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TITLE PAGE

Utility of preoperative Neutrophil / Lymphocyte ratio (NLR) as a new objective prognostic tool in endoscopically treated upper tract urothelial carcinoma. A retrospective evaluation.

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Runninghead: NLR as an objective prognostic tool in endoscopic UTUC management

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ABSTRACT (249words)

Introduction

This exploratory retrospective analysis examined any potential prognostic role of pre-operative NLR for progression free survival (PFS) and time to endoscopically verified upper tract or bladder recurrence free survival (RFS), in upper tract urothelial cancer (UTUC) patients selected for endoscopic treatment with subsequent endo-surveillance.

Patients and Methods

Eligibility criteria were natural orifice endoscopically retrogradely treated low-risk and imperative UTUC patients treated between 2005-2019, with biopsy confirmed diagnosis and 12 months minimum follow-up. For PFS, optimal NLR cut-off value was derived by log-rank test. Subsequently, both PFS and RFS were assessed for differences using Kaplan–Meier survival curves and log-rank test. Multivariate proportional Cox regression analysis adjusted for clinico-pathological variables was performed to examine end-points for NLR independent prognostic significance.

Results

There were 100 eligible patients (63 truly low-risk and 37 imperative cases). The optimal PFS log-rank test NLR cut-off value was 2.7. NLR $\geq$ 2.7 was significantly associated with shorter PFS (p=0.01), and shorter upper tract RFS (p=0.03), but not with bladder RFS (p=0.90). Only positive high-grade cytology (HR 5.92, 95% CI 2.140 – 16.35, p=0.002) and NLR$\geq$2.7 (HR 4.28, 95% CI 1.34 – 13.72, p=0.014) independently predicted PFS in multivariate analysis. Recurrence and progression were not significantly linked in the low-risk subset.

Conclusions

This exploratory analysis showed that baseline NLR evaluation before first endoscopic UTUC treatment may be a valuable predictor and prognosticator of defined disease progression and of upper tract recurrence risk. In conjunction with high-grade urine cytology, NLR may improve risk stratification to optimize future individualized management.

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MANUSCRIPT (2481)

Introduction

European Association of Urology (EAU) guidelines [1] state that endoscopic treatment for low-risk upper tract urothelial cancer (UTUC) may reduce radical nephro-ureterectomy (RNU) or partial ureterectomy morbidity, without compromising oncological outcomes or renal function, and is the preferred approach in low-risk cancers, with non-inferior survival. Consequently, this option should be discussed in all confirmed low-risk cases, irrespective of contra-lateral kidney status, while retaining RNU as the "gold standard" treatment for the high-risk UTUC population, regardless of tumor location [2].

Technical instrument improvements have contributed to expand endoscopic UTUC treatment indications, along with introduction of new ablative dual-energy technologies [3]. Together, they may help to expand the present limits of treating larger low-risk lesions beyond current guideline recommendations. However, endoscopic biopsy, grading and staging accuracy improvements, all vital for optimal management decision making, lack tangible progress. This leaves an ongoing unmet need for reliable objective predictive and prognostic factors in endoscopically treated UTUC patients, including those treated imperatively after appropriate multi-disciplinary team consultation.

Established prognosticators include tumor grade, size, focality, lymphovascular invasion, and hydro-uretero-nephrosis as a muscle invasion surrogate [4, 5]. Recent studies have linked inflammation to cancer development and progression [6-8]. Neutrophil / Lymphocyte ratio (NLR) has been shown to reflect the extent of systemic inflammation involved in neoplasia [9], pointing to its emerging role as a pre-operative prognostic biomarker in RNU-UTUC patients [10-12], and was incorporated as a new risk factor into current EAU guidelines [1]. However, any potential prognostic value in the natural orifice retrograde endoscopically treated-UTUC population remains unexplored. This retrospective analysis aimed to address this deficiency.

