Prognostic implications of immediate PSA response to early salvage radiotherapy

Robert M. Turner II, MD,[1] Jonathan G. Yabes, PhD,[2] Elen Woldemichael, BS,[1] Melvin M. Deutsch, MD,[3] Ryan P. Smith, MD,[3] Robert S. Werner, MD,[3] Bruce L. Jacobs, MD,[1] Joel B. Nelson, MD[1]

[1]Department of Urology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA
[2]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[3]Department of Radiation Oncology, UPMC Cancer Center, Pittsburgh, Pennsylvania, USA

TURNER II RM, YABES JG, WOLDEMICHAEL E, DEUTSCH MM, SMITH RP, WERNER RS, JACOBS BL, NELSON JB. Prognostic implications of immediate PSA response to early salvage radiotherapy. *Can J Urol* 2016;23(6):8568-8575.

Introduction: *Up to 25% of men with prostate cancer who undergo radical prostatectomy will recur. In this setting, salvage radiotherapy may cure patients with local recurrence, but is unable to cure those with occult metastatic disease. The objective of this study is to examine how prostate-specific antigen (PSA) response to radiotherapy predicts subsequent disease progression and survival.*

Materials and methods: *Using a prospectively populated database of 3089 men who underwent open radical prostatectomy, 212 patients (7%) were identified who received early salvage radiotherapy for biochemical recurrence. The main outcome was time to disease progression after salvage radiotherapy. Patients were stratified by PSA response after radiotherapy: 1) PSA < 0.1 ng/mL, 2) persistently detectable PSA, and 3) rising PSA.*

Results: *Patients received salvage radiotherapy at a median PSA of 0.20 ng/mL (IQR 0.10-0.30 ng/mL). At a median follow up of 47.3 months, a total of 52 (25%) patients experienced disease progression. On multivariable analysis, both persistent PSA (HR 5.12; 95% CI 1.98-13.23) and rising PSA (HR 16.55; 95% CI 6.61-41.48) were associated with increased risk of disease progression compared to those with PSA < 0.1 ng/mL after adjusting for pre-radiotherapy PSA, Gleason score, margin status, stage, and time to radiotherapy. Only rising PSA was associated with an increased risk of cancer-specific and all-cause mortality.*

Conclusions: *PSA response is associated with the risk of disease progression following salvage radiotherapy. This information can be used to counsel patients on the potential need for additional therapy and identify those at greatest risk for progression and cancer-related mortality.*

Key Words: radical prostatectomy, prostate cancer, prostate-specific antigen, recurrence, biomarker

Introduction

Radical prostatectomy is a treatment option for men with clinically localized prostate cancer that affords excellent long term cancer-specific survival; however, as many as 25% of men are expected to recur.[1,2] Although biochemical recurrence does not invariably result in poor patient outcomes, patients with prostate-specific antigen (PSA) recurrence have a higher risk of metastatic progression and cancer-related mortality.[3] While adjuvant radiotherapy may be considered for patients at high risk for recurrence, salvage radiotherapy remains the only potentially curative option for men in whom PSA relapse has occurred.[4-10]

Previous studies have evaluated pre-radiotherapy predictors of biochemical recurrence and/or cancer-related mortality after salvage radiotherapy.[7,9,11-14] These reports have highlighted the importance of timely delivery of radiotherapy and guided patient selection. However, none have examined the association between the immediate PSA response following treatment and cancer-related outcomes, including risk of progression and cancer-specific mortality.

Accepted for publication September 2016

Address correspondence to Dr. Robert M. Turner II, UPMC Mercy Professional Building, 1350 Locust St., Suite G100A, Pittsburgh, PA 15219 USA

For this reason, the prognostic implications of the immediate PSA response immediately following early salvage radiotherapy were evaluated. Such information could provide additional information to patients and clinicians regarding the risk of subsequent disease progression and potentially inform decisions regarding the need and timing of additional therapy.

