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Research Article

Observation with or without late radiotherapy is equivalent to early radiotherapy in high-risk prostate cancer after radical prostatectomy: A SEER-Medicare analysis on trends, survival outcomes, and complications

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ABSTRACT

Background: We aimed to illustrate national trends of post-radical prostatectomy (RP) radiotherapy (RT) and compare outcomes and toxicities in patients receiving eRT versus observation with or without late radiotherapy (lRT).

Methods: Utilizing the Surveillance, Epidemiology, and End Results (SEER)-Medicare data from 2001 to 2011, we identified 7557 patients with high-risk pathologic features after RP (≥pT3N0 and/or positive surgical margins). Our study cohort consisted of patients receiving RT within 6 months of surgery (eRT), those receiving RT after 6 months (lRT), and those never receiving RT (observation). Another subcohort, delayed RT (dRT), encompassed both lRT and observation. Trends of post-RP RT were compared using the Cochran–Armitage trend test. Cox regression models identified factors predictive of worse survival outcomes. Kaplan–Meier analyses compared the eRT and the dRT groups.

Results: Among those with pathologically confirmed high-risk prostate cancer (PCa) after RP, 12.7% (n = 959), 13.2% (n = 1710), and 74.1% (n = 4888) underwent eRT, lRT, and observation without RT, respectively. Of these strategies, the proportion of men on observation without RT increased significantly over time (p = 0.004). The multivariable Cox regression model demonstrated similar outcomes between the eRT and the dRT groups. At a median follow-up of 5.9 years, five-year overall and cancer-specific survival outcomes were more favorable in the dRT group, when compared to the eRT group.

Conclusions: A blanket adoption of the eRT in high-risk PCa based on clinical trials with limited follow-up may result in overtreatment of a significant number of men and expose them to unnecessary radiation toxicity.

1. Introduction

Radical prostatectomy (RP) remains the gold standard surgical treatment for patients with clinically localized prostate cancer (PCa).[1] For some patients, surgery alone may not provide long-term oncologic control, particularly in those with adverse pathologic features. These patients are at risk for biochemical recurrence (BCR) and eventual progression of disease after surgery. To reduce BCR rates, adjuvant radiotherapy (RT) has been recommended to treat post-RP patients with adverse pathologic characteristics such as extracapsular extension (ECE), seminal vesicle invasion, or positive surgical margin (PSM).[2–4] Currently, American Urologic Association/American Society of Radiation Oncology (AUA/ASTRO)

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guidelines, backed by randomized clinical trial data, support offering adjuvant RT to high-risk patients.[1,4]

Despite the oncologic benefits of adjuvant RT, it may lead to potential overtreatment and unnecessarily expose patients to radiation toxicities.[2,5,6] Salvage RT given to post-RP patients with a prostate-specific antigen (PSA) relapse represents an effort to reduce overtreatment while maintaining the oncologic benefits of RT.[7] However, some critics argue that salvage RT compromises the efficacy of RT, fearing that in waiting for PSA elevation, high-risk patients miss a narrow treatment window and that the disease becomes no longer 'salvageable'.[8]

Multiple retrospective and prospective studies have demonstrated that adjuvant RT may offer more favorable survival, when compared to salvage RT; however, patient selection in these prior studies may have driven these conclusions. Patients who were candidates for post-RP RT based on pathologic features and underwent observation without recurrence may not be captured in these prior studies as they received neither adjuvant nor salvage RT.

Therefore, comparing patients who received adjuvant RT versus the sum population of those undergoing observation with and without salvage radiation may provide a more clinically relevant finding. In this study, we aimed to examine the national trend of post-RP radiation utilization and compare outcomes in those receiving early RT (eRT) (within 6 months of RP) versus those observations with or without late RT (dRT) (after 6 months following RP) groups. We examine their survival outcomes and complication rates using a large population-based database.

2. Materials and methods

2.1. Study Cohort

Our study was approved by the institutional review board (IRB) at the Rutgers Cancer Institute of New Jersey. We used Surveillance, Epidemiology, and End Results (SEER)—Medicare database, which links patient demographic and tumor-specific data collected by SEER cancer registries to health care claims for Medicare enrollees. Our study cohort was defined to include patients with non-metastatic high-risk PCa characterized by pT3 and/or PSM (Fig. 1).

