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Clinical-Prostate cancer

Variation in management of lymph node positive prostate cancer after radical prostatectomy within a statewide quality improvement consortium

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Abstract

Background: Patients with lymph node positive (pN+) disease found at the time of radical prostatectomy with pelvic lymphadenectomy for clinically localized prostate cancer (CaP) are at high risk of disease persistence and progression. Contemporary management trends of pN+ CaP are not well described.

Materials and methods: Patients in the Michigan Urologic Surgery Improvement Collaborative (MUSIC) with clinically localized prostate cancer who underwent radical prostatectomy between 2012 and 2023 with cN0/pN+ disease were identified. The primary outcome was to evaluate patient and practice-level factors associated with time to secondary post-RP treatment. Secondary outcomes included practice-level variation in management of pN+ CaP and rates of secondary treatment modality. To assess factors associated with secondary treatment, a Cox proportional hazards model of a 60-day landmark analysis was performed.

Results: We identified 666 patients with pN+ disease. Overall, 66% underwent secondary treatment within 12 months post-RP. About 19% of patients with detectable post-RP PSA did not receive treatment. Of patients receiving secondary treatment after 60-days post-RP, 34% received androgen deprivation therapy (ADT) alone, 27% received radiation (RT) alone, 36% received combination, and 4% received other systemic therapies. In the multivariable model, pathologic grade group (GG)3 (HR 1.5; 95%CI: 1.05−2.14), GG4-5 (HR 1.65; 95%CI: 1.16−2.34), positive margins (HR 1.46; 95%CI: 1.13−1.88), and detectable postoperative PSA ≥0.1 ng/ml (HR 3.46; 95%CI: 2.61−4.59) were significantly associated with secondary post-RP treatment. There was wide variation in adjusted practice-level 12-month secondary treatment utilization (28%−79%).

Conclusions: The majority pN+ patients receive treatment within 12 months post-RP which was associated with high-risk pathological features and post-RP PSA. Variation in management of pN+ disease highlights the uncertainty regarding the optimal management. Understanding which patients will benefit from secondary treatment, and which type, will be critical to minimize variation in care.

Keywords: Prostate cancer; Lymph node metastases; Adjuvant therapy; Pelvic lymph node dissection

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1. Introduction

There is a paucity of level 1 evidence to guide management of lymph node positive (pN+) prostate cancer (CaP) found at the time of radical prostatectomy (RP). One randomized clinical trial (ECOG 3886) has shown improved overall survival in pN+ men who receive immediate and lifelong androgen deprivation therapy (ADT) [1,2], and the addition of early radiation therapy (RT) to ADT has also been associated with improved survival in multiple retrospective studies [3]. Appropriate patient selection for early secondary treatment remains controversial, and societal guidelines have indicated that both initial observation and adjuvant treatment are appropriate options in the setting of an undetectable PSA [4,5]. Concerningly, the presence of a persistently detectable PSA after RP is particularly strongly associated with local recurrence and distant metastases [6].

The presence of lymph node metastases at the time of RP confers a high-risk of disease progression and death in men presumed to have clinically localized CaP [7]. However, pN+ CaP represents a spectrum of disease, and long-term oncologic outcomes of men with pN+ disease are heterogeneous [8]. The 15-year prostate cancer specific mortality for men with lymph node metastases is 22%–30% [7]. Although pN+ CaP is associated with worse overall and metastasis-free survival, as many as 30% of pN+ patients will have no evidence of biochemical recurrence 10 years post-RP [9]. As a result, initial observation is a tempting strategy for select men with pN+ disease wishing to avoid the morbidity of post-RP radiation or lifelong ADT.

In this study, we aimed to assess contemporary management patterns of pN+ CaP identified at RP in a diverse statewide consortium [10]. We hypothesized that disease factors would be associated with treatment selection, but that practices would display significant variability in management given the lack of high-level evidence to guide decision-making.

2. Materials and Methods

2.1. MUSIC

MUSIC is a quality improvement consortium which includes greater than 90% of all urologic practices in the state of Michigan and comprises academic, private, and community practices. MUSIC Prostate is a prospectively collected and maintained prostate cancer data set. Abstractors at each MUSIC site review the primary medical record to collect and enter demographic and clinicopathologic patient parameters pertaining to treatment and follow-up at fixed intervals. Each MUSIC practice has obtained an exemption or approval by the local institutional review board for participation in the collaborative.