Materials and methods

Study population

Between November 1999 and April 2014, 3089 men underwent radical prostatectomy at the University of Pittsburgh Medical Center by a single surgeon and were followed in a prospectively populated and longitudinally maintained database. A total of 462 men (15%) had biochemical recurrence following radical prostatectomy, of which 212 received early salvage radiotherapy, as defined as a PSA level of 0.5 ng/mL or less prior to radiotherapy.[15]

Pre-radiotherapy evaluation consisted of a history and physical examination. No patient had clinically or radiographically apparent local, regional, or distant disease. No patient received any adjuvant therapy prior to salvage radiotherapy. After radiotherapy, patients were followed at regular intervals with clinical assessments and PSA measurements, and underwent hormonal manipulation only after documentation of biochemical or clinical disease progression.

Outcomes

The primary outcome was time to disease progression, as defined as either initiation of androgen deprivation therapy or radiographic evidence of metastatic disease. Initiation of androgen deprivation therapy in the absence of metastatic disease was the result of a joint decision by the patient and physician that considered the absolute PSA level, PSA kinetics, as well as patient comorbidities and goals.

Secondary outcomes included overall and prostate cancer-specific survival. There were no deaths observed in patients with Gleason 3 + 3 = 6 disease and only one death in a patient with 3 + 4 = 7 disease; therefore, pathologic Gleason scores were categorized as ≤ 7 or 8-10 for purposes of analysis. No deaths were observed for any patient with pathologic node-positive disease (pN1); therefore pN1 patients were categorized with those patients with locally advanced disease at the time of radical prostatectomy (T3-4).

The primary predictor was PSA response to early salvage radiotherapy. For each patient, the initial PSA level drawn 3-6 months following treatment was compared with the pre-radiotherapy PSA. Patients were categorized into three groups according to PSA response after radiotherapy: undetectable PSA (initial post-radiotherapy PSA < 0.1 ng/mL, n = 99), persistent PSA (initial post-radiotherapy PSA detectable but not higher than the pre-radiotherapy PSA, n = 68), and rising PSA (post-radiotherapy PSA higher than the pre-radiotherapy PSA, n = 45). Most PSA determinations were performed at the University of Pittsburgh laboratory using a two-site immunoenzymetric PSA assay. The assay's lower limit of PSA detection is 0.1 ng/mL; therefore, undetectable PSA is defined as all PSA values < 0.1 ng/mL. Some patients were followed by other physicians and had PSA values determined at other laboratories.

Statistical analysis

Demographic, clinical, and pathologic characteristics of the study population were compared among groups using analysis of variance for normally distributed continuous variables, the Kruskal-Wallis test for non-normally distributed continuous variables, and Chi-square or Fisher exact tests for categorical variables.

The main outcomes, progression-free survival and overall survival, were analyzed using techniques for survival data. Time to event was calculated from the completion date of radiotherapy. The Kaplan-Meier method was used to estimate survival probabilities for each of the PSA response groups. Univariable analyses were performed using the log rank test and Cox proportional hazards model for categorical and continuous variables, respectively. Cox proportional hazards models were used to calculate unadjusted and adjusted hazards ratios for PSA response. Variables used in the adjusted models included those that had $p < 0.05$ in the univariable analyses and other clinicopathological confounders, as sample size permitted.

Competing risks analysis was used to examine associations with prostate cancer-specific mortality, treating deaths from other causes as a competing event. Cumulative incidence was calculated nonparametrically for each of the PSA response groups. Univariable analysis used Gray's test[16] and a Fine and Gray proportional subdistribution hazards model[17] for categorical and continuous variables, respectively. The Fine and Gray proportional subdistribution hazards model is a Cox type model for competing risks regression. Instead of the marginal hazards function, it models the hazards of the subdistribution, or cumulative incidence function. Unadjusted subdistribution hazards ratios for the PSA groups were calculated using the proportional subdistribution hazards model. Adjusted analysis was not pursued due to the small number of prostate cancer-specific deaths.

Statistical analyses were performed using R (version 13.2)[18] using the packages dpylr[19] for data manipulation, compareGroups[20] for descriptive tables, ggplot2[21] for graphics, survival[22] for survival analysis, and riskRegression[23] for competing risks. Statistical significance was defined as $p < 0.05$. The University of Pittsburgh institutional review board approved the study protocol.