Information on the incidence of cancer was available from 16 SEER areas from January 1, 2001, through December 31, 2011, which covers 25% of the US population.[9] Staging of the cancer was performed according to the American Joint Committee on Cancer criteria.[10]

2.2. Definitions of Variables

The patient cohort was categorized into the following three treatment groups. The eRT group consisted of those who received RT within 6 months after RP. The late radiotherapy (lRT) group consisted of those who received RT beyond 6 months after RP. The observation group consisted of post RP patients without RT. Lastly, the delayed radiotherapy (dRT) group was defined to include those who were observed as well as those who received RT after 6 months, representing the sum of the observation and lRT groups. Complications included adverse outcomes occurring within 12 months after RP when comparing the eRT and dRT groups. In contrast, when comparing the eRT and lRT groups, adverse outcomes were assessed within 12 months after RT.

Adjunctive androgen deprivation therapy (ADT) was defined as RT plus any ADT delivered 2 months before RT until any time 3 years after radiation. Salvage ADT was given 3 years after RT.[11] PSA data were not used in our analysis, nor in the definition of eRT, lRT, or dRT.[12] Complications associated with treatment were identified with ICD-9-CM and HCPCS codes from Medicare files (Supplementary Material 1).

2.3. Statistical Analyses

Pearson's chi-square test was used to compare sociodemographic and tumor characteristics when comparing the eRT and dRT groups. The Cochran–Armitage trend test examined the treatment patterns over years.

Cox proportional hazards regression models were employed to identify factors predictive of worse survival outcomes, including age, treatment strategies, and other relevant variables. The Kaplan–Meier survival analyses were used to compare overall survival (OS) and cancer-specific survival (CSS) for the eRT and dRT groups, and to determine five-year OS and CSS outcomes.

Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R statistical package, version 3.5.1 (https://www.r-project.org/). A two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1. Cohort Characteristics and National Trends

Among 7557 post-RP patients who met inclusion criteria, 12.7% ($n = 959$) received eRT within 6 months following RP. Those who were observed and received RT after 6 months as needed accounted for 87.3% ($n = 6598$), representing the dRT group. In this latter group, 4888 (74.1%) patients never underwent radiation treatment (Fig. 1).

Comparing the eRT and dRT groups in terms of pathologic characteristics, there were significant differences in tumor stage and Gleason score patterns ($P < 0.01$) (Table 1). The eRT group contained a lower proportion of organ-confined disease (14.50% vs. 32.59%) and a greater proportion of ECE (24.92% vs. 14.19%) compared to the dRT group. While adjunctive ADT was more commonly used in the eRT group when compared to the dRT group (52.55 vs. 16.96; $P < 0.01$), salvage ADT was exclusively used in the dRT setting (0.15 vs. 0; $P = 0.63$) (Table 1). A steady increase in men who were managed with observation was noted (p trend $= 0.004$) (Fig. 2).

3.2. Survival Analyses

At a median follow-up of 5.9 years (95% Confidence Interval (CI): 5.8, 6.0), there were 837 deaths in the cohort of 7557 men, of which 199 were attributed to prostate cancer. Older age at diagnosis is predictive of worsening OS during the study period (age $\geq$ 70 vs. age < 70: Hazard Ratio (HR) 1.26 (1.02, 1.56)). However, older age is not predictive of CSS (age $\geq$ 70 vs. age < 70: HR 0.99 (0.64, 1.53)). Extra-capsular disease with pathologic staging $\geq$ pT3 confers worse OS and CSS when compared to those with an organ-confined disease (pT3−NXM0 vs. pT2+N0M0: HR 1.57 (1.04, 2.39) for OS and HR 2.46 (95% CI: 1.04, 5.85) for CSS).

A similar trend, with a higher HR, was observed in patients with pT4 staging when compared to men with an organ-confined disease (OS—PT4N0M0 vs. PT2+N0M0: HR 3.15 (1.87, 5.32); CSS—HR 3.59 (95% CI: 1.32, 9.74)). A Gleason score of 8 – 10 also predicted cancer-specific mortality when compared to those with Gleason 6 disease (CSS—HR 8.52 (2.99, 24.32)). Types of radiation therapy, eRT vs. dRT, had similar effects on both OS and CSS when adjusted for pathologic staging and Gleason grades (eRT vs. dRT: OS—HR 0.94 (0.70, 1.27); CSS—HR 0.69 (0.42, 1.11)) (Table 2).

