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Impact of Tumor Regional Involvement on Active Surveillance Outcomes: Validation of the Cumulative Cancer Location Metric in a US Population.

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Title: Impact of Tumor Regional Involvement on Active Surveillance Outcomes: Validation of the Cumulative Cancer Location Metric in a United States Population

Running Title: CCLO Validation in a US Active Surveillance Population

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STRUCTURED ABSTRACT

Background: Treatment progression for men on active surveillance (AS) for prostate cancer (PCa) is driven primarily by grade and volume progression on isolated prostate biopsies (PBx). As PCa is a multifocal disease, regional disease progression over time should be accounted for.

Objective: To validate the utility of the Cumulative Cancer Location (CCLO) metric, which assesses regional core involvement, as described by Erickson et al., in predicting AS outcomes in a North American cohort.

Design, setting, and participants: Single institutional retrospective chart review of all AS patients evaluated between 2015-2017.

Outcome Measurements and Statistical Analysis: CCLO defined as total number of cancer-positive sextant locations among all PBx to that point in time (range 1-6). Baseline demographics and clinical characteristics of the entire cohort were stratified by CCLOΔ, defined as the difference between the first and last CCLO. CCLOΔ then correlated to progression to treatment and treatment outcomes.

Results: 261 men met inclusion criteria. Though mean number of biopsies was slightly higher in the CCLOΔ 3-5 cohort than the CCLOΔ 0-2 cohort (p=0.006), mean AS follow-up time (3.3 years) was not significantly different (p=0.327). As CCLOΔ increased, the proportion of men remaining on AS decreased while the proportion of men receiving treatment increased (p<0.001). In men undergoing radical prostatectomy, higher CCLOΔ was not associated with higher rates of Gleason 7-10 (p=0.38) or pT3 (p=0.52) disease. However, as CCLOΔ increased, upgrading from final PBx to RP pathology increased while downgrading decreased (p=0.12). In Kaplan-Meier analyses, lower CCLOΔ and lower initial CLO score were associated with the highest 5-year treatment-free survival rates (p<0.001).

Conclusion: Higher regional cancer core involvement is associated with higher rates of progression to treatment in AS patients. The CCLO metric is a potentially useful modality in stratifying patients for treatment in AS patients among the North American cohort, while not compromising disease outcomes.

Patient Summary: In the North American population, cumulative cancer-positive locations among biopsies can be used to predict active surveillance outcomes in men with prostate cancer.

Keywords: active surveillance, prostate cancer, cumulative cancer location

INTRODUCTION

Since its introduction, widespread screening with serum prostate-specific antigen (PSA) has facilitated earlier detection of prostate cancer (PCa).[1] Although the detection rate of PCa has increased, a significant proportion of newly diagnosed PCa are found to be clinically localized low-risk disease.[2,3] With improved understanding of the indolent natural history of these low risk prostate cancers, active surveillance (AS) has emerged as the standard of care for men with low-risk disease, based on the strength of multiple prospective series that have demonstrated excellent cancer-specific and overall survival without sacrificing an opportunity for cure in men who progress to higher risk disease.[4-8]

While significant variation exists among AS protocols and international guidelines, eligibility criteria for AS typically include a combination of PSA level, PSA density, clinical stage, and prostate biopsy (PBx) data (% positive cores and core volume) on both diagnostic and confirmatory biopsy.[9-12] In men followed on AS, progression to intervention is most commonly due to pathologic upgrading or increased tumor volume, but clinicians may also consider PSA kinetics and radiographic upstaging.[13,14] Treatment progression due to pathologic upgrading, increased tumor volume and fast PSA doubling times are reported in 35-50%, 2-63% and 21-44% of AS cohorts, respectively. Progression to definitive treatment due to patient anxiety has also been reported at rates of 6-9%.[4-6]

Ultimately, the decision to proceed to intervention is driven by the results of the latest PBx, often considered in isolation from prior PBx results. Given the multifocal nature of PCa and the sampling error that accompanies freehand transrectal ultrasonography (TRUS) PBx,[15-19] Erickson et al. described a novel method that considers the location of positive cores and regional involvement over time.[20] They first described cumulative cancer locations (CCLO) as a distinct and powerful predictor of AS outcomes (Supplementary Figure 1). Herein, we validate the utility of the CCLO metric in predicting AS outcomes in a North American cohort.

