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The Timing of Salvage Radiotherapy After Radical Prostatectomy: A Systematic Review

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Summary

A comprehensive systematic review of salvage radiotherapy (SRT) after radical prostatectomy identified 41 studies encompassing 5597 patients. Only prostate-specific antigen (PSA) level before SRT and RT dose had a significant and independent association with relapse-free survival. Progressively better tumor control rates are achieved with a lower PSA at initiation of SRT and when higher RT doses are delivered. This study provides Level 2a evidence for initiating SRT at the lowest possible PSA. Early salvage RT at a PSA level <0.2 ng/mL may be an equivalent strategy to adjuvant RT.

Purpose: Salvage radiotherapy (SRT) after radical prostatectomy can potentially eradicate residual microscopic disease. Defining the optimal patient and treatment factors is essential and is particularly relevant within the context of adjuvant vs early vs delayed postoperative radiotherapy (RT).

Methods and Materials: A systematic review of all published SRT studies was performed to identify the pathologic, clinical, and treatment factors associated with relapse-free survival (RFS) after SRT. A total of 41 studies encompassing 5597 patients satisfied the study entry criteria. Radiobiologic interpretation of biochemical tumor control was used to provide the framework for the observed relationships.

Results: Prostate-specific antigen (PSA) level before SRT ($P<.0001$) and RT dose ($P=.0052$) had a significant and independent association with RFS. There was an average 2.6% loss of RFS for each incremental 0.1 ng/mL PSA at the time of SRT (95% CI, ~2.2-3.1). With a PSA level of 0.2 ng/mL or less before SRT, the RFS approached 64%. The dose for salvage RT in the range of 60-70 Gy seemed to be on the steep part of the sigmoidal dose–response curve, with a dose of 70 Gy achieving 54% RFS compared with only 34% for 60 Gy. There was a 2% improvement in RFS for each additional Gy (95% CI, ~0.9-3.2). The observed dose–response was less robust on sensitivity analysis.

Conclusions: This study provides Level 2a evidence for initiating SRT at the lowest possible PSA. Dose escalation is also suggested by the data. Progressively better tumor control rates with SRT after radical prostatectomy are achieved with a lower PSA at initiation and with a higher RT dose. Early salvage RT may be an equivalent strategy to adjuvant RT. © 2012 Elsevier Inc.

Keywords: Prostate cancer, Prostate-specific antigen, Salvage radiotherapy, Prostatectomy

Introduction

The eradication of microscopic residual disease after radical prostatectomy can potentially be achieved with the use of salvage radiotherapy (SRT) after a demonstrated biochemical recurrence, or with adjuvant radiotherapy (ART) within the immediate postoperative setting but in the absence of measurable disease. There are numerous retrospective single-institution studies and a few

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pooled-analyses studies of SRT (1, 2), but no randomized trial of SRT has ever been conducted. From these retrospective studies were identified several favorable prognostic criteria, including a positive surgical margin, pathologically organ-confined disease, low Gleason grade, prostate-specific antigen (PSA) level before SRT below a certain threshold, longer time interval to failure, and longer PSA doubling times (1, 2). Some of these factors are biologically related to the likelihood of persistent local vs systemic disease, and some relate to the burden of residual disease. Despite the multitude of retrospective studies, many critical questions remain that are vague or simply unanswered, namely, the optimal timing for SRT and the optimal treatment specifics.

For ART, however, three randomized trials, EORTC 22911 (3), ARO 9602 (4), and SWOG 8794 (5), have shown superior PSA relapse-free survival (RFS) in favor of ART compared with an observation arm for patients at high risk, defined as pT3a or b, or with a positive surgical margin. One of these trials showed that this improvement in biochemical RFS also translated into distant metastases-free survival and overall survival advantages (5). By design, however, because the control arm was only an observation arm, these trials cannot answer the question whether ART is superior to or equal to SRT, especially if SRT were to be initiated early (*ie*, at the earliest time of confirmed biochemical failure). Although three open randomized controlled trials examining the timing of SRT are currently under way, RADICALS (6), GETUG-17 (7), and RAVES (8), their results are many years away.

