# Anatomic Patterns of Recurrence Following Biochemical Relapse after Post-Prostatectomy Salvage Radiation Therapy: A Multi-Institutional Study

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**ABSTRACT**

Objectives: To characterize the frequency and detailed anatomic sites of failure for patients receiving post-radical prostatectomy (RP) salvage radiation therapy (SRT).

Materials/Methods: A multi-institutional retrospective study was performed on 574 men who underwent SRT between 1986 and 2013. Anatomical recurrence patterns were classified as lymphotropic (lymph nodes only), osteotropic (bone only), or multifocal if both were present. Isolated first failure sites were defined as sites of initial clinically detected recurrence that remained isolated for at least 3 months.

Results: The median follow-up post-SRT was 6.8 years. The 8-year rates of local, regional, and distant failure for patients undergoing SRT were 2%, 6%, and 21%, respectively. Of the 128 of 574 men (22%) who developed a clinically detectable recurrence, 17%, 50%, and 31% were

lymphotropic, osteotropic, and multifocal, respectively. The tropic nature of metastases was prognostic for distant metastases-free survival (DMFS) and prostate cancer specific survival (PCSS); the 10-year rates of DMFS were 18%, 5%, and 7% ($p<0.01$), and PCSS were 78%, 68%, and 56% ($p<0.01$), for lymphotropic, osteotropic, and multifocal failure patterns, respectively.

Conclusions: We demonstrate that tropism for metastatic site has significant prognostic impact on PCSS in men treated with SRT. Radiographic local failure is an uncommon event after SRT when compared to historical data of patients treated with surgery monotherapy. However, distant failure remains a challenge in this patient population and warrants further therapeutic investigation.

Keywords: Prostate cancer, radical prostatectomy, salvage radiotherapy, patterns of failure

## Introduction

Understanding patterns of treatment failure is critical in defining how best to further escalate or de-intensify therapy. In prostate cancer, the primary pattern of failure following definitive radiation therapy (RT) or radical prostatectomy (RP) is local. Despite the great concern for micrometastatic disease, even men who have high risk prostate cancer most commonly recur locally, accounting for approximately 50% of all clinically detectable recurrences following prostatectomy or definitive RT (1-3). Importantly, local control has been demonstrated to correlate with the development of distant metastases (DM) as well as prostate-cancer specific survival (4-7).

For men that choose to undergo RP for high risk disease it is important to counsel them on the high recurrence rates following surgery alone with estimated 5-year rates of biochemical failure of 50-75% (8). The use of adjuvant radiotherapy (ART) can reduce progression rates by 50% as demonstrated in 3 randomized controlled trials (3, 9, 10). However, the use of ART occurs in <10% of men who undergo RP who have high risk features, and it is increasingly common for patients to undergo salvage RT (SRT) once they have biochemically recurred (11). Given the increased utilization of surgery for high risk disease, and continued low rate of ART use, the patterns of failure in this setting are poorly described (12).

The patterns of failure after SRT are critical to better understand how to improve patient outcomes. For this reason, we aimed to characterize the patterns of failure after SRT and to determine if predominant tropic patterns of failure are prognostic for patient outcomes. Herein, we report results of a large multicenter study assessing patterns of failure for a cohort of men treated with RP followed by SRT.

## Materials and Methods

### Patient Selection

A multi-institutional study was performed on 574 men who underwent a RP with a standard pelvic lymph node dissection and then received post-operative external beam SRT between 1986 and 2013. These men were selected from a cohort of 657 consecutively treated men receiving adjuvant or salvage radiation therapy following prostatectomy. Excluding men whom received adjuvant radiation and those with positive pelvic lymph nodes resulted in 574

remaining men. Analysis of these men was approved by local institutional review boards at all involved institutions.

