Trends and Predictors of Adjuvant Therapy for Adverse Features Following Radical Prostatectomy: An Analysis From Cancer of the Prostate Strategic Urologic Research Endeavor

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OBJECTIVE To determine trends and predictors of adjuvant therapy in patients with adverse features at radical prostatectomy (RP), and to investigate the associations of adjuvant therapy and adverse feature type with survival.

METHODS From the Cancer of the Prostate Strategic Urologic Research Endeavor registry (1990-2017), 2209 men with adverse features (pT3N0M0 disease and/or positive surgical margins), and 108 men with positive lymph nodes (pN1) at RP were identified. Temporal trends were evaluated, and predictors of adjuvant therapy were assessed with multivariate logistic regression. Kaplan-Meier analysis and competing risks regression were used to test cumulative incidence and risk of all-cause and prostate cancer-specific mortality.

RESULTS Of 2209 men with adverse features and pN0 disease, 89 (4.0%), 82 (3.7%), and 30 (1.4%) received adjuvant external beam radiation therapy (ERBT) alone, androgen deprivation therapy (ADT) alone, or combined EBRT and ADT, respectively. Of 108 men with pN1 disease, 54 (50%) received ADT with or without EBRT. Adjuvant treatment for patients with adverse features decreased from 13.3% (1990-1994) to 6% or less (2005-2017, P_{trend} <.001). Patients with margin positive pT3a (odds ratio 4.13; 95% confidence interval 2.21-7.73; P<.01) and margin positive pT3b disease (odds ratio 7.09; 95% confidence interval 3.66-1.73; P<.01) had greater odds of receiving adjuvant therapy compared to patients with margin negative pT3a disease. Adverse feature type was associated with prostate cancer-specific mortality in univariate analysis (log-rank P <.01), but not in competing risks regression (P= .06).

CONCLUSION Adjuvant therapy declined for men with adverse features at RP. Providers do not treat all adverse feature types the same way, despite broad treatment recommendations in guidelines. UROLOGY 131: 157–165, 2019. © 2019 Elsevier Inc.

A substantial body of evidence exists to help guide primary treatment decisions for clinically localized prostate cancer. However, a relatively smaller evidence base informs the use of adjuvant therapy following radical prostatectomy (RP). Adverse features found at RP—positive surgical margins (R+), extracapsular extension (pT3a), and seminal vesicle invasion (pT3b)—have historically been treated with observation, external beam radiation therapy (EBRT), or early androgen deprivation therapy (ADT).[1-3] Treatment options for lymph node positive (pN1) disease at RP have included adjuvant ADT and/or EBRT, or observation with treatment only after disease recurrence.[4-6]

Current guidelines from the National Comprehensive Cancer Network (NCCN), the American Urological Association, and the American Society for Radiation Oncology recommend that patients with adverse features at the time of RP should be offered the options of adjuvant EBRT or expectant management.[7,8] Guidelines provide a single treatment recommendation for R+, pT3a, and pT3b disease. However, outcomes vary based on the type of adverse feature and the patient's clinical risk classification.[9] For example, disease-free survival at 5 years is

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approximately 80% for patients with positive margins alone, and approximately 50% for patients with positive margins and pT3a.[10] While men with positive margins and pT3a disease are at increased risk of local recurrence, men with pT3b disease are at increased risk of distant metastasis.[11]

Evidence regarding the use of adjuvant therapy for adverse features and pN1 disease has evolved since the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry was initiated in the 1990s.[12] Changes in clinical practice during this time, such as the increased use of ultrasensitive prostate-specific antigen (PSA) assay, have influenced how clinicians evaluate the risk associated with adverse features found at RP and may also have an impact on their decision to offer adjuvant treatment. Therefore, we expect there has been considerable variation in practice patterns. The objectives of this study were to determine patterns of adjuvant therapy in patients with adverse features (R+, pT3a, or pT3b) at RP, to identify predictors of the receipt of adjuvant therapy, and to investigate the associations between adjuvant therapy and adverse feature type with all-cause and prostate cancer-specific morality (PCSM). Secondarily, a subanalysis was performed for patients with pN1 disease at RP.

METHODS

Data Source

Data were abstracted from the CaPSURE database, a national registry of men with biopsy-proven prostate adenocarcinoma. CaPSURE began accrual in 1990 and has enrolled men from 43 primarily community-based urology practices representing 28 states across the United States. Patients provide written consent with supervision of the central institutional review board at the University of California San Francisco. Patients are treated according to their physician's usual practices, and are followed until time of death or withdrawal from the registry. Gleason grading is performed by pathologists at the practice where the patient is treated and followed. Cause of death is determined using state-issued death certificates, National Death Index, and reports from local study coordinators. Details have been reported previously.[12,13]

Study Cohorts

The study cohort included men who were diagnosed with clinically localized prostate cancer or extracapsular extension (stage cT3aN0M0 or lower disease) between 1990 and 2017, underwent RP, and had adverse features (R+, pT3a, and pT3b) or pN1 disease at surgical pathology. We defined adverse features by a composite of margin status and pathologic T-stage, creating the following groups: pT2 margin positive, pT3a margin negative, pT3a margin positive, pT3b margin negative, and pT3b margin positive. We defined adjuvant therapy as EBRT and/or ADT starting within 6 months after RP, with no detectable PSA prior to treatment. Salvage therapy was defined as EBRT and/or ADT starting 6 or more months after RP, or earlier if PSA was detectable right after RP and prior to post-RP treatment. Types of adjuvant therapy were grouped as EBRT, ADT, or combined ADT and EBRT.

