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ORIGINAL ARTICLE

Variation in the use of postoperative radiotherapy among high-risk patients following radical prostatectomy

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BACKGROUND: We used data from the Michigan Urological Surgery Improvement Collaborative (MUSIC) to investigate the use of adjuvant and salvage radiotherapy (ART, SRT) among patients with high-risk pathology following radical prostatectomy (RP).
METHODS: For patients with pT3a disease or higher and/or positive surgical margins, we examined post-RP radiotherapy administration across MUSIC practices. We excluded patients with <6 months follow-up, and those that failed to achieve a postoperative PSA nadir $\leqslant 0.1$. ART was defined as radiation administered within 1 year post RP, with all post-nadir PSA levels <0.1 ng ml^{-1}. Radiation administered >1 year post RP and/or after a post-nadir PSA $\geqslant 0.1$ ng ml^{-1} was defined as SRT. We used claims data to externally validate radiation administration.
RESULTS: Among 2337 patients undergoing RP, 668 (28.6%) were at high risk of recurrence. Of these, 52 (7.8%) received ART and 56 (8.4%) underwent SRT. Patients receiving ART were younger ($P=0.027$), more likely to have a greater surgical Gleason sum ($P=0.009$), higher pathologic stage ($P<0.001$) and received treatment at the smallest and largest size practices ($P=0.011$). Utilization of both ART and SRT varied widely across MUSIC practices ($P<0.001$ and $P=0.046$, respectively), but practice-level rates of ART and SRT administration were positively correlated ($P=0.003$) with lower ART practices also utilizing SRT less frequently. Of the 88 patients not receiving ART and experiencing a PSA recurrence $\geqslant 0.2$ ng ml^{-1}, 38 (43.2%) progressed to a PSA $\geqslant 0.5$ ng ml^{-1} and 20 (22.7%) to a PSA $\geqslant 1.0$ ng ml^{-1} without receiving prior SRT. There was excellent concordance between registry and claims data $\kappa=0.98$ (95% CI: 0.94–1.0).
CONCLUSIONS: Utilization of ART and SRT is infrequent and variable across urology practices in Michigan. Although early SRT is an alternative to ART, it is not consistently utilized in the setting of post-RP biochemical recurrence. Quality improvement initiatives focused on current postoperative radiotherapy administration guidelines may yield significant gains for this high-risk population.

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INTRODUCTION

Although three prospective randomized clinical trials have evaluated the impact of adjuvant radiotherapy (ART) on long-term outcomes following radical prostatectomy (RP), there is no consensus surrounding its use. These phase 3 trials—SWOG 8794, EORTC 22911 and ARO 96-02—have all reported results after more than 10 years of follow-up, and each study demonstrated significantly lower rates of biochemical progression with ART compared with the control arm.[1–3] However, the results were mixed, and in some cases conflicting, regarding more distant end points such as metastasis-free and overall survival. For example, in contrast to EORTC 22911 and ARO 96-02, SWOG 8794 is the only trial to have demonstrated improved overall survival with ART. These studies were somewhat heterogeneous, though, with one-third of patients in the SWOG and EORTC studies having a PSA >0.2 ng ml^{-1} at study entry. In addition, salvage radiotherapy (SRT) was not mandated in the control arm in any of these studies and was often given later than would typically be recommended or not at all.

As a result, there are few guidelines surrounding the administration of postoperative radiation in patients at high-risk of local recurrence after RP. According to European Association of Urology (EAU) guidelines, patients at high risk of local failure (defined by positive surgical margin or seminal vesicle invasion) should be offered either immediate ART or early SRT at a PSA $\leqslant 0.5$ ng ml^{-1}.[4] Combined guidelines from the American Urological Association and American Society for Radiation Oncology state that high-risk patients (defined by the presence of positive surgical margins, extraprostatic extension or seminal vesicle invasion) should be offered ART but make no recommendation that it be given.[5] In the absence of strong recommendations in favor of ART, and given concerns surrounding overtreatment, urologists have tended not to recommend ART, with a recent study of the National Cancer Database reporting a rate of 9.9% in a high-risk cohort.[6] However, beyond similar population-based and single-institution studies, there is little data regarding how post-RP radiotherapy is utilized in high-risk patients.

