International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Utilization of Salvage Radiation Therapy for Biochemical Recurrence After Radical Prostatectomy

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Received Oct 5, 2018. Accepted for publication Jan 6, 2019.

Summary

Salvage radiation therapy (SRT) utilization for men with biochemical recurrence after radical prostatectomy is low and widely variable across urology practices. Patient and tumor-level factors alone do not explain this heterogeneity. Urology practices more likely to use SRT

Purpose: For men with biochemical recurrence after radical prostatectomy (RP), salvage radiation therapy (SRT), especially "early" SRT (PSA level $\leq$0.5 ng/mL), is a potentially curative option; however, its utilization is not well defined. We sought to determine factors associated with SRT utilization as well as variation in its administration.

Materials and Methods: Patients with localized prostate cancer undergoing RP at 33 practices participating in the statewide Michigan Urological Surgery Improvement Collaborative between 2012 and 2016 were prospectively followed. Eligible patients had at least 1 post-RP PSA level $\geq$0.1 ng/mL with $\geq$6 months of follow-up after the first detectable PSA level. Patients undergoing adjuvant radiation therapy were excluded. SRT utilization and clinical and pathologic patient characteristics were examined.

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Conflict of interest: T.M.M. is supported by a U.S. Department of Defense Physician Research Training Award (W81XWH-14-1-0287), Prostate Cancer Foundation Young Investigator Award, and by the A. Alfred Taubman Medical Research Institute. He is also is a consultant/advisor for and receives research funding from Myriad Genetics. D.E.S. is funded by the Prostate Cancer Foundation. M.L.C. participated in the Astellas-Medivation speakers' bureau. K.R.G. is a consultant/advisor for Lumenis and Boston Scientific and receives salary support from Blue Cross Blue Shield of Michigan as the codirector of the Michigan Urological Surgery Improvement Collaborative. D.C.M. receives salary support from Blue Cross Blue Shield of Michigan as the director of the Michigan Urological Surgery Improvement Collaborative and the Michigan Value Collaborative. J.E.M. is a consultant/advisor for and has ownership in HistoSonics Inc. Michigan Urological Surgery Improvement Collaborative is funded by Blue Cross Blue Shield of Michigan.

Supplementary material for this article can be found at https://doi.org/10.1016/j.ijrobp.2019.01.006.

Acknowledgments—The authors acknowledge the significant contribution of the clinical champions, urologists, and data abstractors in each participating MUSIC practice (details for specific participating urologists and practices can be found at www.musicurology.com). They also acknowledge the support provided by the Value Partnerships program at BCBSM.

https://doi.org/10.1016/j.ijrobp.2019.01.006

overall are more likely to administer it across all patient subgroups examined. Higher-risk disease characteristics predict SRT use. This presents an important quality improvement opportunity to facilitate identification of patients who may benefit from SRT and address its variable utilization.

Results: Of 1010 eligible patients with a detectable PSA level, 29.5% underwent SRT. Of patients who received SRT, 46.9% either reached a PSA ≥0.2 ng/mL or were treated before reaching that PSA level. A total of 30.6% of patients had a PSA level ≥0.5 ng/mL without undergoing prior SRT; of this group, 42.1% later received SRT. After adjusting for patient and practice level factors, positive surgical margins, higher T stage, and higher grade group were all associated with receipt of SRT ($P < .05$). Even after adjusting for patient and tumor characteristics, significant variation remained in the adjusted rate of SRT utilization across practices sites, ranging from 7% (95% confidence interval, 3%-17%) to 73% (95% confidence interval, 45%-90%, $P < .001$). Practices were grouped into tertiles based on SRT utilization, and those practices that used SRT more frequently overall were more likely to administer SRT across all patient-based predictors of SRT utilization.

Conclusions: SRT utilization is low among men with a detectable post-RP PSA level, with significant variation in practice-level SRT utilization that cannot be explained by patient factors alone. Factors suggesting higher-risk disease were predictors of SRT administration. These data support the potential to expand the use of SRT, particularly among sites with low utilization.