Treatment

All men were treated with external beam SRT with the use of either three-dimensional conformal RT or intensity-modulated RT. SRT was defined as post-RP radiation delivered in the presence of a detectable PSA (most common reason) or commencing greater than 4 months following RP. The clinical target volume (CTV) was defined as the prostate bed. The planning target volume consisted of the CTV plus a uniform 0.5- 1.0 cm expansion, dependent on the use and modality of daily imaging. The median dose delivered to the planning target volume (PTV) was 68.4 Gy with an interquartile range (IQR) of 64.8 to 68.4 Gy, delivered in daily 1.8 Gy fractions. Men with high-risk clinicopathologic features were selectively treated to the pelvic lymph nodes (19%, n=23) and/or received neoadjuvant and concurrent androgen deprivation therapy (ADT) (25%, n=31), at the treating physician's discretion. If pelvic lymph nodes were treated they received 45 Gy in 1.8 Gy daily fractions.

End points

Clinically detected recurrences were discovered primarily through CT based imaging or bone scintigraphy. Lymph node recurrences were most commonly identified on CT based imaging. Lymph nodes were considered suspicious if > 8 mm in size in the pelvis or > 1 cm in the retroperitoneum, or with abnormal shape (rounded), loss of a fatty hilum, inhomogeneity, or clear increase in size of a lymph node from prior imaging in the appropriate clinical context, such as a rising PSA. All imaging was read by radiologists at one of the treating institutions; however there was no repeat central review for this analysis. Imaging was typically performed at the time of post-radiation biochemical recurrence, and then as clinically indicated following this (normally at least every 6 months for men with metastatic disease). The locations of first disease recurrence or metastatic site were grouped as local (prostate bed), confined to pelvic lymph nodes (external and internal iliac, presacral, and obturator lymph node stations), retroperitoneal/abdominal lymph nodes, thoracic lymph nodes, bone, or viscera. An isolated site of first recurrence was defined as any recurrence limited to a single anatomic location in any of the above groupings for at least 3 months before discovery of additional sites of involvement, as

proposed by Zumsteg and Spratt et al (2). Men were also grouped based on their pattern of failure and were defined as having lymphotropic, osteotropic, or multifocal patterns of failure. All patients with visceral failures had multi-site failure, and as such are included in the multifocal pattern of failure. Lymphotropic and osteotropic patterns of failure were defined as metastatic disease confined to lymph nodes or bone alone, respectively, for at least two years from initial clinical detection before discovery of involvement of an additional site (2). Patients with multiple anatomic locations involved within the first two years of a clinically detected recurrence were defined as having a multifocal pattern of failure. The time to a recurrence was defined as the time from the date of salvage radiation therapy to the date of the imaging study that identified radiographic evidence of recurrence.

Biochemical failure following SRT was defined as a rising prostate-specific antigen (PSA) level ≥0.2 ng/mL from the post-SRT PSA nadir, or any PSA level ≥ 0.5 ng/mL. Prostate-cancer specific mortality (PCSM) was defined as a death in any man with progressive metastatic disease or castration-resistant prostate cancer. The time to development of metastases and PCSM was assessed from the time of biochemical failure following RP.

Statistical analysis

Descriptive statistics were used to describe first sites of failure as well as patterns of failure. Adjusted Kaplan-Meier methods controlling for patient age at the time of RT were used to assess distant metastases-free survival (DMFS) and prostate cancer-specific survival (PCSS) from the time of post-RP biochemical failure. A step-wise multivariate model was created using Cox-proportional hazards analysis for DMFS and PCSS. For all statistical analyses, two-tailed P-values of ≤0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS version 21.0 (SPSS Inc., Chicago, IL USA) and MedCalc V16.4.3 (MedCalc Software, Mariakerke, Belgium).

## Results

Patient characteristics

The median follow-up post-SRT was 6.8 years (IQR 3.9-10.2). The median time from RP to SRT was 24 months (IQR 11-49). Patient characteristics for the men who developed metastases can be found in **Table 1**; 74.2% of men had high-risk prostate cancer based on NCCN

criteria at the time of prostatectomy, 75.5% had Gleason grade group 3-5 (Gleason 4+3 to 10) disease (8, 13, 14), 69.9% were pathologic stage T2b-T4, and the median pre-RT PSA was 0.7 ng/mL (interquartile range [IQR] 0.4-1.4).

