Research Article

Twelve-year outcomes of prostate cancer after radical prostatectomy for T3 and/or positive margins managed with surveillance or salvage radiation therapy, based on risk groups☆

Barry W. Goy [a],*, In-Lu Amy Liu [b]

[a] Department of Radiation Oncology, Kaiser Permanente, Los Angeles Medical Center, Los Angeles, CA, USA
[b] Department of Research and Evaluation, Kaiser Permanente, Pasadena, CA, USA

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ABSTRACT

Background: To assess 12-year outcomes on radical prostatectomy with T3/positive margins, while categorizing patients into risk groups.
Methods: From 2004 to 2007, 862 radical prostatectomy patients had T3/positive margins. Management included surveillance (54.8%), salvage radiation therapy (SRT) (36.8%), and primary androgen deprivation therapy (ADT) (8.5%). Freedom from biochemical failure, metastasis-free-survival (MFS), prostate cancer—specific survival (PCSS) were estimated using Kaplan-Meier. Multivariable analysis established prognostic factors that affected PCSS, which were used to form risk groups. Subanalysis was performed on SRT patients.
Results: Median follow-up was 12.1 years. T3b, Gleason score (GS), and detectable postoperative PSA independently lowered PCSS. Very—low-risk (VLR) were GS 6. Low-risk (LR) were GS $3 + 4$ with T3a or positive margins, but undetectable postoperative PSA <0.1. High-risk (HR) were T3b with GS 7-10, or any GS 7-10 with T3a/b and positive margins, but undetectable PSA. Ultra—high-risk (UHR) were detectable PSA with GS 7-10. Median time to first salvage treatment for VLR, LR, HR, and UHR were 11.1, 10.8, 5.3, and 0.6 years, $p < 0.001$. The 12-year freedom from biochemical failure for VLR, LR, HR, UHR were 60.2%, 52.9%, 28.4%, and 0%, $p < 0.001$. For 12-year MFS, 99.1%, 97.8%, 88.6%, and 63.6%, $p < 0.001$. For 12-year PCSS, 99.5%, 99.4%, 93.5%, and 78.9%, $p < 0.001$. For subanalysis of 317 SRT patients, 10-year MFS were 100.0%, 97.0%, 88.2%, and 84.6%, $p = 0.008$.
Conclusions: Outcomes of VLR/LR yields excellent results using surveillance or SRT as initial management, in which adjuvant radiation therapy or ADT plus SRT can be avoided. For HR, early SRT or adjuvant radiation therapy can be considered reasonable, and UHR patients may benefit from ADT plus immediate SRT.

1. Introduction

The role and timing of radiation therapy after radical prostatectomy (RP) is controversial. Historically, many patients who underwent RP with adverse features of T3 disease and/or positive surgical margins were followed with surveillance, and later underwent salvage radiation therapy (SRT) at the time of biochemical failure. This allowed some patients to avoid side effects of radiation therapy, if they had been cured by RP or had indolent recurrence. South West Oncology Group (SWOG) 8794 performed a randomized trial of RP patients with either T3 disease and/or positive surgical margins and found improved MFS and OS in those that underwent immediate adjuvant radiation therapy (ART) to the prostate fossa.[1] However, 32-35% of patients in this study had a detectable postoperative prostate-specific antigen (PSA), which should by definition categorize these patients as salvage patients, as these patients already had failed by PSA. Also, only 33.2% of those in the control arm received SRT, which represents an underutilization of SRT, if 32-35% already failed immediately post-RP. The European Organization for Research and Treatment of Cancer

22911 and the Arbeitsgemeinschaft Radiologische Onkologie (ARO) 96-02 are randomized trials that did not show improvement in MFS or OS with ART for T3 and/or positive margin patients.[2,3] Our goal was to analyze a large number of patients with T3 disease and/or positive surgical margins with long-term follow-up and analyze oncologic outcomes with surveillance and SRT, while producing risk categories to assess which patients may benefit the most from early SRT or ART.

2. Methods

2.1. Patient characteristics

Our study included all RP patients at our integrated, multi-facility heath care system who pathologically had adverse factors of pathologic T3a (extracapsular extension), T3b (seminal vesicle invasion), and/or positive margins, from January 2004 to December 2007. Those with microscopic bladder neck involvement were staged as T3a.[4] Gleason score (GS) assessment and grouping was based on the International Society of Urologic Pathology consensus conference.[5] Patients who had clinically T3a/b disease based on digital rectal exam did not undergo RP. Weighted Charlson co-morbidity score was assigned to each patient to assess overall health status.