In this study, we aimed to understand the real-world administration of ART and SRT in men at high risk of local recurrence following RP. Given the lack of consensus surrounding postoperative radiation in these patients, we hypothesized that rates of ART and SRT would be highly variable across practices. Using data from the Michigan Urological Surgery Improvement Collaborative (MUSIC), encompassing nearly 85% of urologists in

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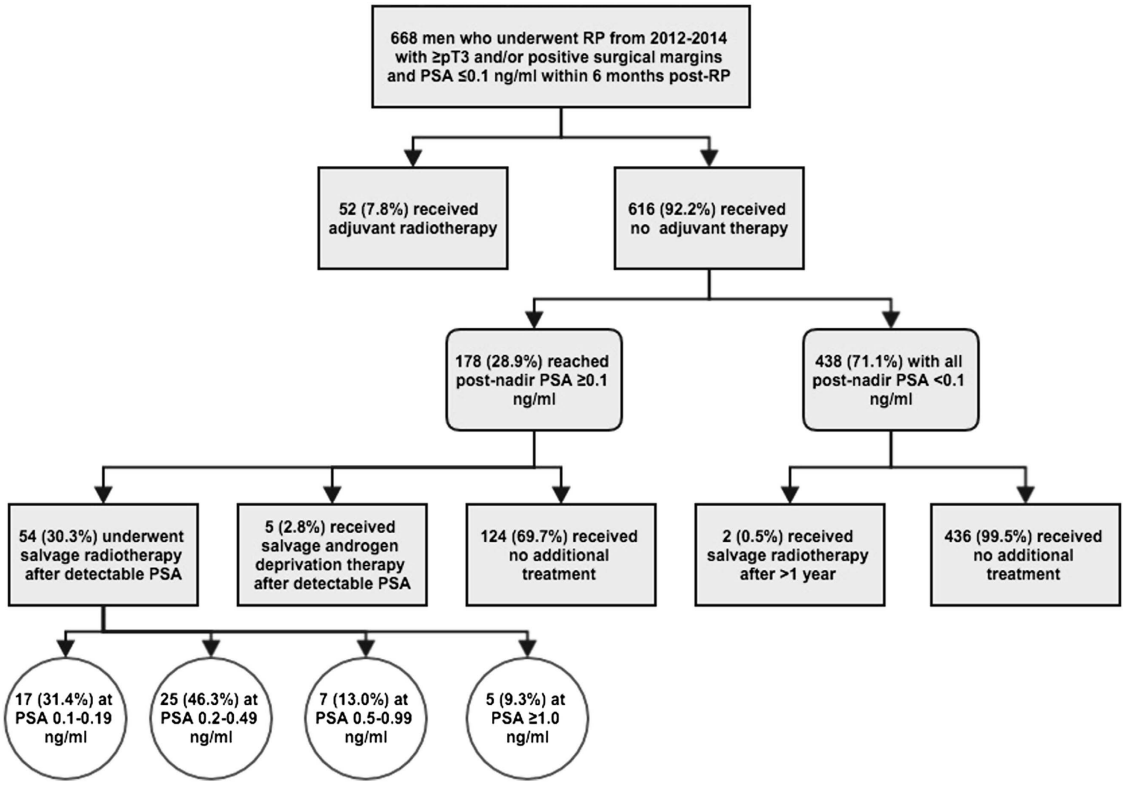

Figure 1. Treatment decisions for patients at high risk of recurrence following radical prostatectomy (RP). Flow chart of the post-prostatectomy treatment decisions for patients with pT3a disease or higher and/or positive surgical margins.

the state of Michigan, we sought to quantify the variation in management according to patient and tumor characteristics and across MUSIC practices.