Results

The clinical, pathological, and demographic information for the study groups are summarized in Table 1. There were no differences in age, race, preoperative PSA, pathologic Gleason score, or stage between groups. There was also no difference in the percentage of patients with an undetectable PSA following radical prostatectomy. Men with an undetectable PSA following salvage radiotherapy were more likely to have had a positive surgical margin ($p = 0.02$) and lower pre-radiotherapy PSA ($p < 0.001$). Men with rising PSA following salvage radiotherapy had a shorter time from prostatectomy to radiotherapy ($p = 0.04$). After radiotherapy, mean time to initial PSA measurement was 4.7 ± 1.5 months.

Over a median follow up after salvage radiotherapy of 47.3 months (IQR 16.3-83.7), 52 men experienced disease progression (39 initiated androgen deprivation therapy and 13 developed of radiographic evidence of metastatic disease). The 5-year estimates of

TABLE 1. **Demographic, clinical, and pathological characteristics of the study population according to first post treatment PSA**

Characteristics	PSA < 0.1 ng/mL (n = 99)	PSA persists (n = 68)	PSA rises (n = 45)	p value[1]
Age, years, mean (SD)	59.8 (5.6)	59.0 (6.3)	60.7 (6.4)	0.34
Race (%)				0.53
White	92 (93)	63 (93)	44 (98)	
Non-white	7 (7)	5 (7)	1 (2)	
Body mass index, kg/m^2, mean (SD)	27.8 (3.4)	29.3 (4.2)	27.5 (3.5)	0.01
Preoperative PSA, ng/mL, mean (SD)	8.1 (6.4)	9.1 (6.2)	8.4 (5.8)	0.58
Pathologic Gleason score (%)				0.19
7 or less	79 (80)	49 (72)	29 (66)	
8-10	20 (20)	19 (28)	15 (34)	
Margin status (%)				0.02
Negative	68 (69)	57 (84)	39 (87)	
Positive	31 (31)	11 (16)	6 (13)	
Pathologic stage (%)				0.28
T2 or less, N0	29 (29)	25 (37)	19 (42)	
T3/T4, N0 or N1	70 (71)	43 (63)	26 (58)	
Percent tumor in gland, mean (SD)	18 (15)	20 (13)	19 (14)	0.71
Largest prostate cancer nodule, cm, mean (SD)	1.7 (0.5)	1.9 (0.7)	1.7 (0.5)	0.09
Undetectable immediate postop PSA (%)				0.27
Yes	93 (94)	64 (94)	39 (87)	
No	6 (6)	4 (6)	6 (13)	
Pre-radiation PSA, ng/mL, median (IQR)	0.17 (0.10-0.20)	0.20 (0.10-0.36)	0.20 (0.16-0.4)	< 0.001
Time to salvage radiotherapy, years, mean (SD)	3.5 (2.5)	4.0 (2.6)	2.8 (2.3)	0.04
Year of radiation, median (IQR)	2009 (2007-2012)	2009 (2007-2012)	2009 (2006-2011)	0.43
Dose of radiation, Gray, median (IQR)	66.6 (66.6-66.6)	66.6 (66.6-66.9)	66.6 (66.6-68.3)	0.73

SD = standard deviation; PSA = prostate-specific antigen; IQR = interquartile range
[1]p values for continuous and categorical variables generated from ANOVA (or Kruskal-Wallis) and chi-square (or Fisher exact) tests, respectively.

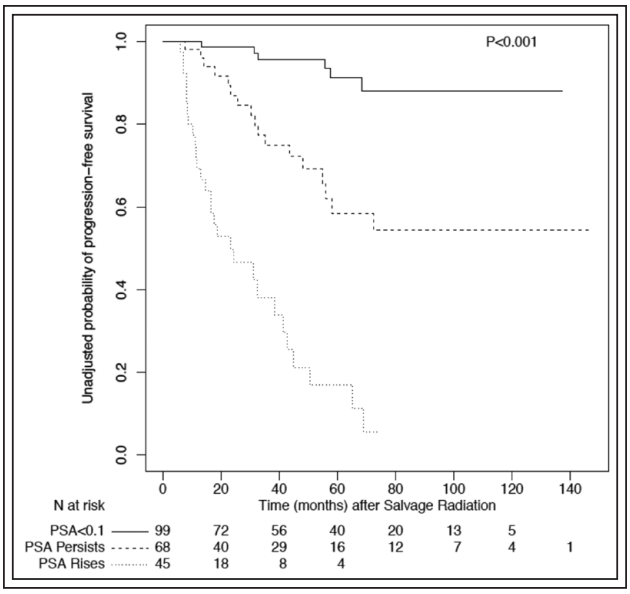

Figure 1. Kaplan-Meier progression free survival curve after salvage radiotherapy.

