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Cumulative Cancer Locations is a Novel Metric for Predicting Active Surveillance Outcomes: A Multicenter Study

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Abstract

Background: Active surveillance (AS) of prostate cancer (PC) has increased in popularity to address overtreatment.

Objective: To determine whether a novel metric, cumulative cancer locations (CCLO), can predict AS outcomes in a group of AS patients with low and very low risk.

Design, setting, and participants: CCLO is obtained by summing the total number of histological cancer-positive locations in both diagnostic and confirmatory biopsies (Bx). The retrospective study cohort comprised three prospective AS cohorts (Helsinki University Hospital: $n = 316$; European Institute of Oncology: $n = 204$; and University of Münster: $n = 89$).

Outcome measurements and statistical analysis: We analyzed whether risk stratification based on CCLO predicts different AS outcomes: protocol-based discontinuation (PBD), Gleason upgrading (GU) during AS, and adverse findings in radical prostatectomy (RP) specimens.

Results: In Kaplan Meier analyses, patients in the CCLO high-risk group experienced significantly shorter event-free survival for all outcomes (PBD, GU, and adverse RP findings; all $p < 0.002$). In multivariable Cox regression analysis, patients in the CCLO high-risk group had a significantly higher risk of experiencing PBD (hazard ratio [HR] 12.15, 95% confidence interval [CI] 6.18–23.9; $p < 0.001$), GU (HR 6.01, 95% CI 2.16–16.8; $p = 0.002$), and adverse RP findings (HR 9.144, 95% CI 2.27–36.9; $p = 0.006$). In receiver operating characteristic analyses, the area under the curve for CCLO outperformed the number of cancer-positive Bxs in confirmatory Bx in predicting PBD (0.734 vs 0.682), GU (0.655 vs 0.576) and adverse RP findings (0.662 vs 0.561) and the added value was supported by decision curve analysis.

Conclusions: CCLO is distinct from the number of positive Bx cores. Higher CCLO predicts AS outcomes and may aid in selection of patients for AS.

Patient summary: For patients on active surveillance for prostate cancer, the cumulative number of cancer-positive locations in diagnostic and confirmatory biopsies is a predictor of active surveillance outcomes.

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1. Introduction

The use of prostate-specific antigen (PSA) screening has led to a decrease in prostate cancer (PC)-specific mortality [1] but has come at the cost of diagnosing and overtreating clinically insignificant cancer [2]. Active surveillance (AS) is an option to reduce the harmful effects of overtreatment [3–5]. However, deferred treatment with radical intention occurs in up to 52% of AS patients within 5 yr of enrollment [6]. Thus, there is an urgent need to distinguish PCs with unfavorable outcomes earlier in AS to avoid disease progression and excess morbidity.

Previous studies have shown that 12-core (bi-sextant) biopsies (Bx) often fail to detect all cancer foci [7,8]. In the PRIAS trial, only patients with two or fewer positive Bxs at each Bx session can be included and remain on AS [9]. However, most AS inclusion and exclusion criteria, if not all, do not consider the location of positive cores, and the cumulative tumor locations in the two first Bxs (diagnostic Bx [DBx] and confirmatory Bx [CBx]) are not routinely assessed. We hypothesized that the tumor burden expressed as cumulative cancer locations (CCLO) may predict AS protocol-based discontinuation (PBD), AS discontinuation due to Gleason upgrading (GU), and adverse pathological findings in radical prostatectomy (RP) specimens from patients undergoing RP after discontinuation of AS.

2. Patients and methods

The institutional review boards (IRBs) of Helsinki University Hospital (HUS; 276/E6/06) and University of Münster (UKM; 2008-485-f-S) approved the study, whereas the European Institute of Oncology (IEO; does not have an IRB) study was conducted according to Declaration of Helsinki principles. All study participants gave written informed consent.