Patients and Methods

All procedures performed in human participant studies were according to host institutional and/or national research committee ethical standards, plus the 1964 Helsinki declaration

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and its later amendments, or comparable ethical standards. For this retrospective data analysis, formal written consent was not required in Italy.

Patient Selection

Natural orifice retrograde endoscopically treated UTUC patients between January 2005 and November 2019 were retrospectively identified in a single national tertiary referral center (Cristo Re Hospital, Rome, Italy).

Inclusion criteria

Endoscopic biopsy-proven UTUC diagnosis and recommendation for natural orifice retrograde endoscopic treatment either aligned with contemporaneous EAU guidelines, or imperative indications (solitary kidney, bilateral UTUC, poor global renal function, palliation, or patients refusing RNU despite appropriate multi-disciplinary consultation recommendations for personal reasons or to avoid dialysis), with willingness to accept rigorous endo-surveillance [3] and have accrued at least 12 months minimum follow-up.

From the 184 patients initially referred, 84 were excluded from analyses (Figure 1). Baseline NLR prognostic value was assessed for progression free survival (PFS - primary outcome), and for time to pathologically verified upper tract (u-RFS) or bladder (b-RFS) urothelial recurrence free survival (secondary outcomes).

Procedure, End Points and Follow Up

Natural orifice retrograde endoscopic diagnostic and therapy technical aspects plus endo-surveillance protocol, were as previously described [3] (Figure S1). No patient received adjuvant intra-renal or bladder instillation therapy. All data were recorded intra- and post-operatively on standardized study proformas. A single uro-pathologist reported all specimens according to the 2009 TNM classification plus 1973 and 2016 [13] WHO grading systems. For analyses, grade 2 tumors were treated as low-grade.

In the low-risk subset, progression was defined by recurrence(s) with grade, size, stage or multifocality greater than the original presenting lesion after complete initial endoscopic visual tumor eradication, and in imperative patients, by new metastases +/-cT2-4 on imaging, new onset hydronephrosis, or persistent bothersome macroscopic haematuria despite endoscopic treatment, requiring a strategy change to RNU +/or palliative

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chemotherapy. All recurrence(s) were targeted biopsy and/or cytologically proven.

Data Analysis

Pre-operative baseline neutrophil (N) and lymphocyte (L) counts from the first endoscopic procedure day, were retrieved from the hospital pathology informatics system. Each NLR value (rounded off to one decimal point between range 2.5 - 3.0) was evaluated by log-rank test for PFS, selecting that which determined the most significant p-value, as per existing literature methodology [10, 12]).

The relationship between NLR and clinico-pathological variables was studied using parametric and non-parametric tests. Survival time to event curves was estimated by the Kaplan-Meier method with log rank testing to compare PFS (primary outcome) and u-RFS / b-RFS (secondary outcomes) between groups.

All outcomes were further analyzed in multivariate Cox proportional hazard regression models, adjusting for clinico-pathological variables, with statistical significance set at $p<0.05$. All analyses were performed with SPSS 25 (IBM Corp., Armonk NY, USA).

Results

One hundred patients met all inclusion criteria for end-point analyses (Figure 1). Patient and tumor characteristics are shown in Table 1. Mean follow-up (SD; range) was 31.7 months (28.3; 12-144). There were 63 non-imperatives and 37 imperative indication patients. Progression and recurrences are summarized in Table 2. RNU and/or chemotherapy were performed for progression as appropriate in 3/63 (4.76%) non-imperatives and 13/37 (35%) imperative patients.

NLR

Mean NLR was 2.99 (SD 2.04; range 0.8 – 16.5). The optimal log rank test calculated NLR cut-off value for PFS, was 2.7 (Table 3), thus dividing patients into groups <2.7 and ≥2.7 for comparison (Table 4).

Primary Outcome Analysis (PFS)

Figure 2 shows Kaplan-Meier analysis with significantly shorter mean estimated PFS (SD; range) of 55.9 months (8.35; 39.5 – 72.2months) for the NLR≥2.7 group versus 100.5 months (7.17; 86.5 – 114.6 months) for the NLR <2.7 group, (p=0.01).

