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Second Transurethral Resection of Bladder Tumor Can Be Safely Omitted in Selected Patients with T1 Non–muscle-invasive Bladder Cancer: Results from the Prospective HuNIRe Trial

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Abstract

Background and objective: Current European Association of Urology guidelines universally recommend a second transurethral resection (ReTUR) for all T1 non–muscle-invasive bladder cancer (NMIBC) cases. However, ReTUR is an invasive and costly procedure that is often negative for residual disease, and may represent overtreatment in appropriately selected patients who have undergone complete initial TUR. Our aim was to report 2-yr oncological outcomes and confirm the safety of a novel, response-guided strategy with selective ReTUR for patients with T1 NMIBC.

Methods: The prospective, observational, multicenter HuNIRe trial enrolled patients with T1 NMIBC from 2020 to 2024. Patients with complete TUR underwent urine cytology at 3–4 wk and cystoscopy at 4–6 wk. ReTUR was performed only if cytology was positive (Paris system 3–6) or disease was detected on cystoscopy; otherwise, patients proceeded directly to bacillus Calmette-Guérin (BCG) induction therapy. The primary endpoints were 2-yr recurrence-free survival (RFS) and progression-free survival (PFS). Secondary endpoints included comparison of outcomes between the groups with and without ReTUR, and between the overall HuNIRe cohort and a retrospective cohort of patients with T1 NMIBC who underwent routine ReTUR. Kaplan-Meier estimates and the log-rank test were used for survival analysis.

Key findings and limitations: A total of 90 patients were prospectively enrolled. The protocol successfully avoided ReTUR in 71% (n = 64) of patients, who proceeded directly to BCG therapy. Only 29% (n = 26) of the patients required ReTUR according to early evaluation; importantly, no patient was upstaged to MIBC at ReTUR. After median follow-up of 26 mo, 2-yr survival rates for the entire cohort were 69% for RFS and 91% for PFS. There were no significant differences between the groups with and without ReTUR in RFS (p = 0.9) or PFS (p = 0.6). Oncological outcomes were also comparable between the

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HuNIRe cohort and a retrospective cohort that underwent routine ReTUR (2-yr RFS: 74% vs 74%; 2-yr PFS: 91% vs 92%).

Conclusions and clinical implications: Results from the HuNIRe trial confirm that a risk-adapted approach to ReTUR in selected patients with T1 NMIBC after complete initial TUR is feasible, although oncological outcomes should be interpreted with caution owing to the short follow-up. This strategy spared 71% of patients from ReTUR, and could support a tailored, response-guided approach rather than the blanket guideline recommendation for ReTUR.

ADVANCING PRACTICE

What does this study add?

This study provides prospective evidence that a response-guided strategy may reduce the use of routine repeat transurethral resection of the bladder in carefully selected patients with T1 non–muscle-invasive bladder cancer. Early urine cytology and cystoscopy reliably identified the minority of patients requiring a second resection. Although no increase in recurrence or progression was observed, these findings must be interpreted in light of the short follow-up. Overall, the study results support a more tailored, data-driven approach than the current universal recommendation.

Clinical Relevance

This prospective study speaks directly to two principles that matter in contemporary NMIBC care – doing the first TURBT well, and avoiding additional intervention when it does not meaningfully improve outcomes. In a highly selected cohort with complete initial resection and detrusor muscle present, a simple, response-guided strategy using early cystoscopy and urine cytology allowed 71% of patients with T1 disease to safely avoid repeat TUR without compromising short-term recurrence or progression outcomes. Importantly, no patient was upstaged to muscle-invasive disease at ReTUR, and 2-yr PFS exceeded 90%, reinforcing the central role of resection quality and early assessment. While longer follow-up is needed and this approach is not suitable for all patients, the HuNIRe trial provides prospective evidence that thoughtful de-escalation, when anchored in high-quality TURBT and objective early evaluation, can reduce morbidity and resource use without risking oncological control. Associate Editor: Ashish M Kamat, M.D.

Patient Summary

We tested a new strategy for patients with noninvasive bladder cancer in which a second surgery is performed only if early urine tests or a telescopic look into the bladder show signs of remaining tumor. Our short-term results show that selected patients could safely avoid this second procedure without worse outcomes. These early results suggest that a personalized approach may reduce unnecessary operations, although longer follow-up is needed to fully assess long-term cancer control.