progression-free survival were 91% in those with an undetectable post-radiotherapy PSA, 58% in those with a persistently detectable but non-rising PSA, and 17% in those with a rising PSA following radiotherapy, Figure 1.

The univariable and multivariable analyses examining predictors of disease progression following early salvage radiotherapy are shown in Table 2.

In univariable analyses, persistent PSA (hazards ratio [HR] 5.3; 95% CI 2.1-13.4) and rising PSA (HR 24.6; 95% CI 10.1-60.0) had significantly higher hazards of progression. Pre-radiotherapy PSA ($p = 0.01$), Gleason score ($p = 0.02$), undetectable postoperative PSA ($p = 0.05$), and time to salvage radiotherapy ($p < 0.001$) were also significantly associated with progression. After adjusting for pre-radiotherapy PSA, Gleason score, margin status, stage, and time to salvage radiotherapy, both persistent PSA (HR 5.12; 95% CI 1.98-13.23) and rising PSA (HR 16.55; 95% CI 6.61-41.48) remained significant predictors of disease progression. The results did not change when detectable postoperative PSA was added to the model.

Overall, 15 men died of any cause during the follow up period. The 5-year estimates of overall survival were 95% in those with an undetectable post-radiotherapy PSA, 94% in those with a persistently detectable but non-rising PSA, and 80% in those with a rising PSA

TABLE 2. **Results of Cox proportional hazards model examining predictors of progression-free survival after salvage radiotherapy**

Characteristic	Univariable analysis		Multivariable analysis[1]	
	Hazards ratio (95% CI)	p value[2]	Hazards ratio (95% CI)	p value
Immediate PSA response		< 0.001		<0.001
PSA < 0.1 ng/mL	reference		reference	
PSA persists	5.29 (2.08-13.40)		5.12 (1.98-13.23)	
PSA rises	24.60 (10.10-60.00)		16.55 (6.61-41.48)	
Pre-radiation PSA, ng/mL	3.27 (1.41-7.61)	0.01	3.53 (1.21-10.28)	0.02
Pathologic Gleason score		0.02		0.20
7 or less	reference		reference	
8-10	1.91 (1.08-3.38)		1.49 (0.81-2.72)	
Margin status		0.10		0.32
Negative	reference		reference	
Positive	0.54 (0.25-1.14)		0.67 (0.30-1.49)	
Pathologic stage		0.32		0.61
T2 or less, N0	reference		reference	
T3/T4, N0 or N1	1.35 (0.75-2.43)		1.20 (0.59-2.45)	
Time to salvage radiotherapy	0.74 (0.63-0.88)	0.001	0.74 (0.61-0.89)	0.002

CI = confidence interval; PSA = prostate-specific antigen

[1]multivariable analysis adjusted for immediate PSA response, pre-radiation PSA, pathologic Gleason score, surgical margins, and pathologic stage

[2]p values for hazards ratios are computed using the log rank or Wald test under a Cox model for categorical or continuous variables, respectively