Five-year OS probabilities of the eRT group and that of the dRT group were not statistically significantly different (0.92 vs. 0.94;

P = 0.95). Similarly, five-year CSS probabilities of both groups were similar as well (0.96 vs. 0.99; P = 0.93). Kaplan–Meier survival curves demonstrate that the dRT group had superior OS and CSS when compared to the eRT group (log rank P < 0.001 for both) (Fig. 3). Subgroup analyses limited to patients with path stage ≥ pT3 and Gleason score ≥4 + 3 still demonstrated similar results (figure not shown). When comparing individuals with RT at different time intervals, eRT versus lRT, both groups had similar OS and CSS (log rank P = 0.78 and 0.85 for OS and CSS, respectively) (figure not shown).

3.3. Adverse Outcomes

Patients who had eRT experienced more complications than those who had dRT in terms of radiation cystitis (0.94% vs. 0.06%; P < 0.01) and radiation proctitis (1.04% vs. 0.09%; P < 0.01). However, a greater proportion of men who had dRT had erectile dysfunction (42.30% vs. 33.68%; P < 0.01) and subsequent procedures to address erectile dysfunction (6.49% vs. 3.96%; P < 0.01) (Table 3).

When comparing two RT groups without those individuals who were observed, namely the eRT versus lRT groups, more complications were seen in the eRT group in terms of urinary incontinence (27.84% vs. 17.84%; P < 0.01), erectile dysfunction (30.76% vs. 21.70%; P < 0.01), and bladder neck contracture (14.60% vs. 9.36%; P < 0.01) (Table 4).

4. Discussion

Despite the AUA/ASTRO guidelines for adjuvant RT for post-RP patients with adverse pathologic features, our study found that 12.6% (959/7557) of eligible patients received RT within 6 months of RP (eRT). Furthermore, we observed an increasing utilization of the observation strategy (p trend = 0.004). Additionally, we