2.2. Therapy and follow-up

Management included only PSA surveillance in 472 patients (54.8%), SRT in 317 (36.8%), and androgen deprivation therapy (ADT) using leuprolide in 73 (8.5%) as first salvage therapy, and 185 (21.5%) eventually received salvage ADT. Patients with lymph node positive disease were excluded from this study. Open RP was performed in 518 (60.1%), laparoscopic RP in 331 (38.4%), and perineal RP in 13 (1.5%) of patients. Lymph node sampling occurred in 53.6% of patients, and the median number of nodes sampled was five. Twenty patients underwent ART and were excluded from this analysis, which was defined as those who underwent prostate fossa radiation with an undetectable postoperative PSA <0.1. Those patients who underwent immediate prostate fossa radiation with a detectable postoperative PSA were classified as immediate SRT, as by definition, these were already considered to have failed biochemically. SRT was delivered using 3-dimensional conformal radiation therapy, using 4-6 fields to the prostate fossa, to a dose of 6480-6660 in 180-200 centigray fractions. Whole pelvis radiation was not used.

Time zero was the day of RP, but for the subanalysis of SRT patients, time zero was the first day of SRT. Freedom from biochemical failure (FFBF) was based on a PSA value of 0.2 ng/ml. We then estimated FFBF, freedom from salvage therapy (FFST), metastasis-free survival (MFS), prostate cancer–specific survival (PCSS), and overall survival (OS). A minimum of 12-months of follow-up from the time of RP was required for this study.

2.3. Statistics

Characteristics of patients were assessed with percentages for categorical factors, and median with ranges were used for continuous factors. Pearson chi-square test was used to test for differences in categorical features between risk groups. Wilcoxon rank-sum test was used to calculate differences in continuous factors between risk groups. Multivariable analysis (MVA) using the Cox proportional hazards model were used to estimate hazard ratios on five outcomes of FFBF, FFST, MFS, PCSS, and OS, establishing various prognostic factors used to categorize risk groups.[6] To assess the validity of these risk groups, Kaplan-Meier estimates were

performed at 5 and 12 years for FFBF, FFST, MFS, PCSS, and OS.[7] The log-rank statistic estimated the differences between risk groups, using a two-sided $P < 0.05$. A sub-analysis of those that underwent SRT was also performed. All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

3. Results

3.1. Patient cohort (Table 1)

The median follow-up was 12.1 years from the day of RP (range 1.0-15.4 years), but the median follow-up of SRT patients measured from the first day of SRT was 9.5 years. The median age was 61.6 years (41.2-78.3). The Charlson score was not significantly different between risk groups. Margin negative patients were significantly higher in the UHR group, p < 0.001 (Table 1). Gleason grouping was lower in the very-low-risk (VLR) and low-risk (LR) compared to high-risk (HR) and ultra-high-risk (UHR), but not statistically different between HR and UHR, p = 0.08. SRT and ADT were significantly higher for HR and UHR compared to VLR and LR, p < 0.001. SRT was borderline significantly higher for UHR compared to HR, p = 0.06, and ADT was significantly higher for UHR compared to HR, p < 0.001.

3.2. Prognostic factors and risk groups (Table 2)

Detectable postoperative PSA drawn at least 5 weeks after RP occurred in 13.8% of patients. T3b was found in 13.7%, and GS 8-10 (group 4, 5) was found in 15.1% of our patients. On MVA, positive margins had lower FFBF and FFST. T3a also had lower FFBF and FFST, and borderline significance for MFS, p = 0.07. T3b had significantly lower FFBF, FFST, MFS and PCSS, while higher Gleason group and detectable postoperative PSA significantly lowered all oncologic endpoints of FFBF, FFST, MFS, PCSS, and OS. Thus, we included these factors in making risk groups of VLR, LR, HR, and UHR. Risk groups were made based on MVA of prognostic factors that independently affected PCSS. The three factors that independently affected PCSS were higher Gleason grouping, pathologic stage (T3b), and detectable postoperative PSA. VLR were any patient with GS 6 (group 1). LR were GS 3 + 4 (group 2) with only T3a or positive margins, but an undetectable postoperative PSA <0.1. HR were T3b with GS 7-10 (groups 2-5), or any GS 7-10 with T3a/b and positive margins but an undetectable postoperative PSA. UHR were those with a detectable postoperative PSA with a GS 7-10 (groups 2-5).

The median PSA prior to salvage therapy was 0.3 for VLR, LR, HR, which is consistent with early SRT, but was 0.7 for the UHR group, in which the post-RP PSA was already detectable, with a median time to treatment of 7 months.

3.3. Group 1 with a detectable postoperative PSA

There were 9.8% (24/246) of group 1/GS 6 patients which had a detectable postoperative PSA. Median follow-up of this subset was 11.7 years (range 2.5-14.3). SRT was done in 22/24 (91.7%) of these patients, and the two patients who underwent surveillance were alive without metastases at 10.0 and 11.7 years. Only one of them developed metastases, but was alive at 11.7 years on ADT. The only death in this group was caused by larynx cancer.

