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Postoperative radiation therapy for patients at high-risk of recurrence after radical prostatectomy: does timing matter?

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Objective

To evaluate among radical prostatectomy (RP) patients at high-risk of recurrence whether the timing of postoperative radiation therapy (RT) (adjuvant, early salvage with detectable post-RP prostate-specific antigen [PSA], or 'late' salvage with a PSA level of >1.0 ng/mL) is significantly associated with overall survival (OS), prostate-cancer specific survival or metastasis-free survival, in a longitudinal cohort.

Patients and Methods

Of 6 176 RP patients in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), 305 patients with high-risk pathological features (margin positivity, Gleason score 8–10, or pT3–4) who underwent postoperative RT were examined, either in the adjuvant (≤6 months after RP with undetectable PSA levels, 76 patients) or salvage setting (>6 months after RP or pre-RT PSA level of >0.1 ng/mL, 229 patients). Early (PSA level of ≤1.0 ng/mL, 180 patients) or late salvage RT (PSA level >1.0 ng/mL, 49 patients) was based on post-RP, pre-RT PSA level. Multivariable Cox regression examined associations with all-cause mortality and prostate cancer-specific mortality and/or metastases (PCSMM).

Results

After a median of 74 months after RP, 65 men had died (with 37 events of PCSMM). Adjuvant and salvage RT patients had comparable high-risk features. Compared with adjuvant, salvage RT (early or late) had an increased association with all-cause mortality (hazard ratio [HR] 2.7, $P = 0.018$) and with PCSMM (HR 4.0, $P = 0.015$). PCSMM-free survival differed by further stratification of timing, with 10-year estimates of 88%, 84%, and 71% for adjuvant, early salvage, and late salvage RT, respectively ($P = 0.026$). For PCSMM-free survival and OS, compared with adjuvant RT, late salvage RT had statistically significantly increased risk; however, early salvage RT did not.

Conclusion

This analysis suggests that patients who underwent early salvage RT with PSA levels of <1.0 ng/mL may have comparable metastasis-free survival and OS compared with adjuvant RT; however, late salvage RT with a PSA level of >1.0 ng/mL is associated with worse clinical outcomes.

Keywords

prostate, postoperative, adjuvant, salvage, radiation therapy, CaPSURE

Introduction

Radical prostatectomy (RP) provides excellent cancer control for those with clinically localised prostate adenocarcinoma [1]. However, despite significant downward migration of stage and increased screening, prostate cancer is still the second leading cause of cancer mortality in men in the USA, with an estimated 30 000 deaths [2,3]. After RP, risk factors for recurrence include preoperative PSA level, Gleason score 8–10, extracapsular extension (ECE), seminal vesicle invasion (SVI), and positive surgical margins, with at least one of these features detected in 38–52% of patients [4,5]. These factors, alone or in combination, lead to a 20–70% risk of biochemical failure at 5 years [6,7]. If untreated, such patients are at an increased risk of distant metastases and prostate cancer mortality [8].

Postoperative radiation therapy (RT) can be delivered as either: (i) adjuvant (RT performed within months of RP without a detectable postoperative PSA level) or (ii) salvage RT (RT only after biochemical recurrence, i.e. a detectable PSA level, occurring after RP). Salvage RT can be further stratified into

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'early' or 'late', based on the threshold for PSA level at the time of recurrence to trigger postoperative RT, such as a PSA level of >1.0 ng/mL [9–12]. Three randomised trials comparing adjuvant RT to observation alone have shown decreased recurrence rates with adjuvant therapy, with one also showing improved overall survival (OS) [13–16]. Another option for high-risk patients is to offer salvage RT at the time of biochemical recurrence, although randomised trial data do not exist comparing adjuvant, early salvage, or late salvage RT and the decision on timing of RT remains controversial [9]. Salvage RT seems to be more effective when delivered when the PSA level is low following recurrence; however, the optimal timing or post-RP PSA level threshold to initiate postoperative RT remains undefined [9–12]. Salvage compared with adjuvant RT would expose fewer patients to the side-effects and costs associated with RT. Although retrospective studies suggest that adjuvant RT improves biochemical progression-free survival (PFS) compared with salvage RT, it is uncertain if adjuvant RT improves OS or prostate cancer-specific survival [9,17–20]. The purpose of the present study was to examine the timing of postoperative RT (adjuvant, early salvage, late salvage) on OS and freedom from prostate cancer-specific mortality and/or metastases (PCSMM) for patients at high-risk of recurrence in a USA disease registry, the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study.