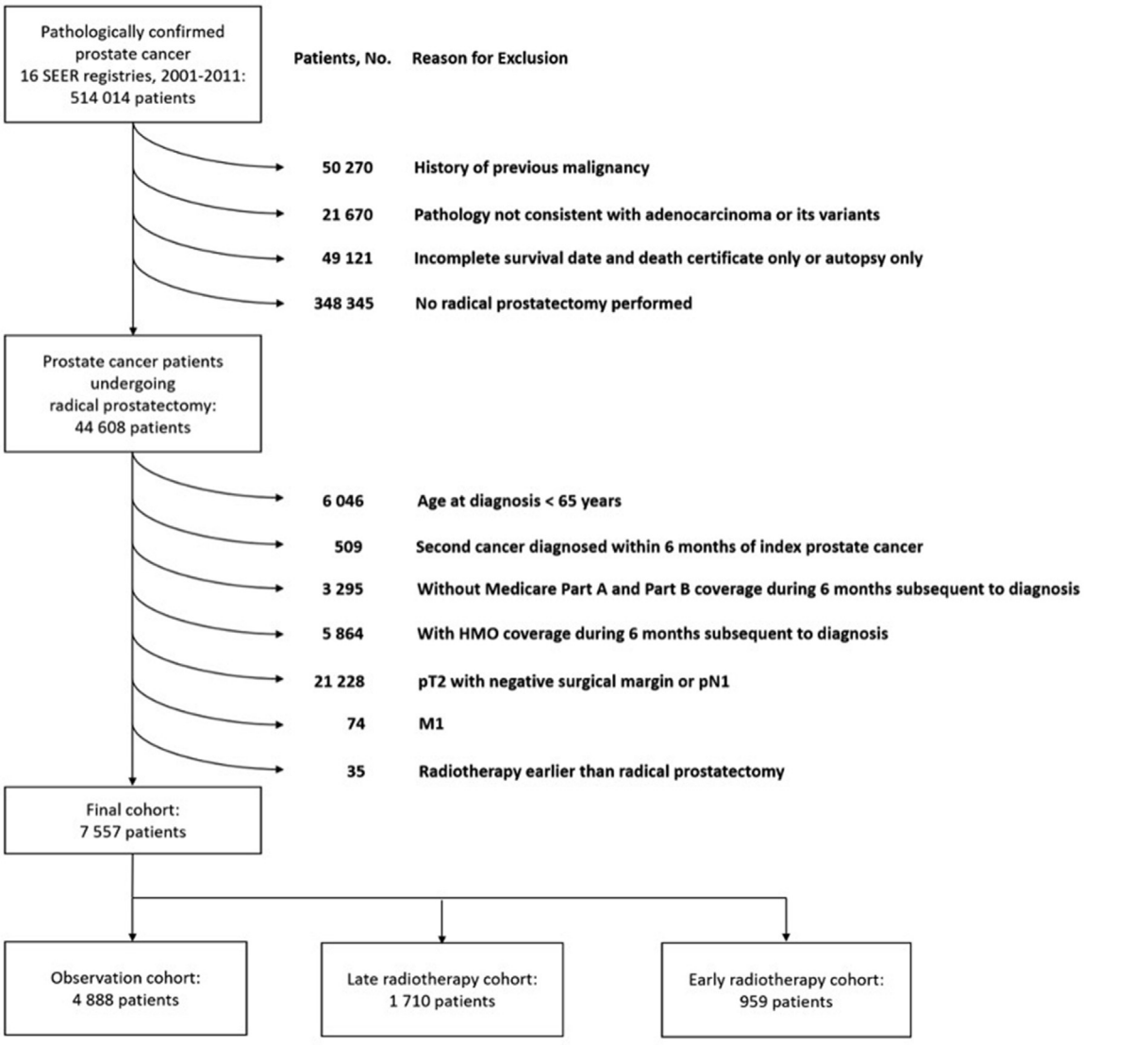

Fig. 1. Flow Chart for Inclusion and Exclusion of Study Population.

Table 1
Demographic and Clinicopathologic Characteristics

Characteristics	RP + eRT (N = 959)	RP + dRT (N = 6 598)	*P*-Value
Age at diagnosis, y (%)			
65–69	62.98	60.84	0.32
70–74	30.66	31.54	
75–79	6.15	6.94	
80–84	0.21	0.64	
85+	0.00	0.04	
Race (%)			
White	82.59	83.84	0.10
Black	7.92	8.52	
Other	9.49	7.49	
Unknown	0.00	0.15	
Hispanic ethnicity (%)			
Not Hispanic	97.71	98.12	0.23
Hispanic	2.29	1.73	
Unknown	0.00	0.15	
Marital status (%)			
Married	82.06	80.65	0.56
Unmarried	14.39	15.34	
Unknown	3.55	4.01	
Tumor stage[a] (%)			
pT2+N0M0	10.64	21.19	<0.01
pT2+NXM0	3.86	11.40	
pT3+N0M0	20.54	10.28	
pT3+NXM0	4.38	3.91	
pT3−N0M0	43.17	38.33	
pT3−NXM0	12.20	12.29	
pT4N0M0	3.96	1.99	
pT4NXM0	1.25	0.61	
Gleason pattern[b] (%)			
3 + 3	6.66	16.76	<0.01
3 + 4	25.52	39.13	
4 + 3	16.64	19.43	
8 − 10	45.35	19.12	
Unknown	5.83	5.55	
Diagnosis year (%)			
2001–2003	24.82	26.30	0.05
2004–2006	24.09	23.02	
2007–2009	28.68	31.49	
2010–2011	22.41	19.19	
SEER registry (%)			
Atlanta	1.46	1.82	<0.01
Connecticut	4.48	5.50	
Detroit	5.84	7.05	
Greater California	23.36	24.60	
Greater Georgia	7.82	6.26	
Hawaii	3.23	1.56	
Iowa	2.82	5.11	
Kentucky	6.99	6.46	
Los Angeles	13.45	11.35	
Louisiana	7.72	7.70	
New Jersey	10.74	7.96	
New Mexico	2.19	2.73	
Rural Georgia	0.00	0.06	
San Francisco	3.13	2.88	
San Jose	2.40	2.39	
Utah	4.37	6.57	
Population of county of residence (%)			
≥ 1 000 000	52.35	50.91	0.60
250 000–999 999	24.92	24.95	
0–249 999	22.73	24.14	
Percentage with less than a high school education in census tract of residence, %[c] (%)			
Bottom quartile (24–100)	26.17	24.11	0.38
Second quartile (13–24)	26.80	26.30	
Third quartile (7–13)	23.57	24.08	
Top quartile (0–7)	23.25	25.01	
Unknown	0.21	0.50	
Median household income in census tract of residence, US$[c] (%)			
Bottom quartile (0–36 916)	24.61	24.95	0.50
Second quartile (36 916–50 213)	25.03	24.86	
Third quartile (50 213–69 539)	26.49	24.64	
Top quartile (69 539–200 014)	23.67	25.05	
Unknown	0.20	0.50	