1. Introduction

For non–muscle-invasive bladder cancer (NMIBC), current European Association of Urology (EAU) guidelines recommend a second transurethral resection (ReTUR) within 2–6 wk in cases of incomplete primary TUR, the absence of detrusor muscle (DM; except for Ta low-grade tumors and primary carcinoma in situ), or any T1 tumor [1]. The rationale is to ensure eradication of residual disease, improve staging accuracy, and ultimately reduce the risk of recurrence and understaging [2]. Several studies have suggested that ReTUR may translate to better oncological outcomes, including lower recurrence and progression rates and better cancer-specific and overall survival [3].

Nevertheless, TUR of bladder tumor (TURBT) is not devoid of risks, with postoperative complication rates approaching 40% [4]. Beyond morbidity, repeated endoscopic procedures can negatively impact psychological wellbeing and quality of life [5]. From a health-system perspective, bladder cancer represents the costliest malignancy to manage on a per-patient basis [6], and rationalization of treatment and follow-up pathways may yield significant resource savings without compromising outcomes [7].

Although ReTUR remains necessary in patients with residual disease or when the specimen lacks DM, it may represent overtreatment in patients who have undergone complete TUR of T1 NMIBC, particularly given recent advances in surgical instrumentation and resection quality [8,9].

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Consequently, we proposed a more conservative approach that avoids routine ReTUR in all patients with T1 NMIBC, and instead bases the decision on early urine cytology and cystoscopy performed after complete initial TUR. We hypothesized that a response-guided strategy provides reliable criteria for safe ReTUR omission in appropriately selected patients with T1 NMIBC, which would challenge the current guideline recommendation for indiscriminate ReTUR in all cases.

We previously demonstrated the feasibility and cost-effectiveness of this strategy [7]. Here we report 2-yr outcomes that confirm the oncological safety of this approach.

2. Patients and methods

2.1. Study design and population

HuNIRe is a prospective, observational, multicenter study that enrolled patients with T1 NMIBC between May 2020 and December 2024 at a tertiary academic referral center and four affiliated hospitals. Patients with a diagnosis of T1 NMIBC who underwent complete TURBT with DM present in the resection specimen were eligible for inclusion.

Patients with a history of prior bacillus Calmette-Guérin (BCG) instillations, previous or concomitant upper tract urothelial carcinoma (UTUC), histological variants, or lymphovascular invasion (LVI) were excluded.

All patients were informed about the rationale and purpose of the study and signed a written informed consent form. The HuNIRe protocol was approved by the institutional review board of the coordinating center (reference number 2503, 08.05.2020, ICH-010) and subsequently endorsed by the local ethics committees of all participating institutions. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Surgeries were performed by two experienced urologists per center, with experience defined as more than 100 TURBTs. The completeness of the resection was reported by the surgeon at the end of the procedure using a dedicated surgical checklist in accordance with the EAU guidelines [1].

Patients with macroscopically incomplete initial resection or lacking DM in the primary TURBT specimen were excluded and underwent ReTUR within 2–6 wk, in accordance with the EAU guidelines [1]. Patients with T1 tumors and complete macroscopic resection underwent urine cytology at 3–4 wk and office-based flexible cystoscopy with both white-light and narrow-band imaging at 4–6 wk after the primary TURBT.

If urine cytology was positive or recurrent/persistent disease was detected on cystoscopy, postcystoscopy ReTUR was performed within 2 wk. Otherwise, patients proceeded directly to an intravesical BCG induction course without ReTUR and then followed the standard BCG schedule.

Follow-up was conducted according to the EAU guidelines, including cystoscopy and urine cytology at 3 mo, every 3 mo thereafter for 2 yr, and then every 6 mo. All patients underwent computed tomography of the upper urinary tract at baseline and annually thereafter. Urine cytology was considered positive for categories 3–6 according to the Paris system [10]. Tumor size was analyzed as a dichotomous variable using a 3-cm cutoff, in accordance with the EAU risk stratification model [1]. All TURBT specimens were centrally reviewed by a dedicated genitourinary pathologist at the coordinating center.

2.2. Endpoints

The primary endpoints were 2-yr progression-free survival (PFS) and recurrence-free survival (RFS) in the entire HuNIRe study population. Progression was defined as the development of MIBC or distant metastases, whereas recurrence was defined as any biopsy-proven tumor in the bladder. To minimize immortal-time bias, follow-up was calculated from the date of ReTUR, or from the 4–6-wk cystoscopy for patients who did not undergo ReTUR, until death or last follow-up. All analyses were repeated after stratifying the cohort according to ReTUR status.