Baseline clinical and sociodemographic characteristics were assessed for associations using ANOVA and Wilcoxon rank-sum tests for continuous variables and Pearson's chi square test for categorical variables. Clinical variables included adverse feature type, year of diagnosis, comorbidities at diagnosis, PSA at diagnosis, and Gleason grade at RP. Clinical risk at diagnosis was calculated according the CAPRA (University of California San Francisco Cancer of the Prostate Risk Assessment) score, and postsurgical risk was assessed with the CAPRA-S score.[14] The Cochran-Armitage test for trend was used to evaluate significance of trends in adjuvant therapy utilization for patient with adverse features at RP, and for patients with pN1 disease at RP.

Outcomes and Analysis

A multivariate logistic regression model was created to evaluate predictors of adjuvant therapy for patients with adverse features at RP. The model was adjusted for age per 10 years, adverse feature type, year of diagnosis, comorbidity count at diagnosis, PSA at diagnosis, and Gleason grade at RP. We also calculated Kaplan-Meier product-limit estimates with time-to-event curves, and compared outcomes by type of adjuvant therapy and by type of adverse feature using the log-rank test. The outcomes for these analyses were all-cause mortality and PCSM. Time to event was calculated from date of RP until event or last follow-up. Our analysis also included a competing risks regression model to test for risk of PCSM among patients with adverse features and/or pN1 disease. The model was adjusted for adjuvant therapy type, salvage therapy type, adverse feature type, Gleason grade at RP, year of diagnosis, and study site type. P values were 2-sided, and the statistical significance threshold was defined as $P<.05$. All analyses were performed using SAS 9.4 for Windows.

RESULTS

Between 1990 and 2017, 6750 men in the CaPSURE registry with stage cT3aN0M0 or lower disease underwent RP. Mean age at diagnosis was 61.9 years (standard deviation 7.0). The lymph node dissection rate for this cohort was 80.2%, with a median of 5 nodes dissected (interquartile range [IQR] 2-8). Of these 6750 men, 2209 (32.7%) had adverse features at RP without pN1 disease, and 108 (1.6%) had pN1 disease at RP. Of the 2209 men in our study with adverse features and no evidence of pN1 disease, 2008 (90.9%) did not receive any adjuvant therapy, 89 (4.0%) received adjuvant ERBT alone, 82 (3.7%) received adjuvant ADT alone, and 30 (1.4%) underwent adjuvant EBRT and ADT (Table 1). Among men with adverse features, 1104 (50.0%) had margin positive pT2 disease, 350 (15.8%) had margin negative pT3a disease, 426 (19.3%) had margin positive pT3a disease, 137 (6.2%) had margin negative pT3b disease, and 192 (8.7%) had margin positive pT3b disease. Following RP, a life table estimated 45% ($n = 487$) of men with adverse features experienced biochemical recurrence within 15 years, with a median time to recurrence of 21.7 (IQR 10.3-43.6) months. Of those with recurrence, 257 (52.8%) received salvage therapy.

Adverse feature type was associated with receipt of adjuvant and salvage treatment (Supplementary Fig. 1). A significantly greater proportion of patients with margin positive pT3b disease received adjuvant treatment compared to patients with margin negative pT3a disease (27.6% vs 3.7%, $P<.01$). Similarly, among those not receiving adjuvant treatment, a greater proportion of patients with margin positive pT3b disease underwent salvage therapy compared to those with margin negative pT3a

Table 1. Characteristics of 2209 patients with adverse features at radical prostatectomy stratified by type of adjuvant therapy