Patients and Methods

Data were abstracted from CaPSURE, a national disease registry initiated in 1995 that accrues men with biopsy confirmed prostate adenocarcinoma who receive treatment at any of 45 (primarily community based) urology practices across the USA. Participating urologists recruited men consecutively at diagnosis and reported initial and follow-up clinical data, including staging tests and treatments. Co-morbidities were recorded at baseline [21]. From 1995 to 1998 accrual was both prospective and retrospective; after 1998 all accrual has been prospective. Patients provided written informed consent under local and central Institutional Review Board supervision.

Patients were treated according to the usual practices of clinicians and were followed until death or withdrawal from the study. Clinicians or next of kin report mortality events, and copies of State death certificates were obtained. PCSM was determined if prostate cancer was listed as a primary, secondary, or tertiary cause of death on the death certificate and if no other malignancy was listed as a higher order cause. Events of PCSM and/or metastases (PCSMM) were determined if a patient either had died or had developed metastases due to prostate cancer. Death from prostate cancer and prostate cancer metastases were examined as separate outcomes, with comparable associations. Because of the high correlation of metastatic disease and prostate cancer-specific death [8], PCSMM was used. Perioperative mortality and/or death from complications associated with surgery contributed to all-cause mortality but not PCSMM. If the patient had been lost to follow-up or the death certificate was not available, then the National Death Index was queried to identify the date and cause of death. Additional details regarding the methodology of CaPSURE have been reported previously [22,23].

In all, eligible CaPSURE patients for our study included 13 805 men accrued through 2009, allowing sufficient follow-up. Of the 6 176 men who underwent RP, we included only those ≥2 years of follow-up (or death ≤24 months) (N = 4 834). Of these patients, we included those with at least one criteria for high risk of recurrence (margin positive if pathological Gleason score ≥7, SVI, ECE, Gleason score 8–10, or pT3–4), and excluded lymph node positive disease or those without postoperative RT, for a total of 305 patients. RT was performed a median (range) of 12 (1–158) months from RP. Adjuvant RT was defined as RT at ≤6 months of RP without a detectable PSA level of >0.1 ng/mL (76 patients, 24.9%); salvage RT was defined as RT >6 months after RP or a PSA level before RT of >0.1 ng/mL (229 patients, 75.1%). Salvage patients were further stratified as early (PSA level of ≤1.0 ng/mL, 180 patients) or late (PSA level of >1.0 ng/mL, 49 patients) based on post-RP PSA level prior to RT.

Patient characteristics in each treatment group were tested for associations using ANOVA or Pearson's chi-square tests as appropriate for continuous and categorical variables including pathological factors such as Gleason score, co-morbid diseases (hypertension, cardiovascular disease, stroke, or diabetes mellitus as reported at first participant questionnaire), treatment characteristics such as neoadjuvant/concurrent hormone therapy use as a part of RT, and also demographic characteristics. To assess risk, the Cancer of the Prostate Risk Assessment Post-surgical (CAPRA-S) score was used, a validated score with a range from 0 to 12 calculated using established risk factors [24,25].

Kaplan–Meier product-limit estimates with time-to-event curves were generated [26] and outcomes by timing of RT were compared using the log-rank test. Outcomes were all-cause mortality and PCSMM. Follow-up time and time to event was from date of RP until event or censor. The median (range) follow-up time was 74 (7–256) months. For each endpoint, the hazard ratio (HR) with Wald 95% CI was calculated for adjuvant, early salvage, and late salvage RT, with reference groups as indicated.

