ORIGINAL RESEARCH

# Correlation of Tumor Location and Biochemical Recurrence in Localized and Locally-Advanced Prostate Cancer in Post-Robotic Radical Prostatectomy Patients

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***Objective***: This study aims to determine the tumor location of prostate adenocarcinoma in patients who underwent Robotic Radical Prostatectomy (RRP) for localized and locally-advanced prostate cancer and the correlation of the tumor location with the incidence of biochemical recurrence.
***Patients and Methods***: The authors reviewed the patient database of a single Urological Oncologist from January 2015 to April 2017 for patients who underwent RRP for localized or locally-advanced prostate cancer. They also reviewed the histopathologic report of the prostatectomy specimens to determine pathologic T-stage, prostate volume, and post-operative Gleason score. The histopathologic examination of specimens was interpreted by a single Urological Pathologist based on the 2014 International Society of Urological Pathology Gleason Scoring System. Eligible patients were then divided into three groups: those with pure anterior tumor location, pure posterior tumor location, and mixed tumor location. Presence of positive surgical margins, mean follow-up period, and biochemical recurrence were determined for these groups. Patient demographic data were analyzed using test of proportions. Correlation of tumor location with biochemical recurrence was derived using Pearson chi-square test.
***Results***: Of the 113 patients included in the study, 63 (55.8%) were clinically-staged T2 patients while 27 (23.9%) and 23 (20.3%) were clinical stage T1 and T3, respectively. On pre-operative prostate biopsy, 27 (23.9%) patients had a Gleason score of 8-10. Thirty-eight (33.6%) and 30 (26.6%) had a Gleason score of 6 (3+3) or 7 (3+4), respectively Average prostate volume was 42.8 grams. Ninety-five (84.1%) of the patients had mixed tumor location, 11 (11.6%) had pure posterior tumor location, and only 7 (6.2%) had pure anterior tumor location. In those with pure anterior or posterior tumor locations, majority were low-grade prostate cancers (Gleason 6(3+3) and Gleason 7(3+4)) while those with mixed tumor location had low to high-grade prostate cancers (Gleason 7 (3+4) and Gleason 7 (4+3.)) Majority of the patients had pathologic T2c and T3a tumors across all groups. Positive surgical margins were present in 31% of those with mixed tumor location and only 0.9% in those with pure anterior or posterior tumor location, respectively. Only 10 patients from the population had biochemical recurrence, 9 of which had mixed tumor location while 1 had pure posterior tumor location. Pearson chi-square test shows no significant relationship between tumor location and biochemical recurrence at 95% CI (p= regional involvement 0.695.) Furthermore, there is a very weak positive correlation (R=0.069) between tumor location and biochemical recurrence.
***Conclusion***: Majority of patients who underwent RRP have mixed tumor location. There is poor correlation between prostate cancer tumor location and biochemical recurrence.

***Keywords***: prostate cancer, biochemical recurrence, radical prostatectomy

## Introduction

Historically, it was reported that prostate adenocarcinoma arises from the peripheral zone in 68%, from the transitional zone in 24%, and from the central zone in 8% of cases.[1] However, due to the advent of improved prostate biopsy techniques and review of radical prostatectomy specimens, more anteriorly located prostate cancers are being detected, which encompasses transitional zone cancers in most cases. These findings have produced investigations on the prognostic impact of tumor location on oncologic outcomes.[2-5] Despite numerous studies, there is still controversy regarding this matter.

Transitional zone prostate cancers are associated with lower Gleason scores and lower incidence of extraprostatic extension and seminal vesicle invasion despite having higher pre-treatment PSA levels and higher tumor volume.[5] This may be attributed to the anterior location of the transitional zone prostate cancers, which are usually detected by conventional transrectal prostate biopsy techniques once these cancers have reached higher tumor volumes and, subsequently, higher tumor stage. In addition, transitional zone prostate cancers have distinct molecular and genetic differences from peripheral zone prostate cancers which may contribute to their relatively indolent clinical course.[6-15]

This study aims to determine the tumor location of prostate adenocarcinoma in patients who underwent RRP for localized and locally-advanced prostate cancer. The correlation of the tumor location of prostate cancer with the incidence of biochemical recurrence will also be determined.

