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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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**Authors**

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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 CCLO $\Delta$ , defined as the difference between the first and last CCLO. CCLO $\Delta$  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 CCLO $\Delta$  3-5 cohort than the CCLO $\Delta$  0-2 cohort ( $p=0.006$ ), mean AS follow-up time (3.3 years) was not significantly different ( $p=0.327$ ). As CCLO $\Delta$  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 CCLO $\Delta$  was not associated with higher rates of Gleason 7-10 ( $p=0.38$ ) or pT3 ( $p=0.52$ ) disease. However, as CCLO $\Delta$  increased, upgrading from final PBx to RP pathology increased while downgrading decreased ( $p=0.12$ ). In Kaplan-Meier analyses, lower CCLO $\Delta$  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

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## 1 INTRODUCTION

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

10

11 While significant variation exists among AS protocols and international guidelines, eligibility  
12 criteria for AS typically include a combination of PSA level, PSA density, clinical stage, and  
13 prostate biopsy (PBx) data (% positive cores and core volume) on both diagnostic and  
14 confirmatory biopsy.<sup>9-12</sup> In men followed on AS, progression to intervention is most commonly  
15 due to pathologic upgrading or increased tumor volume, but clinicians may also consider PSA  
16 kinetics and radiographic upstaging.<sup>13,14</sup> Treatment progression due to pathologic upgrading,  
17 increased tumor volume and fast PSA doubling times are reported in 35-50%, 2-63% and 21-  
18 44% of AS cohorts, respectively. Progression to definitive treatment due to patient anxiety has  
19 also been reported at rates of 6-9%.<sup>4-6</sup>

20

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

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## 28 PATIENTS AND METHODS

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

44

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

49 progression stratified by CCLOΔ in the entire cohort and sub-stratified by initial CLO; results  
50 were compared with the log-rank test. All statistical tests were two-tailed and a p-value of  
51 <0.05 was considered statistically significant. Analyses were completed using SPSS®, version  
52 23.0.

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## 53 RESULTS

### 54 Patient demographics

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

59

### 60 Clinical outcomes

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

65

### 66 Treatment indications and modalities

67 Table 3 and Supplementary Table 1 summarizes the treatment indications and treatment  
68 modalities utilized within each CCLOΔ cohort, respectively. Across all subsets, the primary  
69 indication for treatment recommendation and receipt **was** pathologic upgrading on PBx,  
70 ranging between 70-80%, while increased tumor volume was a much less common indication  
71 (20-30%). Radical prostatectomy (RP) was the most common treatment modality, with 54.7% of  
72 men receiving RP and 45.3% receiving radiation therapy **with or without** hormonal therapy.

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

75

#### 76 Analysis of Radical Prostatectomy pathology

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

82

#### 83 Progression of disease

84 Figure 1 depicts treatment-free survival (TFS) based on CCLO $\Delta$  for the entire population. Men  
85 with CCLO  $\Delta$ 0 had the best treatment-free survival (5-year TFS 78%), while men with CCLO  $\Delta$ 1-5  
86 had a much higher rate of progression to treatment (5-year TFS 35-58%) ( $p < 0.001$ ). Further  
87 stratification based on patients initial CLO (Figure 2) demonstrated distinct populations with  
88 superior TFS. Men with the best TFS (5-year TFS 90%) were those with initial CLO 1 and CCLO  $\Delta$ 0  
89 (Figure 2A).

90

91 The swimmer's plots in Figure 3 depicts the entire patient cohort stratified by treatment  
92 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.

95

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## 96 DISCUSSION

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

110

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

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

125

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

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

145

146 Within our cohort, 42% of patients were recommended treatment while 34% eventually  
147 underwent treatment. These rates are consistent with prior literature regarding progression to  
148 treatment in the AS population.<sup>21</sup> In contrast to Erickson et al., who found that higher CCLO was  
149 independently associated with adverse RP findings, in our subset of patients who underwent  
150 RP, higher CCLO $\Delta$  was not associated with an increased rate of Gleason 7-10 pathology on RP  
151 ( $p=0.38$ ) or non-localized pT3 upstaging ( $p=0.52$ ).<sup>20</sup> Interestingly, we found that as CCLO $\Delta$   
152 increased, there was a suggestion, although not statistically significant, of increased upgrading  
153 from final PBx to RP pathology ( $p=0.12$ ). However, in our cohort, 5.8% and 36.5% of patients  
154 had Gleason  $\geq 8$  disease and pT3 disease, respectively, on final RP pathology, which was  
155 consistent with previously reported rates in the literature for Gleason 8-10 upgrading (8.7-  
156 9.2%) and pT3 upstaging (27.7-43.0%).<sup>24,25</sup> Consistent with our data, Dall'Era et al. also found no  
157 association between time on AS and adverse pathological outcomes at the time of RP.<sup>26</sup> Overall,