MATERIALS AND METHODS

Michigan urological surgery improvement collaborative

MUSIC is a quality improvement collaborative funded by Blue Cross Blue Shield of Michigan (BCBSM). Established in 2011, this initiative tracks all newly diagnosed prostate cancer patients seen at participating practices.[7] There are 42 participating practices, representing a diverse set of academic and community practice settings. Each MUSIC practice obtained an exemption or approval for participation from a local institutional review board.

Study population and identification of postoperative radiotherapy

Patients with pT3 or greater disease and/or positive surgical margins after undergoing RP at a participating practice from March 2012 through March 2014 were identified. Patients that had <6 months of follow-up after RP or did not reach a nadir PSA $\leqslant 0.1$ ng ml^{-1} within 6 months post RP were excluded. Those with node-positive disease were included, as long as they met these criteria. Patients were followed over time, and the administration of postoperative radiotherapy was abstracted from patient records. ART was defined as radiation administered $\leqslant 1$ year post RP, with all post-nadir PSA levels <0.1 ng ml^{-1}. SRT was defined as radiation administered >1 year post RP and/or after a post-nadir PSA $\geqslant 0.1$ ng ml^{-1}. MUSIC does not provide recommendations to providers regarding postoperative radiotherapy administration. Trained abstractors at each site enter data into a web-based registry. Abstractors are prompted to review the medical record for postoperative PSA values at 10 weeks post RP and every 6 months from the most recent PSA value abstracted.

Data validation

As described elsewhere, MUSIC has protocols to ensure data accuracy.[8–10] This includes standard operating procedures and variable definitions, such as the distinction between ART and SRT. In addition, there are regular abstractor training sessions and site visits with data audits. To ensure accurate classification of ART and SRT, we reviewed the timing of each patient's post-RP radiation therapy administration and his corresponding PSA level. In the rare instances with apparent inconsistencies, we reviewed medical records and reclassified patients when indicated. We also externally validated the postoperative radiation treatment data by comparing BCBSM claims with MUSIC registry data. As ART and SRT cannot be reliably distinguished using insurance claims, we grouped these together and assessed the receipt of any postoperative radiotherapy for prostate cancer.

Among men in the study cohort with BCBSM insurance, we obtained all claims data ($n=144$). On the basis of our prior work,[8,11] we used Current Procedural Terminology and International Classification of Diseases, ninth revision, codes (ICD9-CM) to define a claims-based algorithm for the receipt of postoperative radiation therapy for prostate cancer (Supplementary Table 1). We then determined the Cohen κ statistic to examine the level of agreement between documentation of post-RP radiotherapy in the MUSIC registry and the presence of post-RP radiotherapy claims.

Statistical analyses

The primary outcome was ART administration, and the secondary outcome was the SRT administration. First, we used chi-square and Fisher's exact tests to compare patient demographic, clinical and pathologic characteristics, as well as practice size based on the receipt of ART. We then fit multivariable logistic regression models to estimate practice-level rates of ART, adjusting for patient age, pathologic stage, Gleason grade and preoperative PSA. For the purpose of model convergence, practices with no ART administered were excluded. Next, we determined the overall use of SRT among patients with a post-nadir PSA $\geqslant 0.1$ ng ml^{-1} and no prior ART. For practices with at least four patients meeting these criteria, we determined the SRT rate, adjusting for the same variables as the ART model. Throughout the manuscript, all reported practice-level rates of ART and SRT administration are adjusted values, whereas reported rates of ART and SRT for the entire cohort are only adjusted when specified. The maximum PSA level before SRT administration was determined for all SRT