Multivariable Cox proportional hazards analysis adjusted for education, co-morbid diseases, and CAPRA-S score, and provided adjusted estimates of relative risk, as described above. Fine and Gray's competing risks regression model was performed to test for differences in cumulative incidence of events of PCSMM by timing of RT while accounting for other deaths and adjusting for CAPRA-S score, co-morbid

diseases, and education [27]. All statistical tests are two-sided, and analyses were performed using the SAS software package (version 9; SAS Institute, Cary, NC, USA). Power calculations were performed with an α of 0.05 using the PS Power and Sample Size software package (version 3.1.2; Vanderbilt University; Nashville, TN, USA). Based on median survival estimates from our data, for the size of the sample, there was 85% power to detect a HR of 1.7 for all-cause mortality and 80% power to detect a HR of 2.0 for PCSMM.

Results

Clinical Characteristics of Study Population, By Postoperative Treatment Group

Of the 305 patients in our study, 65% had margin positive disease with pathological Gleason score ≥7, 37% had Gleason score 8–10, and 68% had stage pT3–4 disease. More patients who received adjuvant RT (76 patients) compared with salvage RT (229 patients) had advanced pT3 or 4 stage, 84% vs 62% ($P < 0.01$, Table 1). There were fewer low-risk patients among adjuvant RT (11%) compared with salvage RT (19%) patients, although not statistically significant ($P = 0.12$). Otherwise, risk factors at diagnosis and surgery were comparable between groups ($P > 0.05$). There was no statistically significant difference in mean ($P = 0.45$) or categorical values ($P = 0.27$) for CAPRA-S scores between patients who received salvage and adjuvant RT. Demographically, RT groups were comparable, except more patients who received adjuvant (75%) compared with salvage (52%) RT ($P < 0.01$) had at least some college education. As a component of RT, more salvage RT patients received concurrent hormone therapy (93%) compared with those who received adjuvant RT (70%, $P < 0.01$). Before adjuvant RT all patients had a PSA level of <0.1 ng/mL and the median (range) time to RT was 3.0 (1.0–5.8) months. Among the salvage RT group, the median (interquartile range, IQR) PSA level before RT was 0.5 (0.3–1.0) ng/mL and the mean (SD) PSA level was 2.4 (10.0) ng/mL with a median (IQR) time to RT of 18.9 (9.0–36.0) months.

Salvage RT patients were further stratified as early (PSA level of ≤1.0 ng/mL, 180 patients) or late (PSA level of >1.0 ng/mL, 49) based on post-RP PSA level before RT. For early salvage RT, the median (IQR) PSA level before RT was 0.4 (0.2–0.6) ng/mL. For late salvage RT, the median (IQR) PSA level before RT was 2.9 (1.5–6.9) ng/mL. Early salvage RT was administered at a median (IQR) of 16 (8–32.5) months from RP, whereas late salvage RT was at a median (IQR) of 25 (12–45) months from RP. The time from RP to RT was statistically significantly different between early and late salvage patients ($P < 0.001$).

At the time of RP, adjuvant, early salvage, and late salvage RT patients had comparable risk of recurrence based on CAPRA-S scores. The CAPRA-S score was not statistically

Table 1 Sociodemographic and clinical factors for patients in each treatment group.