Secondary endpoints included: (1) comparison of outcomes between patients who underwent ReTUR after the 4–6-wk cystoscopy (ReTUR group) and those who did not (patients with negative cystoscopy and urine cytology at 4–6 wk); and (2) comparison of outcomes between HuNIRe patients and a retrospective cohort of patients with high-grade (HG) T1 NMIBC who underwent routine ReTUR. This retrospective cohort was identified from an institutional database of more than 600 patients treated with intravesical BCG from 2010 to 2020. Patients with incomplete or missing data were not included in the database and were therefore not eligible for analysis.

2.3. Statistical analysis

Descriptive statistics were used to summarize the study cohort. Results for categorical variables are reported as the frequency and proportion, and for continuous variables as the median with interquartile range (IQR).

RFS and PFS were estimated using the Kaplan-Meier method and were compared between groups using the log-rank test. Median follow-up was calculated via the reverse Kaplan-Meier method.

Univariable Cox proportional-hazards regression models were used to evaluate associations between study groups and the times to recurrence and progression. A two-sided p value <0.05 was considered statistically significant. All analyses were performed using Stata/SE v18 (StataCorp, College Station, TX, USA).

3. Results

3.1. Outcomes in the HuNIRe cohort

Of 107 eligible patients, 90 were enrolled in the study. Seventeen patients were excluded because of concomitant UTUC (n = 2), prior BCG exposure (n = 8), the presence of histological variants (n = 6), or LVI (n = 1).

The median age was 75 yr (IQR 68–81) and the majority of the patients were male (n = 75; 83%). Most patients presented with primary bladder cancer (n = 69; 76%). Patient characteristics are summarized in Table 1. Twenty-eight

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Table 1 – Baseline characteristics of the 90 patients enrolled in the HuNIRe trial

Parameter	Result
Median age, yr (IQR)	75 (69–81)
Recurrent tumor, *n* (%)	21 (23)
Tumor diameter >3 cm, *n* (%)	29 (32)
Multifocal tumor, *n* (%)	21 (23)
Carcinoma in situ, *n* (%)	7 (8)

IQR = interquartile range.

patients (31%) had their lesion removed via the en-bloc technique; all resections were performed with bipolar energy.

Twenty-six patients (29%) underwent ReTUR after protocol-defined early evaluation, of whom 11 (12%) had positive urine cytology at 3–4 wk and 15 (17%) had suspicious cystoscopy findings at 4–6 wk. Patients with negative cytology and cystoscopy proceeded, as per protocol, directly to BCG induction. All ReTUR procedures were performed within 8 wk of the initial TURBT.

Pathological findings at ReTUR included Ta low grade (LG) in one patient (4%), Ta HG in six (23%), T1 HG persistence in four (15%), and carcinoma in situ (CIS) in eight (31%), while seven patients (27%) had no residual disease. No patient had progressed to MIBC.

In the subgroup with positive urine cytology as the indication for ReTUR, pathology revealed Ta HG in one case (9%), T1 HG in three cases (27%), CIS in five cases (45%), and no residual disease in two cases (18%). In the subgroup with suspicious or positive cystoscopy as the indication for ReTUR, pathology revealed Ta LG in one case (7%), Ta HG in five cases (33%), T1 HG in one case (7%), CIS in three cases (20%), and no residual disease in five cases (33%).

After median follow-up of 26 mo (IQR 14–38), 24 patients had experienced recurrence, including five with progression to MIBC.

Kaplan-Meier estimates for RFS and PFS are shown in Fig. 1. At 2 yr, survival rates for the overall cohort were 69% (95% confidence interval [CI] 56–80%) for RFS and 91% (95% CI 80–96%) for PFS.

Baseline characteristics of the HuNIRe cohort stratified by ReTUR status are summarized in Table 2. Kaplan-Meier curves for RFS and PFS stratified by ReTUR status are presented in Fig. 2 and show no statistically significant differences between the groups (log-rank $p = 0.7$ and $p = 0.6$, respectively). The 2-yr RFS rate was 74% (95% CI 65–81%) for the ReTUR group and 69% (95% CI 53–80%) for the group without ReTUR. The 2-yr PFS rate was 91% (95% CI 77–96%) for the ReTUR group and 93% (95% CI 87–96%) for the group without ReTUR.