Table 1. Distribution by clinicopathologic characteristics in each risk group

Characteristic	*All patients*		*No adjuvant XRT*		*Adjuvant XRT*		P[a]
	N	%	N	%	N	%	
All	668		616	92.9	52	7.1	
Age at diagnosis							
<55	104	15.6	91	14.8	13	25.0	
55–64	291	43.6	265	43.0	26	50.0	
$\geqslant 65$	273	40.9	260	42.2	13	25.0	0.027
Race							
White	507	75.9	469	76.1	38	73.1	
African American	63	9.4	58	9.4	5	9.6	
Other	18	2.7	18	2.9	0	0.0	0.64[b]
Charlson comorbidity index							
0	446	66.8	408	66.2	38	73.1	
1	140	21.0	130	21.1	10	19.2	
$\geqslant 2$	81	12.1	77	12.5	4	7.7	0.52
PSA at diagnosis							
0–4 ng ml^{-1}	101	15.1	94	15.3	7	13.5	
4.1–10 ng ml^{-1}	415	62.1	387	62.8	28	53.8	
10.1–20 ng ml^{-1}	94	14.1	83	13.5	11	21.2	
>20 ng ml^{-1}	35	5.2	29	4.7	6	11.5	0.08
Surgical Gleason sum							
2–6	47	7.0	47	7.6	0	0	
7	494	74.0	458	74.4	36	69.2	
8–10	118	17.7	102	16.6	16	30.8	0.009
Pathologic stage							
T2	227	34.0	223	36.2	4	7.7	
T3a	322	48.2	298	48.4	24	46.2	
$\geqslant$T3b	118	17.7	94	15.3	24	46.2	<0.001[b]
Surgical margins							
Negative	253	37.9	233	37.8	20	38.5	
Positive	415	62.1	383	62.2	32	61.5	0.93
Extraprostatic extension							
No	255	38.2	248	40.3	7	13.5	
Yes	412	61.7	367	59.6	45	86.5	<0.001
Seminal vesicle invasion							
No	544	81.4	517	83.9	27	51.9	
Yes	119	17.8	95	15.4	24	46.2	<0.001
Lymph node invasion							
N0/Nx	621	93.0	576	93.5	45	86.5	
N1	40	6.0	34	5.5	6	11.5	0.11
Practice size							
$\leqslant 4$ urologists	126	18.9	111	18.0	15	28.8	
5–10 urologists	235	35.2	226	36.7	9	17.3	
>10 urologists	307	46.0	279	45.3	28	53.8	0.011

Abbreviation: XRT, radiation therapy. [a]All *P*-values from chi-squared except where indicated. [b]Fisher's exact test.

patients. All statistical testing was performed using SAS v.9.3 (SAS Institute, Cary, NC, USA) at the 5% significance level.

RESULTS

Patient characteristics and association with ART

Among 2337 consecutive patients undergoing RP during the study period, 668 (28.6%) met the inclusion criteria. These patients were managed at 23 urology practices, and Figure 1 displays the flow of post-RP treatment decisions. The median patient age was 64 years (interquartile range = 58–68 years) and the median pre-treatment PSA was 6.12 ng ml^{-1} (interquartile range = 4.50–8.94 ng ml^{-1}). Among the entire cohort, 227 (34.0%) were stage pT2, 322 (48.2%) were pT3a, 118 (17.7%) were $\geqslant$pT3b and 412 (62.1%) had positive surgical margins (Table 1). Patients were followed for a median of 15 months post RP (interquartile range = 11–21 months), and 178 (28.9%) reached a post-nadir PSA $\geqslant 0.1$ ng ml^{-1} (Figure 1). A total of 52 patients (7.8%) received ART, 56 (8.4%) underwent SRT and 5 (0.8%) underwent salvage androgen deprivation, whereas 555 patients (83.1%) have received no additional therapy to date. Only 2/438 patients (0.5%) with all post-nadir PSA levels <0.1 ng ml^{-1} received radiotherapy after >1 year of follow-up. The clinicopathologic characteristics of the entire cohort, stratified by ART administration, are presented in Table 1. Patients that received ART tended to be younger ($P=0.027$) and were found to have more aggressive pathological tumor features, including higher stage ($P<0.001$) and Gleason grade ($P=0.009$). ART use also varied by practice size ($P=0.01$), with the smallest and largest size practices utilizing ART more frequently. Pre-treatment PSA and nodal status were not significantly associated with ART, although there did appear to be trends towards greater ART utilization in patients with higher pre-treatment PSA levels and patients with node-positive disease.