## Patients and Methods

The authors reviewed the patient database of a single Urological Oncologist from January 2015 to April 2017 for patients who underwent RRP for localized or locally-advanced prostate cancer. All procedures were performed by the said Urological On-cologist via a standardized 6-port transperitoneal technique utilizing the da *Vinci Surgical System Si* robot. Pelvic lymph node dissection was done upon the discretion of the surgeon. The age of the patients at surgery, pre-operative PSA levels, clinical T-stage, and pre-operative biopsy Gleason score were recorded. Pre-operative prostate biopsies were done via the transrectal or transperineal approach.

They also reviewed the histopathologic report of the prostatectomy specimens to determine pathologic T-stage, prostate volume, and post-operative Gleason score of eligible patients. The histopathologic examination of specimens was interpreted by a single Urological Pathologist and reports were based on the 2014 International Society of Urological Pathology Gleason Scoring System.[16] Although the whole mount histologic preparations were not available, a thorough review was conducted to include sections from the anterior and posterior base, midgland, and apical regions of the prostate from both right and left prostatic lobes to determine which of these locations had cancer involvement.

Eligible patients were then divided into three groups: those with pure anterior tumor location, pure posterior tumor location, and mixed tumor location. Presence of positive surgical margins, mean follow-up period, and biochemical recurrence were determined for these groups. Biochemical recurrence (BCR) is defined as two consecutive post-operative PSA levels of > 0.2 ng/ml on follow-up according to the European Urological Association Guidelines on Prostate Cancer.[17] Patients with biochemical recurrence were offered adjuvant androgen deprivation therapy and those presenting with positive surgical margins were offered external beam radiotherapy.

Patient demographic data were analyzed using test of proportions. Correlation of regional involvement with BCR was derived using Pearson chi-square test.

## Results

A total of 113 localized and locally-advanced prostate cancer patients who underwent RRP were included in this study (Table 1). Sixty-three (55.8%) were clinically staged T2 patients while

27 (23.9%) and 23 (20.3%) were clinical stage T1 and T3, respectively. On pre-operative prostate biopsy, 27 (23.9%) patients had a Gleason Score of 8-10. Thirty-eight (33.6%) and 30 (26.6%) had a Gleason scores 6 (3+3) or 7 (3+4), respectively. Average prostate volume was 42.8 grams. Ninety-five (84.1%) of the patients had mixed tumor location, 11 (11.6%) had pure posterior tumor location, and only 7 (6.2%) had pure anterior tumor location.

**Table 1**. Patient demographics

| | |
|---|---|
| Age (average years) | 64.8 |
| Pre-op PSA | 12.3 |
| Clinical T-stage | |
| T1 | 27 (23.9%) |
| T2 | 63 (55.8%) |
| T3 | 23 (20.3%) |
| Pre-op Gleason Score | |
| 6(3+3) | 38 (33.6%) |
| 7(3+4) | 30 (26.6%) |
| 7(4+3) | 18 (15.9%) |
| 8 to 10 | 27 (23.9%) |
| Prostate volume (average grams) | 42.8 |
| Post-op Gleason Score | |
| 6(3+3) | 26 (23.0%) |
| 7(3+4) | 56 (49.6%) |
| 7(4+3) | 16 (14.1%) |
| 8 to 10 | 15 (13.3%) |
| Pathologic T-stage | |
| T2a | 5 (4.4%) |
| T2b | 5 (4.4%) |
| T2c | 64 (56.7%) |
| T3a | 20 (17.7%) |
| T3b | 19 (16.8%) |
| Prostate Region Involved | |
| Anterior | 7 (6.2%) |
| Posterior | 11 (11.6%) |
| Mixed | 95 (84.1%) |

In those with pure anterior or posterior tumor locations, majority were low-grade prostate cancers (Gleason 6(3+3) and Gleason 7(3+4)) while those with mixed tumor location had low to high-grade prostate cancers (Gleason 7 (3+4) and Gleason 7 (4+3.)) Majority of the patients had pathologic T2c and T3a tumors across all groups. Positive surgical margin was present in 31% of those with mixed tumor locaiton and only 0.9% in those with pure anterior or posterior tumor locations, respectively. Only 10 patients from the population had biochemical recurrence, 9 of which had mixed tumor location while 1 had pure posterior tumor location. (Table 2)

Pearson chi-square test shows no significant relationship between tumor location and biochemical recurrence at 95% CI (p= regional involvement 0.695). Furthermore, there is a very weak positive correlation (R=0.069) between tumor location and biochemical recurrence.