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Multivariate analysis including age, grade, tumor size, focality, cytology, and NLR (Table 5), showed that only positive high grade-cytology (HR 5.92, 95% CI 2.14 – 16.35, p=0.002) and NLR≥2.7 (HR 4.28, 95% CI 1.34 – 13.72, p=0.014) independently predicted PFS. When stratifying by grade alone, NLR was significantly more predictive for PFS in the "low-grade" subset (p=0.034) than in the high-grade subset (p=0.125). When stratifying by low-risk (n=63), log rank test for PFS again remained significant (p=0.029), versus the high-risk subset (p=0.06). However, these findings in high-grade/risk patients are most likely explained by under-powering (being selected for natural orifice retrograde endoscopic treatment for imperative reasons only).

Secondary Outcomes Analysis (u-RFS and b-RFS)

Figure 3 shows u-RFS curves at log rank test (p=0.03) with significantly shorter mean estimated survival of 21.5 months (SD 5.5; range 10.7 – 32.4months) for NLR≥2.7 versus 44.6 months (SD 8.15; range 28.6 – 60.6 months) for the NLR<2.7 cohort.

For b-RFS, the curves were not significantly different at log rank test (p=0.90), with mean 20.9 months (SD 3.5; range 14.1 – 27.8months) for NLR≥2.7, versus 56.7 months for NLR<2.7 (SD 18.4; range 20.6 – 92.9 months). Multivariate analysis showed no significant predictors for recurrence (Table 6).

PFS and u-RFS or b-RFS were not significantly linked on Chi square test (p>0.05). Moreover, in the non-imperative truly low-risk subset, log rank test differences for u-RFS (p=0.11) and b-RFS (p=0.98) were also insignificant.

Discussion

The fundamental twin UTUC natural orifice retrograde endoscopic treatment goals are a) to accurately characterize and control "low-risk" disease, with tumor recurrence monitoring for biological change to detect more aggressive features that require promptly timed strategy change (avoiding under-treatment and loss of opportunity for cure where cure is needed and safely possible), and b) to optimize safe renal functional preservation to avoid radical surgery and renal replacement therapy (dialysis) morbidity and mortality in frail elderly patients. This strategy primarily depends on defining "risk" based on retrospective RNU population data [1] inherently biased towards being fitter with higher progression risk tumors. This leaves "accurate" grading on small natural orifice retrograde

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endoscopic biopsy samples as the best surrogate for predicting pathological stage (the correlation between the two being recognized long ago [14]). However, this strategy is far from foolproof due to the inherent current limitations of UTUC biopsy grading and staging, endoscopic tumor sizing, and accurate urine cytology, thereby creating an opportunity for better objective predictors to guide optimal future individualized patient management as an unmet medical need.

This retrospective exploratory single center analysis is the first to explore the potential predictive and prognostic application of baseline NLR as an objective biomarker in natural orifice retrograde endoscopically treated UTUC patients, to fulfill the ongoing unmet need for optimized safe renal preservation. The analysis revealed significant predictive utility for both high-grade cytology (HR 5.92, p=0.002) and baseline NLR $\geq$2.7 (HR 4.28, p= 0.014) for shorter PFS, with early and maintained Kaplan-Meier curve separation (Figure 2). Moreover, the Kaplan-Meier plots, also showed early and sustained NLR group separation for u-RFS (significant log rank test p=0.03), but not for b-RFS (Figure 3). The novel finding that NLR remained an independent significant PFS predictor in multivariate analysis, even in the truly low-risk ($p<0.029$) / low-grade ($p<0.034$) subsets after excluding imperative cases, emphasizes its utility beyond endoscopic biopsy tumor grade and stage (with their inherent potential limitations – vide infra), tumor size as listed in current guidelines [1], and multi-focality. These subset findings are the opposite of the past radical nephro-ureterectomy literature, which would have contained a variable percentage of patients with no or low-risk UTUC, who were over-treated and could have been managed endoscopically in a tertiary referral center with specialized expertise-equipment, but in many instances, they are still simply not referred for such management.