Introduction

Many men with adverse pathologic findings at the time of radical prostatectomy (RP) for clinically localized prostate cancer (PCa) experience biochemical failure, with rates >50% in high-risk cohorts.[1] Although adjuvant radiation therapy (ART) is a guideline-based option for many of these men, it is rarely used.[2,3] Nevertheless, salvage radiation therapy (SRT), administered for a postoperative prostate-specific antigen (PSA) level ≥0.1 ng/mL, is associated with increased prostate cancer–specific survival, with earlier SRT at a lower PSA level associated with improved freedom from biochemical failure and distant metastasis.[4,5] SRT is most effective when delivered at PSA levels <0.5 ng/mL.[6-9] However, previous work in the Michigan Urological Surgery Improvement Collaborative (MUSIC) indicated SRT utilization may be infrequent and variable across diverse urology practices.[3] We sought to understand SRT utilization across this collaborative by examining potential factors driving SRT administration, timing of delivery, and variation in administration.

Methods

Data source

MUSIC is a quality improvement collaborative funded by Blue Cross Blue Shield of Michigan that uses trained abstractors and a web-based registry to track patients with

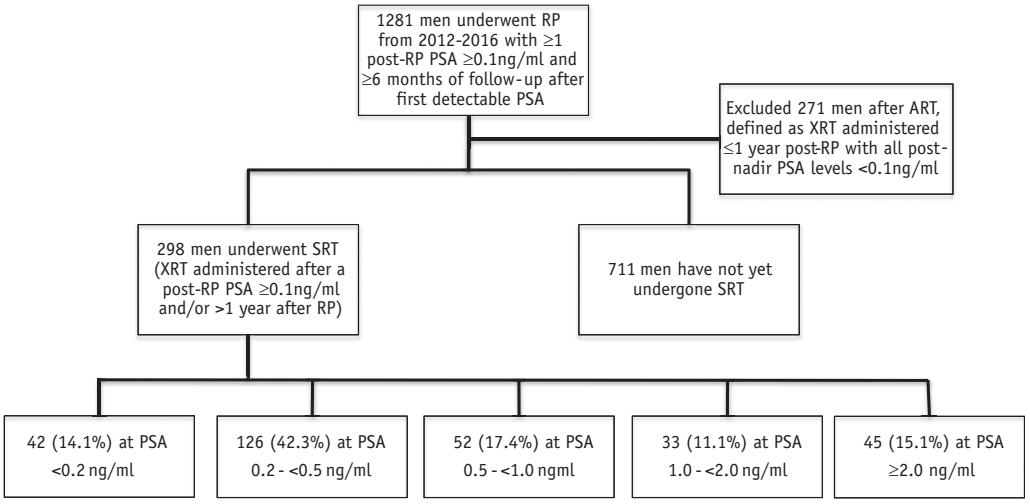

Fig. 1. Diagram of cohort selection criteria. *Abbreviations:* ART = adjuvant radiation therapy; PSA = prostate-specific antigen; RP = radical prostatectomy; SRT = salvage radiation therapy; XRT = radiation therapy.

Table 1 Patient characteristics by SRT utilization and factors associated with SRT utilization

Variable	SRT* (n = 298)	No SRT* (n = 712)	*P* value
Post-RP maximum PSA			
<0.2 ng/mL	42 (14.1)	373 (52.5)	<.001
0.2 to <0.5 ng/mL	126 (42.3)	159 (22.4)	
0.5 to <1 ng/mL	52 (17.4)	69 (9.7)	
1 to <2 ng/mL	33 (11.1)	22 (3.1)	
≥2 ng/mL	45 (15.1)	88 (12.4)	
PSA doubling time			
<3 mo	5 (6.1)	7 (2.0)	<.001
3-9 mo	44 (53.7)	47 (13.4)	
9-15 mo	18 (22.0)	37 (10.5)	
≥15 mo	15 (18.3)	260 (74.1)	
Surgical margins			
Negative	130 (43.6)	428 (60.1)	<.001
Positive	168 (56.4)	284 (39.9)	
Extraprostatic extension			
Positive	206 (69.1)	262 (36.8)	<.001
Negative	92 (30.)	450 (63.2)	
Seminal vesicle invasion			
Not present	210 (70.5)	606 (85.1)	<.001
Present	88 (29.5)	106 (14.9)	
Pathologic T stage			
T2	84 (28.2)	435 (61.1)	<.001
T3/4	214 (71.8)	277 (38.9)	
Pathologic N stage			
N0/Nx	259 (86.9)	662 (93.0)	.002
N1	39 (13.1)	50 (7.0)	
Pathologic Gleason score			
6	8 (2.8)	122 (17.5)	<.001
7	174 (60.0)	439 (63.0)	
8-10	108 (37.2)	136 (19.5)	
Race			
African American	38 (12.8)	107 (15.0)	.69
White	235 (78.9)	541 (76.0)	
Other	5 (1.7)	17 (2.4)	
Unknown	20 (6.7)	47 (6.6)	
Charlson Comorbidity Index			
0	200 (67.1)	508 (71.3)	.17
1	53 (17.8)	126 (17.7)	
≥2	45 (15.1)	78 (11.0)	
Insurance status			
Private	183 (61.4)	422 (59.3)	.52
Government	99 (33.2)	260 (36.5)	
Other	14 (4.7)	23 (3.2)	
None	2 (0.7)	7 (1.0)	
Practice setting			
Private	155 (52.0)	379 (53.2)	.72
Academic	143 (48.0)	333 (46.8)	
Length of follow-up (mo)	26.0 (10.0)	23.7 (11.6)	.002
Age (y) Mean (SD)	63.1 (7.0)	63.2 (7.4)	.87