A total of 128 of 574 men (22.3%) developed clinically detectable recurrent prostate cancer following biochemical recurrence post-RP. No patient experienced a distant recurrence without a preceding biochemical recurrence. An additional 3 men had a local only recurrence without developing metastases. The median time to post-RP biochemical recurrence for these 128 men was 11.9 months (IQR 5.0-24.8). The median time from post-RP BF to development of metastases was 32.5 months (IQR 11.4-64.2).

Patterns of isolated first recurrences

**Table 2** demonstrates the sites of isolated first recurrences as well as the total distribution of clinically detectable recurrences. 104 patients (developed an isolated first recurrence (i.e. disease located to a single site for at least 3 months). The most common site of isolated first failure was bone (63.5%), followed by retroperitoneal/abdominal lymph nodes (12.5%) and then pelvic lymph nodes (11.5%). Only one patient with an isolated pelvic lymph node failure received pelvic nodal irradiation. This was a left obturator node failure and was within the radiation treatment field. Isolated local first failures were rare with 5 in total (4.8%).

Overall patterns of failure

From our entire cohort of 574 men receiving post-RP SRT 8-year incidences of all anatomic sites of failure were calculated (**Table 3**) (2). 8-year actuarial rates of local failure were 2.2%, pelvic nodal failure was 6.0%, and distant failure was 21.0% (**Figure 1**). Men with NCCN high risk disease at time of RP had 8-year rates of local, regional, and distant failure of 2.5%, 6.2%, and 29.1%, respectively.

Metastatic tropism and impact on outcome

The tropism of recurrences was able to be determined for 120 of the 128 men (93.8%) who developed metastases. 62 men had osteotropic disease (51.7%), 19 had lymphotropic disease (15.8%), and 34 men had multifocal disease (28.3%). Men with multifocal disease had higher pre-RT PSA values compared to men with lymphotropic or osteotropic disease, although

this difference did not reach statistical significance; otherwise patient characteristics were similar between these three groups (**Supplemental Table 1**). On further univariate analysis, the pre-SRT PSA was not associated with either the trophic nature of metastases nor the development of isolated versus multifocal metastases when assessed as a categorical variable, with commonly utilized thresholds of 0.2 ng/mL and 0.5 ng/mL, nor as a continuous variable (all p>0.1). The tropic nature of metastases was prognostic for DMFS and PCSS. The 10-year rates of DMFS were 18%, 5%, and 7% (p=0.046, **Figure 2A**), and PCSS were 78%, 68%, and 56% (p=0.039, **Figure 2B**), for lymphotropic, osteotropic, and multifocal failure patterns, respectively.

Lastly, we created multivariate models to assess for predictors of metastases and PCSM following SRT and biochemical recurrence, respectively. When assessing for predictors of metastases while controlling for grade group, pre-RT PSA, surgical margin status, pathologic T-stage, use of ADT during RT, and pelvic nodal irradiation (**Table 4**), retained variables in the model included grade group 5 (HR 2.2, 95% CI 1.4-3.5, p<0.001), seminal vesicle invasion (HR 2.4, 95% CI 1.5-3.6, p<0.001), pre-SRT PSA (HR 1.2, 95% CI 1.1-1.3, p<0.001) and the presence of a positive surgical margin (HR 0.4, 95% CI 0.3-0.6, p<0.001). When assessing for predictors of PCSM while controlling for grade group, recurrence tropism, pre-RT PSA, surgical margin status, pathologic T-stage, use of ADT during RT, and age (**Table 4**), the only variables retained in the model were grade group 5 (HR 2.4, 95% CI 1.2-4.7, p=0.01) and multifocal metastatic tropism (HR 2.1, 95% CI 1.1-4.0, p=0.02).

## Discussion

In a large multicenter study with long-term follow-up we have demonstrated multiple key findings that we believe are of interest to the urologic oncology community. First, local failure is an infrequent event after SRT. Second, pelvic nodal failure, especially isolated pelvic nodal failure rates are uncommon despite the omission of pelvic nodal RT in most patients and the lack of extended pelvic lymph node dissections in our cohort. Third, distant failure appears to be the most common form of failure after SRT in contrast to surgery monotherapy or definitive radiotherapy. Finally, we validate that tropism for metastatic failure is prognostic for not only time to metastatic disease but also prostate cancer specific survival.