Study characteristic	Adjuvant RT, *n* (%)	Salvage RT, *n* (%)	*P**
Number of patients	76	229	
Age at diagnosis, years			
≥46–59	27 (36)	77 (34)	0.91
60–69	40 (53)	121 (53)	
≥70	9 (12)	31 (14)	
Race			
Other	5 (7)	24 (10)	0.33
Caucasian	70 (93)	205 (90)	
Unknown	1	0	
Education			
High school	15 (25)	92 (48)	<0.01
College	44 (75)	100 (52)	
Unknown	17	37	
BMI, kg/m^2			
16–24.9	16 (30)	36 (20)	0.32
25–29.9	25 (45)	93 (50)	
≥30	14 (25)	55 (30)	
Unknown	21	45	
Comorbidities			
None	38 (57)	93 (47)	0.65
1	17 (25)	66 (34)	
2	11 (16)	35 (18)	
3	1 (1)	2 (1)	
4	0	1 (1)	
Unknown	9	32	
PSA at diagnosis, ng/mL			
0.4–10	39 (55)	126 (58)	0.37
10.1–20.0	23 (32)	53 (25)	
>20.0	9 (13)	37 (17)	
Unknown	5	13	
Diagnostic risk[†]			
Low	8 (11)	41 (19)	0.12
Intermediate	33 (46)	74 (34)	
High	31 (43)	105 (48)	
Unknown	4	9	
CAPRA-S score[‡]			
0–2	4 (6)	7 (3)	0.27
3–5	25 (37)	97 (47)	
6–11	39 (57)	102 (50)	
Unknown	8	23	
Mean (SD) score	5.9 (2.3)	5.7 (2.1)	0.45
Year of surgery			
1987–1999	57 (75)	103 (45)	<0.01
2000–2005	19 (25)	126 (55)	
Pathological T stage			
pTx	8 (11)	21 (9)	<0.01
pT2	4 (5)	65 (28)	
pT3 or 4	64 (84)	143 (62)	
Pathological Gleason score			
2–6	14 (19)	22 (10)	0.11
7	34 (46)	118 (53)	
8–10	26 (35)	83 (37)	
Unknown	2	6	
Margin status			
Negative	13 (21)	25 (14)	0.24
Positive	50 (79)	149 (86)	
Unknown	13	55	
ADT with RT			
No	12 (30)	6 (7)	<0.01
Yes	28 (70)	81 (93)	
Unknown	36	142	

*ADT, androgen-deprivation therapy; BMI, body mass index; *Pearson chi-square comparison does not include values unknown; [†]D'Amico risk class [33] modified to include T2c with intermediate; [‡]CAPRA-S score derived using PSA level at diagnosis (0–6 ng/mL = 0, 6–10 ng/mL = 1, 10–20 ng/mL = 2, >20 ng/mL = 3), pathological Gleason score (≤6 = 0, 3+4 = 1, 4+3 = 2, ≥4+4 = 3), margin status (no = 0, yes = 2), ECE (no = 0, yes = 1), SVI (no = 0, ye s= 2), and lymph node involvement (no = 0, yes = 1).*

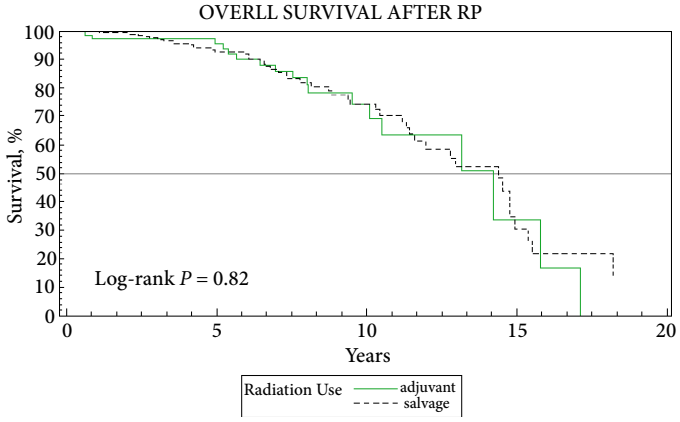
significantly different ($P = 0.38$) between adjuvant (mean [SD] 5.9 [2.3]), early salvage (mean [SD] 5.6 [2.2]), and late salvage RT (mean [SD] 6.0 [2.2]).

OS

At a median follow-up of 6.2 years, there were 65 all-cause deaths and 37 PCSMM events (28 prostate cancer-specific deaths and nine distant metastases). Kaplan–Meier curves show comparable OS for those who received adjuvant and salvage RT (log-rank $P = 0.82$; Fig. 1). In our multivariate model (Table 2) adjusting for CAPRA-S score, co-morbid diseases, and education, salvage RT compared with adjuvant RT had an increased HR of mortality (2.7, 95% CI 1.2–6.1, $P = 0.018$). Additional adjustment for concurrent hormone therapy use with RT or adjustment for age did not significantly alter risk estimates (results not shown). Specific high-risk subgroups were also examined. Compared with adjuvant RT, salvage RT was associated with overall mortality among all pathological Gleason score 8–10 patients (HR 9.6, 95% CI 1.7–53.9, $P = 0.010$).