Univariable Cox regression analysis revealed similar estimated hazards of recurrence and progression for the no-ReTUR and ReTUR groups, with wide CIs reflecting limited event numbers (recurrence: HR 1.19, 95% CI 0.49–2.90; progression: HR 1.19, 95% CI 0.08–7.10).

3.2. Comparison of the HuNIRe cohort and a retrospective cohort

We then compared oncological outcomes between the overall HuNIRe cohort and a retrospective cohort of patients who had undergone standard ReTUR after complete resection. Baseline characteristics of the retrospective cohort were summarized in Supplementary Table 1. A total of 34 of these patients experienced recurrence, including 14 who progressed to MIBC. Median follow-up was 55 mo (IQR 31–97). Pathological findings at ReTUR in the retrospective cohort were negative in 54 patients (56%), Ta LG in six (6%), Ta HG in seven (7%), CIS in 16 (17%), and T1 HG in 14 (14%).

The 2-yr RFS rate was 74% (95% CI 65–81%) in the retrospective cohort. Kaplan-Meier estimates for RFS in both cohorts are presented in Fig. 3A, with no significant difference evident (log-rank $p = 0.7$).

The 2-yr PFS rate in the retrospective cohort was 92% (95% CI, 85–96%). Kaplan-Meier curves for PFS for the retrospective and HuNIRe cohorts are shown in Fig. 3B, with no significant difference evident (log-rank $p = 0.4$).

Univariable Cox regression analysis revealed no significant differences between the retrospective and HuNIRe cohorts in time to recurrence (HR 1.11, 95% CI 0.64–1.90; $p = 0.70$) or time to progression (HR 0.61, 95% CI 0.21–1.80; $p = 0.40$).

4. Discussion

This study demonstrates the feasibility of a risk-adapted approach to ReTUR in patients with T1 NMIBC after complete initial resection. Importantly, to the best of our knowledge, this is the first prospective study investigating a risk-adapted approach aimed at reducing overtreatment while preserving oncological safety in this patient subset.

Patients with T1 NMIBC represent a group at high risk of recurrence and progression, which typically require aggressive treatment. However, a second TUR reveals no residual disease in most cases, which suggests that the procedure could potentially be safely omitted, which would offer benefits for both the patient and the health care system.

Notably, 71% of the study patients avoided ReTUR and proceeded directly to BCG induction. This translates to a meaningful reduction in patient burden, sparing the need for a second hospitalization, an additional endoscopic intervention, and exposure to anesthesia, which is an important consideration given that the median age of patients with bladder cancer is approximately 70 yr and comorbidities are common [11]. In addition to improving patient experience, this strategy has potential cost-saving implications via substantial reductions in the number of surgical procedures performed, as previously demonstrated [7].

Nevertheless, 29% of the patients enrolled had positive postoperative cytology or cystoscopy and underwent ReTUR and additional diagnostic procedures beyond the standard pathway. Although this results in slightly higher diagnostic costs for this subgroup, overall resource utilization remains favorable given the avoidance of surgery in the majority of patients [7].

Although only 10/26 patients (38%) who underwent ReTUR had clinically relevant findings (HG Ta or T1), and the remaining cases (T0, Ta LG, or CIS) would not be expected to derive a direct therapeutic benefit from ReTUR, this should be interpreted in the context of current guide-