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

160

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

169

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

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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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181 CONCLUSION

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

186

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## FIGURE LEGENDS

Table 1: Patient demographics

	All	CCLO Δ0	CCLO Δ1	CCLO Δ2	CCLO Δ3-5	p-value
<b>Total, N (%)</b>	261 (100.0)	91 (34.9)	80 (30.7)	62 (23.8)	28 (10.7)	---
<b>Age, years (mean ± SD)</b>	69.5 ± 7.3	68.7 ± 7.4	69.6 ± 8.1	70.5 ± 6.2	69.5 ± 7.3	0.551
<b>PSA, ng/mL (mean ± SD)</b>	5.3 ± 2.8	5.2 ± 2.8	5.4 ± 2.8	5.5 ± 2.5	5.2 ± 3.2	0.904
<b>Number of PBx (mean ± SD)</b>	3.1 ± 1.4	2.8 ± 1.2	3.1 ± 1.4	3.2 ± 1.4	3.8 ± 1.5	0.006
<b>Time on AS, years (mean ± SD)</b>	3.3 ± 2.5	3.1 ± 2.5	3.6 ± 2.6	3.0 ± 2.4	3.7 ± 2.6	0.327
<b>Initial CLO (median)</b>	1	1	1	1.5	1	---
<b>Final CCLO (median)</b>	2	1	2	3.5	4	---
<b>Gleason Score at 1<sup>st</sup> PBx</b>						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)	
<b>Clinical T-stage</b>						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)	
<b>Risk Stratification</b>						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

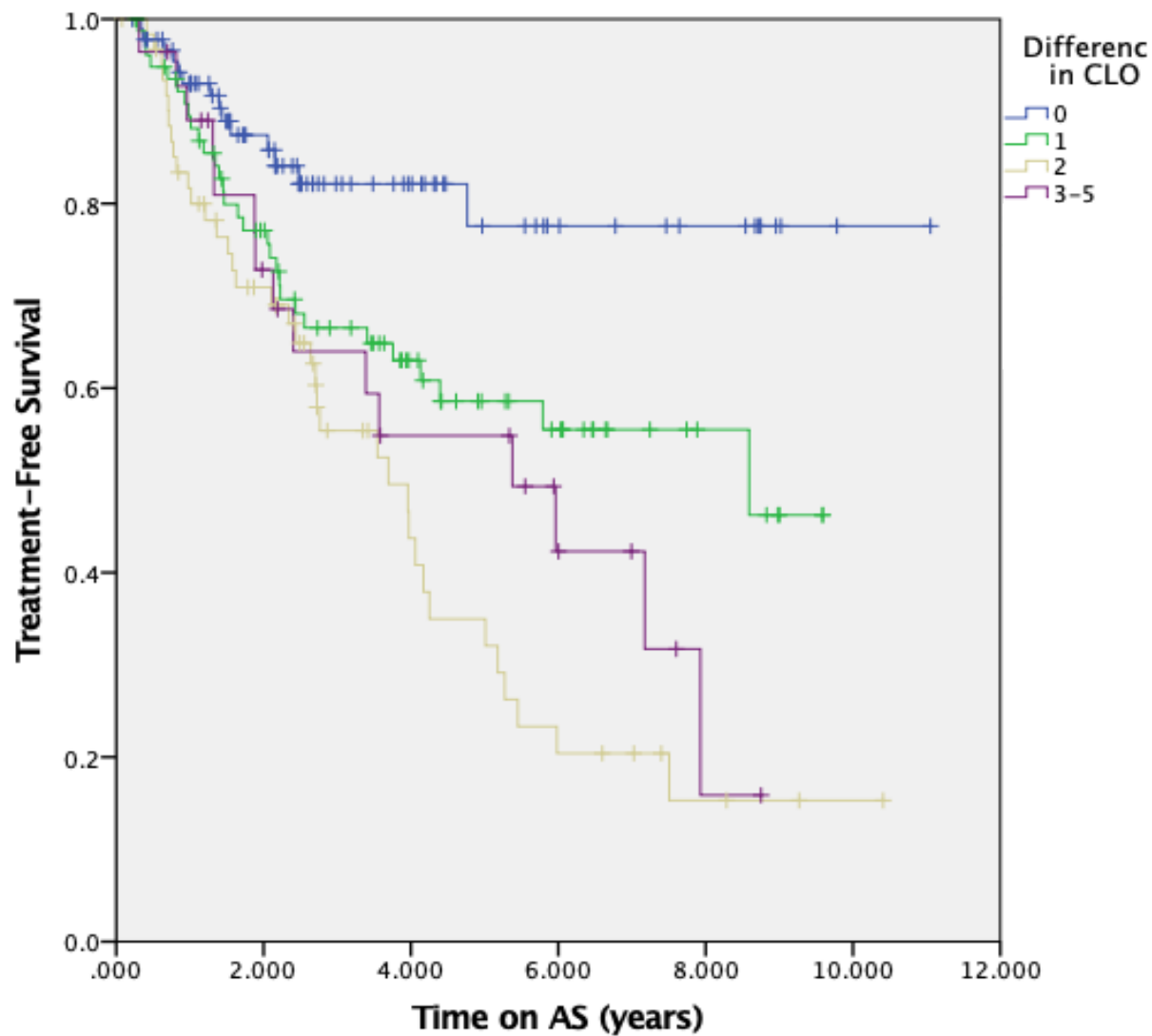
Treatment requested: patients who voluntarily opted out of AS to undergo definitive treatment