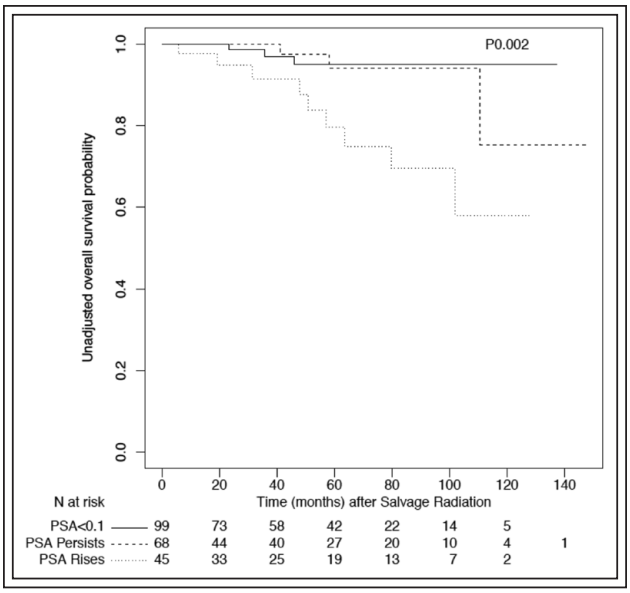

Figure 2. Kaplan-Meier overall survival curve after salvage radiotherapy.

following radiotherapy, Figure 2. The univariable and multivariable analyses examining predictors of overall survival following salvage radiotherapy are demonstrated in Table 3. In univariable analysis, rising PSA had significantly higher hazards of death (HR 6.2; 95% CI 1.7-22.8). Gleason score ($p < 0.001$) was also significantly associated with death from any cause. After adjusting for Gleason score, rising PSA remained a significant predictor of overall survival (HR 4.4; 95% CI 1.1-16.7).

Overall, 12 men died of prostate cancer during the follow up period. The 5-year estimates of cancer-specific mortality were 4% in those with an undetectable post-radiotherapy PSA, 3% in those with a persistently detectable but non-rising PSA, and 18% in those with a rising PSA following radiotherapy ($p = 0.002$). Of nine patients with a rising PSA following radiotherapy who died, 8 (89%) died of prostate cancer. On univariable analysis, rising PSA was a predictor of prostate cancer-specific mortality (subdistribution HR 8.0; 95% CI 1.7-37.8). Gleason score ($p = 0.003$), undetectable postoperative PSA ($p = 0.02$), and time from radical prostatectomy to radiotherapy ($p = 0.01$) were also significantly associated with prostate cancer-specific death, Table 4.

Discussion

Immediate PSA response to early salvage radiotherapy appears to be a strong predictor of subsequent disease progression. Those men with a persistently detectable or rising PSA 3-6 months following radiotherapy were more likely to require androgen deprivation therapy or develop metastatic disease. Specifically, the estimated 5-year progression free survival was 91% in those men who achieved an undetectable PSA compared with 58% in those with a persistently detectable but non-rising PSA and 17% in those patients with a rising PSA. Thus, immediate PSA response likely identifies those patients with occult metastatic disease at highest risk of progression. Furthermore, men with persistently detectable but non-rising PSA, despite having an increased risk of disease progression, had similar cancer-specific and overall survival as those men who had an undetectable PSA following radiotherapy.

The prognostic value of serum PSA evaluations during the course of late salvage radiotherapy has

TABLE 3. **Results of Cox proportional hazards model examining predictors of overall survival**

Characteristic	Univariable analysis		Multivariable analysis[1]	
	Hazards ratio (95% CI)	p value	Hazards ratio (95% CI)	p value [2]
Immediate PSA response		0.002		0.03
PSA < 0.1 ng/mL	reference		reference	
PSA persists	1.42 (0.29-7.02)		1.00 (0.19-5.08)	
PSA rises	6.16 (1.67-22.80)		4.36 (1.14-16.65)	
Pathologic Gleason score		< 0.001		0.004
7 or less	reference		reference	
8-10	5.66 (1.89-16.90)		5.22 (1.71-15.91)	

CI = confidence interval; PSA = prostate-specific antigen
[1]multivariable analysis adjusted for immediate PSA response and pathologic Gleason score
[2]p values for hazards ratios are computed using the log rank or Wald test under a Cox model for categorical or continuous variables

TABLE 4. **Results of competing risk regression analysis examining predictors of prostate cancer-specific mortality**