There are two principal dilemmas after radical prostatectomy: deciding when and how to provide optimally successful SRT and whether, in the absence of any measurable disease, ART can or should be safely deferred until biochemical failure is confirmed. To explore which disease and treatment factors are essential, we performed the first systematic review of all published SRT studies to identify the pathologic, clinical, and treatment factors associated with RFS after SRT. Radiobiologic interpretation of biochemical tumor control was used to provide the framework for understanding the observed relationships.

Methods and Materials

Study selection criteria

A comprehensive and systematic review of all indexed published reports in the English language of salvage radiotherapy after radical prostatectomy was performed from Medline. Manual search of all reference lists from these publications was also performed to identify any additional studies not identified electronically. To satisfy the uniformity criteria for systematic review, studies were required to (*1*) report Kaplan-Meier RFS at 3-5 years; (*2*) report the median pre-SRT PSA level, the median RT dose, and the use of androgen deprivation therapy (ADT); and (*3*) report all surgical pathologic factors (margin status, extracapsular extension, seminal vesicle invasion, pathologic Gleason grade, and nodal status). Studies not providing complete information or reporting only mean values for factors (as opposed to median) were excluded to avoid skewness and outlier effects. Relapse was uniformly defined as a rise in PSA level of 0.2 ng/mL or higher after SRT. Time to failure was uniformly defined as time from SRT until relapse. In sum, 63 studies were reviewed, 41 met the selection criteria, and 22 were excluded.

Statistical analysis

Clinical, pathologic, and treatment factors associated with RFS were analyzed with the Spearman rank correlation test and considered significant when $P<.05$. The Spearman statistic was chosen because it is nonparametric and does not assume a linear relationship and therefore makes the least assumptions on the data. It yields the correlation coefficient rho (which ranges from -1 to $+1$) and a P value. Robustness was performed by using Grubbs' test to remove outliers at a level of $P<.05$ (two-tailed) and repeating the analysis. Removing outliers is useful to investigate their influence on the relationships. Analysis was performed with MedCalc statistical package (MedCalc Software, Belgium, version 11.6, 2011).

Biologic relationship between postoperative PSA level and RFS

To help interpret any association that might be observed, we propose an original radiobiologic framework for the expected relationship between PSA level before SRT and tumor control, as follows. We know that tumor control probability (TCP) after radiotherapy can be classically modeled by Poisson statistics, which is commonly expressed as:

$$\mathrm{TCP} = e^{-\mathrm{NS}}$$

where N is the number of tumor cells and S is the surviving fraction after radiotherapy. For prostate cancer we use the PSA RFS (bNED) as a surrogate for tumor control. We can also safely assume, at least to first order, that measurable postoperative PSA level will be proportional to the disease burden (*ie*, the number of cancer cells) for all but the highly undifferentiated tumors. Therefore, the relationship between bNED and PSA will have the general form $\mathrm{bNED} \sim e^{-\mathrm{PSA}*c}$ (where c is the fitted scaling constant). This relationship is fitted to the data by the weighted least-squares method using the solver function within Excel (Microsoft). Goodness of fit is assessed by the Pearson correlation coefficient, a statistic which measures the linear dependence, is invariant to scale, and yields r that ranges between -1 and $+1$.

Sigmoidal dose–response relationship

Tumor control vs dose commonly reveals a sigmoidal relationship, often called a logistic curve. To interpret any observed relationship between dose and RFS, we use the standard TCP equation given by:

$$\mathrm{TCP} = e^{([d-\mathrm{TCD}_{50}]/k)} / \left[1 + e^{([d-\mathrm{TCD}_{50}]/k)}\right]$$

where d is total dose, TCD_{50} is the dose to achieve 50% tumor control, and k is a fitting parameter related to the slope at the TCD_{50} dose point (9). The proportional gain in TCP per additional Gray within the steep part of the TCP curve is given by the parameter Slope_{50}, defined by $\mathrm{Slope}_{50} = 25/k$ (in units of %/Gy). As above, we use the bNED as a surrogate for tumor control. This relationship is fitted to the data by the weighted least-squares method and assessed with the Pearson test.

Results

From a review of all studies published between 1995 through 2010, a total of 41 series encompassing 5597 patients satisfied the entry criteria for systematic review and are listed in Table 1.