(*continued on next page*)

Table 1 (*continued*)

Characteristics	RP + eRT (N = 959)	RP + dRT (N = 6 598)	*P*-Value
Adjunctive ADT use after RP (%)			
Yes	52.55	16.96	<0.01
No	47.45	83.04	
Salvage ADT use after RP (%)			
Yes	0.00	0.15	0.63
No	100.00	99.85	

Abbreviations: eRT, early radiotherapy; dRT, delayed radiotherapy; RP, radical prostatectomy; ADT, androgen deprivation therapy; SEER, Surveillance, Epidemiology, and End Results.

[a] "+" and "−" in tumor stage represent positive and negative surgical margins.

[b] Data collection for Gleason pattern in SEER began in 2004, and the number of patients involved in Gleason pattern distribution in the RP + dRT group and those in the RP + eRT group were 4 863 and 721, respectively.

[c] Educational level and median household income were based on census tract data (year 2000). The top educational quartile represents the highest educated group.

observed similar OS and CSS between the eRT and dRT groups. Radiation toxicity impacted the eRT group more than the dRT group, and this finding persisted even when the observation-only patients were removed from the dRT group.

With comparable survival outcomes and significantly less treatment-related toxicities seen in the dRT group, our findings suggest that an increasing proportion of patients might safely adopt the strategy of initial observation followed by radiation as needed. This may preserve the oncologic benefits of RT and spare many patient radiation toxicities.

The magnitude of oncologic benefits from adjuvant radiation demonstrated in prior studies may be overstated by study population selection.[2] Adjuvant radiation has been incorporated into the NCCN guidelines based on two randomized prospective studies (EORTC and SWOG).[4,13–15] Although these studies demonstrated benefit from adjuvant RT when compared to the control group, these comparisons might have been biased because no uniform treatments were rendered to patients on recurrence in the observation cohort. Without prompt interventions, these affected individuals are bound to experience poor survival outcomes, which led to controversial recommendation.

In this regard, our study demonstrates that 74% of men who are eligible for eRT do not recur with observation because they did not require lRT. Simultaneously, we found similar survival outcomes in the dRT group when compared to the eRT group in terms of both OS and CSS. Furthermore, Kaplan–Meier survival analyses comparing the eRT and the dRT group uniformly show the survival advantage of the dRT group (Fig. 3). Similar survival outcomes are seen from the subgroup analysis with men with patients with path stage ≥ pT3 and Gleason score ≥4 + 3, suggesting the persistently uneven distribution of "very high-risk" features between the eRT group and the dRT group.

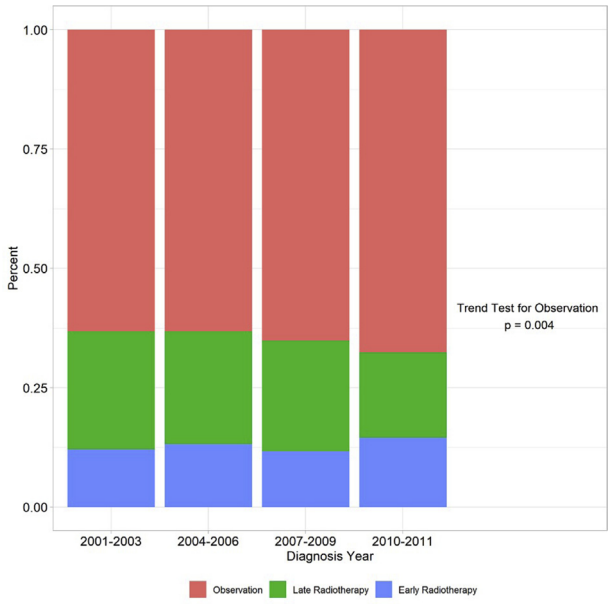

Fig. 2. Trends of Radiotherapy Post-Prostatectomy.