Additionally, associations of adjuvant, early salvage, and late salvage RT with OS were examined (Fig. 2, log-rank $P = 0.614$), with 10-year estimates for late salvage of 63.3%, early salvage of 80.6% and adjuvant treatment of 74.5%. Compared with late salvage RT, there was no significant difference in OS with adjuvant (log-rank $P = 0.63$) or early salvage RT (log-rank $P = 0.31$). Additionally, in Table 3, after adjusting for confounding covariates, compared with adjuvant RT as the reference group, early salvage RT had a HR of 2.3 ($P = 0.060$), while late salvage RT had an increased association with all-cause mortality (HR 3.3, $P = 0.009$). The association with OS was comparable between early and late salvage RT ($P = 0.32$).

Fig. 1 Kaplan–Meier curves of OS after RP, stratified by adjuvant (solid) and salvage (dashed) RT (log-rank $P = 0.82$).



PCSMM-Free Survival

Kaplan–Meier curves of PCSMM-free survival between adjuvant and salvage RT patients are shown in Fig. 3 (log-rank $P = 0.45$). In our multivariable model (Table 4), salvage RT compared with adjuvant RT was associated with an increased risk of PCSMM (HR 4.0, 95% CI 1.3–12.0, $P = 0.015$). To demonstrate robustness, non-prostate cancer-related deaths were accounted for by using Fine and Gray competing risks regression in a multivariable model, which showed a similar increased risk of PCSMM for salvage RT (HR 3.7, 95% CI 1.2–12.0, $P = 0.028$) compared with adjuvant RT. Similar associations were shown within high-risk subgroups, with salvage RT associated with an increased risk of PCSMM among those with positive margins (HR 7.0, $P = 0.017$) but not among pathological Gleason score 8–10 disease (HR 5.0, $P = 0.081$).

When association with PCSMM was examined by adjuvant, early salvage, and late salvage RT, there was a statistically significant difference in the proportion of PCSMM among patients who received adjuvant (10.5%), early salvage (7.8%), and late salvage (30.6%) RT (chi-square $P < 0.001$). PCSMM-free survival was significantly different across subgroups (Fig. 4, log-rank $P = 0.026$), with 10-year estimates of 71% for late salvage, 84% for early salvage, and 88% for adjuvant RT. Although there was a statistically significant difference in PCSMM between late and early salvage RT (log-rank $P = 0.011$), and also between late salvage and adjuvant RT (log-rank $P = 0.049$), there was no statistically significant

Table 2 Associations with all-cause mortality of multivariable survival analysis of salvage vs adjuvant RT among all patients and in high-risk subgroups.

Variable	All-cause mortality					
	All patients		Gleason 8–10*		Margin positive disease†	
	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Adjuvant RT	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Salvage RT (early or late)	2.68 (1.18–6.08)	0.018	9.59 (1.71–53.85)	0.010	2.44 (0.90–6.60)	0.080
CAPRA-S	1.15 (1.01–1.32)	0.037	1.23 (0.99–1.54)	0.068	1.41 (1.16–1.71)	<0.001
Co-morbidities	1.51 (1.05–2.18)	0.028	1.89 (1.10–3.24)	0.021	1.02 (0.62–1.69)	0.942
Education‡	1.06 (0.58–1.93)	0.861	1.14 (0.48–2.70)	0.774	0.96 (0.42–2.15)	0.911

**Gleason 8–10 patients only (N = 81; 25 events); †Margin positive disease (N = 148; 29 events); ‡College vs high-school education.*

Fig. 2 Kaplan–Meier curves of OS after RP, stratified by adjuvant (green line), early salvage (pre-RT PSA level of ≤1.0 ng/mL; black dash), and late salvage RT (pre-RT PSA level of >1.0 ng/mL; orange long dash) (log-rank $P = 0.614$). Survival was not statistically significantly different in pair-wise comparisons between adjuvant, early salvage, and late salvage RT patients (log-rank all $P > 0.10$). The 10-year OS estimates among adjuvant RT was 74.5%, among early salvage was 80.6%, and among late salvage RT was 63.3%.