Abbreviations: PSA = prostate-specific antigen; RP = radical prostatectomy; SD = standard deviation; SRT: salvage radiation therapy; Nx = regional lymph nodes cannot be assessed. N0 = no evidence of lymph node metastases.

Cell values may not total to the cohort sample size because of missing data.

* Values are presented as the number (percent).

Table 2 Patient characteristics by SRT utilization and factors associated with SRT utilization*

Variable	Odds ratio	95% Confidence interval	*P* value
Post-RP maximum PSA	1.11	0.99-1.25	.071
Surgical margins			
Negative	Reference	Reference	-
Positive	1.63	1.17-2.27	.004
Pathologic T stage			
T2	Reference	Reference	-
T3/4	3.13	2.15-4.55	<.001
Pathologic N stage			
N0/Nx	Reference	Reference	-
N1	1.10	0.63-1.92	.73
Pathologic Gleason score			
6	Reference	Reference	Reference
7	3.74	1.70-8.25	.001
8-10	5.38	2.32-12.51	<.001
Race			
African American	0.89	0.53-1.51	.67
White	Reference	Reference	-
Other	0.73	0.23-2.29	.29
Unknown	0.78	0.38-1.62	.51
Charlson Comorbidity Index			
0	Reference	Reference	-
1	0.94	0.62-1.43	.78
≥2	1.16	0.71-1.89	.55
Insurance status			
Private	Reference	Reference	-
Government	0.96	0.65-1.43	.85
Other	1.11	0.49-2.51	.81
None	0.84	0.13-5.21	.85
Practice setting			
Private	Reference	Reference	-
Academic	0.50	0.23-1.05	.07
Length of follow-up (mo)	1.04	1.02-1.05	<.001
Age	0.97	0.95-1.00	.06

Abbreviations: Nx = regional lymph nodes cannot be assessed. N0 = no evidence of lymph node metastases; PSA = prostate-specific antigen; RP = radical prostatectomy; SRT = salvage radiation therapy.

* Values are also adjusted for practice through random effect.

newly diagnosed PCa across a consortium of urology practices.[10] There is excellent concordance among data in the registry and private insurance claims for radiation therapy administration.[3]

Patient population and characteristics

We identified all patients who underwent RP from 2012 to 2016 with ≥1 post-RP PSA level ≥0.1 ng/mL and ≥6 months of follow-up subsequent to this first detectable PSA level. We excluded patients who underwent ART, defined as radiation administered ≤1 year after RP with all postnadir PSA levels <0.1 ng/mL. SRT was defined as