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
<b>Treatment recommended, N (%)</b>	<b>Total</b>	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)
<b>Treatment received, N (%)</b>	<b>Total</b>	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

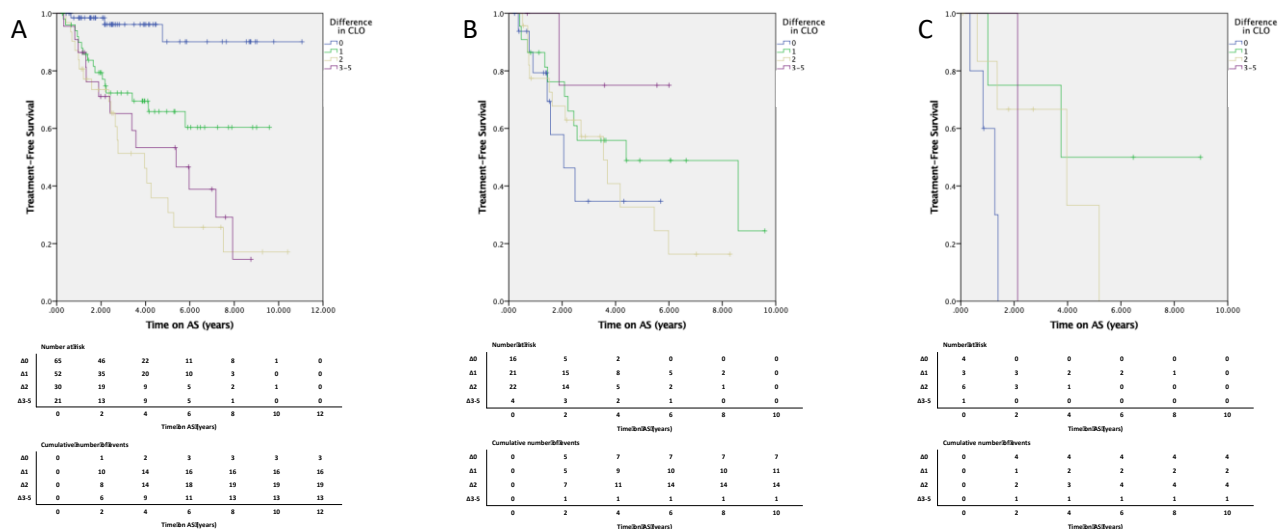


	Number at risk						
	0	2	4	6	8	10	12
$\Delta 0$	90	54	25	12	8	1	0
$\Delta 1$	79	53	30	17	6	0	0
$\Delta 2$	61	37	15	7	3	1	0
$\Delta 3-5$	27	17	11	6	1	0	0