Characteristic	All Subjects	ERBT Only	ADT Only	EBRT + ADT	None	*P*
Number of subjects (%)	2209	89 (4.0)	82 (3.7)	30 (1.4)	2008 (90.9)	
Age at diagnosis, mean (SD)	61.9 (7.0)	60.7 (6.3)	64.7 (6.9)	62.1 (6.2)	61.8 (7.0)	<.01
Follow up months since RP, median (IQR)	82.5 (41.6-148)	115.3 (62.3-176.4)	84.8 (34.8-152)	93.2 (52.6-164.8)	80.8 (40.9-147.1)	<.01
Adverse feature						<.01
pT3a, margin negative	350 (15.8)	6 (6.7)	5 (6.1)	2 (6.7)	337 (16.8)	
pT2, margin positive	1104 (50.0)	27 (30.3)	14 (17.1)	2 (6.7)	1061 (52.8)	
pT3, margin positive	426 (19.3)	32 (36.0)	21 (25.6)	11 (36.7)	362 (18.0)	
pT3b, margin negative	137 (6.2)	9 (10.1)	14 (17.1)	5 (16.7)	109 (5.4)	
pT3b, margin positive	192 (8.7)	15 (16.9)	28 (34.1)	10 (33.3)	139 (6.9)	
Year of diagnosis						<.01
1990-1994	308 (13.9)	28 (31.5)	10 (12.2)	3 (10.0)	267 (13.3)	
1995-1999	385 (17.4)	24 (27.0)	13 (15.9)	7 (23.3)	341 (17.0)	
2000-2004	981 (44.4)	29 (32.6)	44 (53.7)	15 (50.0)	893 (44.5)	
2005-2009	268 (12.1)	5 (5.6)	6 (7.3)	1 (3.3)	256 (12.7)	
2010-2017	267 (12.1)	3 (3.4)	9 (11.0)	4 (13.3)	251 (12.5)	
Salvage therapy						<.01
None	1765 (79.9)	64 (71.9)	42 (51.2)	15 (50.0)	1644 (81.9)	
ADT only	224 (10.1)	25 (28.1)	32 (39.0)	15 (50.0)	152 (7.6)	
EBRT only	119 (5.4)	0 (0.0)	1 (1.2)	0 (0.0)	118 (5.9)	
EBRT + ADT	101 (4.6)	0 (0.0)	7 (8.5)	0 (0.0)	94 (4.7)	
Race						.92
White	1902 (86.1)	78 (87.6)	67 (81.7)	27 (90.0)	1730 (86.2)	
Black	230 (10.4)	9 (10.1)	12 (14.6)	3 (10.0)	206 (10.3)	
Latino	23 (1.0)	0 (0)	1 (1.2)	0 (0)	22 (1.1)	
Other	54 (2.4)	2 (2.2)	2 (2.4)	0 (0)	50 (2.5)	
Comorbidities						.71
0	362 (16.4)	19 (21.3)	13 (15.9)	7 (23.3)	323 (16.1)	
1-2	975 (44.1)	43 (48.3)	39 (47.6)	11 (36.7)	882 (43.9)	
≥3	383 (17.3)	13 (14.6)	15 (18.3)	6 (20.0)	349 (17.4)	
Missing	489 (22.1)	14 (15.7)	15 (18.3)	6 (20.0)	454 (22.6)	
PSA at diagnosis (ng/mL)						.11
0-4	239 (10.8)	9 (10.1)	4 (4.9)	3 (10.0)	223 (11.1)	
>4-10	1365 (61.8)	48 (53.9)	47 (57.3)	15 (50.0)	1255 (6.5)	
>10-20	366 (16.6)	22 (24.7)	19 (23.2)	7 (23.3)	318 (15.8)	
>20	151 (6.8)	6 (6.7)	10 (12.2)	4 (13.3)	131 (6.5)	
Missing	88 (4.0)	4 (4.5)	2 (2.4)	1 (3.3)	81 (4.0)	
Clinical CAPRA score						<.01
Low (0-2)	740 (33.5)	15 (16.9)	13 (15.9)	4 (13.3)	708 (35.3)	
Intermediate (3-5)	706 (32.0)	29 (32.6)	29 (35.4)	15 (50.0)	633 (31.5)	
High (6-10)	198 (9.0)	10 (11.2)	20 (24.4)	9 (30.0)	159 (7.9)	
Missing	565 (25.6)	35 (39.3)	20 (2.4)	2 (6.7)	508 (25.3)	

Continued

Table 1. Continued

Characteristic	All Subjects	ERBT Only	ADT Only	EBRT + ADT	None	*P*
Gleason grade group at diagnosis						<.01
GG1 or lower	729 (33.0)	43 (48.3)	24 (29.3)	8 (26.7)	1117 (55.6)	
GG2	818 (37.0)	20 (22.5)	18 (22.0)	7 (23.3)	453 (22.6)	
GG3	304 (13.8)	10 (11.2)	17 (20.7)	7 (23.3)	211 (10.5)	
GG4-5	322 (14.6)	11 (12.4)	21 (25.6)	8 (26.7)	179 (8.9)	
Missing	36 (1.6)	5 (5.6)	2 (2.4)	0 (0.0)	48 (2.4)	
Gleason grade group at RP						<.01
GG1 or lower	729 (33.0)	22 (24.7)	5 (6.1)	3 (10.0)	699 (34.8)	
GG2	818 (37.0)	39 (43.8)	23 (28.0)	4 (13.3)	752 (37.5)	
GG3	304 (13.8)	8 (9.0)	21 (25.6)	8 (26.7)	267 (13.3)	
GG4-5	322 (14.6)	18 (20.2)	30 (36.6)	15 (50.0)	259 (12.9)	
Missing	36 (1.6)	2 (2.2)	3 (3.7)	0 (0.0)	31 (1.5)	
CAPRA-S score						<.01
Low (0-2)	379 (17.2)	7 (7.9)	0 (0.0)	1 (3.3)	371 (18.5)	
Intermediate (3-5)	1138 (51.5)	39 (43.8)	30 (36.6)	7 (23.3)	1062 (52.9)	
High (6-10)	461 (20.9)	34 (38.2)	44 (53.7)	21 (70.0)	362 (18.0)	
Missing	231 (10.5)	9 (10.1)	8 (9.8)	1 (3.3)	213 (10.6)	

ADT, androgen deprivation therapy; CAPRA, Cancer of the Prostate Risk Assessment; EBRT, external beam radiotherapy; GG, grade group; PSA, prostate-specific antigen; RP, radical prostatectomy; SD, standard deviation.

disease (32.3% vs 12.6%). Higher pathologic Gleason grade and clinical CAPRA score were significantly associated with receipt of adjuvant therapy ($P<.01$).

Figure 1 shows trends of adjuvant and salvage treatment from 1990 to 2017 among the 2209 men with adverse features. Use of adjuvant treatment decreased across years of diagnosis from 13.3% (1990-1994), to 9.0% (2000-2004), to 6% (2010-2017; P_{trend} <.001). Among patients with adverse features who did not receive adjuvant treatment, salvage treatment also decreased from 35.4% (1990-1994) to 6% (2010-2017; P_{trend} <.001). The use of adjuvant EBRT alone significantly decreased over time (P_{trend}<.001). There was no significant trend in the use of either ADT alone (P_{trend} = .88) or combined therapy with EBRT and ADT (P_{trend} = .84).