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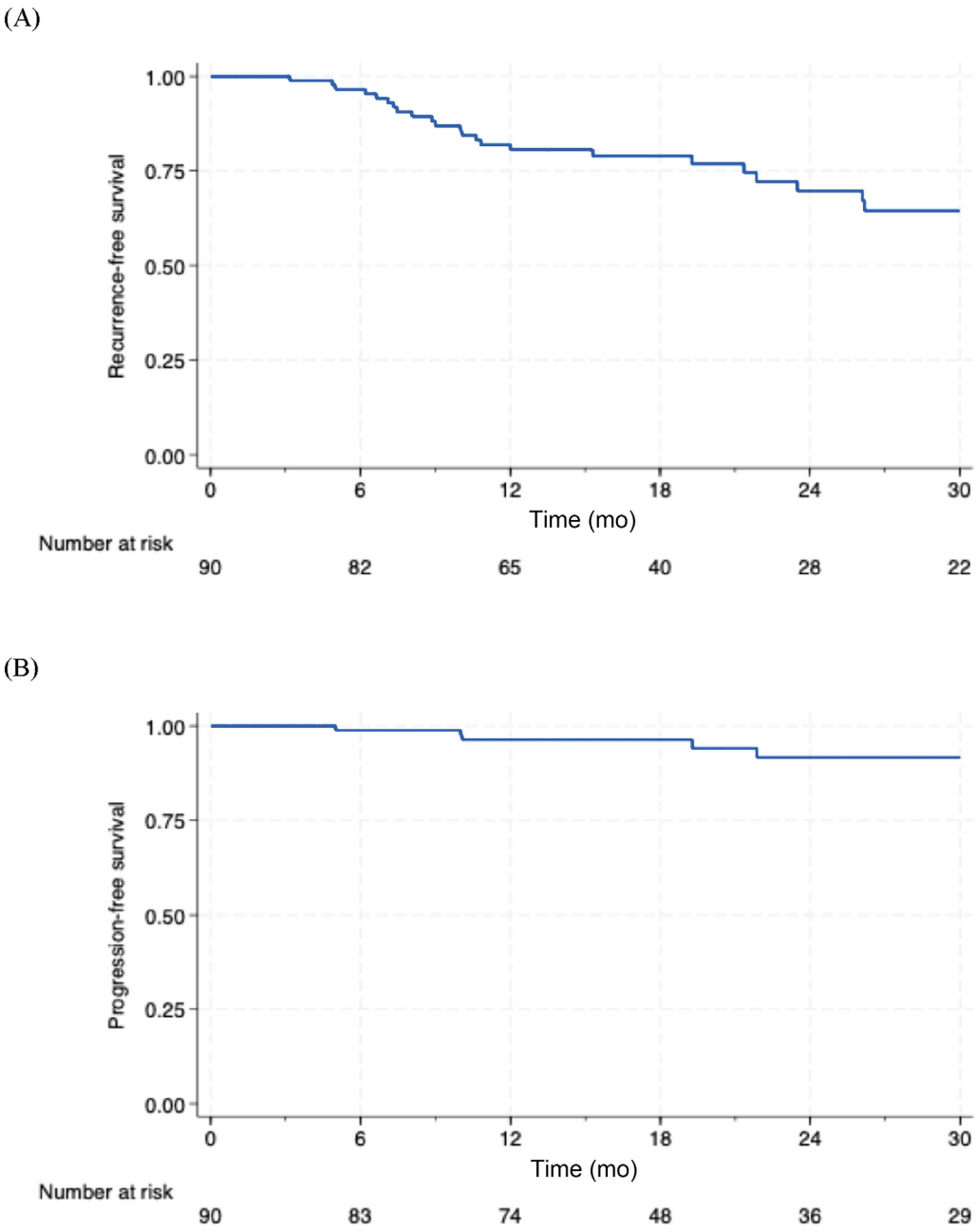

Fig. 1 – Kaplan-Meier estimates of (A) recurrence-free survival and (B) progression-free survival in the HuNIRe cohort (*n* = 90).

Table 2 – Baseline characteristics of the 90 patients enrolled in the HuNIRe trial stratified by ReTUR status

Parameter	No ReTUR (*n* = 64)	ReTUR (*n* = 26)
Median age, yr (IQR)	75 (67–82)	76 (71–81)
Recurrent tumor, *n* (%)	16 (25)	5 (19)
Tumor diameter >3 cm, *n* (%)	21 (33)	8 (38)
Multifocal tumor, *n* (%)	13 (20)	8 (31)
Carcinoma in situ, *n* (%)	4 (6.5)	3 (12)

IQR = interquartile range; ReTUR = repeat transurethral resection after cystoscopy.

line recommendations for routine ReTUR for all T1 tumors. Within this framework, our risk-adapted strategy allowed 71% of patients to be safely spared a second procedure.

Second, none of the patients who underwent ReTUR experienced upstaging to MIBC. This finding may appear unexpected, as upstaging rates at ReTUR reported in the literature range from 0% to 45% [12]. However, most of the data available are from multicenter retrospective studies lacking standardized quality control of the initial TUR [13]. A recent systematic review that included 24 studies and 4678 patients revealed a median upstaging rate of 4% [14].