The findings that UTUC recurrence and progression did not appear to have cause-and-effect linkage, is akin to low-risk bladder-origin UC. However, as with the bladder, there is a clearly a small low-intermediate grade-risk patient subset in whom aggressive tumor biology was actually under-estimated, leading to occasional sudden, unexplained, unexpected, metastatic occurrence in a minority. Hence, it is arguable that although accepted guideline “risk” factors are useful, they are not infallible and may occasionally misrepresent actual tumor biology. This study presents the first evidence that objective baseline inflammatory markers (NLR) may correctly identify these unique cases early on, if

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they produce a more vigorous host inflammatory response, allowing earlier re-classification for a more aggressive management and surveillance strategy – truly personalized medicine.

Our other interesting finding that cytology also independently predicted progression along with NLR in the natural orifice retrograde endoscopic-UTUC treatment setting, may partly be related to the fact that technically, cytology material was optimized by routinely collecting pre-operatively voided urine and regular interval washings throughout the endoscopic biopsy-ablation-resection procedure, to maximize cell yield for pathological analysis.

Prospective studies on this subject are currently lacking. This study differs from the existing literature, which exclusively analyzed NLR's predictive value only in RNU patients, making them inherently biased towards greater tumor burden and higher risk features, compared to only 37% of our study imperative subset. Furthermore cut-off values are not directly comparable, as our study NLR values were recorded specifically on the day of 1st endo-diagnosis/treatment, while timing was poorly specified before RNU (which usually occurs at a variable interval after endo-diagnosis, if performed), in the existing literature.
The Dalpiaz et al [10] retrospective study reported that NLR $\geq$2.7 was associated with shorter overall survival and cancer specific survival (CSS) in 171 patients undergoing RNU or segmental ureterectomy, but again, exact timing of pre-operative blood draw from which NLR was derived, was unspecified. Nevertheless, their findings that both NLR$\geq$2.7 and pT-Stage predicted shorter CSS, were broadly concordant with this analysis where NLR$\geq$2.7 and cytology predicted for shorter PFS (which may lead to shorter CSS if not cured by timely salvage management). It is likely that pT-Stage in our multivariate analysis was insignificant due to the inherent natural orifice retrograde endoscopic sampling limitations aimed at obtaining sufficient tumor material for "accurate grading" as the best available staging surrogate. Technically, endoscopic biopsy risks under-estimating stage by erring towards safety to minimize risk of breaching upper urinary tract integrity, thus avoiding seeding tumor cells outside and compromising later salvage options if-when needed. Accurate tumor grading, is also subjective with an element of intra- and inter-observer pathology reporting variation (especially in lower grade categories), and errors may be

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further compounded by natural orifice retrograde endoscopic tumor sampling variances that are dependent on a range of factors including tumor location, intra-renal collecting system anatomy, tumor size and morphology, operator skill, available sampling accessories and biopsy protocol used.

In another retrospective study [15], pre-operative NLR>3 and hydronephrosis >Grade 2, both independently prognosticated for shorter CSS and Recurrence free survival (RFS) after RNU in multivariate analysis. While shorter CSS might be aligned with our results, hydronephrosis grade is subjectively variable through lack of international standardization, and was not pertinent to natural orifice retrograde endoscopically treated UTUC patients where both bladder and entire affected upper urinary tract are directly visualized. Furthermore, RFS after endoscopic treatment and RNU are not directly comparable due to intrinsic disease and population differences.