2.2. Study population

For this study, all men with CaP between March 2012 and May 2023 who had RP with pelvic lymph node dissection were considered ($n = 16{,}672$). Patients who underwent any pre-operative systemic or localized therapy (such as previous radiation or ablative therapy) were excluded ($n = 480$). Given that individuals undergoing surgery in the setting of known regional (cN+) or metastatic disease (cM+) are a unique subset of patients, we focused only on patients with clinically localized disease (cN0). Therefore, men with pre-operative imaging demonstrating distant metastases ($n = 232$) or positive lymph nodes ($n = 126$) were excluded. Those men coded as having metastatic disease on final pathology were excluded ($n = 47$). Men without post-RP follow up in the registry, such as post-operative PSAs or treatments, were also excluded ($n = 15$). The analytic cohort consisted of 666 men with pN+ disease at the time of RP (Supplemental Figure 1).

2.3. Outcomes

The primary outcome was to assess patient and practice-level factors associated with time to receipt of secondary post-RP therapy. A secondary treatment was defined as receipt of any adjuvant or salvage therapy after RP including monotherapy ADT or RT, combination ADT + RT, or other systemic therapy, regardless of the PSA value at which therapy was started. Combination therapy was considered if a second treatment was initiated within 90 days of the first post-RP treatment. For example, men who received RT within ninety days of ADT were classified as combination therapy. Secondary outcomes of interest included assessment of practice-level variation in management of pN+ CaP and specific type of secondary treatment modality. We also evaluated the association of initial post-RP PSA at 30–60 days post-RP (≥0.1 ng/ml, <0.1 ng/ml, or no PSA) with receipt of secondary treatment. Additionally, we examined later secondary treatment rate of men who did not receive treatment at 12 months post-RP.

2.4. Statistical analysis

Demographic, clinical, and pathologic patient factors were reported as counts and proportions or medians with interquartile range. The Kaplan-Meier estimate of time-to-secondary treatment was used to estimate treatment probability within 12-months of RP. To evaluate for patient, disease, and practice-level factors associated with time to secondary treatment, we used a time-to-event analysis with a landmark at 60-days post-RP to account for immortal person-time bias. A 60 day post-RP landmark was chosen to ensure all independent variables are collected prior to starting time-to-secondary treatment, including first post-RP PSA, which is typically collected 30- to 60-days after surgery. First post-RP PSA was a PSA value collected between 30- and 60-days post-RP unless a patient did not have a PSA drawn in that window; a PSA measured prior to 30-days was used if available, otherwise the post-RP PSA was set to missing. Patients were excluded from the landmark if

they had received treatment within 60-days of RP or had a follow up time less than 60-days. Sensitivity analysis with a landmark of 90-days post-RP was performed; there was a high percentage of secondary treatment causing significant drop out so 60-days was used. To assess for outcomes of those who did not receive treatment for at least 12-months, a second landmark analysis was conducted of men with no treatment at 12-months post-RP. PSA for this analysis was the last PSA drawn prior to 12-months post-RP. Probability of secondary treatment was calculated using the Kaplan-Meier method from the 60-day and 12-months landmark times separately. PSA group differences were tested using log-rank tests.

A mixed-effects multivariable Cox proportional hazards model was used to identify patient and practice specific factors associated with time to receipt of post-RP treatment with a 60 day landmark. The model included a random effect to account for surgeon clustering. Variables of interest included final pathologic grade group (GG: 2, 3, 4-5), pathological T-stage (pT2, pT3-4), surgical margins (positive or negative), race (White, African American, Other, Unknown), type of practice (academic, community/private, hybrid), age (continuous), and post-operative PSA (≥0.1 ng/ml, <0.1 ng/ml, or no PSA). Hybrid urology practice was defined as a private practice that works with urology residents. We calculated adjusted secondary treatment probability at 12-months post-RP in practices seeing greater than 5 pN+ patients using the 60-day landmark Cox model with practice as a fixed effect. Statistical significance was set at a P of 0.05 and statistical analysis was performed with SAS 9.4 (SAS Institute, Cary, NC).