3.4. ADT with SRT

The majority of SRT patients did not receive combined ADT. For VLR and LR, only 3.4% (4/119) received ADT, and for HR and UHR, 3.5% (7/198) received combined ADT. The median duration of combined ADT was 3 months (range 3-12) for all risk groups.

Table 1
Patient cohort characteristics.

	Very low risk (n = 246), GS6	Low risk (n = 224), GS 3 + 4 with T3a or + margin, but PSA<0.1	High-risk (n = 297), T3b with GS 7-10, T3a/b and +margin, but PSA <0.1	Ultra high risk (n = 95), detectable PSA with GS 7-10	*P* value
Age (years)					<0.001
Median	58.5	62.4	63.8	62.2	
Range	(41.2-75.7)	(42.6-78.3)	(46.2-77.6)	(42.1-76.0)	
Race					0.11
Asian	22 (8.9%)	27 (12.1%)	22 (7.4%)	3 (3.2%)	
Black	42 (17.1%)	48 (21.4%)	63 (21.2%)	19 (20%)	
Hispanic	50 (20.3%)	41 (18.3%)	67 (22.6%)	18 (19.0%)	
White	127 (51.6%)	98 (43.8%)	140 (47.1%)	54 (56.8%)	
Unknown	5 (2.0%)	10 (4.5%)	5 (1.7%)	1 (1.1%)	
Charlson comorbidity index					0.57
1-2	186 (75.6%)	159 (71.0%)	210 (70.7%)	70 (73.7%)	
≥ 3	60 (24.4%)	65 (29%)	87 (29.3%)	25 (26.3%)	
Pathologic stage					<0.001
2a	17 (6.9%)	10 (4.5%)	5 (1.7%)	3 (3.2%)	
2b	12 (4.9%)	9 (4.0%)	8 (2.7%)	3 (3.2%)	
2c	162 (65.9%)	153 (68.3%)	63 (21.2%)	23 (24.2%)	
3a	48 (19.5%)	52 (23.2%)	143 (48.2%)	33 (34.7%)	
3b	7 (2.9%)	0 (0%)	78 (26.3%)	33 (34.7%)	
Margins					<0.001
Positive	210 (85.4%)	172 (76.8%)	231 (77.8%)	54 (56.8%)	
Negative	36 (14.6%)	52 (23.2%)	64 (21.6%)	40 (42.1%)	
Unknown	0 (0%)	0 (0%)	2 (0.7%)	1 (1.0%)	
Gleason group					<0.001, but HR vs UHR p = 0.08
Group 1 (GS 6)	246 (100%)		-	-	
Group 2 (3 + 4)	-	224 (100%)	88 (29.6%)	39 (41.1%)	
Group 3 (4 + 3)	-	-	112 (37.7%)	23 (24.2%)	
Group 4 (8)	-	-	58 (19.5%)	20 (21.0%)	
Group 5 (9-10)	-	-	39 (13.1%)	13 (13.7%)	
Median pre-op PSA	5.3 (1.0-43.6)	6.1 (1.2-71.4)	7.5 (0.9-73.2)	11.0 (0.9-92.5)	<0.001
Median PSA prior to salvage	0.3 (0.2-27.0)	0.3 (0.2-7.7)	0.3 (0.2-1324.0)	0.7 (0.2-60.0)	0.74
Lymph node sampling - yes	68 (27.6%)	120 (53.6%)	203 (68.3%)	71 (74.7%)	<0.001
Median number of LN's (range)	5 (1-21)	5 (1-33)	5 (1-41)	5 (1-27)	0.89
Salvage radiation (%)	65/246 (26.4%)	54/224 (24.1%)	142/297 (47.8%)	56/95 (58.9%)	<0.001
Initial salvage ADT (%)	4/246 (1.6%)	9/224 (4.0%)	27/297 (9.1%)	33/95 (34.7%)	<0.001
Follow-up (years)					0.004
Median	12.1	12.1	12.2	11.5	
Range	1.3-15.2	1.0-15.4	1.4-15.3	1.0-15.3	

Table 2
Multivariable analysis of prognostic factors.