Characteristic	Univariable analysis	
	Subdistribution hazards ratio* (95% CI)	p value**
Immediate PSA response		0.002
PSA < 0.1 ng/mL	reference	
PSA persists	1.38 (0.20-9.64)	0.74
PSA rises	8.01(1.70-37.81)	0.009
Age	1.09 (0.97-1.21)	0.14
Race***		0.44
White	reference	
Non-white	--	
Body mass index	0.87 (0.70-1.07)	0.19
Preoperative PSA	0.99 (0.83-1.16)	0.86
Pathologic Gleason score		0.003
7 or less	reference	
8-10	5.42 (1.66-17.64)	
Margin status		0.15
Negative	reference	
Positive	0.25 (0.03-2.06)	
Pathologic stage		0.57
T2 or less, N0	reference	
T3/T4, N0 or N1	1.41 (0.44-4.53)	
Percent tumor in gland	0.99 (0.95-1.04)	0.81
Largest prostate cancer nodule	0.88 (0.38-2.04)	0.77
Pre-radiation PSA	3.19 (0.51-19.80)	0.21
Undetectable Immediate Postoperative PSA		
Yes	reference	
No	4.19[1.34;13.14]	0.01
Time to salvage radiotherapy	0.42 [0.21;0.83]	0.01
Year of radiation	1.08 (0.82-1.42)	0.58
Dose of radiation	0.84 (0.48-1.48)	0.55

CI = confidence interval; PSA = prostate-specific antigen
a multivariable analysis was not performed due to the limited number of prostate cancer-specific deaths
*subdistribution hazards ratio is the risk of prostate cancer-specific death accounting for the fact that non prostate-cancer specific deaths occur
**p values for subdistribution hazards ratios are computed using the Gray's test or Wald test under a Fine and Gray competing risk model or Gray's test for categorical or continuous variables, respectively
***there were no prostate cancer-specific deaths among non-whites

previously been studied.[24] In a series of 41 patients who received 59.4-66 Gy of radiation at a mean PSA of 2.51 ng/mL, serum PSA levels were evaluated following receipt of 30 Gy and 45 Gy. At a mean follow up of 30.9 months, the authors found that serum PSA evaluations at 30 Gy did not predict for biochemical or clinical disease-free outcomes. However, serum PSA at 45 Gy was independently associated with subsequent biochemical and clinical progression. Despite the limitations of a small sample size and short follow up, these findings suggest that PSA response may provide patients with prognostic information during the course of therapy as well.

To guide patient selection, previous studies have evaluated pre-radiotherapy predictors of biochemical recurrence and/or cancer-related mortality after salvage radiotherapy.[7,9,11-14] This analysis supports the

findings of others that pre-radiotherapy PSA[9,10,12] and pathologic Gleason score of 8-10[9,11,25] are significant predictors of disease progression. While the optimal PSA cut off for starting early salvage radiotherapy has yet to be determined, this study adds to the growing body of evidence that initiating radiotherapy at very low PSA levels is associated with improved outcomes. One must balance this benefit with the possible risk of overtreatment of patients with a slowly rising detectable PSA that may never develop a clinically significant relapse. Gleason 8-10 disease is an independent predictor of progression and all-cause mortality; this highlights the increased likelihood of occult metastases, even at low PSA levels, in patients with poorly differentiated tumors.

Time from radical prostatectomy to salvage radiotherapy is also an independent predictor of subsequent disease progression in the early salvage setting. While detectable "ultrasensitive" PSA levels has been demonstrated to predict subsequent biochemical recurrence,[26-29] it increases the risk of overtreatment.[30] While Stephenson et al demonstrated the prognostic significance of a PSA doubling time > 10 months, the ability to extrapolate the clinical importance of PSA doubling time to lower levels has been questioned.[31,32] While it is plausible that shorter time from surgery to radiotherapy acts as a proxy of the dynamic of PSA increase and is associated with worse outcomes, this finding differs from Briganti et al, who reported no association between time from surgery to radiotherapy and risk of biochemical recurrence.

A clinically relevant finding in this study was that men with persistently detectable but non-rising PSA had similar cancer-specific and overall survival as those men who had an undetectable PSA following radiotherapy. The notion that many with detectable and stable PSA can achieve long term survival is supported by Ying and colleagues, who recently reported a cancer-specific survival of 73% at 10 years in 34 men who experienced biochemical recurrence following early salvage therapy.[25] Those with early PSA failure within 1 year of radiotherapy had cancer specific survival of 50% at 10 years compared with 90.5% in those with a late failure. This supports the concept that the immediate PSA response to radiotherapy provides patients and clinicians with valuable prognostic information regarding the likelihood of long term survival.