Local failure after RP monotherapy or definitive RT (+/- ADT) is the most common site of recurrence and is estimated to occur in 10-50% of patients based on pre-treatment

characteristics. Furthermore, ~50% of all recurrences are local (1-3). We demonstrate that when utilizing two forms of local therapy (i.e. surgery and SRT), as in our multicenter cohort, that only 5.5% of all recurrences had a local component to them. Furthermore, the cumulative 8-year radiographic local failure rate was only 2.2%. These data demonstrate the high efficacy of SRT to eliminate local disease, and as such, that further dose-escalation beyond 68.4 Gy is unlikely to result in demonstrable improvements in local control.

While surveillance CT imaging is a part of the standard of care for assessing men with recurrent prostate cancer, as done in our study, it has been demonstrated to have poor sensitivity and specificity in the detection of both local recurrence and lymph node metastases (15). As such the true rate of both local recurrence and lymph node metastases in our series is also likely underreported. None-the less, our very low 8-year pelvic lymph node recurrence (6.0%) suggests that these are not common occurrences for men receiving SRT. Furthermore, none of the patients in our cohort received an extended pelvic lymph node dissection, and <20% of patients received pelvic nodal RT, which questions the potential benefit of elective pelvic nodal RT. Similar rates of pelvic recurrences have been reported from patients undergoing definitive radiotherapy without pelvic nodal RT with 8-year rates of pelvic lymph node failure ~4% (2). However, the benefit of pelvic nodal RT in the salvage setting will definitively be answered by RTOG 0534 which is now closed and the data is maturing.

While local and regional control were excellent following SRT, development of metastases remained a common event with approximately 20% of the men in our cohort developing metastatic disease by 8-years post-SRT. Furthermore, men with NCCN high risk disease had nearly a 30% rate of distant metastases at 8-years post-SRT. There are multiple potential explanations for these findings. First, these patients underwent SRT with a median time between RP and SRT of 24 months. This time interval potentially allows locally persistent disease to spread to regional or distant sites. This raises the question of whether ART may be ideal to not only achieve excellent local control, but also improve rates of DMFS by eradicating local disease before it can disseminate. This idea is supported by a detailed patterns of failure analysis of the SWOG 8794 randomized trial of RP +/- ART, where at a median follow-up of 10 years only 7% of patients who received ART had developed metastases (1). Patients in our analysis also had a median pre-SRT PSA level of 0.7 ng/mL. Recent evidence suggests improved metastasis-free survival when men receive salvage radiation therapy when the PSA

level is ≤ 0.5 ng/mL, and even further improved when the pre-SRT PSA is ≤ 0.2 ng/mL (16, 17). As such, the elevated pre-SRT PSA levels in our cohort may have in part contributed to the overall high rate of metastatic progression, and when possible we would recommend initiation of SRT at the time of biochemical recurrence before the pre-SRT PSA elevated above 0.5 ng/mL and preferably with the pre-RT PSA as close to 0.2 ng/mL as possible.

Another possible explanation for the high distant failure observed in our analysis is that ADT was given to only ~25% of men, and ADT has been shown pre-clinically to be a potent radiosensitizer (18-20). Additionally, prospective randomized trials (GETUG-AFU 16 and RTOG 9601) have recently demonstrated improved progression free survival with the addition of ADT to SRT, primarily in men with pre-SRT >0.7 ng/mL. Furthermore, RTOG 9601 has long-term follow-up and has demonstrated improvement in DMFS and overall survival with the addition of ADT to SRT (21, 22). Our study demonstrated that men with grade group 5, pT3b, and a high pre-SRT PSA all independently confirmed an increased risk for distant failure following SRT. Therefore, the addition of ADT should strongly be considered for men with any of these risk factors.

Other measures by which to decrease rates of DM in this setting are needed in addition to ADT. For men receiving post-operative RT, two prospective trials have demonstrated the safety of docetaxel in combination with post-RP RT (23, 24). Preliminary results from RTOG 0621, which assessed the addition of ADT and docetaxel following adjuvant RT, showed improved progression-free survival compared to historical rates following adjuvant RT alone (24). Given the encouraging early results with docetaxel in combination with either definitive (25) or post-RP RT (24), and the high-rate of progression to metastatic disease for men receiving SRT, additional research is warranted assessing docetaxel or alternative systemic therapies in the context of SRT.