Although there was no association between surgical margin status and ART use across the cohort as a whole, we evaluated three distinct combinations of pathological stage and margin status to determine the incremental effect of each local recurrence risk factor on ART administration. Only 4/227 patients (1.8%) with pT2 margin-positive disease received ART, whereas 20/253 (7.9%) with pT3 margin-negative and 28/188 (14.9%) with pT3 margin-positive tumors received ART ($P<0.001$, Supplementary Table 2).

Data validation

For the 144 men in the study cohort with BCBSM insurance, there was excellent concordance $\kappa=0.98$ (95% CI: 0.94–1.0) between the registry and claims data (Supplementary Table 3).

Variation in use of ART and SRT

ART use varied widely by MUSIC practice, with adjusted site-specific rates ranging from 0 to 67% ($P<0.001$, Figure 2). The adjusted mean probability of ART across the entire cohort was 8.2% (95% CI: 7.2–9.1%). Among patients not receiving ART, a total of 178 reached a post-nadir PSA $\geqslant 0.1$ ng ml^{-1} with 54 (30.3%) undergoing subsequent SRT and 4 (2.2%) receiving salvage androgen deprivation. Again, rates of SRT administration varied significantly by practice, with adjusted rates ranging from 0% to 67% at the 14 evaluable practices ($P=0.046$, Figure 3). The adjusted mean probability of SRT among these patients was 31.4% (95% CI: 28.1–34.7%). Furthermore, as shown in Figure 4, adjusted practice-level rates of ART and SRT administration were highly correlated, with practices that more frequently administered ART also more commonly administering SRT to patients with a detectable PSA $\geqslant 0.1$ ng ml^{-1} (Pearson's $r=0.73$, $P=0.003$).

Timing of SRT administration

Among patients who developed a detectable post-nadir PSA, salvage therapies were initiated at variable PSA levels (Figure 5). SRT was administered to 17/90 patients (18.9%) with a PSA between 0.1 and 0.19 ng ml^{-1}, 25/50 (50.0%) between 0.2 and 0.49 ng ml^{-1}, 7/18 (38.9%) between 0.5 and 0.99 ng ml^{-1} and 5/20 (25.0%) with a PSA $\geqslant 1.0$ ng ml^{-1}. Of the 88 patients with a PSA recurrence $\geqslant 0.2$ ng ml^{-1}, 38 (43.2%) progressed to a PSA $\geqslant 0.5$ ng ml^{-1} and 20 (22.7%) to a PSA $\geqslant 1.0$ ng ml^{-1} without receiving prior SRT.

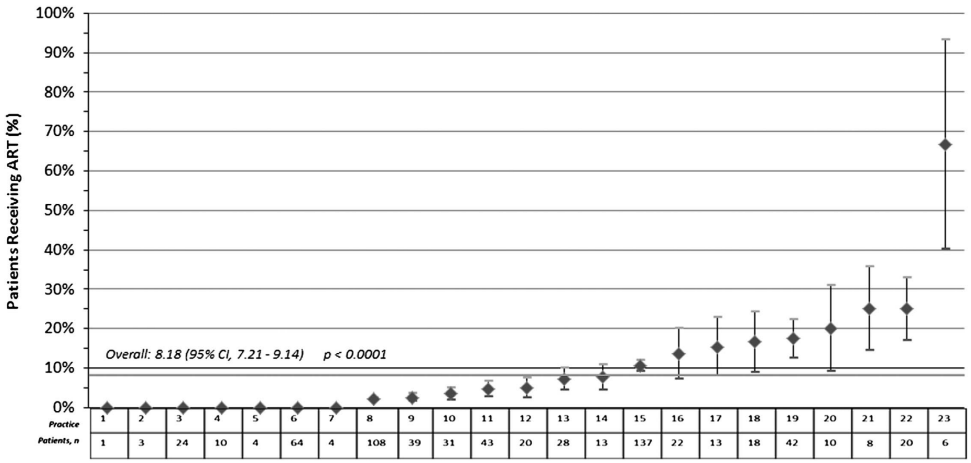

Figure 2. Adjusted likelihood of adjuvant radiation therapy administration for men with pT3 or greater disease and/or positive surgical margins, stratified by MUSIC practice. Rates were adjusted for patient age, pathologic stage, Gleason grade and preoperative PSA. The overall adjusted probability was 8.2% (95% CI: 7.2–9.1), and there was significant variation across practice sites ($P < 0.001$). ART, adjuvant radiotherapy; CI, confidence interval; MUSIC, Michigan Urological Surgery Improvement Collaborative.