3. Results

We identified 666 patients in MUSIC who had pN+ disease at the time of RP and met inclusion criteria from March 2012 through May 2023 (Supplemental Figure 1). The clinical characteristics of all men with pN+ disease are summarized in Table 1. Highlighting the high risk nature of this cohort, 294 men (44%) had GG4 or higher disease at RP, 597 (90%) had pT3-4 disease, and 402 (60%) had a positive surgical margin. The median initial post-RP PSA was 0.1 ng/ml (IQR: 0.09−0.69 ng/ml).

In the entire cohort, 66% of pN+ men underwent secondary treatment within 12-months of RP (Fig. 1). Median time to secondary treatment was 5.3-months post-RP (95%CI: 4.5−5.9 months). Among men who underwent secondary treatment within 60-days of RP, 94 (83%) received ADT monotherapy, 13 (12%) received combination ADT+RT, and 3 (2.7%) received RT monotherapy (Fig. 2). Among men who underwent secondary treatment between 60-days and 12-months post-RP, 97 (34%) received ADT monotherapy, 103 (36%) received combination ADT+RT, 77 (27%) received RT monotherapy, and 12 (4.2%) patients received other systemic therapy (Fig. 2). Among those who received secondary therapy after 12-months, 16 (40%) underwent ADT monotherapy, 12 (30%) combination ADT+RT, 11 (28%) received RT monotherapy, and 1 (2.5%) received other systemic therapy.

Table 1
Clinicopathologic Patient Characteristics of pN+ Patients.

Characteristic	N (%)
Age: Median (IQR)	65 (59−70)
Pre-Op PSA: Median (IQR)	9.2 (6.2−16.2)
Gleason Grade Group (GG)	
GG2	130 (20%)
GG3	236 (35%)
GG4	56 (8.4%)
GG5	238 (36%)
Missing	6 (0.9%)
pT3-4	597 (90%)
Positive margin	402 (60%)
Race	
White	461 (69%)
African American	116 (17%)
Other	27 (4.1%)
Unknown	62 (9.3%)
Practice type	
Academic	134 (20%)
Private/Community based	73 (11%)
Hybrid	459 (69%)
Post-RP PSA (30-60 d): Median (IQR)	0.1 ng/ml (0.09−0.69)

We next evaluated patient and practice level factors associated with time to secondary treatment. Clinical and pathological characteristics of men included and excluded in the 60 day landmark analysis are compared in Supplementary Table 1. There were 145 men excluded at the 60 day landmark; of whom 32 had not had follow up and 113 had received secondary treatment prior to 60 days post-RP. Of the 521 pN+ included in the 60-day landmark, 289 received secondary therapy by 12-months post-RP. Pathologic GG3 (HR 1.5; 95%CI: 1.05−2.14) and GG4-5 (HR 1.65; 95%CI: 1.16−2.34) were associated with secondary treatment compared with GG2 (Wald chi-square $P = 0.017$). Additionally, positive surgical margin (vs negative) (HR 1.46; 95%CI: 1.13−1.88, $P = 0.004$) was associated with secondary treatment post-RP (Table 2). First post-RP PSA ≥0.1 ng/ml (HR 3.46; 95%CI: 2.61−4.59) was strongly associated with secondary treatment compared to PSA <0.1 ng/ml. A proportion of men had no available PSA data prior to 60-days after RP which was also associated with secondary treatment (HR 2.09; 95%CI: 1.40−3.11). Urology practice type was associated with time to secondary treatment (Wald chi-square $P = 0.010$), as academic (HR 1.8; 95%CI: 1.00−3.24) and hybrid (HR 1.96; 95%CI: 1.20−3.20) practices were associated with higher secondary treatment rate relative to private practices.

In men with a detectable post-RP PSA ≥0.1 ng/ml, 81% (95%CI: 76%−86%) underwent secondary treatment by 12-months compared to 34% (95%CI: 28%−41%) of men with PSA <0.1 ng/ml ($P < 0.001$, Fig. 3). There were 79 patients who did not have a post-RP PSA within 60-days of