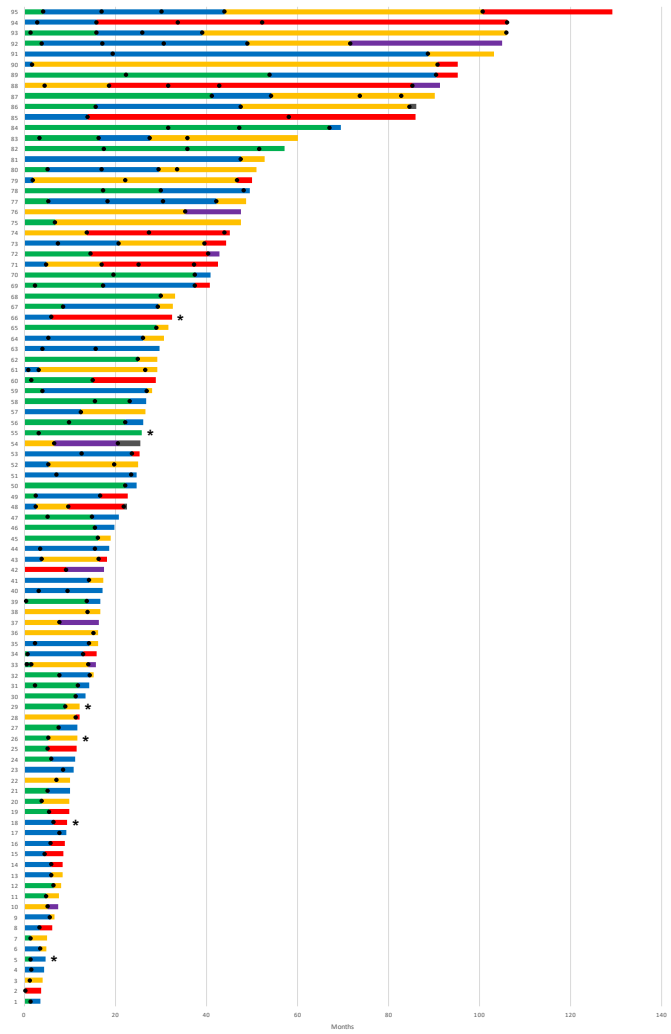
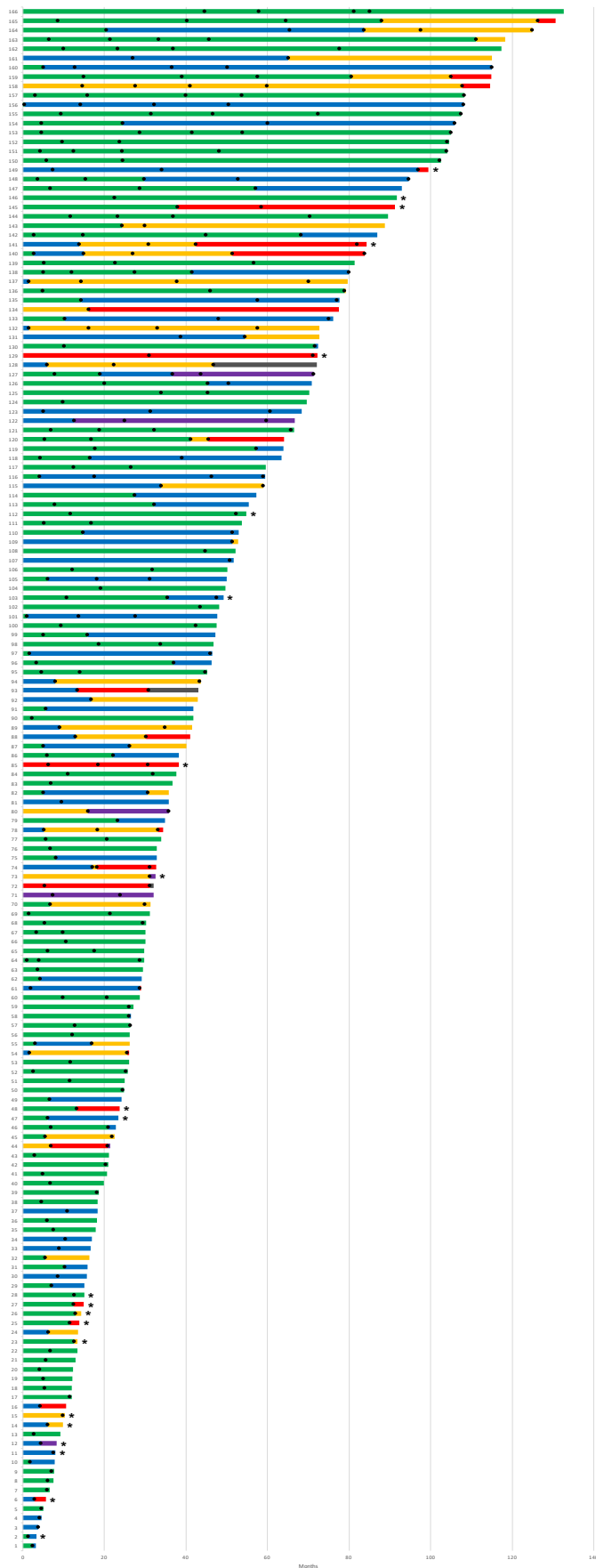
	Cumulative number of events						
	0	2	4	6	8	10	12
$\Delta 0$	0	10	13	14	14	14	14
$\Delta 1$	0	17	26	29	29	30	30
$\Delta 2$	0	17	28	36	37	37	37
$\Delta 3-5$	0	7	11	13	15	15	15