PATIENTS AND METHODS

Following institutional review board approval, retrospective chart review was performed on all AS patients evaluated in our institution between 2015-2017. At our institution, we utilize the AUA guidelines for active surveillance in men with very-low risk and low risk patients with localized PCa, and highly selective low volume localized intermediate risk PCa.[12] Men on active surveillance are followed routinely with PSA testing every 6 months and a PBx every 2 years; PBx may be completed earlier if there is evidence of a rising PSA or abnormal DRE. Patient demographics (age, race, clinical stage, preoperative PSA), clinical outcomes (AS progress, progression to treatment, PCa treatment modality), and radical prostatectomy (RP) pathology synoptic reports were also recorded. Pathology reports of all PBx for individual patients were abstracted for date of procedure, number and location of positive cores, and total Gleason score. Each PBx was reviewed and given a cancer location (CLO) score based on sextant location containing any positive cancer cores as described by Erickson et al.[20] Cumulative CLO (CCLO) was defined as the sum of all CLOs in all PBx to that point in time, while CCLOΔ was defined as the difference between the CCLO of the most recent PBx and the CLO of the first PBx (Supplementary Figure 1).

All patients were stratified based on CCLOΔ scores (0, 1, 2, 3-5), which was then correlated to AS clinical outcomes. Descriptive statistics for demographic and outcome comparisons were performed using analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. Kaplan-Meier survival curves were generated to evaluate treatment-free

progression stratified by CCLOΔ in the entire cohort and sub-stratified by initial CLO; results were compared with the log-rank test. All statistical tests were two-tailed and a p-value of <0.05 was considered statistically significant. Analyses were completed using SPSS®, version 23.0.

RESULTS

Patient demographics

Table 1 highlights key demographic data for the entire cohort and stratified by CCLOΔ. Age, initial PSA, clinical T-stage and risk stratification were not significantly different amongst CCLOΔ cohorts. Although the mean number of PBx increased with higher CCLOΔ (p=0.006), the time on active surveillance was not significantly different amongst cohorts (p=0.327).

Clinical outcomes

Table 2 summarizes clinical outcomes stratified by CCLOΔ. Within the entire cohort, most patients remained on AS (55.2%), while 42.5% were recommended treatment, with 34.1% agreeing to undergo treatment. As CCLOΔ increased, the proportion of men remaining on AS decreased and the proportion of men receiving treatment increased (p<0.0001).

Treatment indications and modalities

Table 3 and Supplementary Table 1 summarizes the treatment indications and treatment modalities utilized within each CCLOΔ cohort, respectively. Across all subsets, the primary indication for treatment recommendation and receipt was pathologic upgrading on PBx, ranging between 70-80%, while increased tumor volume was a much less common indication (20-30%). Radical prostatectomy (RP) was the most common treatment modality, with 54.7% of men receiving RP and 45.3% receiving radiation therapy with or without hormonal therapy.

Among the 6 (6.3%) patients who requested treatment due to anxiety, 4 (66.7%) underwent RP while 2 (33.3%) underwent radiotherapy.

Analysis of Radical Prostatectomy pathology

Supplementary Table 2 highlights the pathology outcomes in the 52 (19.9%) men who discontinued AS and underwent RP. Of the 4 patients who voluntarily discontinued AS, 2 had Gleason 3+3 disease and 2 had Gleason 3+4 disease; all 4 had pT2 disease. A higher CCLOΔ was not significantly associated with higher rates of intermediate risk (Gleason 7) disease, high risk (Gleason 8-10) disease or non-localized pT3 disease.

Progression of disease

Figure 1 depicts treatment-free survival (TFS) based on CCLOΔ for the entire population. Men with CCLO Δ0 had the best treatment-free survival (5-year TFS 78%), while men with CCLO Δ1-5 had a much higher rate of progression to treatment (5-year TFS 35-58%) ($p < 0.001$). Further stratification based on patients initial CLO (Figure 2) demonstrated distinct populations with superior TFS. Men with the best TFS (5-year TFS 90%) were those with initial CLO 1 and CCLO Δ0 (Figure 2A).

The swimmer's plots in Figure 3 depicts the entire patient cohort stratified by treatment receipt. Figure 3A are patients who remained on AS, including men who were recommended

93 treatment but refused. Figure 3B are patients who received treatment, including those who

94 chose treatment based on personal choice.