These findings should be considered in the context of several limitations. First, this is a single-institution retrospective analysis with risk of unmeasured bias and potential for unaddressed confounding variables; however, the study is strengthened by use of a large prospectively collected and longitudinally maintained dataset. Second, the primary endpoint of disease progression was defined as initiation of androgen deprivation or development of radiographic evidence of metastatic disease. While the decision to begin androgen deprivation therapy in the absence of metastatic disease is somewhat arbitrary in that it is dependent on physician and patient preferences, it could be argued that this endpoint is more relevant to patients than the biochemical outcome of PSA recurrence, however it may be defined. Nonetheless, these findings may not be generalizable to those who adopt a program of adjuvant radiotherapy. Three prospective randomized trials have shown that adjuvant radiotherapy improves the outcomes of men at high risk for localized recurrence.[33-35] Based on these findings, the American Society for Radiation Oncology and the American Urological Association jointly published a guideline recommending that adjuvant radiotherapy be offered to all men who meet inclusion criteria for the aforementioned studies. Alternatively, the much more commonly applied approach using early salvage radiotherapy attempts to reduce the risk of overtreatment associated with adjuvant radiotherapy and still has excellent long-term outcomes.[8,10] Results of several ongoing prospective studies will further guide clinical practice in terms of indication and timing of postoperative radiotherapy.

Conclusion

Early salvage radiotherapy affords excellent cancer control for many patients with biochemical recurrence following radical prostatectomy. Immediate PSA response is a strong predictor of subsequent disease progression. In addition, those men with persistently detectable but non-rising PSA had similar cancer-specific and overall survival as those men who had an undetectable PSA following radiotherapy. These findings provide clinicians and patients with important prognostic information that is obtained early in the period following radiotherapy and may reassure those patients who have a persistently detectable but stable PSA.

Disclosures

Robert M. Turner II, MD is supported in part by the National Institutes of Health Institutional TL1 award (5TL1TR000145-10).

Bruce L. Jacobs, MD, MPH is supported in part by the National Institutes of Health Institutional KL2 award (KL2TR000146-08), the GEMSSTAR award (R03AG048091), the Jahnigen Career Development Award, and the Tippins Foundation Scholar Award. □