P value (95% CI) hazard ratio	Freedom from biochemical failure	Freedom from-salvage therapy	Metastasis-free survival	Prostate cancer−specific survival	Overall survival
Age (≥62vs < 62)	P = 0.71 (0.8-1.2) HR = 0.97	P = 0.32 (0.7-1.1) HR = 0.90	P = 0.06 (1.0-2.6) HR = 1.59	P = 0.14 (0.9-3.4) HR = 1.69	P < 0.001 (1.8-4.1) HR = 2.74
Race (black vs nonblack)	P = 0.70 (0.8-1.2) HR = 0.96	P = 0.39 (0.7-1.2) HR = 0.89	P = 0.07 (0.3-1.0) HR = 0.53	P = 0.09 (0.1-1.2) HR = 0.40	P = 0.07 (1.0-2.2) HR = 1.45
Charlson score (≥3 vs < 3)	P = 0.82 (0.8-1.2) HR = 1.02	P = 0.25 (0.9-1.4) HR = 1.14	P = 0.42 (0.5-1.4) HR = 0.81	P = 0.17 (0.3-1.3) HR = 0.58	P = 0.16 (0.9-1.9) HR = 1.30
Pathologic stage (T3b vs T2)	P < 0.001 (1.3-2.3) HR = 1.75	P < 0.001 (1.4-2.6) HR = 1.91	P < 0.001 (2.6-10.1) HR = 5.11	P = 0.003 (1.6-9.8) HR = 3.99	P = 0.34 (0.8-2.1) HR = 1.28
Pathologic stage (T3a vs T2)	P = 0.002 (1.1-1.8) HR = 1.43	P = 0.02 (1.1-1.7) HR = 1.35	P = 0.07 (1.0-3.7) HR = 1.89	P = 0.85 (0.4-2.8) HR = 1.09	P = 0.94 (0.7-1.6) HR = 1.02
Margins (positive vs negative)	P = 0.004 (1.1-1.7) HR = 1.39	P = 0.002 (1.2-1.9) HR = 1.48	P = 0.28 (0.8-2.2) HR = 1.32	P = 0.20 (0.8-3.5) HR = 1.64	P = 0.58 (0.7-1.7) HR = 1.13
Detectable postop PSA (yes vs no)	P < 0.001 (14.4-24.3) HR = 18.72	P < 0.001 (8.0-13.2) HR = 10.26	P < 0.001 (2.9-7.7) HR = 4.74	P < 0.001 (1.9-7.7) HR = 3.87	P = 0.005 (1.2-2.9) HR = 1.89
Gleason group (group 3, 4, 5 vs 1, 2)	P < 0.001 (1.9-2.9) HR = 2.35	P < 0.001 (1.5-2.4) HR = 1.93	P < 0.001 (2.0-6.0) HR = 3.47	P < 0.001 (2.6-14.1) HR = 6.08	P = 0.002 (1.3-2.6) HR = 1.81
LN sampling (yes vs no)	P = 0.002 (1.1-1.7) HR = 1.36	P < 0.001 (1.2-1.9) HR = 1.54	P = 0.85 (0.5-1.7) HR = 0.95	P = 0.18 (0.3-1.3) HR = 0.60	P = 0.57 (0.6-1.3) HR = 0.90

3.5. Second-line systemic therapy

Taxane-based chemotherapy, abiraterone, and/or enzalutamide, were given in 37/862 (4.3%) of patients due to progression after ADT and/or SRT. For VLR and LR, only 1/246 (0.4%) and 1/224 (0.4%) received the above therapy vs 18/297 (6.1%) for HR, and 17/95 (17.9%) for UHR, p < 0.001.

3.6. Main oncologic outcomes

Median time to first salvage treatment for VLR, LR, HR, and UHR were 11.1, 10.8, 5.3, and 0.6 years, p < 0.001. FFBF at 12 years were 60.2% and 52.9% for VLR and LR patients, but drops precipitously to 28.4% for HR, and was 0% for UHR, and corresponding values of FFST follow that of FFBF. MFS at 12 years was extremely high at 99.1% and 97.8% for VLR and LR groups, but significant drops are seen for HR and UHR at 88.6% and 63.6%. PCSS at 12 years were 99.5%, 99.4%, 93.5%, and 78.9%, and OS 91.8%, 91.8%, 81.0%, 69.9% for VLR, LR, HR and UHR, following a similar pattern of decline (Table 3, Figs. 1−5).

Analysis of causes of death reveal that most men survived in this healthy group of surgical patients, but prostate cancer was the most common cause of death in the HR and UHR groups, p = 0.007 (Table 4).

SRT was performed on 317 patients, of which 65 were VLR, 54 LR, 142 HR, and 56 UHR. Subanalysis of 317 SRT patients showed 10-year FFBF for VLR, LR, HR, and UHR of 74.8% (63.4-88.3), 44.2% (31.2-62.5), 26.2% (18.8-36.6), and 15.9% (8.0-31.6), p < 0.0001. The 10-year MFS for these SRT patients were 100.0% (100.0-100.0), 97.0% (91.3-100.0), 88.2% (82.0-94.9), and 84.6% (74.6-95.9), respectively, p = 0.008 (Table 5).