Table 2 displays results from a binomial multivariate logistic regression model of the 2209 patients with adverse features with receipt of adjuvant therapy as the outcome. In comparison to patients with margin negative pT3a disease, patients with margin positive pT3a disease had approximately 4 times greater odds of receiving adjuvant therapy (odds ratio [OR] 4.13; 95% confidence interval [CI] 2.21-7.73; $P<.01$), and patients with margin positive pT3b had approximately 7 times greater odds (OR 7.09; 95% CI 3.66-1.73; $P<.01$). Year of diagnosis was associated with a 6% reduced odds of undergoing adjuvant therapy per 1-year increase (OR 0.94; 95% CI 0.91-0.97; $P<.01$).

In the univariate Kaplan-Meier analysis of all-cause mortality among the 2209 patients with adverse features at RP stratified by adjuvant treatment type, there were not significant differences in rates of all-cause mortality (log-rank P= .05; Supplementary Fig. 2) between patients treated with EBRT, ADT, EBRT and ADT, and patients not receiving adjuvant therapy. However, there were significant differences in the rates of PCSM (log-rank P = .03; Supplementary Fig. 3).

Our subanalysis of 108 men with positive lymph nodes (pN1) at RP revealed that 52 patients (48.1%) did not receive adjuvant therapy, 47 (43.5%) received ADT alone, 7 (6.5%) were treated with both ADT and EBRT, and 2 (1.9%) underwent EBRT alone. The median number of nodes dissected was 7 (IQR 5-12), the median number of positive nodes was 1 (IQR 1-2), and the median percent positive was 16.7% (IQR 12.5-33.3). There was not a significant temporal trend in the proportion of patients receiving adjuvant treatment for pN1 disease (Supplementary Fig. 4). However, the use of ADT appeared to increase between 1990 and 2009, and then decreased from 2010 to 2017. Among patients who did not receive adjuvant treatment, salvage therapy decreased significantly across the study period (P_{trend}<.001). There were no significant differences in all-cause mortality (log-rank P= .07; Supplementary Fig. 5) or PCSM (log-rank P= .28; Supplementary Fig. 6) between pN1 patients receiving and not receiving adjuvant treatment.

Lastly, we aggregated the 2209 men with adverse features at RP and the 108 men with pN1 disease at RP. We performed Kaplan-Meier analyses of all-cause mortality and PCSM among the combined 2317 men, stratified by adverse feature type (Supplementary Figs. 7 and 8). In these univariate analyses, there were significant differences in all-cause mortality (log-rank P <.01) and PCSM (log-rank P <.01) between patients with different adverse feature types. The association between adverse feature type and PCSM was not significant in multivariable competing risk regression analysis adjusted for clinical factors including receipt of adjuvant and salvage treatment (Table 3).

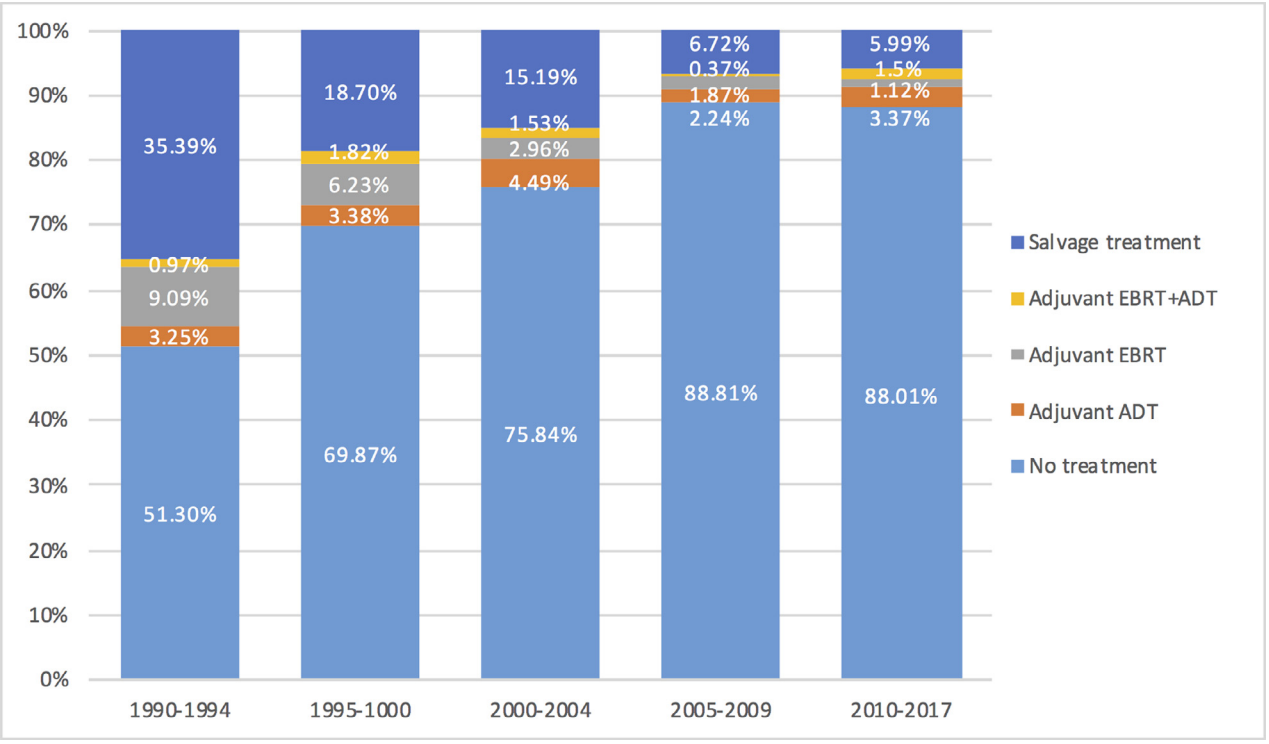

Figure 1. Adjuvant treatment trends from 1990 to 2017 for patients with adverse features at radical prostatectomy ($N = 2209$). (Color version available online.)