When adjusting for patient and neoplasm features that may portend poorer outcomes, age-adjusted multivariable Cox regression demonstrated a Gleason score of 8 – 10 (OS—HR 1.52 (1.06, 2.18; CSS—HR 8.52 (2.99, 24.32)) and pT4N0M0 (OS—HR 3.16 (1.87, 5.32); CSS—HR 3.59 (1.32, 9.74)) as predictors of worse survival outcomes. Older age at diagnosis is predictive of worsening OS, but similar CSS, during the study period (OS—age ≥ 70 vs. age <70: HR 1.26 (1.02, 1.56); CSS—HR 0.99 (0.64, 1.53). Timing of radiation (eRT vs. dRT) did not independently predict worse survival outcomes.

Our analysis is consistent with the study of Fossati *et al.* who showed no long-term differences in terms of distant metastasis and mortality when comparing adjuvant RT against initial observation followed by early salvage RT.[16] On the other hand, a recent randomized control trial from the FinnProstate Group with 250 enrolled patients showed the opposite. The lower BCR was seen in the adjuvant RT group when compared to those who were observed. However, it is critical to note that lower BCR did not translate into superior OS or CSS. Moreover, it should also be emphasized that 57.3% (70/122) in the observation group remained progression free.[17] Therefore, both our study and this recent trial support that observation followed by future radiation upon recurrence may provide an acceptable alternative to automatic early intervention with RT. Moreover, many studies that report superior oncologic outcomes of adjuvant RT in comparison to salvage RT often utilize heterogeneous and highly elevated PSA levels at which salvage RT was initiated.[18]

In addition to survival outcomes, a discussion of treatment-related toxicities is a critical outcome for post-RP patients facing choices between eRT and dRT. It is previously reported that urinary symptoms are typically well tolerated and the majority of patients achieved the baseline symptoms after both eRT and dRT.[5] Similarly, Shumway *et al.* demonstrated that post-RP patients generally tolerate RT in both adjuvant and salvage settings in a retrospective review of 85 patients.[19] However, our study clearly demonstrated an increased risk of radiation cystitis (P < 0.01) and required procedures for bladder neck contracture following eRT (P = 0.01) when compared to the dRT setting (Table 3).

Worse complications seen in patients with the eRT group, when compared to the lRT group, may indicate that RT in the immediate postoperative setting may interfere with tissue healing and compromise the recovery of urinary function (urinary incontinence: 27.8% vs. 17.8%, P < 0.01) (Table 3). Those who underwent eRT also had more bladder neck contracture and thus required

Table 2
Multivariable Cox Proportional Hazards Regression Analyses for Overall and Prostate Cancer-Specific Survivals

Characteristics	Overall Survival HR (95% CI)	PCa-Specific Survival HR (95% CI)
Age at diagnosis		
65–69	1.00 (reference)	1.00 (reference)
≥ 70	1.26 (1.02, 1.56)	0.99 (0.64, 1.53)
Treatment		
eRT	1.00 (reference)	1.00 (reference)
dRT	0.94 (0.70, 1.27)	0.69 (0.42, 1.11)
Tumor stage[a]		
pT2+N0M0	1.00 (reference)	1.00 (reference)
pT2+NXM0	1.17 (0.74, 1.85)	0.80 (0.21, 3.04)
pT3+N0M0	1.20 (0.77, 1.87)	0.90 (0.33, 2.44)
pT3+NXM0	1.17 (0.62, 2.22)	1.26 (0.33, 4.78)
pT3−N0M0	1.72 (1.23, 2.42)	1.61 (0.74, 3.49)
pT3−NXM0	1.57 (1.04, 2.39)	2.46 (1.04, 5.85)
pT4N0M0	3.15 (1.87, 5.32)	3.59 (1.32, 9.74)
pT4NXM0	1.11 (0.27, 4.57)	NA[b]
Gleason pattern		
3 + 3	1.00 (reference)	1.00 (reference)
3 + 4	0.93 (0.66, 1.30)	1.08 (0.34, 3.36)
4 + 3	0.83 (0.56, 1.24)	1.77 (0.55, 5.76)
8 − 10	1.52 (1.06, 2.18)	8.52 (2.99, 24.32)