Despite the rigor in collecting our data there are multiple limitations that must be acknowledged. First, our analyses are limited by their retrospective nature. Second, the use of MRI and more advanced functional imaging were not used which have been shown to have increased sensitivity in detecting recurrent/metastatic disease (10). Therefore, all of our failure rates are likely underestimated. Additionally, biopsies of recurrent/metastatic sites were not performed to document true pathologic evidence of prostate cancer. However, CT imaging and

bone scans remain standard of care imaging studies for men with recurrent/metastatic prostate cancer.

In closing, while local failures are rare following SRT these men remain at increased risk for progression to metastatic disease. As demonstrated in recent randomized trials, the use of ADT in the setting should strongly be considered, especially for men with high pre-SRT PSA, and future clinical trials are needed to assess the possible benefits of treatment intensification with docetaxel, second generation anti-androgens, or other novel therapies, as well as companion biomarkers to better select patients for treatment intensification.

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**Figure Legends**

**Figure 1**. Cumulative incidence of all failures stratified by location (local, regional, or distant) for the entire cohort of men receiving post-prostatectomy salvage radiation therapy from time of salvage radiotherapy.

**Figure 2**. Impact of tropic nature on A) distant metastasis-free survival, and B) prostate cancer-specific survival from the time of biochemical failure after salvage radiotherapy.

**Table 1. Characteristics for men developing post-SRT metastases**

| Variable | N= or median (IQR) | % |
|---|---|---|
| Age (years) | 63.8 (57.7-68.2) | |
| Pre-RP PSA (ng/mL) | 7.0 (4.8-12.5) | |
| Pre-SRT PSA (ng/mL) | 0.7 (0.4-1.4) | |
| Grade Group (Gleason Score) | | |
| 1 (≤6) | 6 | 4.9 % |
| 2 (3+4=7) | 24 | 19.5 % |
| 3 (4+3=7) | 41 | 33.3 % |
| 4 (8) | 19 | 15.4 % |
| 5 (9-10) | 33 | 26.8 % |
| pTstage | | |
| T2a | 37 | 30.1 % |
| T2b/c | 46 | 37.4 % |
| T3a-T4 | 40 | 32.5 % |
| NCCN risk group | | |
| Low | 0 | 0 % |
| Intermediate | 33 | 25.8 % |
| High | 95 | 74.2 % |
| Positive margins | 56 | 45.5 % |
| Positive Lymph nodes | 5 | 4.7 % |
| SRT Dose (Gy) | 68.4 (64.8-68.4) | |
| Pelvic nodal RT | 23 | 19.2 % |
| Concurrent ADT | 31 | 25.2 % |
| ADT duration (months) | 6.6 (4.0-15.1) | |

Abbreviations: SRT=salvage radiation therapy, RP=radical prostatectomy, PSA=prostate-specific antigen, pTstage=pathologic T stage, Gy=Gray, ADT=androgen deprivation therapy

| Table 2. Distribution of clinically detectable recurrences | *Isolated first recurrence site (104 patients with isolated first failure) | | All clinically detectable recurrence sites (238 total involved sites in 128 patients) | |
|---|---|---|---|---|
| | n | % | n | % |
| **Local failure** | 5 | 4.8% | 13 | 5.5% |
| **Pelvic lymph nodes** | 12 | 11.5% | 35 | 14.7% |
| **Retroperitoneal/Abdominal Lymph nodes** | 13 | 12.5% | 41 | 17.2% |
| **Thoracic lymph nodes** | 3 | 2.9% | 15 | 6.3% |
| **Bone** | 66 | 63.5% | 102 | 42.9% |
| **Visceral** | 5 | 4.8% | 32 | 13.4% |

*Isolated first recurrence site defined as metastatic disease confined to a single location listed above for at least 3 months before involvement of a second site