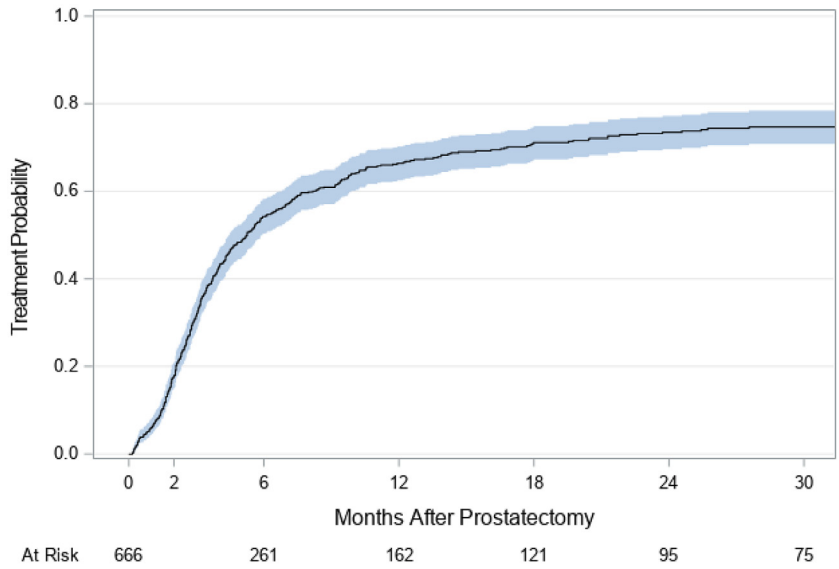

Figure 1. Probability of Post-RP Secondary Treatment of pN+ Patients (With 95% Confidence Limits).

RP, and the cumulative incidence of secondary treatment by 12-months was 64% (95%CI: 52%–76%).

There were 17 practice sites that managed greater than 5 patients with pN+ CaP. There was wide variation in rate of secondary treatment at 12 months across practices in MUSIC. The adjusted proportion of patients undergoing a secondary treatment within 12 months of RP ranged from 28% to 79% in practices treating greater than 5 patients with pN+ disease (Wald chi-square $P < 0.001$, Fig. 4).

We next assessed the treatment patterns of patients who did not receive secondary treatment for the first 12 months post-RP. Clinical and pathological characteristics of patients not receiving secondary treatment at 12-months post-RP are listed in Supplementary Table 2. The probability of undergoing treatment within the following 12-months was 21% (95%CI 15%–29%, Supplemental Figure 2). 53% (95%CI: 36%–72%) of men with a PSA ≥0.1 ng/ml detected 12-months post-RP had secondary treatment by

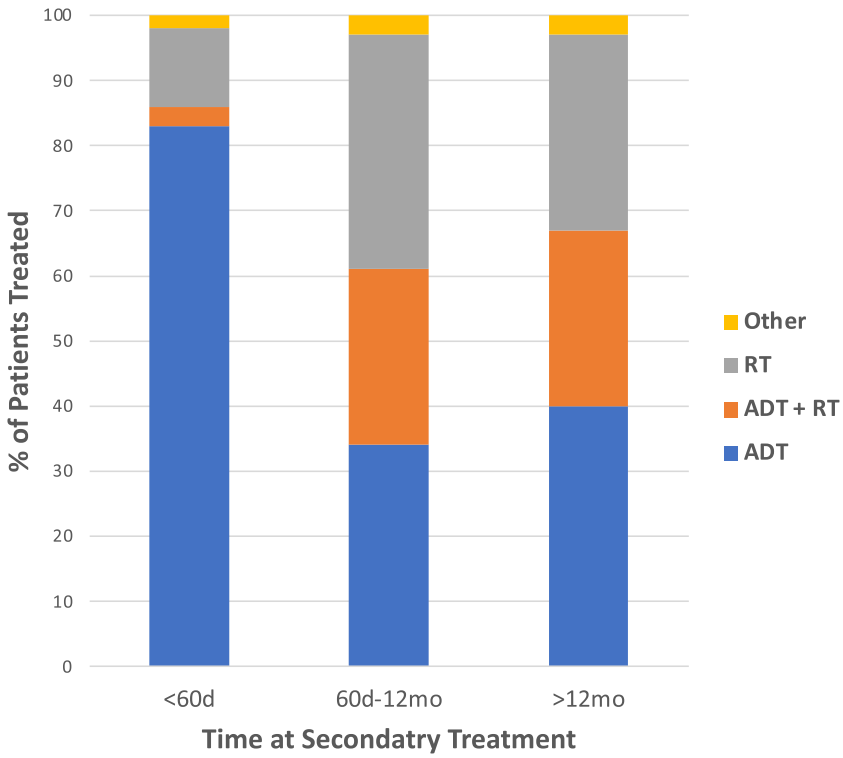

Figure 2. Frequency of Secondary Treatment Modality of pN+ Patients.