Tan et al [16] found that a 2.5 NLR cut off in 717 RNU patients, was a useful prognosticator for CSS, overall survival, RFS and metastasis free survival, only in high-grade disease patients. In our study, not only was grade accounted for, but patients were also sub-stratified by risk class. In the low-risk/low-grade subsets, NLR $\geq$2.7 remained significant for predicting shorter PFS, but not for predicting either upper tract or bladder recurrence. This suggests that urothelial recurrence anywhere in natural orifice retrograde endoscopically treated low-risk UTUC patients, does not appear to be directly aligned with progression, just as with low-risk bladder origin urothelial carcinoma. Upper tract recurrence may also have been influenced by the use of two different complementary ablation energies which allowed reduced bleeding especially in vascular lesion(s), thanks to the Thulium:YAG coagulation effect, while periodically removing the necrotic layer with Holmium:YAG mode to show up eventual residual tumour tissue requiring further ablation [3].

The Vartolomei et al [11] meta-analysis included 9 studies with 4385 RNU patients, concluding that increased pre-treatment NLR (variable cut-off between 2-3) predicted overall survival (pooled HR 1.64 95% CI; 1.23-2.17), RFS (pooled HR 1.60 95% CI; 1.16-2.20) and CSS (pooled HR 1.73 95% CI; 1.23-2.44) in multivariate analysis. Others have also reported that higher NLR was associated with higher intra-vesical recurrence after RNU [17], but our analysis found no such association in natural orifice retrograde

endoscopically treated patients, and in the truly low-risk subset, recurrence and progression were not found to be directly linked.

Study limitations included small sample size, a single national referral center experience, retrospective exploratory analysis, incomplete survival data due to hospital management and care records systems change making it impossible to track personal records of early database patients [3], and inclusion of an imperative indications patient subset encompassing those refusing RNU at the outset for personal reasons despite counseling to the contrary (a "real life" situation reflecting frail elderly UTUC patients with other co-morbidities). However, these were offset by findings that confirmed proof of concept for the test hypothesis and inform future study power calculations. A 1st prospectively enrolled single center validation cohort study examining the same variables and end-points has been ongoing since 2017.

Conclusions

Baseline NLR evaluation before first conservative natural orifice retrograde endoscopic UTUC evaluation and treatment may provide valuable, readily available, affordable and objective prognostic information for disease progression free survival, and for upper tract but not bladder recurrence risk. It complemented high-grade cytology, and may help to individualize management plans in future. The absence of a significant link between PFS and u-RFS or b-RFS suggests that recurrence alone did not portend for progression in the truly low-risk subset.

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Abbreviations used (if used 3 or more times)

EAU	European Association of Urology
UTUC	Upper tract urothelial cancer
RNU	Radical nephro-ureterectomy
NLR	Neutrophil Lymphocyte Ratio
PFS	Progression free survival
u-RFS	Upper tract recurrence free survival
b-RFS	Bladder recurrence free survival
CSS	Cancer specific survival
RFS	Recurrence free survival
HR	Hazard ratio
CI	Confidence intervals
SD	Standard deviation

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Table 1: Eligible patient population characteristics (n=100)

Age (Years)		n
Overall	Median	72.50
	Mean (SD; range)	71.08 (10.4; 40-91)
	≥70	60
	Mean (SD; range)	77.98 (5.19; 70-91)
	<70	40
	Mean (SD; range)	60.76 (7.00; 40-69)
Sex		
	Male	79
	Female	21
NLR		
	Mean (SD; range)	2.99 (2.04; 0.80-16.57)
	<2.7	55
	≥2.7	45

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Table 2: Progression (as defined) and endo-surveillance urothelial recurrence rates

	Total	Non-imperative subset	Imperative subset	p
Patients	100	63	37	
Progression	16	3 (4.76%)	13 (35.14%)	0.001*
Upper tract recurrence	66	34 (53.97%)	32 (86.49%)	0.001*
Bladder recurrence	39	25 (39.68%)	14 (37.8%)	0.86

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Table 3: Optimal NLR cut-off in log rank test for progression free survival