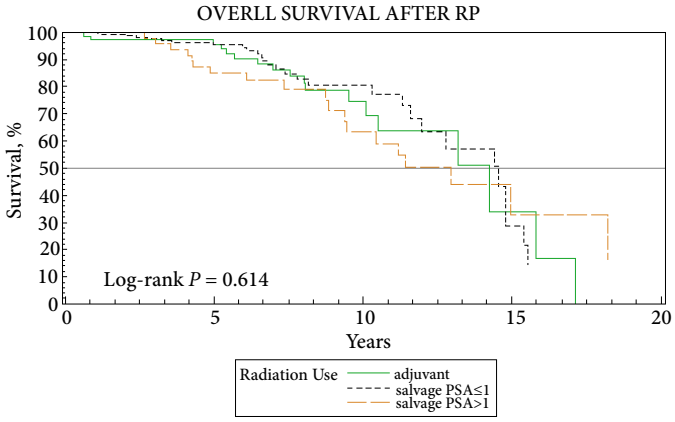


Table 3 Associations with all-cause mortality of multivariable survival analysis of postoperative RT in the adjuvant, early salvage, or late salvage setting, among all patients.

Variable	All-cause mortality among all patients	
	Adjusted HR (95% CI)	*P*
Adjuvant RT	1.00 (Reference)	
Early salvage RT	2.31 (0.97–5.52)	0.060
Late salvage RT	3.28 (1.34–8.03)	0.009
CAPRA-S	1.15 (1.01–1.32)	0.042
Co-morbidities	1.42 (0.96–2.09)	0.080
Education*	1.03 (0.56–1.89)	0.917

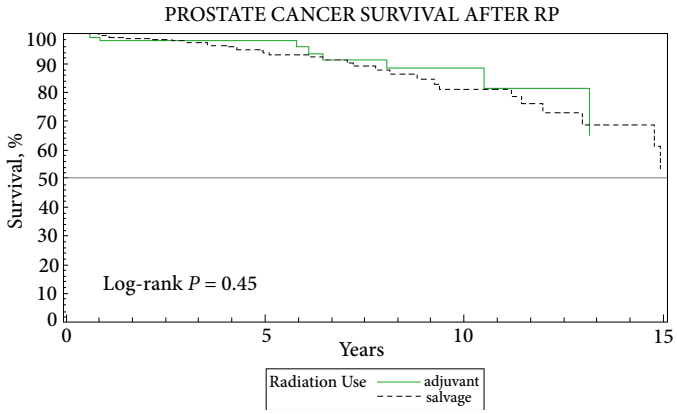
College vs high-school education.

difference between adjuvant and early salvage RT groups (log-rank $P = 0.93$). Additional analyses by adjuvant, early, and late salvage RT, controlling for decade of RP showed rates of PCSMM differed across RT groups (Cochran-Mantel-Haenszel Test $P = 0.004$). Additionally, Table 5 shows in our multivariable model, compared with adjuvant RT, early salvage RT did not have an increased association with PCSMM ($P = 0.11$), although late salvage RT had an increased association with PCSMM (HR 5.7, $P = 0.003$) compared with adjuvant RT.

Discussion

By analysing patients at high-risk of recurrence after RP from an observational, longitudinal registry, clinical outcomes were examined for adjuvant compared with salvage RT, further stratified by early and late salvage (PSA level of ≤1.0 and >1.0 ng/mL, respectively). This allowed for examination of

Fig. 3 Kaplan–Meier curves of survival from PCSMM after RP, stratified by adjuvant (solid) and salvage RT (dashed) (log-rank $P = 0.45$).



clinical outcomes rather than surrogate endpoints, such as biochemical recurrence. If early salvage and adjuvant RT had comparable clinical outcomes, then a policy of early salvage RT would avoid the cost and toxicity of over-treatment of those who would not benefit from postoperative RT.

Three randomised controlled trials (Southwest Oncology Group [SWOG] 8794, European Organisation for the Research and Treatment of Cancer [EORTC] 22911, and ARO 96-02) have all shown decreased rates of recurrence for those treated with adjuvant RT compared with observation [13–16], with SWOG 8794 showing improved distant metastasis free-survival ($P = 0.016$) and 10-year OS (74% vs 66%, $P = 0.023$) [13]. Although 22.5–33.2% of patients assigned to observation arms ultimately received salvage postoperative RT [13–15], it was not possible to extrapolate that adjuvant RT improved clinical outcomes compared with salvage RT.