Furthermore, our finding reflects the highly select nature of the population, all of whom underwent complete initial TUR with confirmed DM; given that upstaging typically arises from inadequate initial staging, its absence in this context is not unexpected.

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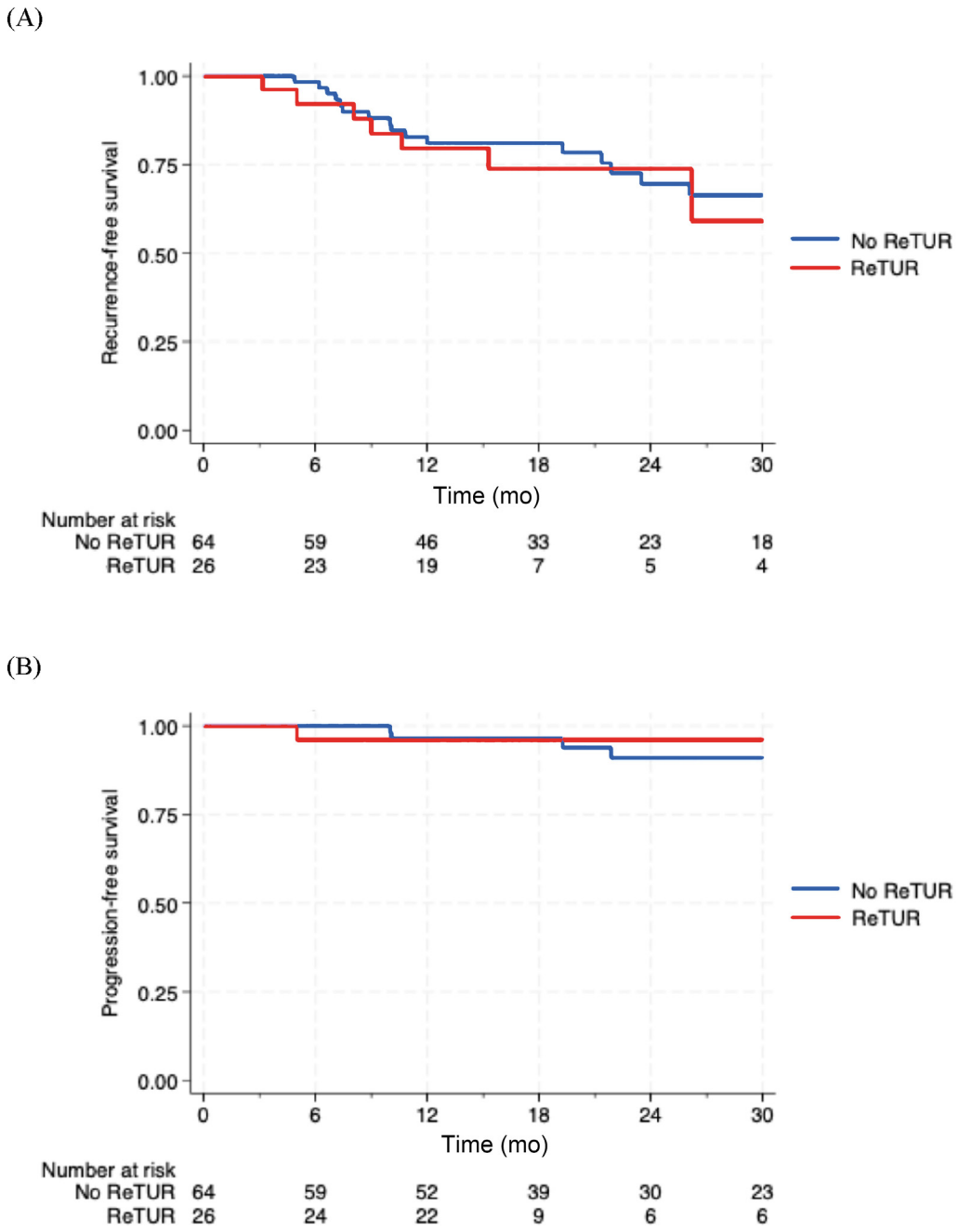

Fig. 2 – Kaplan-Meier estimates of (A) recurrence-free survival and (B) progression-free survival in the HuNIRe cohort (*n* = 90) stratified by repeat transurethral resection (ReTUR) status.