NLR cut off	p
3.0	0.871
2.9	0.401
2.8	0.278
2.7	0.011
2.6	0.017
2.5	0.072

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Table 4: Group characteristics according to 2.7 NLR cut-off value

Characteristics	NLR<2.7	NLR ≥2.7	p
Patients	55	45	
Mean Follow up months (SD)	38.95 (33.56)	22.80 (16.51)	0.002*
Minimum Follow up: 12 months	21 (38.2%)	21 (46.7%)	0.39
Median Age (years) (IQR)	71 (60-78)	74 (67-80)	0.58
Patients with Tumor Multi-focality (%)	16 (29%)	21 (47%)	0.07
Patients with High-grade (%)	12 (22%)	11 (24%)	0.75
Median Largest Tumor Diameter in mm, (IQR)	15 (10-15)	15 (10-17)	0.13
Patients with High-grade Cytology (%)	5 (9%)	19 (42%)	0.01*

* = significant p-value

Table 5: Multivariate Cox regression analysis (stepwise backward Wald) of clinico-pathological variables for the prediction of progression free survival

Cytology		HR (CI 95%)	p-value
	Negative	1 (reference)	
	Positive High Grade	5.62 (2.01 – 15.68)	0.001*
NLR			
	<2.7	1 (reference)	
	≥2.7	4.23 (1.31 – 13.66)	0.016*
Grade			
	Low	1 (reference)	
	High	-	0.116
Size			
	<20 mm	1 (reference)	
	≥20 mm	-	0.147
Focality			
	Single	1 (reference)	
	Multiple	-	0.671
Age			
	< 70 years	1 (reference)	
	≥ 70 years	-	0.701

* indicates significant p-value

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Table 6: Multivariate Cox regression analysis (stepwise backward Wald) of clinico-pathological variables for the prediction of upper tract and bladder recurrence free survival.

Clinical variable		Upper tract RFS		Bladder RFS	
Cytology		HR (95% CI)	p value		p value
	Negative	1 (reference)		1 (reference)	
	Positive High Grade		0.427		0.367
NLR					
	<2.7	1 (reference)		1 (reference)	
	≥2.7		0.207		0.703
Grade					
	Low	1 (reference)		1 (reference)	
	High		0.117		0.616
Size					
	<20 mm	1 (reference)		1 (reference)	
	≥20 mm		0.140		0.660
Focality					
	Single	1 (reference)		1 (reference)	
	Multiple		0.472		0.308
Age					
	< 70 years	1 (reference)		1 (reference)	
	≥ 70 years		0.972		0.582

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FIGURES

Figure 1: Flow diagram of the entire patient cohort

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Figure 2: Kaplan-Meier Plots for Progression Free Survival (primary outcome)