For salvage RT, most retrospective studies focused on biochemical PFS [11,12,28–31]. A nomogram derived from a multi-institutional cohort predicted improved PFS with lower pre-RT PSA level, lower Gleason score, longer PSA doubling-time, positive surgical margins, ADT use, and node negative disease [11]. A recent review showed PSA level before salvage RT was significantly related to recurrence-free survival ($P < 0.001$), with a 2.6% decrease in recurrence-free survival per 0.1 ng/mL PSA level increase at salvage RT, arguing for initiation of salvage RT at the lowest detectable PSA level [12]. Other retrospective studies comparing adjuvant vs salvage RT reported improved biochemical PFS [18–20]. However, prior studies were not sufficiently powered to examine OS or prostate cancer-specific survival.

Findings from the present CaPSURE study further confirmed the protective effects of adjuvant compared with salvage RT but extend these results to harder clinical endpoints. In our present analyses, compared with adjuvant RT, salvage RT had

Table 4 Associations with PCSMM of multivariable survival analysis of salvage compared with adjuvant RT among all patients and in high-risk subgroups.

Variables	PCSMM					
	All patients		Gleason 8–10 patients only*		Margin positive disease only†	
	Adjusted HR (95% CI)‡	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Adjuvant RT	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Salvage RT (early or late)§	3.96 (1.30–12.03)	0.015	4.97 (0.82–30.00)	0.081	7.01 (1.42–34.62)	0.017
CAPRA-S	1.17 (0.99–1.39)	0.068	1.21 (0.92–1.58)	0.167	1.38 (1.09–1.75)	0.009
Co-morbidities	1.71 (1.07–2.72)	0.025	2.03 (1.03–4.01)	0.040	1.55 (0.84–2.85)	0.163
Education§	2.62 (1.10–6.22)	0.030	2.25 (0.67–7.54)	0.187	2.67 (0.86–8.30)	0.089

**Gleason 8–10 patients only (N = 81; 14 events); †Margin positive disease (N = 148; 18 events); ‡For all patients, Fine and Gray competing risks analysis adjusting for CAPRA-S score, co-morbidities, and education had an increased adjusted HR for salvage RT (adjusted HR 3.71, 95% CI 1.15–11.96, P = 0.028) compared with adjuvant RT for prostate cancer clinical progression; §College vs high-school education.*

Fig. 4 Kaplan–Meier curves of survival from PCSMM after RP, stratified by adjuvant (green line), early salvage (pre-RT PSA level of ≤1.0 ng/mL; black dash), and late salvage RT (pre-RT PSA level of >1.0 ng/mL; orange long dash) (log-rank $P = 0.026$). Survival was not statistically significantly different between adjuvant and early salvage RT patients (log-rank $P = 0.93$). There was a statistically significant difference between late salvage compared with early salvage RT (log-rank $P = 0.011$) and also with adjuvant RT (log-rank $P = 0.049$). The 10-year estimates of PCSMM-free survival were ≈71% for late salvage (PSA level of >1.0 ng/mL), 84% for early salvage (PSA level of ≤1.0 ng/mL), and 88% for adjuvant treatment.

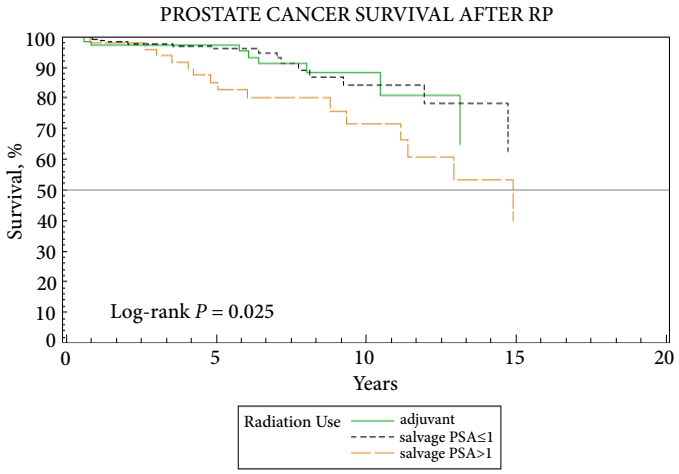


Table 5 Associations with PCSMM of multivariable survival analysis of postoperative RT in the adjuvant, early salvage, or late salvage setting, among all patients.