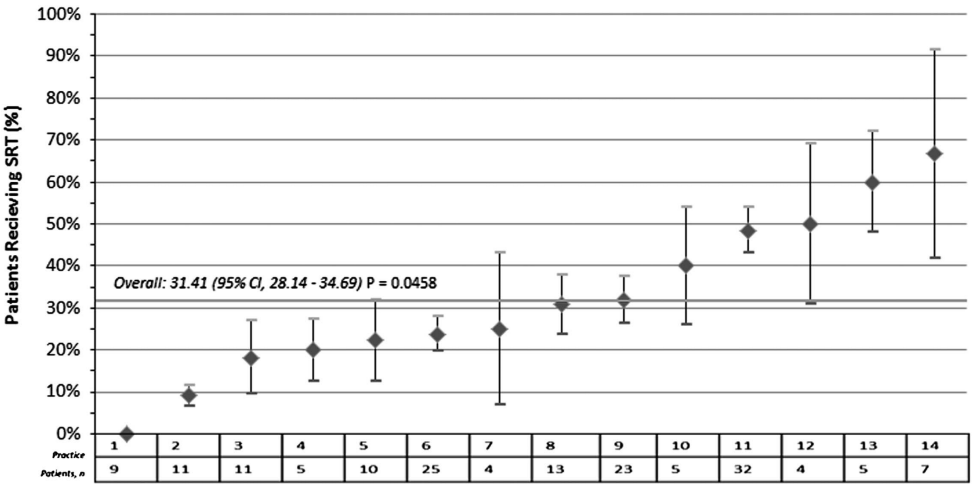

Figure 3. Adjusted likelihood of salvage radiation therapy administration for men not receiving ART and with a rising PSA $\geqslant 0.1$ ng ml^{-1}, stratified by MUSIC practice. Rates were adjusted for patient age, pathologic stage, Gleason grade and preoperative PSA. Only practices with at least four eligible patients were included. The overall rate was 31.4% (95% CI: 28.1–34.7) and there was significant variation across practice sites ($P = 0.046$). ART, adjuvant radiotherapy; CI, confidence interval; MUSIC, Michigan Urological Surgery Improvement Collaborative.

DISCUSSION

Using the data from diverse urology practices, we investigated the use of ART and SRT for patients at high risk of local recurrence post RP. Younger patients and those with higher tumor stage and grade were more likely to receive ART, and margin status also appeared to be a driver of ART decisions in patients with pT3 disease. Across the entire high-risk cohort, the adjusted probability of ART administration was relatively low (8.18%) and highly variable across practices. Furthermore, SRT administration among patients with a post-prostatectomy PSA $\geqslant 0.1$ ng ml^{-1} also varied significantly across practices and was closely related to a given practice's tendency to utilize any form of postoperative radiation. Notably, many patients reached PSA levels $\geqslant 1.0$ ng ml^{-1} without undergoing salvage treatment.

In the context of earlier studies reporting low rates of postoperative radiotherapy administration for patients with adverse pathologic features, ART rates in Michigan are not surprising.[6,12–14] However, a key limitation of these population-based investigations is the inability to clearly differentiate ART from SRT due to a lack of post-prostatectomy PSA data and granular follow-up information. In contrast, our study provides unique insight into the patient characteristics and practice patterns that appear to drive ART and SRT use in high-risk patients.