Table 1A Clinical, pathologic, and treatment factors for salvage RT studies that meet the criteria for systematic review

Study (ref. nos. in Table 1B)	*n*	FU (mo)	prePSA (ng/mL)	bNED (%)	Time (y)	m+ (%)	ECE+ (%)	Dose (Gy)	ADT (%)	GS 8-10 (%)	SV+ (%)	LN+ (%)
Stephenson et al, 2007 (1)	1540	53	1.10	32.0	6.0	51	65	64.8	14	22	24	3
Buskirk, et al 2006 (3)	368	60	0.70	46.0	5.0	51	36	64.8	15	17	25	0
Pazona et al, 2005 (4)	223	56	0.80	40.0	5.0	46	45	63.0	5	17	18	2
Ward et al, 2004 (5)	211	50	0.60	66.0	5.0	55	13	64.0	0	n/a	36	1
Cremers et al, 2010 (6)	197	40	0.59	59.0	5.0	72	53	63.0	0	18	15	0
Loeb et al, 2008 (7)*	192	53	0.70	56.0	5.0	81	81	63.0	0	13	19	0
Neuhof et al, 2007 (8)	171	39	1.10	35.0	5.0	26	32	63.0	30	13	18	0
Maier et al, 2004 (9)	170	49	1.20	55.4	5.0	n/a	14	68.0	16	25	9	0
Pisansky et al, 2000 (10)	166	52	0.90	46.0	5.0	13	34	64.0	4	16	31	0
Wiegel et al, 2009 (11)†	162	42	0.33	54.0	3.5	57	30	66.0	0	n/a	18	0
King and Spiotto, 2008 (12)	122	48	0.50	51.0	5.0	57	27	67.8	56	26	34	0
Katz et al, 2003 (13)	115	42	0.87	46.0	4.0	54	57	66.6	39	25	27	0
Brooks et al, 2005 (14)	114	76	0.90	41.5	5.0	66	52	64.0	11	20	22	7
Moreira et al, 2009 (15)	102	50	0.60	65.0	5.0	71	32	66.0	0	13	18	0
MacDonald et al, 2008 (16)	194	66	1.40	38.0	3.0	51	29	n/a	0	25	15	2
MacDonald et al, 2004 (17)	60	50	0.69	45.0	5.0	12	n/a	64.0	0	15	12	0
Choo et al, 2002 (18)	36	50	0.80	26.0	4.0	75	53	60.0	14	41	33	0
Choo et al, (2002)	26	40	1.20	39.0	4.0	57	34	60.0	4	11	23	0
Choo et al, (2002)	36	47	3.70	14.0	4.0	41	53	61.5	22	28	11	0
Anscher et al, 2000 (19)	89	48	1.40	50.0	4.0	75	69	66.0	9	26	34	3
De Meerleer et al, 2008 (20)	87	30	0.70	67.0	5.0	44	55	74.8	56	0	n/a	0
Song et al, 2002 (21)‡	61	36	0.80	39.0	4.0	67	15	66.6	48	23	20	5
Catton et al, 2001 (22)	59	44	2.80	19.0	5.0	66	29	60.0	0	29	25	0
Quero et al, 2008 (23)	59	38	1.40	41.0	5.0	60	34	66.0	12	29	24	2
Chawla et al, 2002 (24)	54	45	1.30	35.0	5.0	80	91	64.8	0	35	26	0
Liauw et al, 2003 (25)	51	46	0.42	56.0	3.0	61	45	65.7	0	18	27	8
Tomita et al, 2009 (26)	51	36	0.25	55.0	3.0	63	39	60.0	0	37	10	0
Symon et al, 2006 (27)	50	40	1.20	54.0	3.0	62	14	66.6	0	18	26	0
Leventis et al, 2001 (28)	49	29	2.10	24.0	5.0	45	48	66.0	0	20	27	0
Jacinto et al, 2007 (29)	43	26	0.87	71.0	3.0	54	49	70.0	0	n/a	2	0
Taylor et al, 2003 (30)	71	35	0.60	66.0	5.0	n/a	44	70.0	49	34	23	0
Nuddel et al, 1999 (31)	69	36	0.95	45.0	3.0	68	29	67.5	0	22	29	0
Schild et al, 1996 (32)	46	37	0.90	50.0	3.0	n/a	50	64.0	0	11	22	0
Morris et al, 1997 (33)§	48	32	1.70	47.0	3.0	71	n/a	62.0	0	71	25	0
Forman et al, 1997 (34)	47	36	1.40	64.0	3.0	n/a	68	66.0	0	38	23	6
Tsien et al, 2003 (35)	57	74	1.20	35.0	5.0	47	67	65.0	0	14	16	0
Vanuyts el et al, 2001 (36)	53	33	0.80	46.0	3.0	68	70	66.0	0	62	0	0
Stockdale et al, 2007 (37)	32	30	0.55	49.0	3.0	78	34	64.0	16	28	13	0
Swanson et al, 2010 (38)	92	167	1.50	35.0	5.0	n/a	52	65.0	0	14	24	0
Crane et al, 1997 (39)	48	55	2.70	24.0	5.0	50	58	60.0	0	35	29	8
Garg et al, 1998 (40)	78	25	1.20	62.0	3.0	n/a	37	66.0	0	35	35	4
Pacholke et al, 2004 (41)	56	69	1.20	39.0	5.0	54	63	60.0	29	45	36	0
Wadasaki et al, 2007 (42)	42	33	0.7	61.0	3.0	40	48	60.0	0	21	21	0
Mean	-	47.5	1.1	46.2	-	56.5	45	64.6	10.4	25.2	22.2	1.2
Minimum	-	25	0.25	14	-	12	13	60	0	0	0	0
Maximum	-	167	3.7	71	-	81	91	74.8	56	71	36	8
Standard deviation	-	22	0.67	13.7	-	16.3	18.2	3.1	16.6	13.5	8.6	2.3