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DISCUSSION

AS has emerged as a standard of care for men with low-risk localized PCa, preserving an opportunity for curative intervention while minimizing overtreatment and associated adverse events. AS is characterized by a 30-40% rate of progression to treatment, driven primarily by grade and volume progression.[21] Progression to treatment is typically determined based on a patient's most recent PBx, often in isolation from their prior PBx history. Even when considering volume of disease, clinicians commonly focus on the number and percentage of positive cores within each PBx rather than the cumulative location of positive cores.[22] In 2018, Erickson et al. found that regional core involvement from the first two PBx (initial and confirmatory) may represent an additional metric to predicting progression of AS patients to treatment, with higher CCLO scores predicting poorer AS outcomes.[20] Importantly, the CCLO scores account for regional tumor burden from all prior PBx rather than the most recent PBx alone. As the study by Erickson et al. was conducted in 3 European centers with relatively homogenous populations, herein we independently validate the CCLO metric in a North American cohort.[23]

While previous studies have established that total number of positive PBx cores is predictive of AS progression, Erickson et al. showed that CCLOΔ was a powerful predictor for AS outcomes. Moreover, their study reports that CCLOΔ outperformed number of positive cores in predicting AS outcomes, with higher CCLOΔ predicting shorter treatment free survival on AS, Gleason score upgrading and adverse findings on RP.[20] In our study, a higher CCLOΔ was also significantly associated with treatment recommendation and treatment receipt ($p<0.0001$).

Kaplan-Meier analyses indicate that patients with higher CCLOΔ have lower 5-year TFS rates. When stratified by initial volume of disease, it appeared that men with an initial CLO 1 and CCLOΔ 0 have the greatest benefit from AS, with 5-year TFS rates exceeding 90%. Even men with initial CLO 1 and CCLOΔ 1-5 had 5-year TFS rates of <65%. These are consistent with findings by Erickson et al., who demonstrated that higher CCLO at the time of confirmatory biopsy predicted significantly shorter TFS when stratified by the number of positive cores.[20] These results indicate that while initial volume of disease impacts AS outcomes, cumulative volume progression over time must also be accounted for.

While Erickson et al. analyzed only the first two PBx (initial and confirmatory), in our study, we examined all PBx in patients during their entire AS follow-up, enabling better capture of temporal volume progression.[20] The mean number of PBx in the entire cohort was 3.1, with some patients receiving up to 7 PBx during follow-up. While it would be easy to presume that a patient's CCLO would increase proportionately with time on AS, we found that time on AS was not significantly associated with CCLOΔ. The swimmer's plot (Figure 3) clearly illustrates the distinct clinical trajectories of each AS patient over time. Most of the patients who remained on AS (Figure 3A) had low CCLOΔ scores throughout their surveillance period; many of the men who remained on AS while having high CCLO scores were recommended treatment but refused. In contrast, when looking at the course of men ultimately progressing to treatment (Figure 3B), most of these men had higher CCLOΔ scores. However, the spread of initial CLO scores is remarkably similar between the groups – indicating that all these men start with low volume

disease, but a few progresses to higher volume regional disease over time. Yet, as seen by the side by side comparison of Figures 3A and 3B, there are a subset of patients who progress to higher volume disease later in their AS follow-up, demonstrating that cumulative volume progression need not always occur early. This reinforces the need for continued follow-up in all AS patients. These findings further suggest that CCLOΔ can be a useful surrogate in predicting outcomes and need for treatment in AS eligible patients in conjunction with other pre-established clinical characteristics.

Within our cohort, 42% of patients were recommended treatment while 34% eventually underwent treatment. These rates are consistent with prior literature regarding progression to treatment in the AS population.[21] In contrast to Erickson et al., who found that higher CCLO was independently associated with adverse RP findings, in our subset of patients who underwent RP, higher CCLOΔ was not associated with an increased rate of Gleason 7-10 pathology on RP (p=0.38) or non-localized pT3 upstaging (p=0.52).[20] Interestingly, we found that as CCLOΔ increased, there was a suggestion, although not statistically significant, of increased upgrading from final PBx to RP pathology (p=0.12). However, in our cohort, 5.8% and 36.5% of patients had Gleason ≥8 disease and pT3 disease, respectively, on final RP pathology, which was consistent with previously reported rates in the literature for Gleason 8-10 upgrading (8.7-9.2%) and pT3 upstaging (27.7-43.0%).[24,25] Consistent with our data, Dall'Era et al. also found no association between time on AS and adverse pathological outcomes at the time of RP.[26] Overall,

the literature supports that men on AS undergoing RP have favorable outcomes, which is likely related to the selective criteria of AS inclusion and the long natural history of low risk PCa.

As for patients who were recommended or received treatment, we found that Gleason upgrading was the most common reason for clinicians to discontinue AS and pursue treatment. In a study of 46 AS patients who subsequently underwent RP, Hong et al. demonstrated that Gleason upgrading from pattern 3 to 4 or 5 was the most common reason for AS discontinuation (45.7%) and is also the most prognosticating factor for unfavorable disease on RP. Increased tumor volume (21.7%) and increased percentage of cancer per biopsy core (8.7%) were among other common reasons for AS discontinuation.[25] These findings suggest the negative predictive value of a low CCLOΔ.