Variables	PCSMM among all patients	
	Adjusted HR (95% CI)	*P*
Adjuvant RT	1.00 (Reference)	
Early salvage RT	2.67 (0.81–8.80)	0.107
Late salvage RT	5.71 (1.81–18.00)	0.003
CAPRA-S	1.17 (0.98–1.39)	0.075
Co-morbidities	1.48 (0.89–2.46)	0.127
Education*	2.51 (1.05–5.97)	0.038

**College vs high-school education.*

worse OS and PCSMM-free survival. When further stratified by adjuvant, early salvage, and late salvage RT, PCSMM-free survival was worst for the late salvage patients while it was comparable for adjuvant and early salvage RT patients. Similarly, compared with adjuvant RT, associations with all-cause mortality were worse with late salvage RT in our multivariate analysis but not with early salvage RT.

Due to the retrospective nature of our present study, it was not possible to replicate the arms of a clinical trial examining a policy of adjuvant compared with early salvage RT; however, the literature remains limited on this topic [9]. Our present study suggested that a policy of early salvage RT may have comparable mortality/metastases outcomes to adjuvant RT, whereas late salvage RT, after PSA levels are ≥1.0 ng/mL, may have worse clinical outcomes. In CaPSURE, the patients who received RT may represent highly selected groups. For patients who undergo salvage RT, all developed evidence of recurrent disease and were not limited to patients with lower PSA levels; whereas for adjuvant RT, a proportion would not develop recurrence even without treatment [12]. Additionally, among patients who underwent late salvage RT, due to limitations of our present data we were unable to further subdivide by pre-RT PSA velocity in a statistically meaningful fashion. However, both adjuvant and salvage RT groups in CaPSURE had comparable risk factors and comparable CAPRA-S scores, showing that after RP, these patient groups had a similar risk of recurrence.

Additionally, further adjustment of confounders was performed, and the results were robust and consistent. Analysis in CaPSURE did have particular strengths as a large, national, community-based registry followed prospectively and uniformly from diagnosis, which may better approximate practice patterns in the community [23]. However, as data were reported from urology practices, there was limited information on radiation dose, radiation modality, and radiation field size.

With the caveat of the limitations of non-randomised data, the present study suggested that late salvage RT at PSA levels

of >1.0 ng/mL had worse clinical outcomes compared with adjuvant RT, although comparisons between adjuvant and early salvage RT were equivocal with trends towards better outcomes with adjuvant RT. However, a recent review suggested that early salvage RT (PSA level of ≤0.2 ng/mL) may have similar efficacy to adjuvant RT [12]. Given that our present study is observational in nature, these results should be considered hypothesis generating and clinical practice should adhere to recently published AUA/American Society for Therapeutic Radiology and Oncology (ASTRO) guidelines [9]. To avoid the inherent limitations of non-randomised data, the results of several ongoing clinical trials examining the role of timing of RT and the addition of hormone therapy must be examined [9,17,32], including the Radiotherapy and Androgen Deprivation in Combination after Local Surgery (RADICALS), the French Groupe d'Etude des Tumeurs Uro-Genitales-17 trial, and the Trans-Tasman Radiation Oncology Group Radiotherapy Adjuvant vs Early Salvage (TROG RAVES) study.

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Conflict of Interest

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Abbreviations: CAPRA-S, Cancer of the Prostate Risk Assessment Post-surgical Score; CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; ECE, extracapsular extension; HR, hazard ratio; IQR, interquartile range; OS, overall survival; PCSM(M), prostate cancer-specific mortality (and metastases); PFS, progression-free survival; RP, radical prostatectomy; RT, radiation therapy; SVI, seminal vesicle invasion; SWOG, Southwest Oncology Group.