We queried all available AS and Bx data at each center (HUS: PRIAS, January 2007–November 2015; IEO: AS, February 2005–June 2016; UKM: PRIAS, September 2006–August 2017) for 609 patients whose data could be obtained (HUS: $n = 316$; IEO: $n = 204$, UKM: $n = 89$). PRIAS criteria restrict inclusion to patients with a maximum of two positive cores of Gleason score (GS) 6 PC, whereas the IEO AS criteria allow for a maximum of three positive GS 6 cores and incorporate two additional transitional-zone (TZ) Bxs in addition to 12-core (bi-sextant) Bx. The IEO AS criteria also allow inclusion of patients with one GS 7 positive core: these patients were excluded from the analysis as we sought to control for GS. The final study database included patients who fulfilled AS inclusion criteria at the time of CBx (1-yr follow-up) and thereafter continued AS (HUS: $n = 149$; IEO: $n = 173$; UKM: $n = 58$). Table 1 lists detailed demographics for the individual AS cohorts and the pooled cohort.

Calculation of CCLO is illustrated in Fig. 1. Standard Bxs are taken according to a normal protocol, and the information for each location is reduced to a dichotomous positive or negative value (Fig. 1A). Locations containing any number of cores with cancer are positive. CCLO is calculated as the cumulative total of the positive locations from both the DBx and CBx (Fig. 1B).

We assessed three outcome variables: AS discontinuation because of GU, PBD, and adverse clinicopathological findings (GS $> 3 + 4$ and/or pT3) in RP specimens. Univariate Fisher's exact tests and Student's *t* tests were used to analyze the associations between clinical variables and outcomes. Kaplan-Meier curves were plotted and were compared using Mantel-Haenszel log-rank tests. Multivariate Cox regression analysis was performed to assess the hazard ratios for the association of clinicopathological variables with outcomes. Receiver operating characteristic (ROC) area under the curve (AUC) and decision curve analysis

Table 1 – Cohort demographics

Characteristic	HUS ($n = 149$)	IEO ($n = 173$)	UKM ($n = 58$)	Pooled ($n = 380$)
Median age at diagnosis, yr (range)	63.2 (40.7–78.2)	64.6 (43.6–78.1)	65.3 (49.7–74.9)	63.6 (40.7–78.2)
Median pre-AS PSA, ng/ml (range)	5.5 (0.9–10)	5.61 (0–50.7)	6.05 (1.7–16.7)	5.68 (0–50.7)
Median PSA-D, ng/ml/ml (range)	0.14 (0.05–0.2)	0.10 (0.02–0.41)	0.14 (0.04–0.31)	0.12 (0.02–0.41)
cT stage at diagnosis, *n* (%)				
T1c	148 (99.3)	159 (91.9)	48 (82.8)	355 (93.4)
T2a	1 (0.7)	14 (8.1)	10 (17.2)	25 (6.6)
No. of positive DBx cores, *n* (%)				
1	116 (77.9)	118 (68.2)	40 (69.0)	274 (72.1)
2	33 (22.1)	48 (27.7)	18 (31.0)	99 (26.1)
3 [a]	NA	7 (4.1)	NA	7 (1.8)
No. of positive CBx cores, *n* (%) [b]				
0	73 (59.9)	93 (53.8)	35 (60.3)	201 (56.9)
1	32 (26.2)	38 (22.0)	20 (34.5)	90 (25.5)
2	17 (13.9)	29 (16.8)	3 (5.2)	49 (13.9)
3 [a]	NA	13 (7.5)	NA	13 (3.7)
Discontinuation, *n* (%) [c]				
Protocol-based	34 (59.6)	37 (56.9)	18 (85.7)	89 (62.2)
Gleason upgrading–based [d]	18 (52.9)	12 (32.4)	13 (56.5)	43 (48.3)
Non–protocol-based	23 (40.4)	28 (43.1)	3 (14.3)	54 (37.8)
Active treatment, *n* (%)				
Radical prostatectomy	30 (52.7)	59 (85.5)	12 (52.2)	101 (67.8)
Radiotherapy	8 (14.0)	10 (14.5)	7 (30.4)	25 (16.8)
Watchful waiting/other	19 (33.3)	0 (0.0)	4 (17.4)	23 (15.4)

HUS = Helsinki University Hospital; IEO = European Institute of Oncology; UKM = University of Münster; PSA = prostate-specific antigen; PSA-D = PSA density; DBx = diagnostic biopsy; CBx = confirmatory biopsy.
[a] The IEO active surveillance criteria allow for three positive cores.
[b] Given the pathology reporting standards of the time, sextant-level data, but not core-level data, were available for some patients.
[c] Four patients in the IEO cohort underwent active treatment but had missing discontinuation data
[d] Gleason upgrading percentage assessed as a proportion of protocol-based discontinuers.

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