Our study is not without its limitations. First, our study design is based on retrospective chart reviews with its inherent limitations. There was no central pathology review of PBx and final RP pathology. Our small sample size may also limit the ability to identify important associations with pathologic outcomes. Having data from a larger number of AS patients would also allow further analysis of patients with higher initial CLO and higher CCLOΔ and their association with AS outcomes. Additionally, regional core data depended on accurate labeling of PBx cores at the time of biopsy. Lastly, as a tertiary care facility, patient selection may be biased towards higher risk individuals and may not reflect the full spectrum of AS disease pathology. However,

178 regardless of these limitations, this cohort still represents a moderate AS cohort with a mean 3-
179 year AS follow-up.

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CONCLUSION

Our findings suggest that regional core involvement of PCa is associated with progression of disease in AS patients. The CCLO metric is a potentially useful modality among the North American cohort for risk stratification in patients managed with AS, without compromising disease outcomes.

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FIGURE LEGENDS

Table 1: Patient demographics

	All	**CCLO Δ0**	**CCLO Δ1**	**CCLO Δ2**	**CCLO Δ3-5**	***p*-value**
Total, N (%)	261 (100.0)	91 (34.9)	80 (30.7)	62 (23.8)	28 (10.7)	---
Age, years (mean ± SD)	69.5 ± 7.3	68.7 ± 7.4	69.6 ± 8.1	70.5 ± 6.2	69.5 ± 7.3	0.551
PSA, ng/mL (mean ± SD)	5.3 ± 2.8	5.2 ± 2.8	5.4 ± 2.8	5.5 ± 2.5	5.2 ± 3.2	0.904
Number of PBx (mean ± SD)	3.1 ± 1.4	2.8 ± 1.2	3.1 ± 1.4	3.2 ± 1.4	3.8 ± 1.5	0.006
Time on AS, years (mean ± SD)	3.3 ± 2.5	3.1 ± 2.5	3.6 ± 2.6	3.0 ± 2.4	3.7 ± 2.6	0.327
Initial CLO (median)	1	1	1	1.5	1	---
Final CCLO (median)	2	1	2	3.5	4	---
Gleason Score at 1st PBx						0.111
3+3, N (%)	243 (93.1)	85 (93.4)	76 (95.0)	54 (87.1)	28 (100.0)	
3+4, N (%)	18 (6.9)	6 (6.6.)	4 (5.0)	8 (12.9)	0 (0.0)	
Clinical T-stage						0.150
cT1, N (%)	238 (91.2)	84 (92.3)	69 (86.3)	57 (91.9)	28 (100.0)	
cT2, N (%)	23 (8.8)	7 (7.7)	11 (13.8)	5 (8.1)	0 (0.0)	
Risk Stratification						0.669
Very low, N (%)	65 (24.9)	22 (24.2)	19 (23.8)	15 (24.2)	9 (32.1)	
Low, N (%)	179 (68.6)	62 (68.1)	57 (71.2)	41 (66.1)	19 (67.9)	
Intermediate, N (%)	17 (6.5)	7 (7.7)	4 (5.0)	6 (9.7)	0 (0.0)	

Abbreviations: PSA – prostate-specific antigen; PBx – prostate biopsy; AS – active surveillance; CLO – cancer location; CCLO – cumulative cancer location