References

1. Mullins JK, Feng Z, Trock BJ, Epstein JI, Walsh PC, Loeb S. The impact of anatomical radical retropubic prostatectomy on cancer control: the 30-year anniversary. *J Urol* 2012;188(6):2219-2224.
2. Boorjian SA, Eastham JA, Graefen M et al. A critical analysis of the long-term impact of radical prostatectomy on cancer control and function outcomes. *Eur Urol* 2012;61(4):664-675.
3. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281(17):1591-1597.
4. Bernard JR, Jr., Buskirk SJ, Heckman MG et al. Salvage radiotherapy for rising prostate-specific antigen levels after radical prostatectomy for prostate cancer: dose-response analysis. *Int J Radiat Oncol Biol Phys* 2010;76(3):735-740.
5. Terai A, Matsui Y, Yoshimura K, Arai Y, Dodo Y. Salvage radiotherapy for biochemical recurrence after radical prostatectomy. *BJU Int* 2005;96(7):1009-1013.
6. Liauw SL, Webster WS, Pistenmaa DA, Roehrborn CG. Salvage radiotherapy for biochemical failure of radical prostatectomy: a single-institution experience. *Urology* 2003;61(6):1204-1210.
7. Goenka A, Magsanoc JM, Pei X et al. Long-term outcomes after high-dose postprostatectomy salvage radiation treatment. *Int J Radiat Oncol Biol Phys* 2012;84(1):112-118.
8. Briganti A, Wiegel T, Joniau S et al. Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: results of a match-controlled multi-institutional analysis. *Eur Urol* 2012;62(3):472-487.
9. Stephenson AJ, Scardino PT, Kattan MW et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007;25(15):2035-2041.
10. Ost P, De Troyer B, Fonteyne V, Oosterlinck W, De Meerleer G. A matched control analysis of adjuvant and salvage high-dose postoperative intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;80(5):1316-1322.
11. Briganti A, Karnes RJ, Joniau S et al. Prediction of outcome following early salvage radiotherapy among patients with biochemical recurrence after radical prostatectomy. *Eur Urol* 2014; 66(3):479-486.
12. Siegmann A, Bottke D, Faehndrich J et al. Salvage radiotherapy after prostatectomy - what is the best time to treat? *Radiother Oncol* 2012;103(2):239-243.
13. Trock BJ, Han M, Freedland SJ et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. *JAMA* 2008;299(23):2760-2769.
14. 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):728-733.
15. Pfister D, Bolla M, Briganti A et al. Early salvage radiotherapy following radical prostatectomy. *Eur Urol* 2014;65(6):1034-1043.
16. Gray RJ. A Class of K-sample tests for comparing the cummulative incidence of a competing risk. *Ann Stat* 1988;16(3): 1141-1154.
17. FIne JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Amer Statist Assoc* 1999; 94(446):496-509.
18. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing;2010.
19. Wickham H, Francois R. dplyr: A Grammar of Data Manipulation. R package version 0.4.1. 2015.
20. Subirana I, Sanz H, Villa J. Building bivariate tables: The compare Groups package for R. *J Stat Softw* 2014;57(12):1-16.
21. Wickham H. ggplot2: elegant graphics for data analysis. New York: Springer;2009.
22. Therneau T. A Package for Survival Analysis in S. version 2.38. 2015.
23. Gerds TA, H.S. T. risk Regression: Risk regression models for survival analysis with competing risks. R package version 1.1.1. 2014.
24. Do T, Dave G, Parker R, Kagan AR. Serum PSA evaluations during salvage radiotherapy for post-prostatectomy biochemical failures as prognosticators for treatment outcomes. *Int J Radiat Oncol Biol Phys* 2001;50(5):1220-1225.
25. Ying J, Wang CJ, Yan J et al. Long-term outcome of prostate cancer patients who exhibit biochemical failure despite salvage radiation therapy after radical prostatectomy. *Am J Clin Oncol* 2015;Epub ahead of print.
26. Sokoll LJ, Zhang Z, Chan DW et al. Do ultrasensitive PSA measurements have a role in predicting long-term biochemical recurrence-free survival in men following radical prostatectomy? *J Urol* 2016;195(2):330-336.
27. Seikkula H, Syvanen KT, Kurki S et al. Role of ultrasensitive prostate-specific antigen in the follow-up of prostate cancer after radical prostatectomy. *Urol Oncol* 2014; Epub ahead of print.
28. Koulikov D, Mohler MC, Mehedint DC, Attwood K, Wilding GE, Mohler JL. Low detectable prostate specific antigen after radical prostatectomy--treat or watch? *J Urol* 2014;192(5):1390-1396.
29. Eisenberg ML, Davies BJ, Cooperberg MR, Cowan JE, Carroll PR. Prognostic implications of an undetectable ultrasensitive prostate-specific antigen level after radical prostatectomy. *Eur Urol* 2010;57(4):622-629.
30. Ciatto S. Editorial comment on: prognostic implications of an undetectable ultrasensitive prostate-specific antigen level after radical prostatectomy. *Eur Urol* 2010;57(4):630.
31. Shimizu F, Matsuyama Y, Tominaga T, Ohashi Y, Fujime M. Inadequacy of prostate-specific antigen doubling time estimates calculated using an ultrasensitive assay of prostate-specific antigen for biochemical failure after radical prostatectomy. *Urol Int* 2007;79(4):356-360.
32. Cary KC, Johnson CS, Cheng L, Koch MO. A critical assessment of post-prostatectomy prostate specific antigen doubling time acceleration--is it stable? *J Urol* 2012;187(5):1614-1619.
33. 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(3):956-962.
34. Bolla M, van Poppel H, Tombal B et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* 2012;380(9858):2018-2027.
35. Wiegel T, Bartkowiak D, Bottke D et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. *Eur Urol* 2014;66(2):243-250.