Abbreviations: ADT = % use of androgen deprivation therapy; Dose = median salvage RT dose in Gray; ECE = extracapsular extension; ECE+ = % + ECE (pT3a); FU = median follow-up time in mo; Gleason Score 8-10 = % with pathologic Gleason Score 8-10; LN+ = % with involved lymph nodes; m+ = % positive margins; n/a = not available; bNED = by Kaplan-Meier % biochemical no evidence of disease; prePSA = median presalvage RT PSA; RT = radiation therapy; Time = y at which bNED reported; SV+ = % with positive seminal vesicles (pT3b).

* Combined ECE+ and margin+.

† Reported Gleason Score 7-10, PSA failure at >0.1 ng/mL.

‡ PSA failure at >0.1 ng/mL.

§ Mean FU.

Table 1B References for salvage radiotherapy series that meet the criteria for systematic review

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Table 1B (*continued*)

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Kaplan-Meier RFS was reported at 5 years for 23 studies and at 3-4 years for the remaining 18 studies. The median follow-up time was an average of 47 ± 22 months, the median pre-SRT PSA had an average of 1.1 ± 0.67 ng/mL (range, 0.25-3.7 ng/mL), the median dose had an average of 64.6 ± 3.1 Gy (range, 60-74.8 Gy), and RFS was an average of 46.2 ± 13.7% (range, 14%-71%).

Only PSA level before SRT (rho = −0.58, $P<.0001$) and RT dose (rho = +0.42, $P=.0052$) had a significant association with RFS. Furthermore, these two factors were not correlated ($P=.44$) and thus were independently associated with RFS. None of the other factors was significant. Because the large pooled analysis series from Stephenson et al. (1) has contributions from eight other series, the analysis was repeated after its exclusion, which did not change in any way the results. Robustness was performed by identifying and eliminating outliers from the analysis using an iterative application of Grubbs' test. Six outliers were found (the series corresponding to PSA level before SRT equal to 3.7, 2.8, and 2.7; RT dose equal to 74.8; and Gleason Score 8-10 equal to 71% and 62%). After removal of these six outliers, PSA level before RT remained significant (rho = −0.49, $P=.0024$), and the significance of RT dose was attenuated ($P=.10$). Because of the potential interaction between ADT use and dose and also confounding PSA relapse, the analysis was repeated after the removal of 13 series wherein ADT was used in >10% of patients. After removal of these series, only PSA level before RT remained significant (rho = −0.62, $P=.0005$). These results are summarized in Table 2. All 28 pairwise correlations between factors were made, revealing only a single correlation between positive margins and Gleason Score 8-10 to be present (Spearman rho = 0.36, $P=.033$).