Table 2: Clinical outcomes for AS

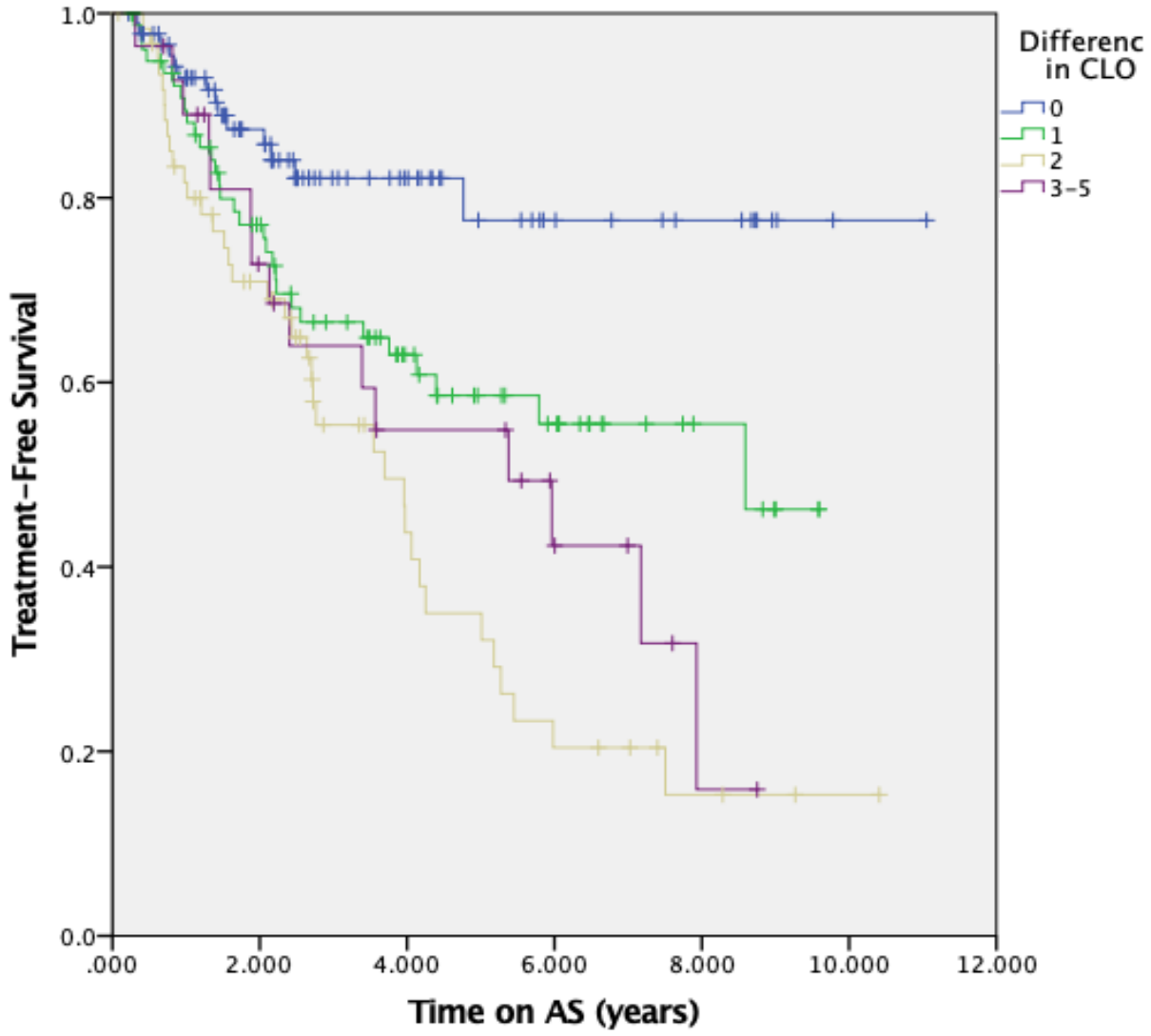
Clinical Outcomes	**All**	**CCLO Δ0**	**CCLO Δ1**	**CCLO Δ2**	**CCLO Δ3-5**	***p*-value**
Total, N (%)	261 (100.0)	91 (100.0)	80 (100.0)	62 (100.0)	28 (100.0)	---
Remained on AS, N (%)	144 (55.2)	71 (78.0)	46 (57.5)	19 (30.6)	8 (28.6)	<0.0001
Treatment recommended, N (%)	22 (8.4)	7 (7.7)	4 (5.0)	6 (9.7)	5 (17.9)	
Treatment received, N (%)	89 (34.1)	12 (13.2)	29 (36.3)	33 (53.2)	15 (53.6)	
Treatment requested, N (%)	6 (2.3)	1 (1.1)	1 (1.3)	4 (6.5)	0 (0.0)	

Legend:
Treatment recommended: patients who were recommended treatment but chose to remain on AS
Treatment requested: patients who voluntarily opted out of AS to undergo definitive treatment
Treatment received: patients for whom treatment was recommended and received

Table 3: Treatment indications

	Indication for treatment	**All**	**CCLO Δ0**	**CCLO Δ1**	**CCLO Δ2**	**CCLO Δ3-5**
Treatment recommended, N (%)	**Total**	22 (100.0)	7 (100.0)	4 (100.0)	6 (100.0)	5 (100.0)
	Gleason upgrading	15 (68.2)	5 (71.4)	3 (75.0)	3 (50.0)	4 (80.0)
	Increased tumor volume	9 (40.9)	2 (28.6)	1 (25.0)	3 (50.0)	3 (60.0)
	Elevated PSA	2 (9.1)	1 (14.3)	0 (0.0)	0 (0.0)	1 (20.0)
Treatment received, N (%)	**Total**	89 (100.0)	12 (100.0)	29 (100.0)	33 (100.0)	15 (100.0)
	Gleason upgrading	72 (80.9)	9 (75.0)	26 (89.7)	25 (75.8)	12 (80.0)
	Increased tumor volume	21 (23.6)	2 (16.7)	5 (17.2)	10 (30.3)	4 (26.7)
	Elevated PSA	7 (7.9)	1 (8.3)	3 (10.3)	1 (3.0)	2 (13.3)