Table 3
Kaplan-Meier estimates with 95% confidence interval at 5 and 12 years.

| Risk group	#subjects	Observed events/#at risk	5-year probability (95% CI)	12-year probability (95% CI)	P
Freedom from biochemical failure					
Very low risk	246	83/108	74.4% (69.1-80.2)	60.2% (53.9-67.3)	<0.001
Low risk	224	94/54	77.7% (72.3-83.5)	52.9% (46.2-60.6)	
High risk	297	200/40	49.5% (44.0-55.6)	28.4% (23.3-34.4)	
Ultra high risk	95	95/1	1.1% (0.1-7.4)	0% (n/a)	
Freedom from salvage therapy					
Very low risk	246	68/71	79.6% (74.6-84.9)	70.9% (65.2-77.1)	<0.001
Low risk	224	62/103	80.9% (75.7-86.3)	68.6% (62.3-75.5)	
High risk	297	166/53	56.1% (50.6-62.1)	40.5% (34.9-46.9)	
Ultra high risk	95	90/1	5.5% (2.2-13.8)	0% (n/a)	
Metastasis-free survival					
Very low risk	246	2/213	99.6% (98.8-100.0)	99.1% (97.9-100.0)	<0.001
Low risk	224	4/158	99.5% (98.6-100.0)	97.8% (95.7-100.0)	
High risk	297	30/134	96.5% (94.4-98.6)	88.6% (84.8-92.6)	
Ultra high risk	95	30/20	83.1% (75.6-91.3)	63.6% (53.6-75.4)	
Prostate cancer−specific survival					
Very low risk	246	1/180	100.0% (100.0-100.0)	99.5% (98.5-100.0)	<0.001
Low risk	224	1/193	100.0% (100.0-100.0)	99.4% (98.4-100.0)	
High risk	297	17/160	99.3% (98.4-100.0)	93.5% (90.5-96.7)	
Ultra high risk	95	15/52	95.2% (90.8-99.9)	78.9% (70.1-88.8)	
Overall survival					
Very low risk	246	18/83	97.9% (96.0-99.7)	91.8% (88.2-95.7)	<0.001
Low risk	224	17/118	98.1% (96.3-100.0)	91.8% (88.0-95.7)	
High risk	297	51/160	97.6% (95.8-99.4)	81.0% (76.3-85.9)	
Ultra high risk	95	26/39	90.8% (85.0-97.1)	69.9% (60.6-80.6)	
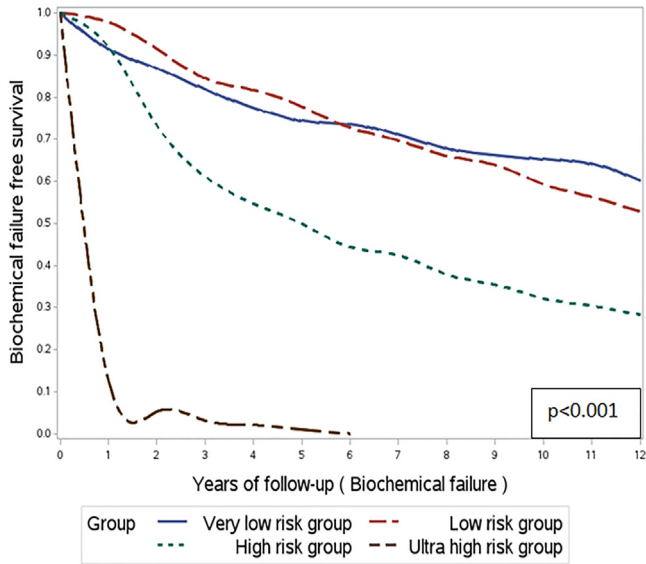
Fig. 1. Freedom from biochemical failure, comparing very–low-risk, low-risk, high-risk, and ultra–high-risk groups.