To further analyze the only two factors associated with RFS, namely, PSA level before RT and dose, we present scatter plots and their fit to the biologic models as described in Methods. Fig. 1 shows the observed relationship between PSA level before SRT vs RFS. The data is fit by the biologic model very well (Pearson $r=0.67$; 95% CI, 0.46-0.81; $P<.0001$). Model fit repeated after removal of outliers and after removal of series with ADT remained significant: (Pearson $r=0.48$; 95% CI, 0.19-0.69; $P=.0025$) and (Pearson $r=0.70$; 95% CI, 0.45-0.85; $P<.0001$), respectively. When averaged over a PSA range of 0-1, there is an observed 2.6% loss of RFS for each incremental 0.1 ng/mL PSA at the time of SRT (95% CI, ∼2.2-3.1). With a pre-SRT PSA level of 0.2 ng/mL or less, the RFS approaches 64%.

Fig. 2 shows the observed dose−response relationship between SRT dose vs RFS. It is very well fit by the sigmoidal relationship (Pearson $r=0.51$; 95% CI, 0.24-0.71; $P=.0005$), with TCD_{50} = 67.8 Gy, and k = 12.13 ($Slope_{50}$ = 2.06%/Gy; 95% CI, ∼0.9-3.2). Model fit repeated after removal of outliers and removal of series with ADT was attenuated but remained significant (Pearson $r=0.33$; 95% CI, 0.002-0.59; $P=.049$) and (Pearson $r=0.35$; 95% CI, −0.03-0.64; $P=.07$), respectively. Dose for salvage RT in the range of 60-70 Gy seems to be on the middle steep part of the sigmoidal dose−response curve, with a dose of 70 Gy achieving 54% RFS compared with only 34% for 60 Gy.

Discussion

This study identifies two of the most influential factors within the context of SRT: PSA level before SRT and RT dose. This study does not imply that the other prognostic and treatment factors (pathologic stage, margin status, Gleason grade, or use of ADT) are not relevant but simply that they are dominated by these other two factors. Systematic reviews of retrospective studies are inherently subject to population heterogeneity effects that tend to average out the relative influence of secondary factors. Therefore, one weakness of this study is that although it does identify the two most influential factors, it cannot exclude the relative importance of the others, particularly within the context of individual patient selection and management. Another weakness is that PSA

Table 2 Clinical, pathologic, and treatment factors associated with relapse-free survival after salvage radiotherapy

	All studies (41 series, 5597 patients)		Studies minus outliers (35 series, 5266 patients)		Studies minus ADT (28 series, 2559 patients)†	
Factor	rho*	*P* value*	rho*	*P* value*	rho*	*P* value*
Presalvage RT PSA	−0.58	<.0001	−0.49	.0024	−0.62	.0005
RT dose	0.42	.0052	0.27	.10	0.27	.17
m+	0.20	.24	0.22	.22	0.21	.32
ECE+	−0.14	.39	−0.18	.20	−0.09	.65
ADT	−0.12	.45	−0.24	.15	−0.16	.42
pGS 8-10	−0.10	.53	0.07	.68	0.01	.98
SV+	−0.10	.54	−0.13	.46	−0.09	.64
LN+	−0.03	.83	0.03	.88	0.13	.51

Abbreviations: +ECE = positive extracapsular extension (pT3a); +m = positive margins; ADT = usage of androgen deprivation therapy; pGS 8-10 = pathologic Gleason Score 8-10; LN+ = involved lymph nodes; RT = radiation therapy; RT dose = salvage RT dose; SV+ = positive seminal vesicles (pT3b).

* rho (ranging from −1 to +1) and associated *P* value are from the nonparametric Spearman rank correlation test.