*Treatment indications are not mutually exclusive



Number at risk

Δ0	90	54	25	12	8	1	0
Δ1	79	53	30	17	6	0	0
Δ2	61	37	15	7	3	1	0
Δ3-5	27	17	11	6	1	0	0
	0	2	4	6	8	10	12

Time on AS (years)

Cumulative number of events

Δ0	0	10	13	14	14	14	14
Δ1	0	17	26	29	29	30	30
Δ2	0	17	28	36	37	37	37
Δ3-5	0	7	11	13	15	15	15
	0	2	4	6	8	10	12

Time on AS (years)

Figure 1: Treatment-free survival for the entire population, stratified by CCLOΔ; Log-rank test: $p < 0.001$.

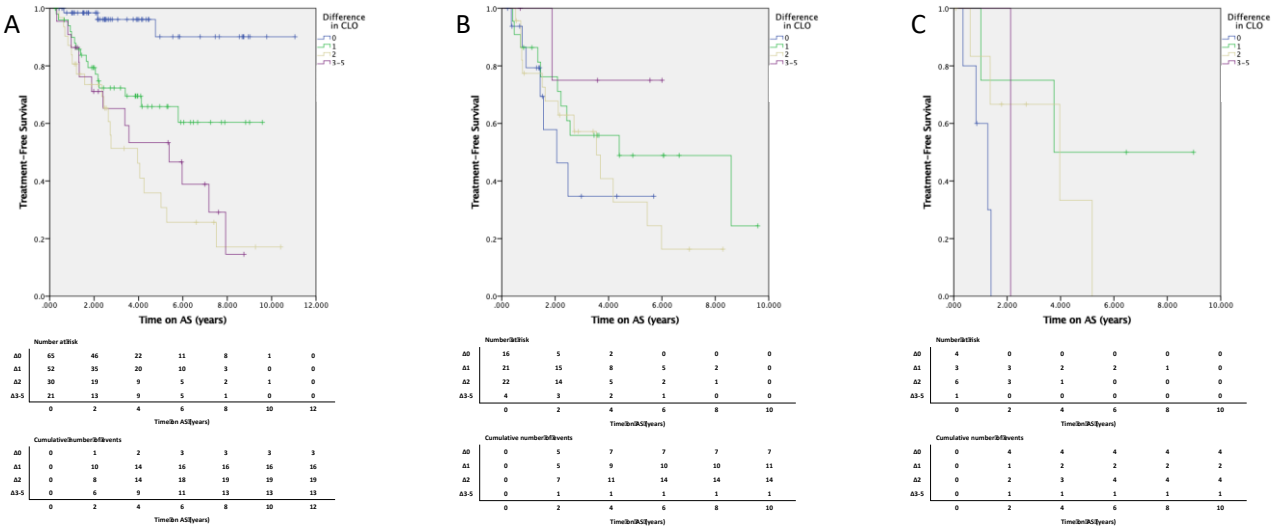


Figure 2: Treatment-free survival stratified by CCLOΔ; Subset analysis of men with initial CLO 1 (Figure 2A), initial CLO 2 (Figure 2B), initial CLO 3 (Figure 2C).