Table 2
Patient and Practice-Level Factors Associated with Secondary Treatment. Multivariable Cox PH model is shown, adjusting for baseline prognostic factors.

Variable	HR	95%CI	*P-value
Age (per 5 year increase)	0.95	(0.88, 1.03)	0.2
Gleason Grade Group (ref: GG2)			**0.017**
GG3	1.5	(1.05, 2.14)	
GG4-5	1.65	(1.16, 2.34)	
pT3-4 (ref: pT2)	1.36	(0.88, 2.10)	0.16
Positive margin	1.46	(1.13, 1.88)	**0.004**
Race (ref: white)			0.6
African American	0.92	(0.67, 1.26)	
Other	0.82	(0.45, 1.50)	
Unknown	0.76	(0.47, 1.24)	
Practice Type (ref: private)			**0.01**
Academic	1.8	(1.00, 3.24)	
Hybrid	1.96	(1.20, 3.20)	
Post-RP PSA (ref: PSA <0.1 ng/ml)			**<0.001**
PSA ≥0.1 ng/ml	3.46	(2.61, 4.59)	
No PSA	2.09	(1.40, 3.11)	

* Adjusted wald chi-square P-value

24-months compared to 12% (95%CI 7%−20%) of patients with an undetectable PSA at 12-months post-RP ($P < 0.001$, Fig. 5).

4. Discussion

In the current study, our findings indicate variable utilization of secondary treatment for the first 12-months post-RP in pN+ men. While most men received early post-RP treatment, 1 out of 3 did not receive treatment. Unfavorable disease-related factors, such as increasing pathologic grade group and positive surgical margins, were associated with a shorter time to secondary treatment. An initially detectable post-RP PSA ≥0.1 ng/ml was also strongly associated with time to secondary treatment; however, 18% of patients with detectable PSA and pN+ disease did not receive treatment. Practice level variability in utilization of secondary treatment in MUSIC underlines a need for quality improvement efforts and additional evidence surrounding who should receive early secondary treatment.

Patient selection for early adjuvant treatment versus observation is challenging given the variable course of pN+ disease and lack of a standard of care for these patients [5]. Adverse histopathologic features such as higher grade group, positive surgical margins, and number of positive lymph nodes are all associated with worse outcomes in pN+ patients [9,11−13]. We found similar adverse pathologic features associated with initiation of secondary post-RP treatment. Prior groups have recommended a risk-adapted approach to select patients for early secondary treatment of pN+ CaP. In a single institution study, Gleason score 8-10, positive margins, and ≥3 positive lymph nodes successfully identified patients with pN+ disease at high-risk of cancer specific mortality [14]. Moreover, detectable post-RP PSA in patients with pN+ disease is a particularly high-risk group, with approximately 50% having a local recurrence and/or distant metastases within 5 years post-RP [6] Observation in the setting of a PSA ≥0.1 ng/ml and pN+ disease should be undertaken with caution as part of a shared decision-making management approach.

That only 33% of patients with pN+ cancer in MUSIC did not receive secondary treatment compares favorably with 1 prior study in which a rate of greater than 50% in a nationwide cohort [15]. This may be related to the lack of a