DISCUSSION

Several large clinical trials have demonstrated that adjuvant EBRT for patients with extraprostatic disease and/or positive margins reduces the risk of disease recurrence.[15-17] Therefore, current guidelines from the NCCN, the American Urological Association, and the American Society for Radiation Oncology recommend that physicians offer adjuvant EBRT without ADT for patients with adverse features at RP. Despite evidence supporting adjuvant EBRT, we found the use of adjuvant EBRT significantly decreased across the study period. We also observed that the odds of receiving

Table 2. Multivariate binomial logistic regression model for predictors of receiving adjuvant therapy for patients with adverse features ($N = 2209$)

Risk Factors	OR and 95% CI	*P* Value	Global *P*
Age, years: (per 10-year increase)	0.89 (0.71-1.13)	.35	.35
PSA at diagnosis (log)	0.94 (0.75-1.18)	.60	.60
Year of diagnosis (per 1-year increase)	0.94 (0.91-0.97)	<.01	<.01
Adverse feature			
pT3a, margin negative	Ref.		<.01
pT2, margin positive	1.07 (0.56-2.05)	.84	
pT3, margin positive	4.13 (2.21-7.73)	<.01	
pT3b, margin negative	4.96 (2.42-10.16)	<.01	
pT3b, margin positive	7.09 (3.66-13.73)	<.01	
Charlson comorbidity index			
0 (ref)	Ref.		.64
1-2	0.97 (0.60-1.57)	.91	
3+	0.87 (0.55-1.36)	.54	
Missing	0.74 (0.43-1.25)	.26	
Gleason grade at RP			
GG1 or lower (ref)	Ref.		<.01
GG2	2.27 (1.40-3.67)	<.01	
GG3	3.56 (2.03-6.23)	<.01	
GG4-5	4.42 (2.63-7.41)	<.01	
Missing	3.55 (1.22-10.31)	.02	

GG, grade group; PSA, prostate-specific antigen; RP, radical prostatectomy.

Table 3. Competing risk model for patients with adverse features or positive lymph nodes at RP ($N = 2317$) with outcome of prostate cancer-specific mortality

Risk Factors	HR and 95% CI	*P* Value	Global *P*
Year of diagnosis (per 1-year increase)	0.95 (0.91-0.99)	.04	.04
Adjuvant therapy			
RP only	Ref.		.83
Adjuvant ADT	1.01 (0.54-1.91)	.97	
Adjuvant EBRT	1.13 (0.50-2.52)	.76	
Adjuvant EBRT + ADT	0.56 (0.15-2.08)	.38	
Salvage therapy			
None	Ref.		<.01
Salvage ADT	6.63 (3.41-12.91)	<.01	
Salvage EBRT	1.83 (0.62-5.36)	.27	
Salvage EBRT + ADT	7.77 (4.08-14.81)	<.01	
Gleason grade at RP			
GG1 or lower	Ref.		.02
GG2	2.01 (0.97-4.16)	.06	
GG3	2.08 (0.91-4.79)	.08	
GG4-5	3.32 (1.63-6.76)	<.01	
Missing	1.90 (0.63-5.69)	.25	
Study site			
Academic	Ref.		.07
Community	1.04 (0.45-2.42)	.93	
Veterans	3.18 (0.92-10.96)	.07	
Adverse feature			
pT3a, margin negative	Ref.		.06
pT2, margin positive	1.22 (0.52-2.87)	.65	
pT3, margin positive	1.26 (0.51-3.15)	.62	
pT3b, margin negative	2.53 (0.96-6.65)	.06	
pT3b, margin positive	2.21 (0.91-5.39)	.08	
pN1	2.91 (1.08-7.84)	.03	

ADT, androgen deprivation therapy; EBRT, external beam radiotherapy; GG, grade group; HR, hazard ratio; RP, radical prostatectomy.

adjuvant therapy significantly differed based on adverse feature type.

Decline in Adjuvant Therapy

Overall, the use of adjuvant therapy for patients with adverse features following RP significantly declined across the study period. This finding is consistent with results from the National Cancer Database.[1,18] Multiple factors likely contribute to the observed decline in adjuvant therapy for patients with adverse features at RP. Patients and providers must weigh the risk of disease recurrence in the absence of adjuvant therapy against the side effects associated with EBRT and ADT. When trial results from the European Organization for Research and Treatment of Cancer and the Southwest Oncology Group were initially reported in 2005-2006, they showed adjuvant EBRT was associated with significant improvement in biochemical progression free survival, but not with significant improvement in overall or metastasis-free survival.[16,19] Without clear evidence of survival benefit, patients and providers may have thought that the risks of postradiation adverse effects outweigh the biochemical progression free survival benefit. Longer term follow-up results published in 2009 from the Southwest Oncology Group trial later demonstrated significant improvement in overall and metastasis-free survival. Despite these findings, we observed a continued decline in adjuvant EBRT.