3.7. Radiation complications

Grade 1-2 urinary morbidity occurred in 8 (2.5%), consisting of hemorrhagic cystitis. Grade 3-4 urinary morbidity occurred in 4 (1.2%), where 2 had anastomotic repairs, 1 had persistent hematuria, and 1 with hematuria requiring hyperbaric oxygen with clots causing retention leading to death from sepsis. Grade 1-2 gastrointestinal bleeding occurred in 6 (1.9%). Grade 3-4 gastrointestinal morbidity occurred in 2 (0.6%), 1 bowel obstruction, and 1 colovesical fistula requiring surgery.[8] Side effects which may also be caused by RP and/or SRT include four (1.3%) artificial urinary sphincter placements after radiation, and 28 (8.8%) bladder neck contractures. Other miscellaneous side effects include one patient experiencing bilateral osteonecrosis of the proximal femur, and another needing total hip replacement, 10 and 21 months after radiation.
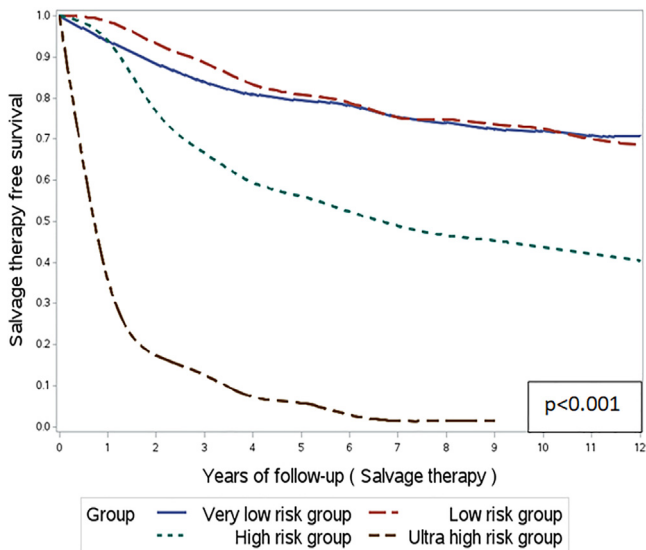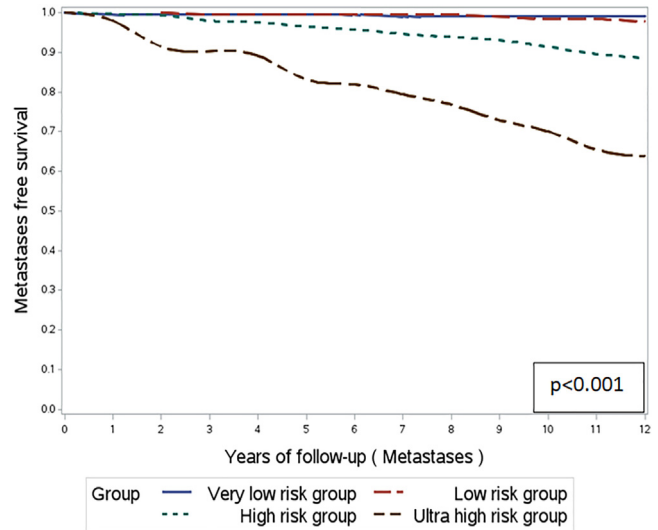

Fig. 3. Metastasis-free survival, comparing very–low-risk, low-risk, high-risk, and ultra–high-risk groups.

4. Discussion

SWOG 8794 randomized patients with T3 and/or positive margins to either ART vs wait-and-see approach, and demonstrated improved MFS for those that underwent ART at 12 years.[1] Some have thought this was a trial comparing ART vs SRT, but this was not the case, since a detectable postoperative PSA was found in 32-35% of patients. Patients with a detectable postoperative PSA should be categorized as salvage patients or immediate SRT, since they already had residual disease after RP, and thus we would consider a wait-and-see approach inappropriate for those with GS 7-10, as evidenced by a 12-year MFS and PCSS of 63.6%, 78.9%, in our study. The only exception to this would be patients with GS 6, where the outcome is excellent in our subgroup analysis with a detectable postoperative PSA. Adjuvant patients should be defined as those with no measurable disease, as was done in the ARO 96-02 study.3 This makes the patients in SWOG 8794 higher risk, as persistence of
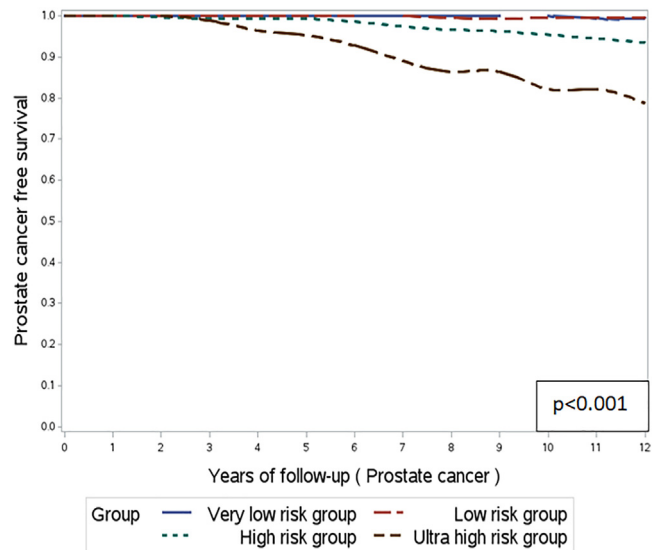

Fig. 2. Freedom from salvage therapy, comparing very–low-risk, low-risk, high-risk, and ultra–high-risk groups.