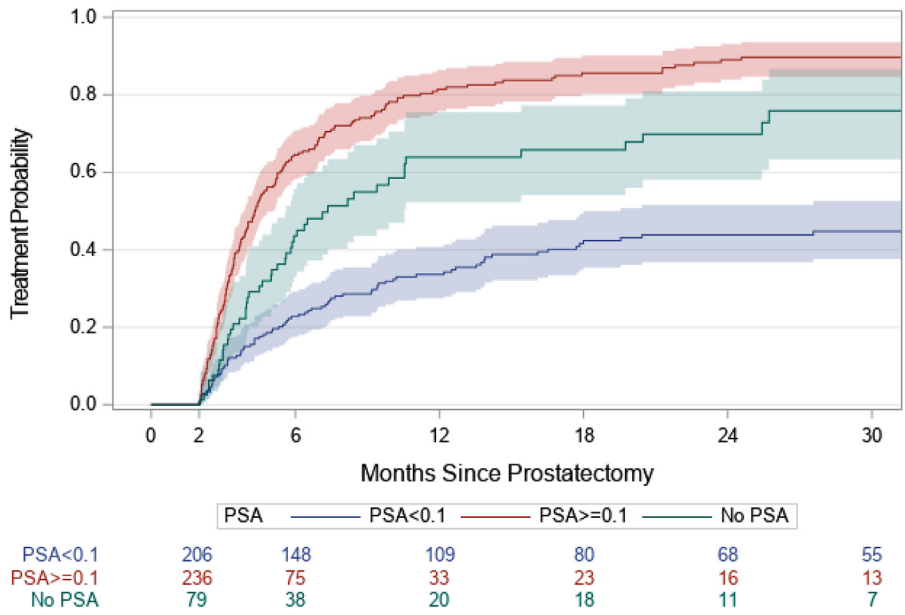

Figure 3. Impact of Initial Post-RP PSA on Rate of Secondary Treatment. (Log-rank P-value < 0.001, PSA within 60 days of RP).

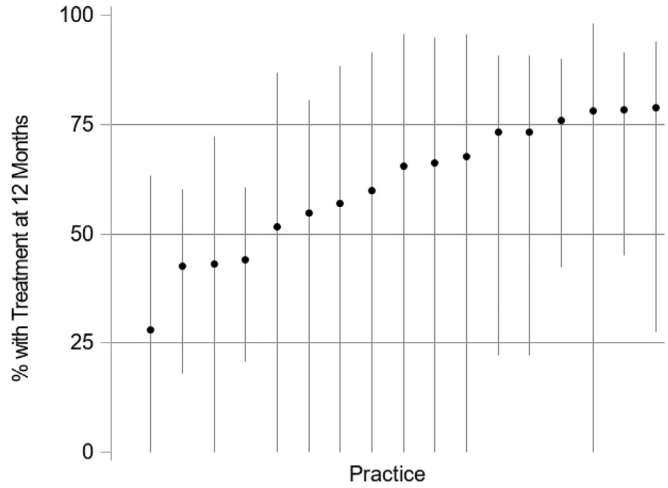

Figure 4. Practice-Level Variation in Management of Patients with pN+ Prostate Cancer. Shown is the Adjusted 12-Month Treatment Proportion with 95% Confidence Intervals By Practice. (Excludes Practices with <5 pN+ Patients, Wald chi-square $P<0.001$).

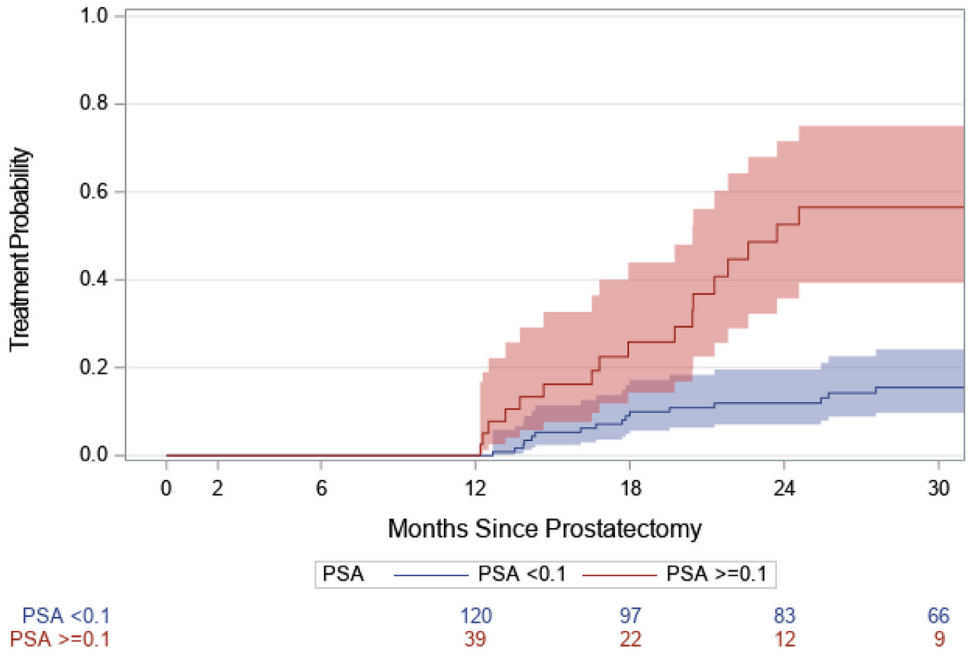

Figure 5. Probability of Secondary Treatment of Men not Receiving Initial Post-RP Treatment Stratified by 12-Month PSA with Number at Risk. (Log-rank P-value <0.001, PSA closest to but prior to 12 months after RP).

standard of care for pN+ patients and also may be related to changing practice patterns or a secondary effect of MUSIC education surrounding earlier use of postoperative therapies, although there was no quality improvement effort specifically directed at management of this patient population.