It is likely that clinicians avoid the risk of overtreatment in the adjuvant setting and instead opt for observation with early salvage therapy for biochemical recurrence, particularly with the increased use of ultrasensitive PSA assays which allow for earlier detection of recurrence. This rationale is supported by a retrospective analysis of CaPSURE, suggesting that patients undergoing early salvage EBRT have similar metastasis-free survival to patients receiving adjuvant EBRT.[20] Interestingly, there is also evidence that clinicians of different specialties have significantly different opinions on the risk of adverse features and the timing of adjuvant therapy.[21,22] Radiation oncologists appear to be more likely to recommend adjuvant radiation therapy for adverse features after RP, while urologists are more likely to recommend early salvage radiation therapy.

While recent large retrospective studies offer conflicting results regarding adjuvant vs early salvage EBRT, 3 ongoing randomized trials will provide higher quality evidence to guide practice.[23,24] Additionally, the development of biomarkers such as Decipher and new imaging modalities such as ^{68}Ga−PSMA−positron emission tomography will likely help to select men for secondary radiation therapy.

Use of Adjuvant ADT

There are limited data to support the use of adjuvant ADT alone or in combination with RT after RP.[25,26]

NCCN guidelines therefore only recommend adjuvant ADT in cases with positive pelvic lymph nodes.[8] Regardless, 5.1% of patients with adverse features at RP received adjuvant ADT with or without EBRT, with no significant change in utilization. A prior study of the Surveillance, Epidemiology, and End Results registry found that approximately 5%-8% of patients with pT3N0M0 disease and/or positive margins received ADT alone following RP.[2] Since their study could not distinguish salvage and adjuvant therapy, the authors postulated that many of these patients were receiving salvage ADT. Our report reveals that adjuvant ADT has been offered to a limited, but significant portion of patients with adverse features who have no evidence of significant biochemical recurrence.

While evidence does not support the use of ADT for adverse features, a randomized control trial by Messing et al[5] showed improved overall survival for patients with positive lymph nodes at RP treated with immediate ADT compared to observation. This evidence may have contributed to the observed increase in adjuvant ADT for patients with pN1 disease between 1990 and 2009.

Treatment by Adverse Feature Type

Institutional guidelines provide a single treatment recommendation for R+, pT3a, and pT3b disease. However, our findings suggest that providers do not treat all adverse feature types the same. In the current study, patients with margin positive pT3b had approximately 7 times greater odds of receiving adjuvant therapy compared to patients with margin negative pT3a disease. Provider recommendations for adjuvant therapy are likely influenced by patient- and surgery-specific factors. For example, Poelaert et al[27] found that among patients with pT3b disease, positive margins, and younger age were independent predictors of EBRT, while assessing lymph node status with pelvic dissection was an independent predictor for ADT.

Potential variability in outcomes between adverse feature types may influence provider recommendations for adjuvant therapy. The association between adverse feature type and PCSM that we observed on univariate analysis did not persist on multivariable analysis. However, prior reports have found differential outcomes based on adverse feature type. For example, there is considerable evidence that positive margins alone are not significantly associated with PCSM.[28,29]

This study has some limitations. First, the CaPSURE database does not represent a random sample of US men. However, the patients accrued in CaPSURE have relatively similar demographics and clinical risk to those included in the Surveillance, Epidemiology, and End Results registry.[14] Second, the observational design of this study carries the limitations of nonrandomized data and risk of selection bias. Therefore, results on oncological outcomes are meant to generate hypotheses rather than guide clinical practice. Third, enrollment into CaPSURE has decreased since 2007 as the study reaches its end. The reduction in enrollment sites could have introduced selection bias. However, follow-up of earlier patients was not affected. Fourth, our definitions of adjuvant and salvage therapy, which are drawn from definitions in prior reports from CaPSURE, do not strictly adhere to guideline definitions.[7,30] In our definition of adjuvant treatment, we included a time criterion (secondary treatment within 6 months of RP with no detectable PSA prior to treatment). Adjuvant therapy is typically administered within 4-6 months following RP; however, we recognize that some patients may have received adjuvant treatment after 6 months.[30] Our definition of salvage therapy included a lower PSA recurrence criterion (>0.1 ng/mL) than guideline definitions of recurrence in order to include patients who received early salvage therapy. Patients with detectable PSA prior to 6 months who underwent post-RP treatment were considered as receiving salvage therapy.

This study also has considerable strengths. Unlike other reports on postprostatectomy treatment trends, we distinguished adjuvant from salvage therapy by using postprostatectomy PSA levels and time of treatment. Further, our study was able to observe treatment trends across a 27-year time period. Prior investigations of adjuvant therapy patterns have reported trends across substantially shorter time periods.[1-3,18] Lastly, while several reports from other registries have focused on trends in the use of adjuvant EBRT, we were able to report trends in the use of adjuvant EBRT and ADT.

CONCLUSION

Data from a longstanding registry of primarily community-based urology practices show the use of adjuvant therapy has declined for men found to have pathologically staged T3 disease and/or positive surgical margins. Despite guideline recommendations supporting adjuvant EBRT, we found the use of adjuvant EBRT significantly decreased. Our findings also reveal that providers do not treat all adverse feature types the same, despite broad treatment recommendations in guidelines.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.05.018.