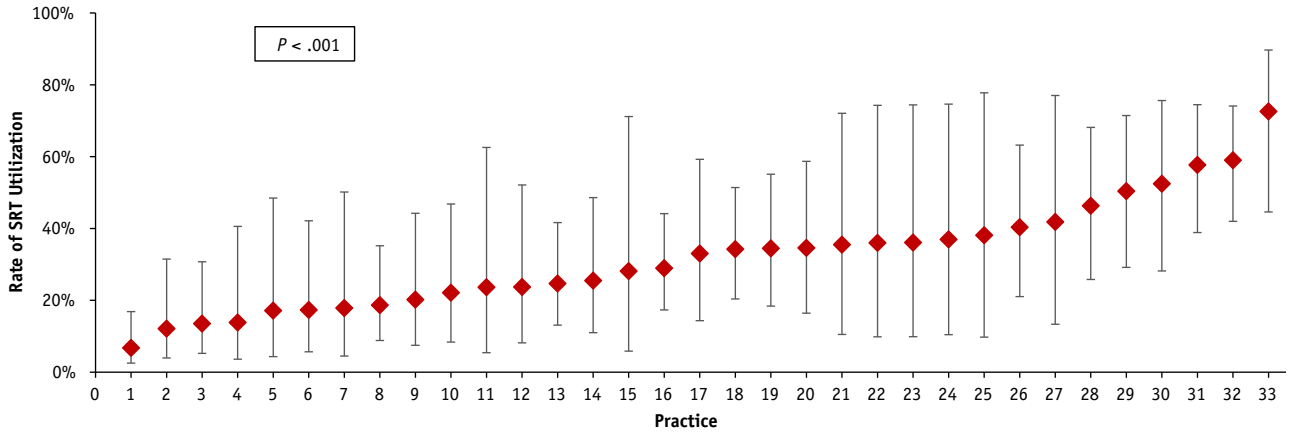

Fig. 2. Adjusted rate of salvage radiation therapy (SRT) utilization in men with biochemical recurrence by the Michigan Urological Surgery Improvement Collaborative practice, adjusted for patient and tumor characteristics.

radiation administered after a post-RP PSA level ≥0.1 ng/mL and/or >1 year after RP (Fig. 1). We examined demographics, surgical pathology findings, and PSA levels. PSA doubling time (PSADT) was calculated as PSADT = log(2)*Time/[log(final PSA) − log(initial PSA)] in patients with ≥3 PSA test results available over ≥6 months.

Statistical analyses

SRT administration was the primary outcome. We compared post-RP maximum PSA, PSADT, demographics, and surgical pathology findings by SRT utilization. Using a mixed effects logistic regression model, we examined the impact of these factors on SRT utilization, adjusting for practice (random effect) and PSA as a continuous variable. PSADT was not assessed in this model owing to a high rate of missingness (42.9%). Using this model, we evaluated variation in adjusted practice-level SRT utilization. We grouped practices into tertiles using the adjusted SRT rate and examined patient characteristics across groups. We repeated the analysis with a Cox proportional hazards model. All statistical analyses were performed using SAS (version 9.4, SAS Institute).

Results

A total of 1010 patients met eligibility criteria, with a median time from RP to PSA recurrence of 3.6 months (interquartile range [IQR], 1.4-12.4 months). Patients were followed for a median of 22.3 months (IQR, 15.4-31.2 months) subsequent to their first PSA level ≥0.1 ng/mL. Two hundred ninety-eight patients (29.5%) underwent SRT. Table 1 shows rates of SRT administration by patient characteristics. Higher post-RP maximum PSA level,