The wide variation in ART and SRT utilization across the diverse MUSIC practices highlights the lack of consensus on this issue.[14–16] Given the mixed and often conflicting data from prior phase 3 trials of ART,[1–3,17–19] physicians appear to have developed highly divergent practice patterns surrounding its administration. Specifically, these data imply that a patient's likelihood of receiving postoperative radiotherapy is highly dependent on the practice where they receive care and that urologists have not coalesced around a given treatment approach. The positive correlation between ART and SRT use by practice suggests that practices tending not to administer ART also infrequently utilize SRT. Further work is needed to better understand the factors driving this variation in care. In addition, two ongoing phase 3 trials (RADICALS and RAVES) comparing ART with early SRT may help

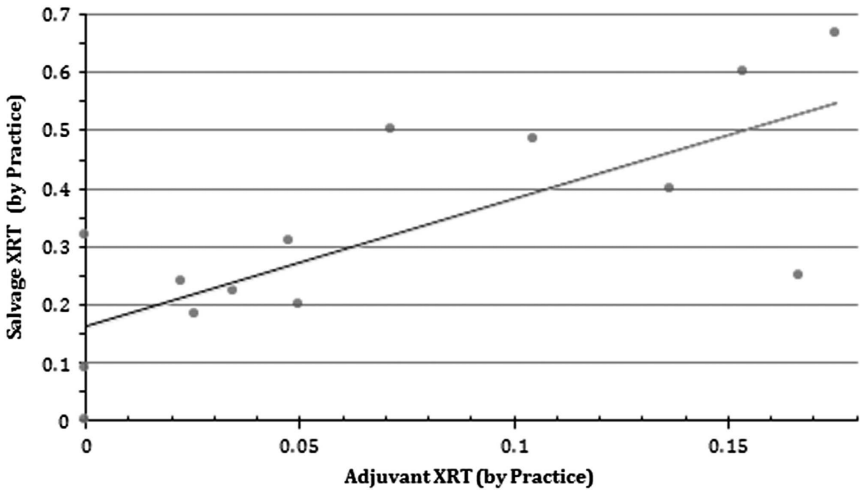

Figure 4. Practice-level rates of salvage versus adjuvant radiation therapy (XRT) administration. There was a significant, positive correlation between rates of ART and SRT administration across practices ($r = 0.73$, $P = 0.003$). ART, adjuvant radiotherapy; SRT, salvage radiotherapy.

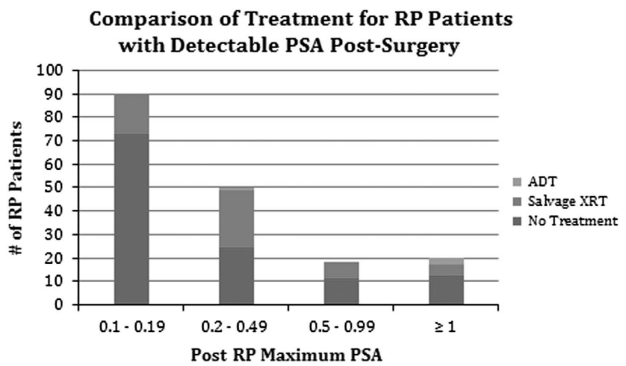

Figure 5. Timing of salvage therapy following radical prostatectomy (RP). Timing of salvage treatments according to maximum post-RP PSA for the 178 patients with a PSA $\geqslant 0.1$ ng ml^{-1} after reaching a nadir PSA $\leqslant 0.1$ ng ml^{-1} within 6 months after surgery. ADT, androgen deprivation therapy; XRT, radiation therapy.

guide decisions and bring more uniformity to the postoperative care of this population.[20,21]

Finally, although there is ongoing debate regarding the relative effectiveness of ART versus early SRT, current guidelines are clear that postoperative radiation should be delivered before a PSA of 0.5 ng ml^{-1}.[4,5,22–24] We found that 25/88 patients (28.4%) that reached a PSA of $\geqslant 0.2$ ng ml^{-1} received SRT before progressing to a PSA of $\geqslant 0.5$ ng ml^{-1}, and an additional 17 patients underwent even earlier SRT. However, 38 patients (43.2%) have progressed to a PSA $\geqslant 0.5$ ng ml^{-1} and 20 (22.7%) to a PSA $\geqslant 1.0$ ng ml^{-1} without receiving prior SRT. These data suggest an opportunity for quality improvement through earlier utilization of SRT.