† Studies in which more than 10% of patients received ADT were removed.

doubling time, known to be an independent indicator of biologic aggressiveness and occult systemic disease, was not routinely available in published SRT series. Last, bias may be introduced when treatments evolve over time, as for example higher doses given more recently because of better techniques and the practice of initiating SRT at lower PSA levels. To that end, we examined the relationship between follow-up length and PSA level before SRT ($P=.59$, rho = 0.09), use of ADT ($P=.63$, rho = 0.08) and dose ($P=.083$, rho = −0.29). Although a weak relationship was seen in the sense of higher doses described in studies with shorter follow-up times, it was not significant.

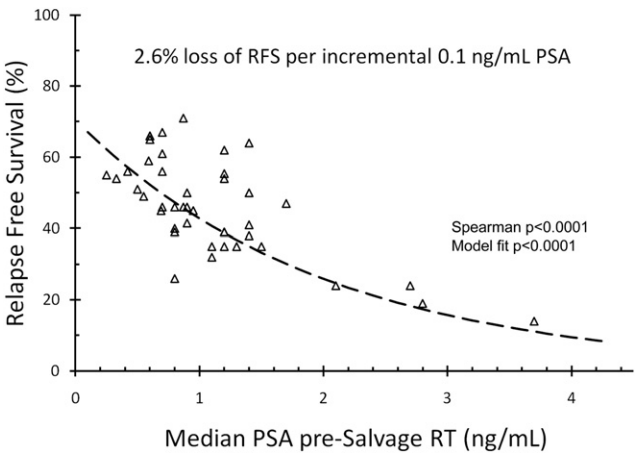

Fig. 1. Relapse-free survival (RFS) vs prostate-specific antigen (PSA) level before salvage radiotherapy (SRT) for all eligible studies. The data is well fit by the biologic tumor control model, RFS ~ e^{-PSA} (dashed curve, $r=0.67$, $P<.0001$). There is an average loss of 2.6% in RFS for each incremental 0.1 ng/mL rise in PSA before SRT. Extrapolating to PSA levels of 0.2 ng/mL or lower, the RFS would be 64% or better.

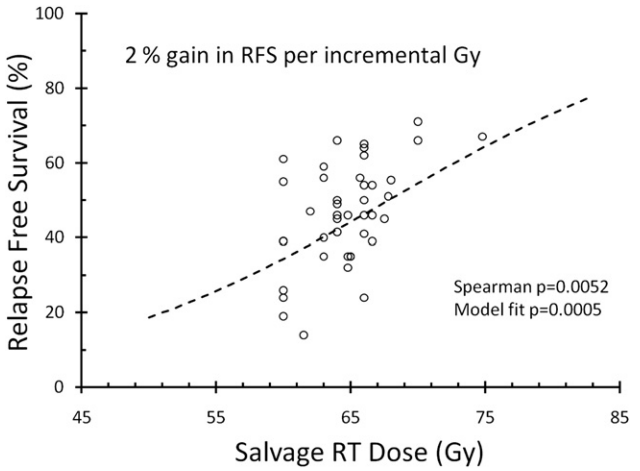

Fig. 2. Relapse-free survival (RFS) vs SRT dose for all eligible studies. The data are well fit by the standard sigmoidal dose−response model, tumor control probability (TCP) = $e^{([d\text{-}TCD_{50}]/k)}/[1+e^{([d\text{-}TCD_{50}]/k)}]$ (dashed curve, $r=0.51$, $P=.0005$). The fitted TCD_{50} = 67.8 Gy, and $Slope_{50}$ (defined as 25/k) = 2.06%/Gy. The data suggest that doses between 60 and 70 Gy are in the middle steep portion of the dose−response curve. There is an average improvement of 2% in RFS for each additional Gy. RT = radiation therapy.

Nevertheless, this large systematic review of retrospective studies shows that these two factors are highly significant and independent in their association with RFS. It provides Level 2a evidence, as defined by the Oxford Centre for Evidence Based Medicine (10), for initiating SRT at the lowest possible PSA. It also suggests that an escalated RT dose, potentially up to 70 Gy or higher, would yield improved outcomes, although this conclusion is attenuated by the sensitivity analyses. This study also provides evidence that early SRT would potentially achieve RFS rates comparable to adjuvant RT. These three points are discussed in turn below.