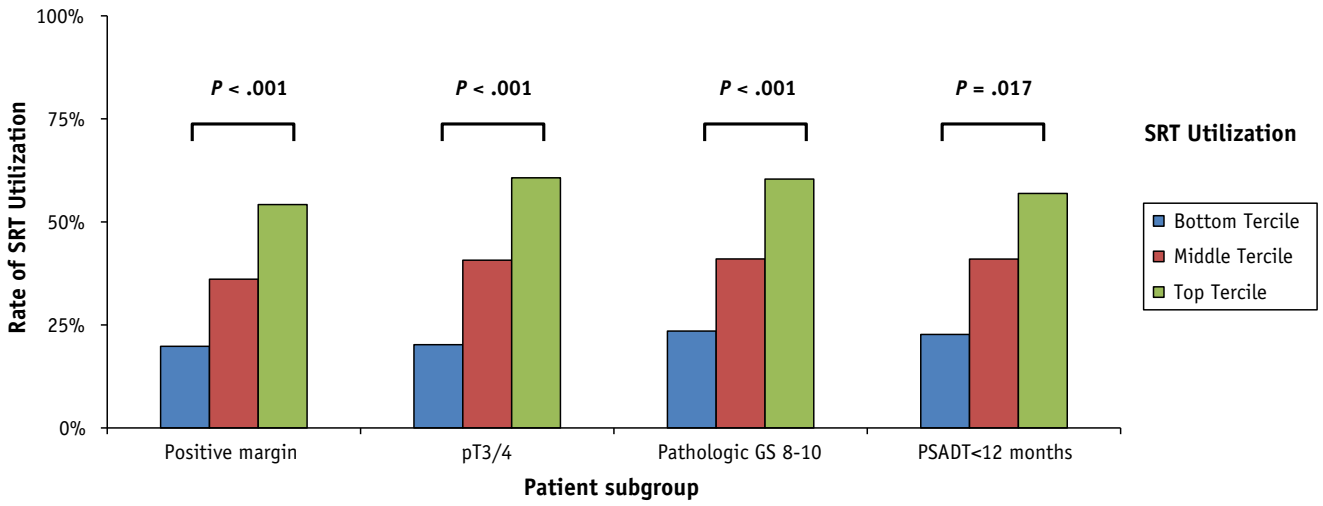

Fig. 3. Rate of salvage radiation therapy (SRT) utilization by patient and tumor characteristics, stratified into tertiles by the practice level–adjusted rate of radiation utilization. Practices using SRT more frequently overall were more likely to administer SRT across all patient-based predictors of SRT utilization. *Abbreviations:* GS = Gleason score; PSADT = prostate-specific antigen doubling time.

shorter PSADT, positive surgical margins, pT3/4 disease, N1 disease, higher Gleason score, and private practices were associated with SRT administration ($P < .001$).

The majority of patients receiving SRT did so at a PSA level <0.5 ng/mL (56.4%); median time to SRT was 3.8 months (IQR, 2.0-6.9 months) after a PSA level ≥0.1 ng/mL. In 309 patients (30.6%) the PSA level reached ≥0.5 ng/mL without prior SRT, with 130 of these patients (42.1%) receiving later SRT. To date, SRT has been administered to 298 of 636 (46.9%) patients who have either reached a PSA level ≥0.2 ng/mL or who were treated before reaching a PSA level of 0.2 ng/mL. Of these, 168 of 636 patients (26.4%) received early SRT at a PSA level <0.5 ng/mL. Table 2 shows the mixed effects logistic regression model examining the impact of patient characteristics on SRT utilization. Positive surgical margins, T3/4 disease, and higher Gleason score remained significant predictors of SRT after adjusting for patient-level factors, length of follow-up, and practice. Private practices were more likely to administer SRT. The same variables were observed to be significant in the Cox model (Table E1; available online at https://doi.org/10.1016/j.ijrobp.2019.01.006).

There was significant variation in the adjusted rate of SRT utilization across practices, ranging from 7% to 73% (Fig. 2, $P < .001$). After grouping practices into tertiles based on adjusted SRT utilization, practices using SRT more frequently overall were more likely to administer SRT across each of the clinically significant patient subgroups (Fig. 3).

Discussion

In this diverse cohort, we found low utilization of SRT in men with a PSA recurrence after RP. This is particularly salient in light of known low utilization of ART and ongoing randomized studies (RADICALS [Radiotherapy and androgen deprivation in combination after local surgery] and GETUG-17 [Groupe des Tumeurs Uro-Genitales]) evaluating the efficacy of early SRT as a substitute for ART. SRT utilization was variable across practices and was more frequent in patients with adverse disease characteristics. Age and comorbidity did not predict SRT use, which is potentially problematic because older men with multiple comorbidities may be less likely to benefit. Of those patients who underwent SRT, approximately half received early SRT (PSA level <0.5 ng/mL). However, of all patients with a PSA recurrence ≥0.2 ng/mL, only 26% received early SRT.

Perhaps most notably, these data indicate marked differences in treatment paradigms across practices. Rates of SRT vary widely among practices, independent of patient characteristics. Furthermore, high-utilization practices were more likely to administer SRT across all pathologic subgroups of patients, suggesting intrinsic practice-level differences surrounding SRT decision- making. These findings can be placed in the context of prior reports demonstrating practice level heterogeneity in radiation administration for PCa, although the underlying drivers of SRT variation cannot be readily determined.[11]

Our study has several limitations. First, although our inclusion criteria required ≥6 months of follow-up after the first PSA value ≥0.1 ng/mL, SRT rates may still increase over time. Second, MUSIC does not track the use of ultrasensitive PSA tests assessing PSA levels <0.1 ng/mL. Third, we were unable to measure certain factors that may affect decisions surrounding SRT administration, such as patient preferences, urinary and sexual function recovery, and financial incentives.

Despite these limitations, our study has implications for patients and providers. A large proportion of men likely to benefit from SRT are not undergoing treatment, suggesting substantial underutilization. The variation across practices suggests that providers have not coalesced around optimal management strategies for men with post-RP biochemical recurrence, despite current published data. This presents an important quality improvement opportunity to identify patients who may benefit from SRT and facilitate guideline concordance through shared decision-making. Given the large number of patients who experience PSA recurrence after RP, coupled with the curative success of SRT, these efforts may markedly affect long-term rates of metastasis and death from PCa.

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