Our analysis has several limitations. First, with a 15-month median follow-up, it is possible that SRT rates may increase over time. However, even within this follow-up period, many patients with a rising PSA post RP reached PSA levels >0.5 ng ml^{-1} without receiving SRT, indicating that early SRT is utilized variably. Second, a small number of patients underwent RP at participating MUSIC practices but were followed after surgery at a non-participating practice, and were excluded. This was necessary to ensure accurate ascertainment of post-RP radiotherapy administration; however, it is unlikely that these patients differed in any systematic way from patients that were followed at one of MUSIC's diverse practices. Third, there are some unmeasured factors, most notably patient preferences factoring in functional status and quality of life, and these undoubtedly affect doctor–patient shared decision-making regarding post-RP radiotherapy. Fourth, MUSIC encompasses a specific geographical region, and it is possible that practice patterns could differ elsewhere. However, given the diversity of practices within Michigan and the inclusion of the majority of practices in the state, these findings are likely to be more widely applicable. Last, our validation of radiotherapy administration was limited to patients with BCBSM health insurance, the major payer for non-Medicare beneficiaries in Michigan. Nevertheless, the data from the MUSIC registry demonstrated excellent concordance with claims.

These limitations notwithstanding, our findings have implications for patients and providers. For patients, the fact that some men received late SRT, and others no salvage therapy at all, suggests opportunities to expand ART and early SRT use for patients with high-risk cancer. For providers, the wide variation across practices demonstrates that there are significant differences in perceptions regarding the relative risks and benefits of post-prostatectomy radiotherapy. A lack of strong evidence for improved prostate cancer-specific survival with ART versus early SRT likely contributes to this finding.[25] Moreover, there may be other factors, such as efforts to minimize morbidity, which differentially influence treatment decisions across the state.

Moving forward, there is a need to better understand why some patients receive ART or early SRT and why others receive neither in the setting of biochemical recurrence.[26] Currently, SRT represents the only potentially curative treatment for patients with a post-RP PSA recurrence, and a number of studies have demonstrated that the effectiveness of SRT is inversely correlated with the PSA level at radiotherapy initiation. Thus, the substantial percentage of patients with early PSA recurrences not receiving SRT suggests an opportunity for quality improvement and increased cure rates. Relevant factors impacting radiotherapy use may include providers' interpretation of the evidence, interpretation of the data surrounding the impact of radiation on functional outcomes and thresholds for treatment, as well as the influence of patient preferences. A better understanding of these factors and the opportunity to engage and learn from practices throughout the statewide collaborative may allow MUSIC to implement targeted efforts to improve the care of men who experience a PSA rise following RP.

Taken as a whole, these data may have implications for developing consensus criteria for identifying patients that would most benefit from ART or early SRT. Given the current level of

evidence favoring ART and early SRT use in the appropriate setting, these quality improvement efforts are likely to yield significant gains for this high-risk population. In addition, recently published data suggest a potential role for genomic classifiers in guiding these treatment decisions.[27,28] With improved risk stratification, either through molecular markers or via comparable strategies, it may be possible to diminish the variation in care and improve cancer outcomes without a significant adverse impact on long-term sexual and urinary function.

CONFLICT OF INTEREST

TMM is a consultant/advisor for and receives research funding from Myriad Genetics. KRG is a consultant/advisor for Lumenis and Boston Scientific, and receives salary support from Blue Cross Blue Shield of Michigan as the co-director of the Michigan Urological Surgery Improvement Collaborative. DCM 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. FYF has a leadership role at PFS Genomics, is a consultant/advisor for Medivation/Astellas, GenomeDx Biosciences and Celgene, and has research funding from Varian, Celgene and Medivation/Astellas. JEM is a consultant/advisor for and has ownership in Histosonics. MLC was part of Astellas-Medivation speaker's bureau. The remaining authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Prostate Cancer and Prostatic Diseases website (http://www.nature.com/pcan)