Abbreviations: eRT, early radiotherapy; dRT, delayed radiotherapy; PCa, prostate cancer; HR, hazard ratio; CI, confidence interval; INF, infinity; SEER, Surveillance, Epidemiology, and End Results.
[a] "+" and "−" in tumor stage represent positive and negative surgical margins.
[b] No death event was found for men in either treatment regimen (RP + dRT or RP + eRT).

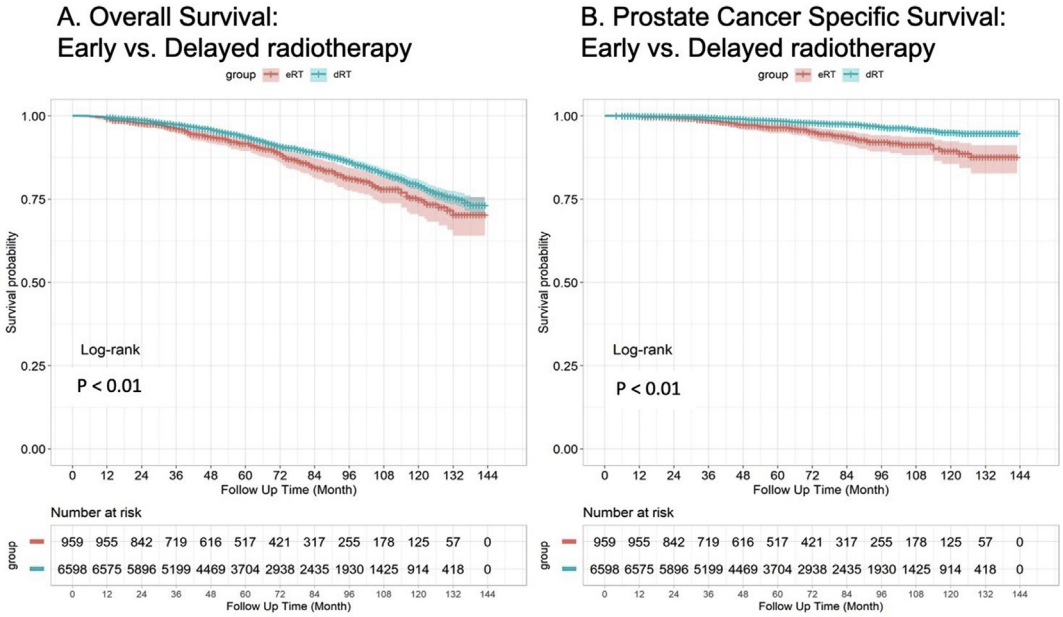

Fig. 3. Overall and Prostate Cancer-Specific Survival: Early versus Delayed Radiotherapy.

more operative procedures, when compared to those who underwent lRT (procedures: 7.72% vs. 2.92%; P < 0.01). Lastly, secondary cancer risks after RT is beyond the scope of this study but may represent important treatment-related side effects.[20]

Despite high-level published data supporting the use of adjuvant RT, only 12.6% of patients received eRT. Interestingly, the increase of observation strategy seen in the period of 2001 and 2011 may coincide with the previous finding (P trend = 0.004). For example, Sineshaw *et al.* reported a steady decrease in postoperative RT within 6 months of RP from 9.1% to 7.3% (P trend <0.001).[21] A trend favoring observation may reflect an improvement in risk-stratification for a better selection of higher-risk patients for upfront radiation to leave the rest for close surveillance.