References

1. Sineshaw HM, Gray PJ, Efstathiou JA, Jemal A. Declining use of radiotherapy for adverse features after radical prostatectomy: results from the national cancer data base. *Eur Urol*. 2015;68:768–774. https://doi.org/10.1016/j.eururo.2015.04.003.
2. Sheets NC, Hendrix LH, Allen IM, Chen RC. Trends in the use of postprostatectomy therapies for patients with prostate cancer: a surveillance, epidemiology, and end results Medicare analysis. *Cancer*. 2013;119:3295–3301. https://doi.org/10.1002/cncr.28222.
3. Hoffman KE, Nguyen PL, Chen MH, et al. Recommendations for post-prostatectomy radiation therapy in the United States before and after the presentation of randomized trials. *J Urol*. 2011;185:116–120. https://doi.org/10.1016/j.juro.2010.08.086.
4. Wong YN, Freedland S, Egleston B, Hitdes G, Schwartz JS, Armstrong K. Role of androgen deprivation therapy for node-positive

prostate cancer. *J Clin Oncol*. 2009;27:100–105. https://doi.org/10.1200/JCO.2007.14.2042.
5. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol*. 2006;7:472–479. https://doi.org/10.1016/S1470-2045(06)70700-8.
6. Briganti A, Karnes RJ, Da Pozzo LF, et al. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pn+ prostate cancer: results of a matched analysis. *Eur Urol*. 2011;37:832–840. https://doi.org/10.1590/S1677-55382011000400025.
7. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part II: recommended approaches and details of specific care options. *J Urol*. 2018; 199:990–997. https://doi.org/10.1016/j.juro.2018.01.002.
8. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in oncology: prostate cancer*. Available at: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed June 24, 2018 .
9. Alkhateeb S, Alibhai S, Fleshner N, et al. Impact of positive surgical margins after radical prostatectomy differs by disease risk group. *J Urol*. 2010;183:145–150. https://doi.org/10.1016/j.juro.2009.08.132.
10. Swanson GP, Lerner SP. Positive margins after radical prostatectomy: implications for failure and role of adjuvant treatment. *Urol Oncol Semin Orig Investig*. 2013;31:531–541. https://doi.org/10.1016/j.urolonc.2011.06.007.
11. Kasibhatla M, Peterson B, Anscher MS. What is the best postoperative treatment for patients with pT3bN0M0 adenocarcinoma of the prostate? *Prostate Cancer Prostatic Dis*. 2005;8:167–173. https://doi.org/10.1038/sj.pcan.4500789.
12. Lubeck DP, Litwin MS, Henning JM, et al. The CaPSURE database: a methodology for clinical practice and research in prostate cancer. *Urology*. 1996;48:773–777. https://doi.org/10.1016/S0090-4295(96)00226-9.
13. Cooperberg MR, Broering JM, Litwin MS, et al. The contemporary management of prostate cancer in the United States: lessons from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), a national disease registry. *J Urol*. 2004;171:1393–1401. https://doi.org/10.1097/01.ju.0000107247.81471.06.
14. Cooperberg MR, Broering JM, Carroll PR. Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis. *J Natl Cancer Inst*. 2009;101:878–887. https://doi.org/10.1093/jnci/djp122.
15. Bolla M, Van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet*. 2012;380:2018–2027. https://doi.org/10.1016/S0140-6736(12)61253-7.
16. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer. JAMA. 2006;296:2329. https://doi.org/10.1001/jama.296.19.2329.
17. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. *Eur Urol*. 2014;66:243–250. https://doi.org/10.1016/j.eururo.2014.03.011.
18. Kalbasi A, Swisher-Mcclure S, Mitra N, et al. Low rates of adjuvant radiation in patients with nonmetastatic prostate cancer with high-risk pathologic features. *Cancer*. 2014;120:3089–3096. https://doi.org/10.1002/cncr.28856.
19. Bolla M, Van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet*. 2005. https://doi.org/10.1016/S0140-6736(05)67101-2.
20. Hsu CC, Paciorek AT, Cooperberg MR, Iii MR, Hsu IJ, Carroll PR. Postoperative radiation therapy for patients at high-risk of recurrence after radical prostatectomy : does timing matter ?2015:713-720. doi:10.1111/bju.13043.
21. Kim SP, Tilburt JC, Karnes RJ, et al. Variation in treatment recommendations of adjuvant radiation therapy for high-risk prostate cancer by physician specialty. *Urology*. 2013;82:807–812. https://doi.org/10.1016/j.urology.2013.04.060.
22. Showalter TN, Ohri N, Teti KG, et al. Physician beliefs and practices for adjuvant and salvage radiation therapy after prostatectomy. *Int J Radiat Oncol Biol Phys*. 2012;82:233–238. https://doi.org/10.1016/j.ijrobp.2011.04.003.
23. Fossati N, Karnes RJ, Boorjian SA, et al. Long-term impact of adjuvant versus early salvage radiation therapy in pT3N0 prostate cancer patients treated with radical prostatectomy: results from a multi-institutional series. *Eur Urol*. 2017;71:886–893. https://doi.org/10.1016/j.eururo.2016.07.028.
24. Hwang WL, Tendulkar RD, Niemierko A, et al. Comparison between adjuvant and early-salvage postprostatectomy radiotherapy for prostate cancer with adverse pathological features. *JAMA Oncol*. 2018 e175230. https://doi.org/10.1001/jamaoncol.2017.5230.
25. Siddiqui SA, Boorjian SA, Inman B, Bagniewski S, Bergstralh EJ, Blute ML. Timing of androgen deprivation therapy and its impact on survival after radical prostatectomy: a matched cohort study. *J Urol*. 2008;179:1830–1837. https://doi.org/10.1016/j.juro.2008.01.022.
26. Iversen P, McLeod DG, See WA, Morris T, Armstrong J, Wirth MP. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. *BJU Int*. 2010;105:1074–1081. https://doi.org/10.1111/j.1464-410X.2010.09319.x.
27. Poelaert F, Joniau S, Roumeguère T, et al. Current management of pT3b prostate cancer after robot-assisted laparoscopic prostatectomy. *Eur Urol Oncol*. 2018. https://doi.org/10.1016/j.euo.2018.05.005.
28. Swindle P, Eastham JA, Ohori M, et al. Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urol*. 2005;174:903–907. https://doi.org/10.1016/j.juro.2008.03.137.
29. Stephenson AJ, Eggener SE, Hernandez AV, et al. Do margins matter? The influence of positive surgical margins on prostate cancer-specific mortality. *Eur Urol*. 2014;65:675–680. https://doi.org/10.1016/j.eururo.2013.08.036.
30. Thompson IM, Valicenti R, Albertsen PC, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO guideline. *J Urol*. 2013;190:441–449. https://doi.org/10.1016/j.juro.2013.05.032.