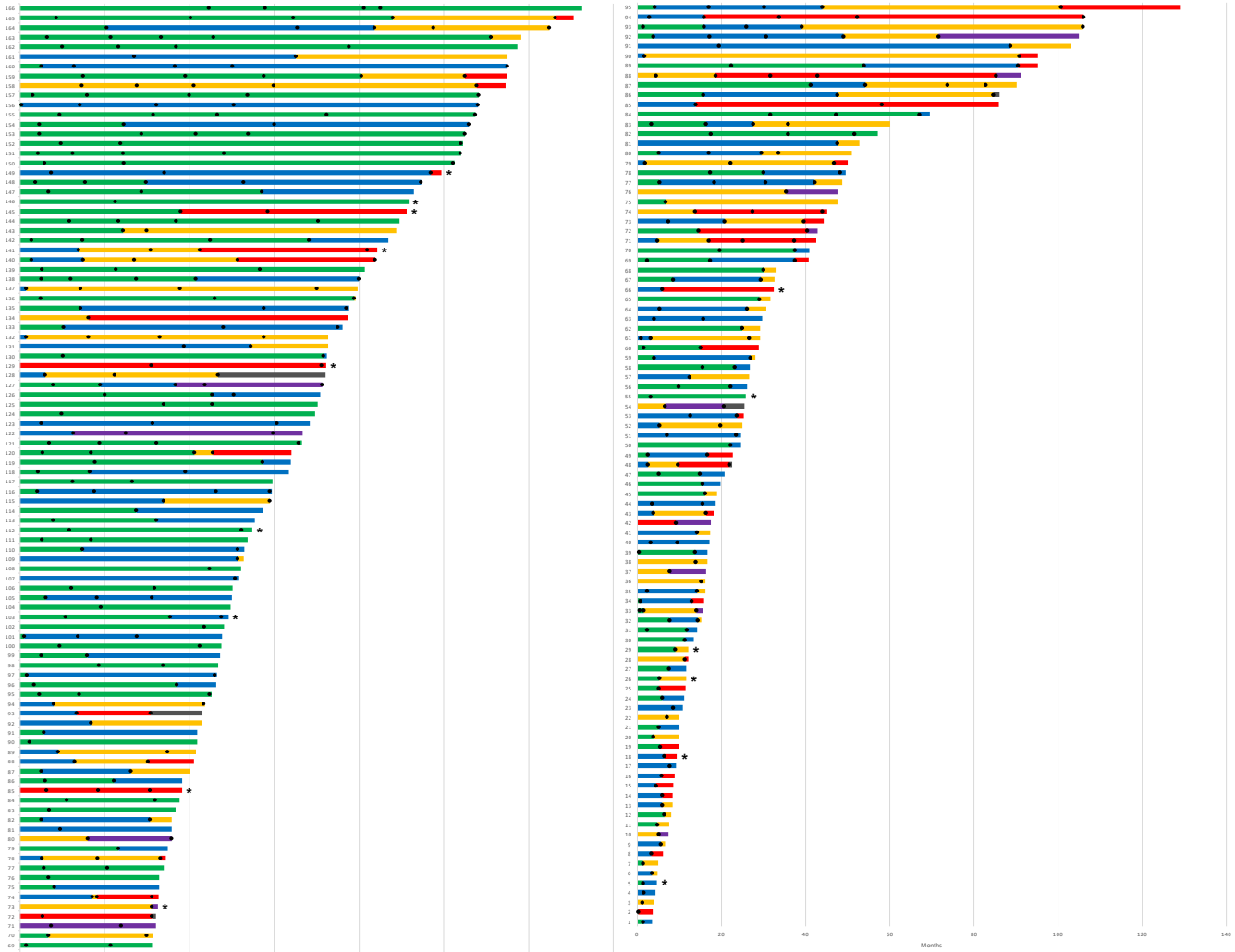

Months
Months
CCLO1
CCLO2
CCLO3
CCLO4
CCLO5
CCLO6
PBx

Figure 3: Swimmer's Plots of the Entire Cohort, separated in men who stayed on AS (Figure 3A) and men who received treatment (Figure 3B).

Legend:

Each ● represents a single biopsy. Color coding represents the CCLO at the time based on all prior biopsies.

In Figure 3A, * represents men recommended for treatment but who refused.

In Figure 3B, * represents men who chose treatment as a personal choice.

SUPPLEMENTARY TABLES

Supplementary Table 1: Treatment modalities

Types of Treatment	**All**	**CCLO Δ0**	**CCLO Δ1**	**CCLO Δ2**	**CCLO Δ≥3**
Total, N (%)	95 (100.0)	13 (100.0)	30 (100.0)	37 (100.0)	15 (100.0)
RP, N (%)	52 (54.7)	10 (76.9)	19 (63.3)	15 (40.5)	8 (53.3)
XRT +/- ADT, N (%)	43 (45.3)	3 (23.1)	11 (36.7)	22 (59.5)	7 (46.7)

Abbreviations: RP – radical prostatectomy; XRT – radiation therapy; ADT – hormonal therapy; CCLO – cumulative cancer location.
*Treatment modalities are not mutually exclusive