## Discussion

Based on the patient population, there was poor correlation between prostate cancer tumor location and biochemical recurrence. Several studies showed contradicting results but with similar clinical implications. In a study done by Augustin, et al. consisting of 307 radical prostatectomy patients, prostate cancer with 70% transitional zone cancer volume had significantly higher chance of biochemical cure compared to those with 30% or less transitional zone cancer volume. However, this association did not retain its significance on multivariate analysis.[2] Similarly, Iremashvlll, et al. concluded that transitional zone tumor origin and the risk of biochemical recurrence do not add important predictive value to the standard prognostic factors (i.e. extraprostatic extension, lymphovascular involvement, seminal vesicle involvement) despite finding out that transitional zone prostate cancers were associated with better biochemical recurrence free-survival.[3] They came to this conclusion by performing an external validation of a nomogram developed by Steuber, et al. which predicted transitional zone involvement.[18] Their results showed that the said nomogram demonstrated poor discriminative ability for transitional zone tumors and no discriminative ability for transitional and mixed cancers.[3] The aforementioned findings may be

**Table 2**. Comparison of anterior, posterior, and mixed tumor location groups

| | Anterior | Posterior | Mixed |
|---|---|---|---|
| Average Pre-op PSA (ng/mL) | 4.1 | 8.8 | 13.3 |
| Post-op Gleason Score | | | |
| 6(3+3) | 4 | 5 | 17 |
| 7(3+4) | 1 | 6 | 49 |
| 7(4+3) | 2 | 0 | 14 |
| 8 to 10 | 0 | 0 | 15 |
| Pathologic T-stage | 0 | | |
| T2a | 0 | 4 | 1 |
| T2b | 0 | 2 | 3 |
| T2c | 6 | 3 | 55 |
| T3a | 1 | 1 | 18 |
| T3b | 0 | 1 | 18 |
| Positive margins | 1 (0.9%) | 1 (0.9%) | 35 (31.0%) |
| Biochemical recurrence | 0 (0.0%) | 1 (0.9%) | 9 (8.0%) |
| Follow-up (months) | 10.7 | 9.5 | 8.8 |

indicative that, based on current literature, tumor location has no clinically-significant prognostic value to prostate cancer patients warranting its routine use in practice.

However, some authors have contradicted the aforementioned findings. Lee, et al. concluded that transitional zone prostate cancers are associated with decreased odds of adverse pathologic findings and demonstrate improved recurrence-free survival. They attributed their findings to several biological differences of transitional zone and peripheral zone cancers. Transitional zone prostate cancers were found to be less susceptible to acquisition of genomic alterations, maintains a diploid DNA status even at large tumor volumes, have lower proliferation indices, and does not contain TMPRSS2-ERG gene rearrangement.[6-14] In addition, peripheral zone cancers have been shown to have increased expression of Ki-67, MMP-2, MMP-9, and Bcl-2 proteins.[6,15] The presence of these proteins, on top of TMPRSS2-ERG gene fusion, may also explain why peripheral zone prostate cancers have poorer clinical outcomes.

A recent study published by Teloken, et al. reported that prostate cancer zonal origin significantly impacts biochemical outcomes in patients with high grade (i.e. Gleason 7(4+3) or above) prostate cancer in patients who underwent radical prostatectomy.[19] In addition, they also reported that low-grade prostate cancers have excellent biochemical recurrence free-survival regardless of zonal origin.[19] These findings may indicate that taking into account the regional involvement of high-grade prostate cancer preoperatively in potential radical prostatectomy may have little prognostic value since these patients usually present with higher tumor stage, thus, may not be offered radical prostatectomy as an initial treatment modality.

Although the anterior prostate primarily consists of the transitional zone, the authors could not disregard the possibility that some cancers may originate from the anterior fibromuscular zone. Determining the exact zonal origin of prostate cancers instead of regional involvement may further consolidate the prognostic significance of such in future studies. In addition, a longer follow-up period will better reflect correlation between regional involvement and biochemical recurrence.

## Conclusion

Based on this cohort of prostate cancer patients who underwent RRP, majority would have mixed tumor location. However, there is

poor correlation between prostate cancer tumor location and biochemical recurrence upon analysis of available data.

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