value at which you would order a C-11 PET or PSMA PET. Enter 0 for "never."**

Gleason 4+5=9, post-prostatectomy, consecutively rising PSA

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Gleason 4+3=7, post-prostatectomy, consecutively rising PSA

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Gleason 10, T3, intact prostate, pre-treatment

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Gleason 4+3=7, T2, intact prostate, pre-treatment

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Gleason 10, T3, post-definitive radiation

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Gleason 4+3=7, T2, post-definitive radiation

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In a patient with newly diagnosed cT2 Gleason 9 prostate cancer with a PSA of 200 ng/mL, who has no evidence of bone metastases by nuclear bone scan and abdominopelvic CT, which of the following would you consider for further workup?

- C-11 PET
- PSMA PET
- No further workup prior to therapy
- Other (specify)

Please specify

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What are the reasons you do not order PSMA PET or C-11 PET more frequently? (Check all that apply)

- Availability
- Cost
- Lack of evidence
- Unsure how to interpret
- Other (specify)

Please specify

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