**Table 3. 8-year cumulative incidence of all anatomic sites of failure**

| | RP+SRT (Overall) | RP+SRT (NCCN High-risk) |
|---|---|---|
| **Local Failure** | *2.2%* | *2.5%* |
| **Pelvic Lymph nodes** | *6.0%* | *6.2%* |
| **Retroperitoneal/Abdominal Lymph nodes** | *4.2%* | *5.7%* |
| **Thoracic lymph nodes** | *1.9%* | *2.6%* |
| **Bone** | *12.3%* | *17.7%* |
| **Visceral** | *2.6%* | *3.1%* |
| **Overall 8-year incidence of local regional failure** | 8.2% | 8.7% |
| **Overall 8-year incidence of distant failure** | 21.0% | 29.1% |

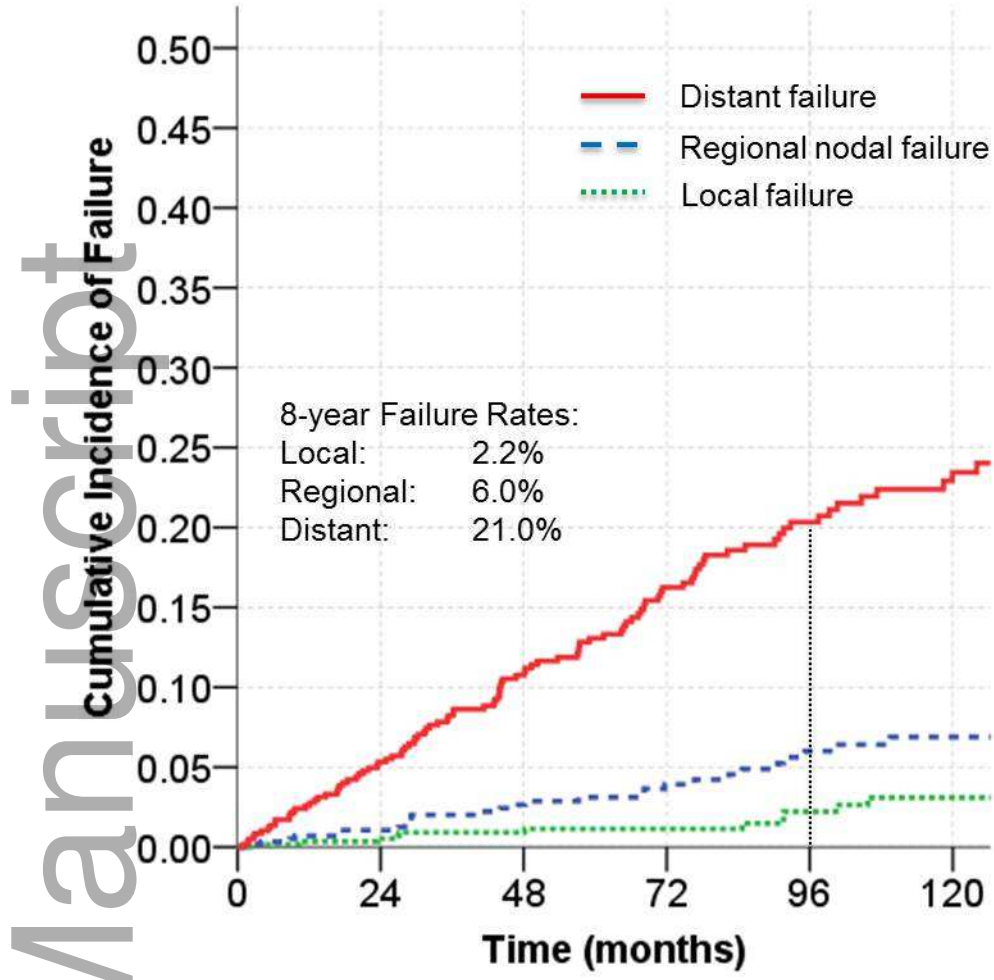
Abbreviations: NCCN, National Comprehensive Cancer Network; RP=radical prostatectomy; SRT=Salvage radiation therapy,