Initiating SRT early: At the lowest possible PSA

Our study shows that PSA level before SRT is significantly associated with RFS ($P<.0001$) and is robust on sensitivity analyses, although rho = −0.58 indicates that this correlation is moderately strong and accounts for only part of the observed variance in RFS. Quantitatively, there is an average 2.6% loss of RFS for each incremental 0.1 ng/mL PSA. With postoperative PSA level being directly proportional to disease burden, this finding is consistent with the higher biologic effectiveness of RT for lower microscopic disease burdens. This hypothesis is supported by the fit of the observed relationship of pre-SRT PSA vs RFS to our exponential biologic model (Fig. 1). Although numerous retrospective studies had shown higher bNED rates with PSA before RT below a certain threshold, typically estimated at 0.5, 1.0, or 2.0 ng/mL (1, 2) it remained unclear whether this was a static threshold, how high that threshold could be before rendering SRT ineffective, and whether this was independently significant from other pathologic or treatment factors. The best evidence to date for the importance of PSA level before RT had been from matched-control analyses of ART vs SRT. Two such

studies have shown that for patients with uniformly matched high-risk pathologic features, a ~20% improvement biochemical RFS was achieved in ART patients in whom PSA was <0.2 ng/mL compared with matched patients receiving SRT whose PSA was greater (median PSA, 0.7-1 ng/mL) (11, 12).

Our study suggests that a continuously progressive loss of tumor control occurs with increasing PSA before SRT. This progressive relationship is consistent with an exponential biologic model that relates PSA level directly with microscopic tumor burden. Thus, the present study places this threshold in the context of a proportional and quantifiable risk for loss of treatment effectiveness. Furthermore, extrapolating this relationship to low PSA levels, SRT would be expected to yield RFS rates of around 64% for pre-SRT PSA in the range of 0.2 ng/mL or below. The conclusion that SRT should be initiated at the lowest PSA level raises the practical question of what that PSA level is. Although well beyond the scope of this study it can be said that, using the ultrasensitive assays in our practice, we consider a rising post-operative PSA >0.05 ng/mL as a reliable indicator of biochemical failure, which justifies the initiation of SRT before PSA reaches a level of >0.2 ng/mL.

Dose–response for SRT

Our study suggests that there is a significant and independent dose–response for SRT ($P = .0052$), although once again rho = 0.42 indicates that this correlation is moderate and accounts for only part of the variance observed in RFS. The narrow span of doses used in nearly all SRT series limits the strength of any analysis of dose–response. For a dose within the range of 60-70 Gy, the dose–response seems to lie within the middle and steep portions of the curve (Fig. 2). The TCD_{50} is only 67.8 Gy. This means that the current recommended minimum dose of 64 Gy for salvage RT by the ASTRO consensus, or the dose used in the three ART trials (60-62 Gy), or the dose used in the ongoing ART vs SRT trials (RADICALS, RAVES, and GETUG), which are in the range of 64-66 Gy, are all still considerably much too low. It is commonly presumed, albeit unproven, that because tumor burden in the postoperative setting is microscopic, only lower effective doses are necessary when compared with what is needed in the definitive setting. Several retrospective studies have suggested quite the contrary: that a dose–response is still seen between 60 and 70 Gy for SRT, and a recent systematic review of the literature has confirmed this (13). Interestingly, the TCD_{50} for definitive prostate RT is not that much different, 66 Gy (13), confirming that prostate cancer is intrinsically rather radioresistant, even if it is present as microscopic tumor burden. A dose–response for the primary (definitive) treatment of prostate cancer has been demonstrated in several randomized trials and a recent pooled analysis (13), and the current standard of care is a high dose of 75.6-80 Gy. It has been shown that dose–response for prostate cancer can seem to be steeper when derived from single series and shallower when derived from pooled analysis or meta-analysis (14). The effects of population and treatment heterogeneity, selection bias, and other confounders on any dose–response will tend to diminish its strength and thus highlight the importance of randomized controlled trials to answer this question.

The evidence presented here highlights the pressing need for, and clinical ramifications of, a randomized controlled trial to establish the appropriate dose for postoperative RT. Indeed, an analysis of the patterns of failure from the EORTC and SWOG adjuvant RT trials demonstrated that treatment failure is predominantly local and that therefore an improvement in local therapy (*ie*, higher dose) will result in improved outcomes (3, 5). One of the main conclusions of the present study is that higher doses are necessary and could be in excess of 70 Gy. There is an observed improvement in RFS of 2% for each incremental Gy of dose. Inasmuch as dose was found to be independent of all other factors, this implies that higher doses would also be necessary even in the adjuvant RT setting.