Our study has several important limitations. First, inherent to our SEER-Medicare database, our study is a retrospective cohort study that contains significant confounders—some controllable but others not. Second, the lack of PSA levels in the data set precludes precise assignment of eRT, as opposed to dRT. Third, limited information on types and doses of radiation is available. It is likely that a substantial heterogeneity exists in this cohort in terms of types of RT and doses. Fourth, complications are not graded based on severity and, hence, may not provide a comprehensive clinical picture. Lastly, the difference in age distribution between the eRT group and the dRT group may be less appreciable due to the limitation of the SEER-Medicare database, which only captures individuals whose ages are greater than or equal to 65.

Table 3
Comparing Complication Rates and Adverse Events: Early versus Delayed Radiotherapy

Characteristics	RP + eRT (N = 959), %	RP + dRT (N = 6598), %	*P*-Value
Urinary incontinence			
Diagnosis	36.08	32.90	0.05
Procedures	1.98	2.27	0.57
Erectile dysfunction			
Diagnosis	33.68	42.30	<0.01
Procedures	3.96	6.49	<0.01
Other genitourinary			
Radiation cystitis	0.94	0.06	<0.01
Hematuria	13.35	14.05	0.56
Bladder neck contracture/urethral stricture			
Diagnosis	21.79	19.22	0.06
Procedure	12.41	9.81	0.01
Urinary fistula	0.52	0.59	0.79
Gastrointestinal			
Radiation proctitis	1.04	0.09	<0.01
Diarrhea	4.90	3.23	<0.01
Rectal bleeding	7.72	5.37	<0.01

Abbreviations: dRT, delayed radiotherapy; eRT, early radiotherapy; RP, radical prostatectomy.

Table 4
Comparing Complication Rates and Adverse Events: Early versus Late Radiotherapy

Characteristics	eRT (N = 959), %	lRT (N = 1710), %	*P*-Value
Urinary incontinence			
Diagnosis	27.84	17.84	<0.01
Procedures	1.25	0.99	0.53
Erectile dysfunction			
Diagnosis	30.76	21.70	<0.01
Procedures	3.96	1.29	<0.01
Other genitourinary			
Radiation cystitis	1.46	0.94	0.22
Hematuria	8.86	6.20	0.01
Bladder neck contracture/urethral stricture			
Diagnosis	14.60	9.36	<0.01
Procedure	7.72	2.92	<0.01
Urinary fistula	0.63	0.06	0.01
Gastrointestinal			
Radiation proctitis	1.77	0.94	0.06
Diarrhea	5.32	5.32	1.00
Rectal bleeding	8.03	6.73	0.21

Abbreviations: eRT, early radiotherapy; lRT, late radiotherapy; RP, radical prostatectomy.

Ultimately, the decision between eRT and dRT will be answered by the multiple prospective randomized trials. Specifically, both RADICALS RT and RAVES trials compare adjuvant RT and salvage RT with primary endpoints of disease-specific survival and biochemical failure, respectively. Other trials including RADICALS HD, GETUG-17, and EORTC 22043-30041 implemented ADT in both comparison arms based on recent evidence of ADT use in improved survival.[22] In the meantime, we recommend that dRT may be the preferred approach over adjuvant RT based on equivalent oncologic outcome and superior quality of life.

5. Conclusions

Our results demonstrated a relatively low utilization of adjuvant RT given within 6 months after RP. In terms of oncologic control, patients who were either observed or had a dRT after 6 months had similar survival rates as those who were given adjuvant RT. Given the similar survival outcomes associated with observation with salvage radiation and better safety profiles with significantly less toxicities, a greater proportion of patients may in fact benefit from an observation with RT as needed as opposed to adjuvant therapy.

Author contributions

Young Suk Kwon: Data curation, Formal analysis, Investigation, Writing of original draft.

Wei Wang: Data curation, Formal analysis, Critical review of manuscript.

Arnav Srivastava: Data curation, Formal analysis, Critical review of manuscript.

Thomas L. Jang: Data curation, Formal analysis, Critical review of manuscript.

Eric A. Singer: Data curation, Formal analysis, Critical review of manuscript.

Rahul R. Parikh: Data curation, Formal analysis, Critical review of manuscript.

Wun-Jae Kim: Data curation, Formal analysis, Critical review of manuscript.

Isaac Yi Kim: Inception of idea, Data curation, Formal analysis, Critical review of manuscript.

Conflicts of interest

None of the contributing authors have any conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2020.10.002.

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