**Table 4. Stepwise multivariable models**

| **Model for distant metastases from time of salvage radiotherapy** | | | |
|---|---|---|---|
| **Retained Variables†** | **HR** | **95% CI** | **p-value** |
| Grade Group 5 | 2.2 | 1.4-3.5 | <0.001 |
| Seminal vesicle involvement | 2.4 | 1.5-3.6 | <0.001 |
| Pre-salvage radiotherapy PSA (continuous) | 1.2 | 1.1-1.3 | <0.001 |
| Positive surgical margins | 0.4 | 0.3-0.6 | <0.001 |
| **Model for prostate cancer specific mortality from the time of biochemical recurrence** | | | |
| **Retained Variables‡** | **HR** | **95% CI** | **p-value** |
| Grade Group 5 | 2.4 | 1.2-4.7 | 0.01 |
| Multifocal metastases | 2.1 | 1.1-4.0 | 0.02 |

†Variables entered but not retained: *pT-stage, ADT use during SRT, Pelvic nodal RT*

‡Variables entered but not retained: *Lymphotrophic, Osteotrophic, Gleason Group 1-4, pre-SRT PSA, Positive surgical margins, pT-stage, ADT use during SRT, Age*

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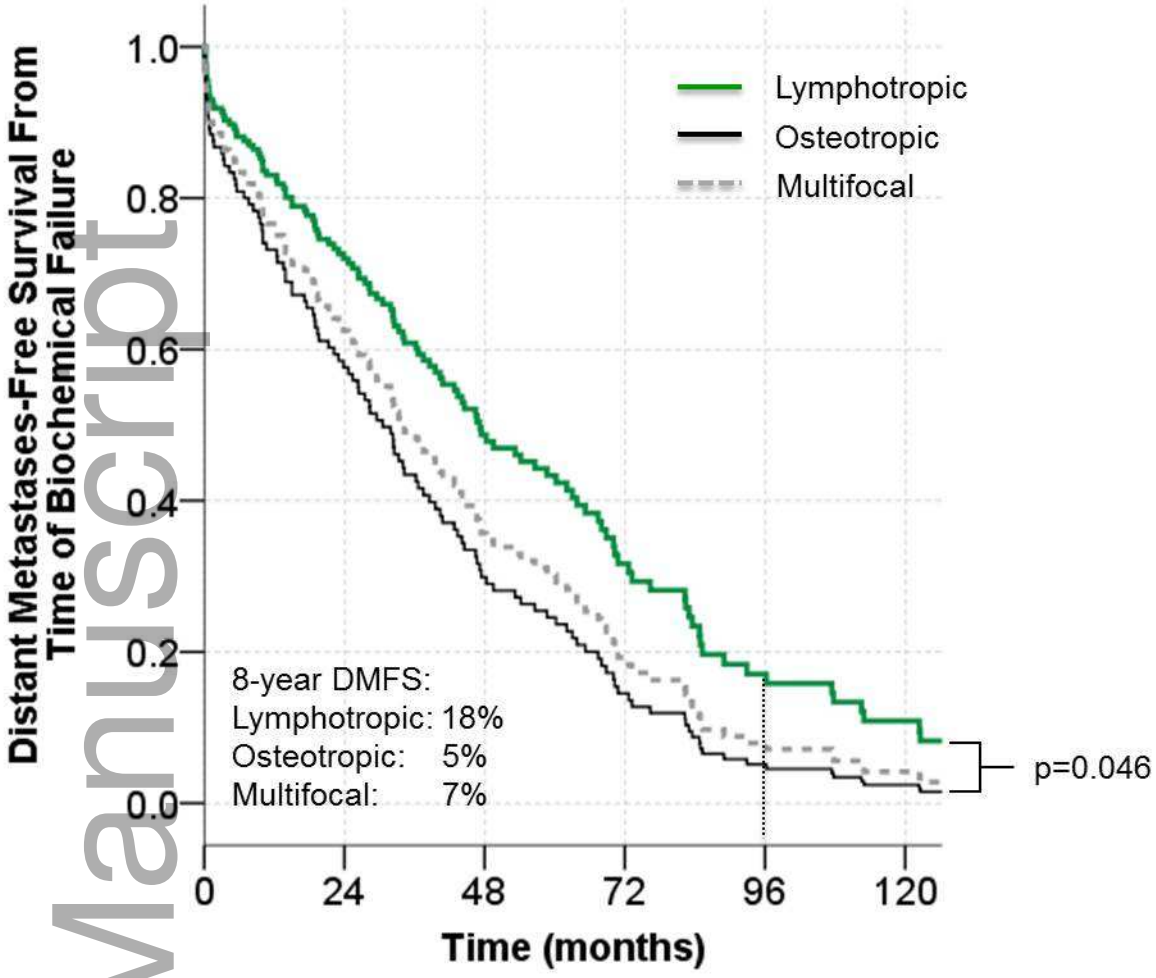