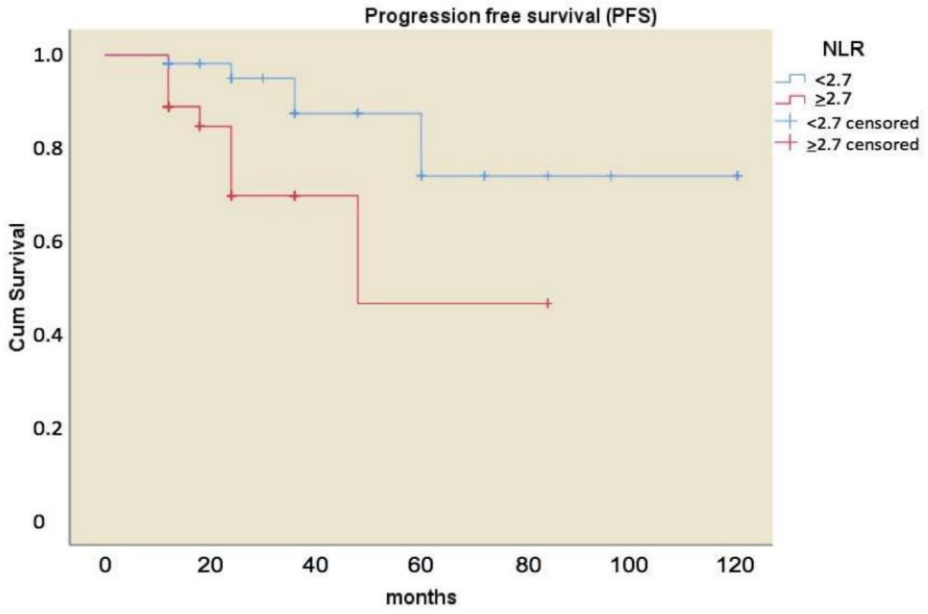

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Figure 3: Kaplan-Meier Plots for Upper Tract Recurrence Free Survival (u-RFS) and Bladder Recurrence Free Survival (b-RFS) as secondary outcomes

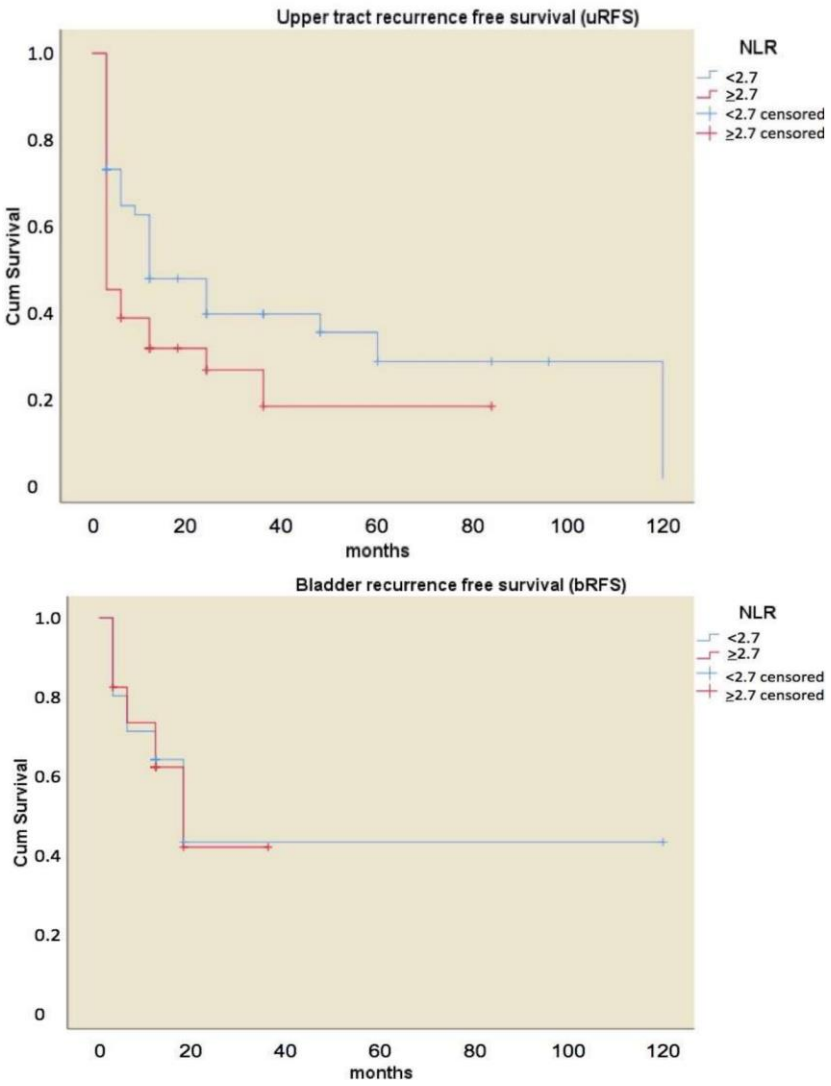

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Figure S1: Endo-surveillance follow-up scheme