Early SRT in relation to ART

Short of a randomized trial, there are many caveats in the attempt to compare ART and SRT, and we are by no means attempting a definitive comparison here. By definition, the primary difference between these two groups of patients is whether or not they have measurable disease, and in principle, "adjuvant" patients should have no measurable disease at all. In fact, many of the patients in the three randomized adjuvant trials did have measurable PSA levels. In the EORTC trial (3), 9% of patients had a PSA >0.2 ng/mL, in the SWOG trial (5) 35% had PSA >0.2 ng/mL, and in the ARO trial (4) (which had access to assays with lower threshold) 20% of patients had PSA >0.05-0.1 ng/mL and 59% of patients had PSA >0.03-0.1 ng/mL. The definition of "adjuvant" becomes slippery, especially within the modern era of ultrasensitive PSA assays with detection thresholds of 0.01 ng/mL.

The mean pathologic characteristics of patients who received SRT are in fact not all that different from those of patients selected for the ART randomized trials. For example, a positive margin was present in 63%, 68%, and 68% in the EORTC, ARO, and SWOG trials, respectively; it was on average 57 ± 16% for the SRT studies (Table 1). Similarly, pT3a was present in 78%, 62%, and 68% for the three trials, respectively; it was on average 45 ± 18% for the SRT studies. Finally, pT3b was present in 25%, 28%, and 10% of the trials, respectively; it was an average of 22 ± 8% in the SRT studies.

The final and most important point to establish when comparisons are made between SRT and ART is the following. Whereas for SRT, all patients actually have disease (measurable by PSA recurrence), there is clearly a proportion of ART patients who are without disease. These patients do not need ART, and that is indeed the crux of the current clinical dilemma. The retrospective adjuvant series in the literature are not usable in this context because they cannot estimate the baseline proportion of patients without disease in their patient populations. The randomized ART trials, however, provide this critical information from their randomized control (observation) arms, where the 5-year bNED rates for the observation arm was 44% in the SWOG trial, 53% in the EORTC trial, and 54% in the ARO trial. Thus, to enable comparison with SRT outcomes, the "raw" bNED for ART must be corrected for the known proportion of patients without disease. The actual bNED with adjuvant RT is then given by the difference in bNED between the RT arm and the observation arm, divided by the proportion of patients with disease:

$$bNED_{ADJ} = [bNED_{RTarm} - bNED_{OBSarm}] / [100 - bNED_{OBSarm}]$$

The raw 5-year bNED rates for the three ART trials are as follows: 70% for the SWOG trial, 74% for the EORTC trial, and 72% for the ARO trial. Consequently, the corrected 5-year bNED rates are 46% for SWOG, 45% for EORTC, and 39% for ARO.

In the present study of SRT, the mean bNED rate was 46 ± 13% (Table 1). Given the similar mean pathologic characteristics

discussed earlier and the mean RT dose (65 ± 3 Gy), the RFS rates between ART and SRT are remarkably comparable. Furthermore, the mean PSA before RT was 1.1 ng/mL for the SRT studies, whereas it was below 0.2 ng/mL for the all ART trials. If one extrapolates the relationship in Fig. 1 for SRT to low PSA levels (<0.2 ng/mL), namely, that of the ART trials, then the bNED approaches 64% for SRT and is substantially higher than the 39%-46% of the ART trials.

Conclusions

Progressively and significantly better tumor control rates with SRT after radical prostatectomy are achieved with a lower PSA at initiation and with a higher RT dose. This study provides Level 2a evidence for initiating SRT at the lowest possible PSA. It also suggests that escalating RT dose would yield higher tumor control rates. The evidence indicates that early SRT can achieve high rates of tumor control, potentially comparable with those of adjuvant RT. Although evidence from a randomized controlled trial of ART vs early SRT is lacking, the current body of evidence supports consideration of a management strategy for patients after radical prostatectomy in which waiting for biochemically demonstrated failure before RT might be both prudent and effective.

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