Fig. 4. Prostate cancer–specific survival, comparing very–low-risk, low-risk, high-risk, and ultra–high-risk groups.
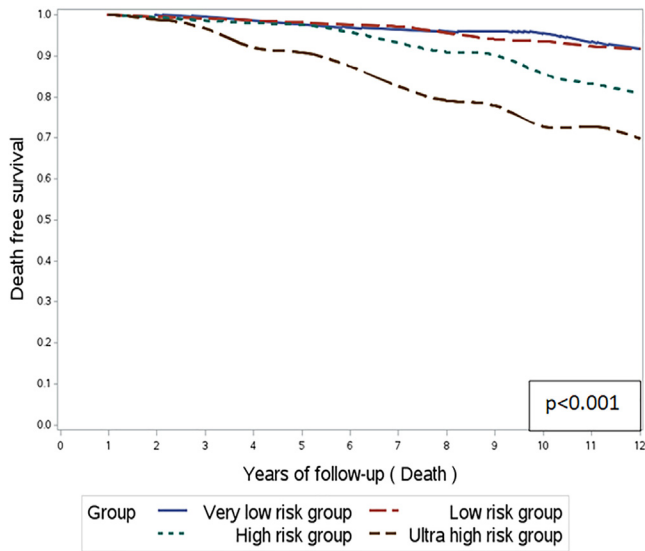
Fig. 5. Overall survival, comparing very−low-risk, low-risk, high-risk, and ultra−high-risk groups.

Table 4
Causes of death.

Cause of death	Very low risk (n = 246)	Low risk (n = 224)	Total (n = 470)	P
Prostate cancer	1 (0.4%)	1 (0.4%)	2 (0.4%)	0.52
Cardiac	3 (1.2%)	7 (3.1%)	10 (2.1%)	
Stroke dementia	3 (1.2%)	3 (1.3%)	6 (1.3%)	
Pulmonary	3 (1.2%)	1 (0.4%)	4 (0.9%)	
Miscellaneous	5 (2.0%)	1 (0.4%)	6 (1.3%)	
Other cancer	7 (2.9%)	7 (3.1%)	14 (3.0%)	
Alive	224 (91.1%)	204 (91.1%)	428 (91.1%)	

Cause of death	High risk (n = 297)	Ultra-high risk (n = 95)	Total (n = 392)	P
Prostate cancer	19 (6.4%)	16 (16.8%)	35 (8.9%)	0.007
Cardiac	6 (2.0%)	0 (0%)	6 (1.5%)	
Stroke dementia	12 (4.0%)	0 (0%)	12 (3.1%)	
Pulmonary	4 (1.3%)	0 (0%)	4 (1.0%)	
Miscellaneous	5 (1.7%)	2 (2.1%)	7 (1.8%)	
Other cancer	15 (5.1%)	8 (8.4%)	23 (5.9%)	
Alive	236 (79.5%)	69 (72.6%)	305 (77.8%)	

PSA after RP was predictive of lower MFS and OS in our study, as well by the authors of the ARO 96-02 study, who performed a follow-up analysis of patients with a persistence of PSA after RP.[9] Also, only 33.2% of those randomized to wait-and-see received SRT in the SWOG 8794 study, which should be considered an underutilization of SRT, or below the standard of care. This explains why the MFS is so much lower, at 61-71%, as opposed to our study where the MFS was 99.1%, 97.8%, 88.6%, and 63.6% in our VLR, LR, HR, and UHR patients. Only our UHR group, in which there was a persistence of PSA after RP, had a similar MFS to that of the SWOG 8794 patients. And it was this group of UHR patients who had the most treatment using not only ADT and immediate SRT, but also abiraterone, enzalutamide, and taxane-based chemotherapy. Two other randomized trials failed to show improvement in MFS with the use of ART, one of which required that patients have an undetectable postoperative PSA.[2,3] Another potential bias of randomized trials exists, where lower risk patient were treated with

Table 5
Comparison of metastasis-free survival between trials.

	SWOG 8794	GETUG-AFU 16	Goy-Liu (current study)
Number patients	425	743	862
Median follow-up (years)	12.7 from RP	9.3 from SRT	12.1 from RP, 9.5 from SRT
Median age	65	66.8-69.5	61.6
Pre-op PSA	10.0	8.1-8.4	6.6
Detectable postop PSA	32-35%	0%	13.8%
Group 4-5 Gleason	9-16%	11%	15.1%
T3b	10-11%	12-13%	13.7%
Metastasis-free survival from date of RP	10-year 71% (ART) 61% (wait-see)	N/A	12-year VLR: 99.1% LR: 97.8% HR: 88.6% UHR: 63.6%
Metastasis-free survival from date of SRT	N/A	10-year 75% (6-month HT + SRT) 69% (SRT)	10-year VLR: 100.0% LR: 97.0% HR: 88.2% UHR: 84.6%

standard of care treatment off-trial, but when a higher risk patient is seen, physicians may consider them for the randomized trial with an experimental arm in addition to the standard of care treatment. When this is done in a multi-institutional fashion, one can obtain large numbers of high-risk patients. This bias would be in favor of finding of a difference in the experimental arm, as in SWOG 8794. For these reasons, the SWOG 8794 results should not be applied to all patients with T3 or positive margins.