Third, we demonstrated that 2-yr RFS and PFS rates did not differ between the study groups with and without ReTUR. This finding supports the effectiveness of the selection strategy, as patients spared from ReTUR did not experience worse oncological outcomes.

Fourth, we compared RFS and PFS outcomes to those for a retrospective cohort of patients who underwent guideline-recommended ReTUR following complete initial TUR. No significant differences in oncological outcomes were observed between the HuNIRe and retrospective cohorts. These findings further support the safety and effectiveness of a risk-adapted approach to ReTUR according to our protocol. Of note, the 2-yr oncological outcomes for the HuNIRe cohort are consistent with those reported for historical series. Sylvester et al [15] reported progression rates of 3.8% at 1 yr and 9.6% at 5 yr in a high-risk cohort of patients not treated with BCG, whereas Lobo et al [16] reported corresponding rates of 3% and 7.4% in a high-risk cohort of patients who received BCG. It should be noted that both cohorts included patients with Ta high-grade tumors in addition to T1 disease.

ReTUR omission for selected patients may prevent overtreatment and avoid delays in initiation of adjuvant therapy. However, the impact of the interval between pri-

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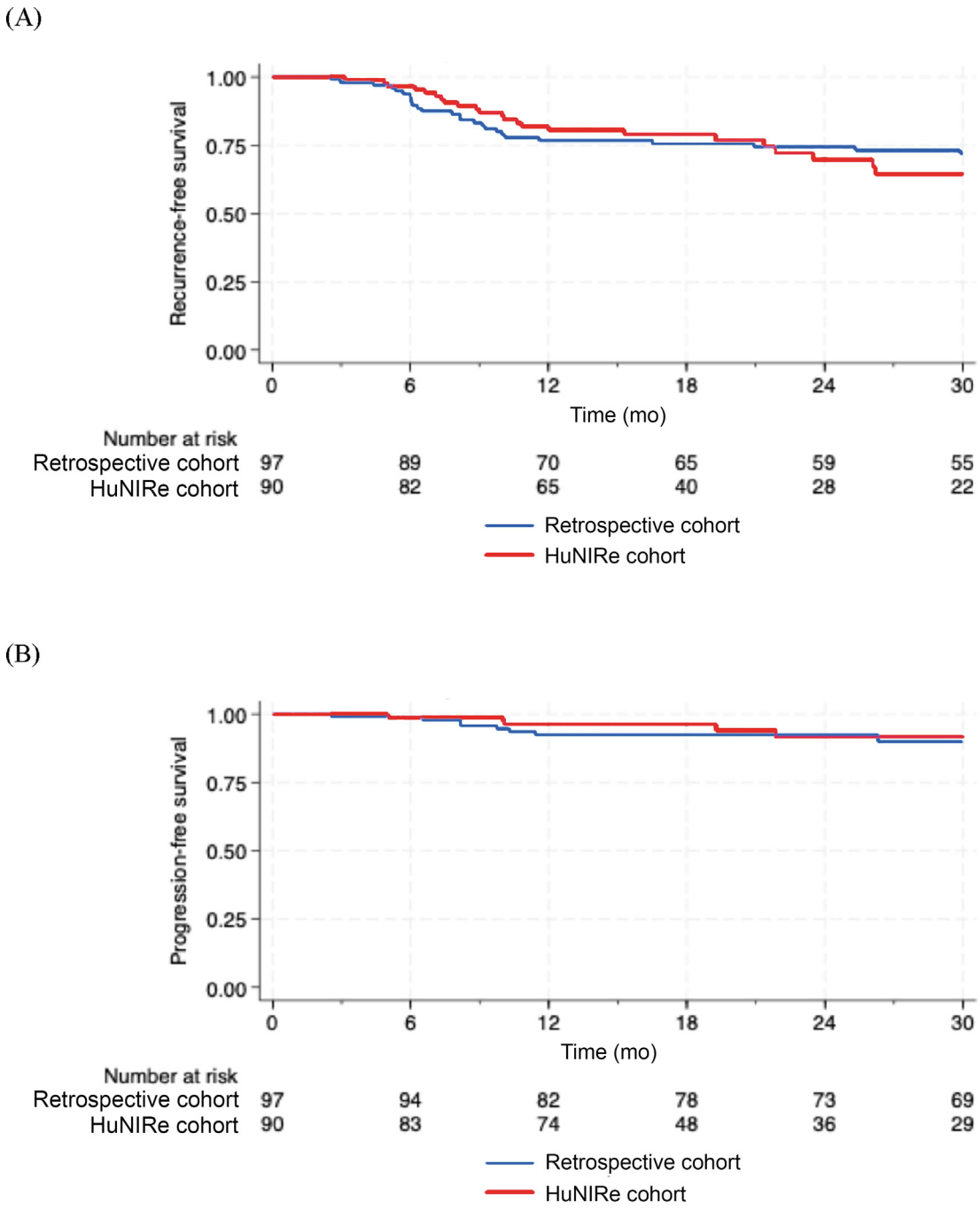