We found variation in post-RP management of pN+ men at the practice level. Academic based urologic practices were more likely to administer secondary treatment by 12-months post-RP compared to community/private practices when adjusting for patient-level factors. Additionally, wide inter-practice variability in rates of utilization of post-RP treatment likely represent the heterogeneity of pN+ disease and lack of consensus on post-RP management.

The optimal therapeutic modality for patients who do undergo post-operative treatment in this setting remains an area of investigation. In fact, NRG GU 008 is an ongoing randomized trial testing salvage radiation therapy with 2 years of a GnRH-directed therapy (control) compared with the same treatment plus 2 years of apalutamide (experimental arm) in patients with pN+ disease. The only other randomized trial in this setting, from a study conducted decades ago, demonstrated that pN+ men randomized to immediate and lifelong ADT had improved overall and metastasis-free survival at a median follow up of 11.9 years compared with men that waited until clinical disease progression prior to starting ADT (Messing trial) [2].

Widespread utilization of ADT monotherapy for pN+ men has been limited by observational studies which have questioned the long-term outcomes of immediate ADT [16]. Among men who underwent immediate secondary treatment prior to 60-days post-RP, the majority received ADT monotherapy. It is possible a proportion of these patients went on to receive later RT (>90-days) after initiation of ADT to preserve post-RP continence.

A substantial proportion of men were treated with RT monotherapy or in combination with ADT, reflecting increasing data supporting the role of RT in this setting. For example, in a retrospective study it was shown that addition of RT to ADT was associated with improved 10 year CSS (86% vs 70%) and OS (74% vs 55%) in a matched cohort [17]. Similar results have been shown in other studies reinforcing the utility of multimodal therapies for pN+ patients [18]. A notable proportion of patients in our cohort underwent RT monotherapy, reflecting the hesitancy to commit men to lifelong ADT, when a proportion of men will be "cured" with RT alone.

PSMA PET CT/MRI has emerged as a far more sensitive and accurate staging modality compared with CT scan and bone scan, and is rapidly being integrated into clinical practice across the United States. Although PSMA PET is good for the identification of lymph node metastasis, it is still not perfect, with a sensitivity of approximately 85% [19]. Although some false negatives exist for patients staged as cN0 with PSMA PET, patients in this subset with pN+ disease typically have a lower disease burden. As a result, men with cN0/pN+ disease with PSMA PET staging may be a lower risk population compared to those with cN0/pN+ disease staged with conventional imaging. Understanding these differences in the era of molecular imaging will be an important priority.

Our study has several limitations. MUSIC does not collect data on number of lymph nodes removed at time of RP or the total number of positive lymph nodes which are an independent predictor for BCR and cancer-specific survival in pN+ men [20,21]. Furthermore, data collection within the MUSIC prostate cancer registry began in 2012. Therefore, analysis of long-term outcomes related to biochemical recurrence, metastasis, and death were not able to be determined.

5. Conclusions

High-risk pathologic disease features and detectable post-RP PSA are associated with secondary treatment for patients with pN+ disease. Practice-level variation underscores the lack of consensus on how best to manage this population. Understanding which patients will benefit from early secondary treatment, and from which type, will likely be made clearer with the availability of PSMA PET to identify lymph node metastases prior to and after RP.

Declaration of competing interest

Robert E. Dess – Jansen (Advisory Board).

Todd Morgan – Tempus (Advisory Board), Myriad Genetics (Research Funding), Stratify Genomics (Advisory Board).

CRediT authorship contribution statement

Daniel Triner: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Stephanie Daignault-Newton:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Udit Singhal:** Writing – review & editing, Methodology. **Michael Sessine:** Writing – review & editing, Methodology, Investigation. **Robert T. Dess:** Writing – review & editing. **Megan E V Caram:** Writing – review & editing. **Tudor Borza:** Writing – review & editing. **Kevin B. Ginsburg:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Brian R. Lane:** Writing – review & editing, Methodology, Conceptualization. **Todd M. Morgan:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2024.03.015.

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