On the other extreme of randomized trials, including patients who are not likely to benefit from the experimental treatment may bias results to show no significant difference in the experimental arm. The Radiotherapy-Adjuvant vs Early Salvage (RAVES) and GET-UG-Association Francaise d' Urologie 17 (GET-UG-17) both showed no significant statistical difference in freedom from biochemical progression/event-free survival at 5 years, comparing ART vs early SRT, although progression was slightly in favor of early SRT, which is counter-intuitive, suggesting an implicit bias in favor of the early SRT arm.[10,11] Interestingly, a substantial number of patients in both of these trials would fall into our LR group, where using surveillance or SRT alone yields 12-year MFS of 97.8% in our study, making it highly unlikely for ART to show any benefit, leading to low numbers of oncologic events in both of these trials. Second, the GET-UG-17 trial also used six months of ADT, making the probability of the oncologic events even more unlikely.[11] Another randomized trial, the RADICAL-RT trial, included patients who only had GS 7-10 and/or a preoperative PSA of ≥10, even without T3 or positive margins, which are patients who are not likely to benefit from local radiation to the prostate fossa.[12] Additionally, short median follow-up of 4.9-6.3 years in these trials will reduce the chances of showing differences in MFS, PCSS, and OS, and we must wait for 10-12 year results from prostate cancer studies, in order to make meaningful conclusions.

The above randomized trials conclude both extremes of treating everybody vs treating nobody with ART. Thus, we formulated risk groups, to assess which patients should be spared the toxicities of ART, and which patients may potentially benefit. Our VLR and LR groups do exceedingly well with surveillance or SRT, with a 12-year MFS of 99.1% and 97.8%, and do not need ART. Our VLR is the only group that does well, despite a detectable postoperative PSA. The reason for this may be these patients are clinically and

pathologically low risk, and would ordinarily undergo active surveillance and probably did not need treatment by contemporary standards. Subanalysis of our patients that underwent SRT of VLR and LR groups showed excellent 10-year MFS of 100.0% and 97.0%, and thus do not require combined ADT in addition to SRT. Their excellent MFS is reflected in their slow biology, which took a median of 11 years to salvage therapy. This is in contrast to the GETUG-Association Francaise d' Urologie 16 trial, which showed improved 10-year MFS with the addition of 6 months of ADT, but their control patients undergoing SRT had only a 10-year MFS of 69%, and the median time to relapse was 30 months.[13] This probably reflects a higher risk population, which had a lower MFS compared to our HR and UHR SRT patients, whose 10-year MFS were 88.2% and 84.6%. Also, our median preoperative PSA was lower than the SWOG 8794 and GET-UG 16 patients (Table 5). Radiation Therapy Oncology Group 9601 also reported a more favorable 12-year incidence of metastatic prostate cancer and deaths from prostate cancer, along with improved OS, with the addition of 2 years of high dose anti-androgen therapy to SRT.[14] However, these patients also appear to be of higher risk, and their control arm of SRT had a 12-year incidence of metastatic disease of 23.0%, which is closer to our UHR patients. Thus, our UHR patients may potentially benefit from combined long-term ADT with immediate SRT, due to lower MFS and PCSS in our UHR group. Our UHR group has a high risk of systemic disease, as it was this risk group which had the highest negative margin rate (Table 1), implying that local therapy has less of an impact for UHR patients.

Future studies may concentrate on our patients classified as HR, which would be the ideal group for a randomized study comparing ART vs early SRT alone. Also, it would be of interest to test whether the addition of ADT in our HR group, and what duration, would improve MFS and PCSS compared to early SRT or ART alone.

In conclusion, post-RP patients with T3/positive margins GS 6 with or without detectable post-operative PSA (VLR), and patients with GS 3 + 4 with T3a or positive margins with an undetectable PSA (LR), do exceedingly well using surveillance or SRT alone at the time of biochemical failure, in which ART or combined ADT with SRT can be avoided. For HR, early SRT or possibly ART may be considered reasonable, since FFBF was only 28.4%, with the most common cause of death for HR and UHR patients being prostate cancer. UHR patients may benefit from combined long-term ADT and immediate SRT.

Disclaimer

The interpretation and reporting of these data are the sole responsibility of the authors. Dr. Goy had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The views expressed in the submitted article are the author's own and are not an official position of the Southern California Kaiser Permanente Medical Group. Kaiser Permanente IRB# 11239.

Conflicts of interest

All authors have no conflict of interest to declare.

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