Fig. 3 – Kaplan-Meier estimates of (A) recurrence-free survival and (B) progression-free survival in the HuNIRe cohort (*n* = 90) and the retrospective cohort (*n* = 97).

mary TUR and BCG induction on oncological outcomes remains a matter of debate. While the current EAU guidelines recommend starting BCG therapy at least 2 wk after TUR without defining an upper time limit [1], recent studies have shown that routine ReTUR delays BCG induction and may negatively affect oncological outcomes [17].

Importantly, a multicenter retrospective study involving patients with HG T1 NMIBC treated with BCG by Gontero et al [18] revealed that the benefit of ReTUR on oncological outcomes was evident only when DM was absent in the initial TUR specimen.

Although DM presence is widely considered a surrogate marker of resection quality and is associated with lower rates of residual disease at ReTUR, this parameter alone is unlikely to be sufficient to guide clinical decision-making given the considerable risk of residual tumor even when DM is present in the initial resection specimen [12,19]. For this reason, our protocol incorporated both postoperative cystoscopy and urinary cytology to improve patient selection and enhance the safety of a risk-adapted approach.

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In addition, several urinary molecular markers for BC detection have been developed over the past decades [20]. Further studies are warranted to integrate these biomarkers into clinical decision-making with the aim of achieving even more accurate patient selection for ReTUR omission.

Our study is not without limitations. The relatively small sample size may have limited the statistical power and the reproducibility of our findings. Moreover, median follow-up of 26 mo does not fully capture long-term recurrence and progression events, which are critical endpoints in T1 NMIBC. In addition, the multicenter setting introduces potential variability that was not accounted for by stratification by center. Finally, the comparative analysis is inherently subject to selection bias, and the retrospective cohort cannot replace the level of evidence provided by a randomized controlled trial. Furthermore, comparisons with the retrospective cohort may be influenced by differential ascertainment of outcomes, as the prospective HuNIRe protocol included standardized early assessment and centralized pathology review, whereas follow-up and pathology in the historical cohort reflect routine clinical practice.

Nonetheless, it is worth emphasizing that randomized trials in this setting, although feasible, would require screening of a very large number of patients and are therefore challenging to conduct [21]. Importantly, most of the previous studies simply compared ReTUR versus no ReTUR. Our methodology offers a conceptually distinct approach consistent with the pragmatic deintensification strategy recently recommended in the EAU guidelines [1]. We do not question the value of ReTUR per se, but rather propose a risk-based selection strategy to identify patients who are likely to derive the greatest benefit from this procedure. We believe that this tailored approach may optimize oncological safety while minimizing unnecessary morbidity and health care resource utilization.

5. Conclusions

In a selected cohort of patients with T1 NMIBC, a response-guided strategy after complete initial TUR was associated with similar short-term oncological outcomes to those after routine ReTUR. Given the nonrandomized design and potential confounding, these findings should not be interpreted as evidence that omission of ReTUR yields equivalent oncological control.

This approach could spare a substantial proportion of patients from ReTUR and may help in reducing patient morbidity, optimizing health care resource utilization, and avoiding unnecessary delays in BCG induction therapy. These findings challenge the blanket recommendation of ReTUR for all T1 tumors and support a tailored, response-guided approach. Future studies with longer follow-up and, ideally, randomized designs are needed to validate these results and inform potential updates to clinical guidelines.

Author contributions: Giovanni Lughezzani had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Contieri, Hurle.
Acquisition of data: Contieri, Paciotti, Beatrici, Fasulo, Avolio, Frego, Finocchiaro, Cella, Collura.
Analysis and interpretation of data: Contieri, Hurle.
Drafting of the manuscript: Contieri, Hurle, Paciotti.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Contieri.
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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2026.01.010.

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