Supplementary Table 2: Analysis of RP patients

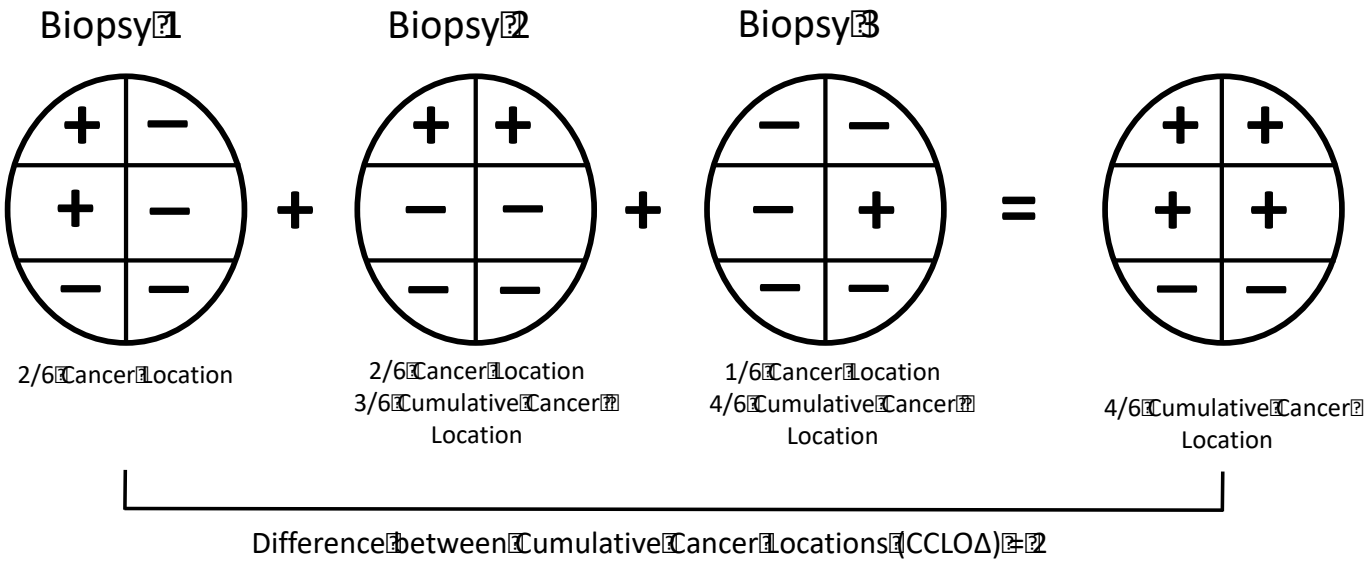
RP outcomes		**All**	**CCLO Δ0**	**CCLO Δ1**	**CCLO Δ2**	**CCLO Δ≥3**	***p*-value**
Total		52 (100.0)	10 (100.0)	18 (100.0)	15 (100.0)	9 (100.0)	---
Gleason score, N (%)	3+3	9 (17.3)	3 (30.0)	2 (11.1)	2 (13.3)	2 (22.2)	0.380
	3+4	31 (59.6)	5 (50.0)	9 (50.0)	12 (80.0)	5 (55.5)	
	4+3	9 (17.3)	1 (10.0)	6 (33.3)	0 (0.0)	2 (22.2)	
	8-10	3 (5.8)	1 (10.0)	1 (5.6)	1 (6.7)	0 (0.0)	
Pathological T-stage, N (%)	pT2	33 (63.5)	7 (70.0)	9 (50.0)	11 (73.3)	6 (66.7)	0.520
	pT3	19 (36.5)	3 (30.0)	9 (50.0)	4 (26.7)	3 (33.3)	

Abbreviations: RP – radical prostatectomy; CCLO – cumulative cancer location

Supplementary Table 3: Gleason Score comparison of final PBx to RP

RP outcomes	**All**	**CCLO Δ0**	**CCLO Δ1**	**CCLO Δ2**	**CCLO Δ≥3**	***p*-value**
Total, N (%)	52 (100.0)	10 (100.0)	18 (100.0)	15 (100.0)	9 (100.0)	---
Pathology downgrade, N (%)	7 (13.5)	3 (30.0)	4 (22.2)	0 (0.0)	0 (0.0)	0.119
Pathology consistent, N (%)	35 (67.3)	7 (70.0)	11 (61.1)	10 (66.7)	7 (77.8)	
Pathology upgrade, N (%)	10 (19.2)	0 (0.0)	3 (16.7)	5 (33.3)	2 (22.2)	

Abbreviations: PBx – prostate biopsy; RP – radical prostatectomy; CCLO – cumulative cancer location



- CLO = Cancer Location
- CCLO = Cumulative Cancer Location

Supplementary Figure 1: A sample patient on active surveillance for prostate cancer with three prior prostate biopsies. Based on individual biopsies, the patient only has up to 2 cancer-positive locations (CLO). After aggregating CLOs among all prior biopsies, cumulative cancer-positive location (CCLO) is 4. The CCLOΔ in this patient, defined by subtracting final CCLO with initial CLO, is 2.