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



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





- 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.

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## SUPPLEMENTARY TABLES

Supplementary Table 1: Treatment modalities

Types of Treatment	All	CCLO $\Delta 0$	CCLO $\Delta 1$	CCLO $\Delta 2$	CCLO $\Delta \geq 3$
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

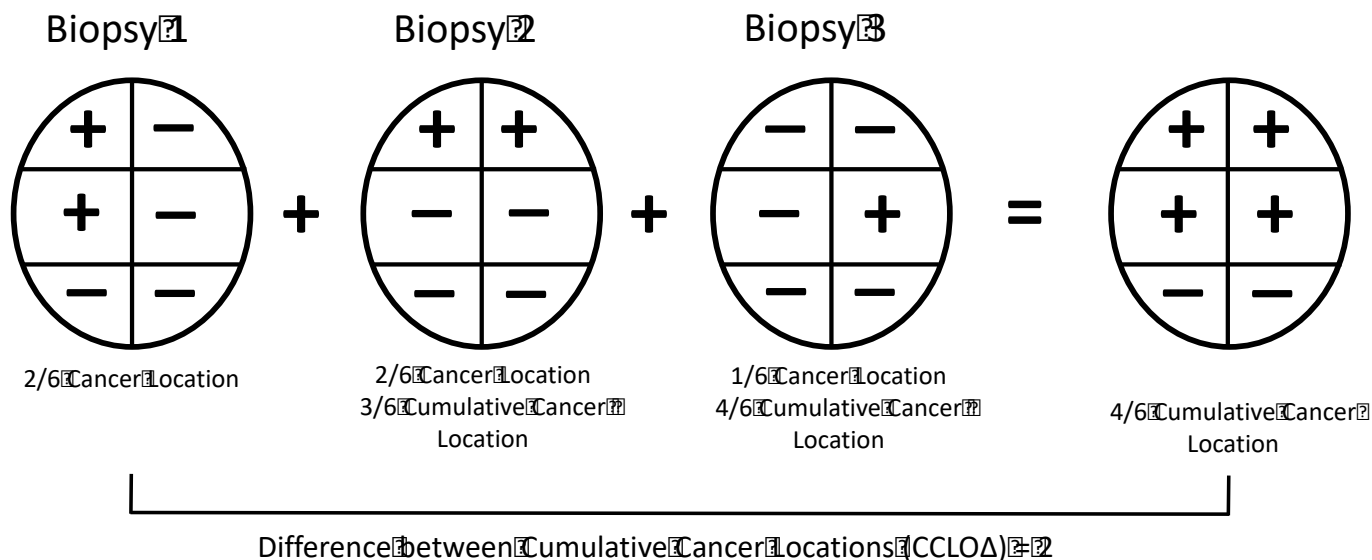
RP outcomes	All	CCLO $\Delta 0$	CCLO $\Delta 1$	CCLO $\Delta 2$	CCLO $\Delta \geq 3$	p-value	
Total	52 (100.0)	10 (100.0)	18 (100.0)	15 (100.0)	9 (100.0)	---	
Gleason score, N (%)	3+3	9 (17.3)	3 (30.0)	2 (11.1)	2 (13.3)	2 (22.2)	0.380
	3+4	31 (59.6)	5 (50.0)	9 (50.0)	12 (80.0)	5 (55.5)	
	4+3	9 (17.3)	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 $\Delta 0$	CCLO $\Delta 1$	CCLO $\Delta 2$	CCLO $\Delta \geq 3$	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 CCLO $\Delta$  in this patient, defined by subtracting final CCLO with initial CLO, is 2.