EDITORIAL COMMENT

Adenocarcinoma of the prostate is a major health concern in the United States, with 31,620 deaths estimated for 2019.[1] A recent population-based study of nearly 400,000 patients found that radical prostatectomy (RP) was the most commonly utilized treatment in the United States for intermediate- and high-risk patients.[2] In men under aged 70 in these risk groups, RP accounted for 48%-82% of first line therapy.[2] These patients with intermediate- and high-risk disease represent the population most to be at high risk for recurrence following RP, historically defined by the presence of extracapsular extension, seminal vesicle involvement, or positive surgical margins. The risk of subsequent biochemical failure in men with these adverse pathologic features ranges from 40% to 70%.[3-7]

The management of men at high risk for recurrence following RP remains contentious. Three randomized trials investigated the potential benefit of adjuvant radiotherapy (RT) in men with positive surgical margins, extracapsular extension, or seminal vesicle involvement.[3,6,7] Two trials found a benefit from adjuvant RT in terms of progression-free survival,[3,7] and 1 trial[8] also found a reduction in the risk of distant metastases and an improvement in overall survival, though survival was not a primary endpoint in any of the studies. Despite these

findings supporting the use of adjuvant radiation, the National Comprehensive Cancer Network guidelines recommend either adjuvant RT or observation in men with high-risk features and a recent international consensus conference was unable to reach agreement on when to recommend adjuvant RT after RP.[9]

The current report on changing practice patterns from 1990 to 2017 among physicians participating in the national CaPSURE project sheds additional light on how these data have been translated into clinical practice, and the findings are disconcerting. Of the 6750 men included, one-third had adverse prognostic features, but <10% received adjuvant treatment. Furthermore, during this time, the use of adjuvant therapy declined by >50%, mostly due to less-frequent use of external beam RT alone. What is most concerning, however, is that among the men given adjuvant therapy, the majority were treated with either androgen deprivation (ADT) alone or a combination of ADT plus RT, rather than RT alone as supported by both the randomized trials and expert opinion.[10] There is no high-level evidence to support the use of either ADT alone or ADT + RT in the adjuvant setting. Furthermore, during the years of the study, 45% of men with adverse features experience a biochemical recurrence with a median time to recurrence of only 21 months. Thus, the ability to predict who ultimately can be spared postoperative therapy was little better than a coin toss. The oft-cited justification for withholding adjuvant RT, that early salvage RT is equally effective as adjuvant RT, is not supported by recent evidence.[11]

Clearly, adjuvant RT in high-risk patients has not gained widespread acceptance in the urologic oncology community. As we await the results of randomized trials comparing adjuvant vs early salvage RT, we should try to avoid personal bias and use the best available evidence to guide therapy recommendations.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7–34.
2. Chen J, Oromendia C, Halpern JA, Ballman KV. National trends in management of localized prostate cancer: a population based analysis 2004-2013. *Prostate*. 2018;78:512–520.
3. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet*. 2012;380:2018–2027.
4. Briganti A, Wiegel T, Joniau S, et al. Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: results of a match-controlled multi-institutional analysis. *Eur Urol*. 2012;62:472–487.
5. Karakiewicz PI, Eastham JA, Graefen M, et al. Prognostic impact of positive surgical margins in surgically treated prostate cancer: multi-institutional assessment of 5831 patients. *Urology*. 2005;66:1245–1250.
6. Thompson Jr IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA*. 2006;296:2329–2335.
7. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. *Eur Urol*. 2014;66:243–250.
8. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol*. 2009;181:956–962.
9. Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: the report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. *Eur Urol*. 2018;73:178–211.
10. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO Guideline. Part II: recommended approaches and details of specific care options. *J Urol*. 2018;199:990–997.
11. Hwang WL, Tendulkar RD, Niemierko A, et al. Comparison between adjuvant and early-salvage postprostatectomy radiotherapy for prostate cancer with adverse pathological features. *JAMA Oncol*. 2018;4: e175230.

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