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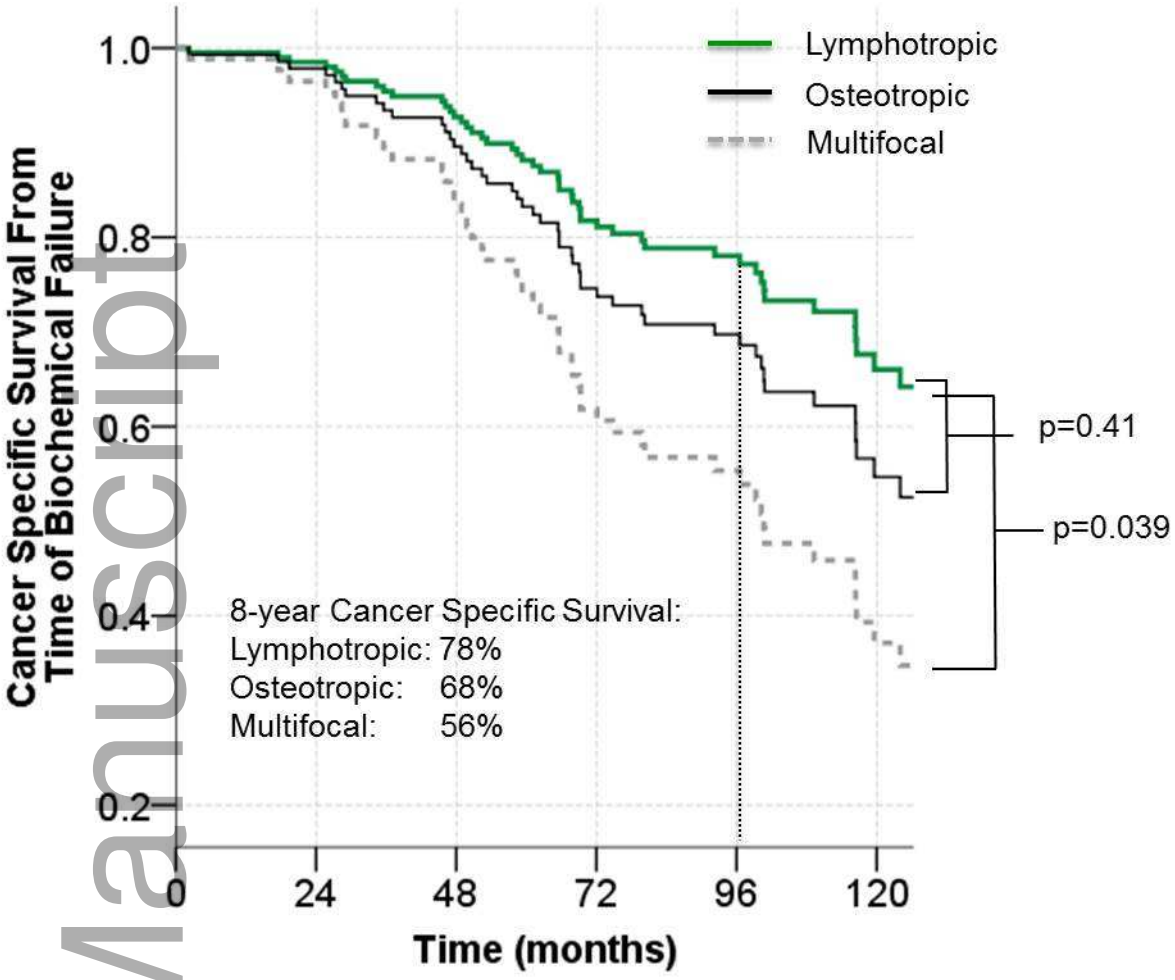


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