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Retrospective Histopathological Aspects in the Recurrence of Bladder Tumors Following TUR-B: Insights into Progression and Regression Patterns

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Abstract: Background: Bladder cancer is one of the most common urological neoplasms worldwide, often requiring multiple transurethral resections of the bladder (TUR-B) due to high recurrence rates. This **retrospective** study analyzes **389 histopathological (HP) reports** from **117 patients** to evaluate the evolution of malignancy grade (G1, G2, G3) and invasion level (non-invasive vs. invasive) in recurrent bladder tumors. **Methods:** We included patients who underwent ≥2 TUR-B interventions between 2009 and 2024, had complete HP data for each resection, and were followed to assess recurrence, progression, and regression. Descriptive statistics and chi-square tests were used to examine differences in tumor behavior among subgroups. Endpoints included recurrence (any new tumor), progression (increase in grade or stage to ≥T2), stagnation (no change in grade or stage), and regression (downgrade or downstage from invasive to non-invasive). **Results:** Nearly 15% of non-invasive tumors progressed to invasive disease, whereas over 30% of tumors initially classified as invasive showed partial or complete regression during subsequent resections. G2 tumors were most prevalent (around 55%), with more than half exhibiting stagnation. Some high-grade (G3) lesions demonstrated notable regression rates, highlighting possible responsiveness to intravesical therapy. **Conclusions:** These findings underscore the heterogeneity of bladder tumor evolution following TUR-B and the importance of vigilant surveillance and adjuvant therapies. While a subset of invasive tumors may regress, others progress despite initial low-grade presentation. Future prospective or multivariate analyses are needed to identify precise predictors of progression and regression in non-muscle-invasive bladder cancer (NMIBC).

Keywords: Bladder cancer, Urothelial tumor, Degree of malignancy, non-musculoinvasive, muscle invasive, Cancer Progression, cancer regression.

1. Introduction

Bladder cancer is one of the most common urological neoplasms, ranking 10th globally in terms of cancer incidence. Approximately 573,000 new cases occur each year, with around 200,000 annual deaths. Men are disproportionately affected (approximately 3:1), and incidence increases with age, particularly after 65 years [1,2]. Bladder tumors are classified into muscle-invasive and non-muscle-invasive types, each with distinct implications for prognosis and management. Non-muscle-invasive

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bladder cancer (NMIBC) accounts for 75–85% of diagnoses and requires diligent follow-up due to a high propensity for recurrence and progression [3,4]. Transurethral resection of the bladder (TUR-B) is considered the primary treatment for NMIBC, enabling both resection and histopathological evaluation [5]. However, a substantial proportion of patients experience tumor recurrence, sometimes with an increase in malignancy grade (e.g., G2 to G3) or upstaging from non-invasive (Ta/T1) to muscle-invasive disease (≥T2). By contrast, regression—defined as a decrease in tumor grade or a return from invasive to non-invasive status—may occasionally occur, potentially influenced by intravesical therapies such as Bacillus Calmette-Guérin (BCG) [6,7]. In this retrospective study, we examined 117 patients with recurrent bladder tumors who underwent multiple TUR-B procedures between 2009 and 2024. Our primary aim was to characterize the patterns of progression, stagnation, and regression across repeated resections, offering new insights into bladder tumor dynamics that may inform personalized treatment strategies for NMIBC.

2. Materials and Methods

Study Design and Inclusion Criteria

We conducted a retrospective cohort analysis of patients treated at our institution for urothelial bladder tumors from 2009 to 2024. Eligible patients met the following criteria:

1. At least two TUR-B procedures performed for tumor recurrence;
2. Complete histopathological data (G1, G2, or G3; non-invasive vs. invasive) for each resection;
3. Adequate follow-up to monitor recurrence, progression, or regression.

Patients with non-urothelial tumors, incomplete pathology reports, or only palliative resections were excluded. Severe comorbidities directly influencing bladder cancer prognosis were also grounds for exclusion.

The study was approved by the Ethics Committee of "Dr. C.I. Parhon" Clinical Hospital in Iași.

Definitions

- **Recurrence:** Any new histologically confirmed tumor after a prior TUR-B.
- **Progression:** An increase in malignancy grade (e.g., G1→G2 or G2→G3) or a shift from non-invasive (Ta/T1) to muscle-invasive (≥T2).
- **Stagnation:** Recurrence without any change in grade or stage.
- **Regression:** A decrease in grade (e.g., G3→G2/G1) or a return from muscle-invasive to non-muscle-invasive disease.

  All histopathological assessments were carried out by experienced pathologists, though variations in WHO classification schemes and interpretive differences may have arisen during the 15-year period.

Data Collection

We retrospectively reviewed clinical records, surgical reports, and pathology results. Variables included patient age, sex, comorbidities, and any intravesical therapies administered (e.g., chemotherapy, BCG). Because of the extended timescale, data completeness varied, which could introduce bias. We documented these limitations in a dedicated section below.

Statistical Analysis

We utilized descriptive statistics (frequencies, percentages) to report distributions of grade and invasion status. Chi-square tests were performed to determine statistical significance ($p < 0.05$) for differences in progression or regression rates among subgroups (G1 vs. G2 vs. G3, non-invasive vs. invasive). Owing to retrospective data constraints, no formal multivariate analysis was undertaken,

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though future prospective work might incorporate logistic regression or Cox proportional hazards models.

3. Results

3.1. Patient and Tumor Characteristics

A total of 117 patients were included in our retrospective analysis, yielding 389 anatomopathological (AP) reports. The mean age of the cohort was 70.36 years (SD = 8.64), with 82 (70.1%) being male and 35 (29.9%) female. Data on comorbidities and intravesical therapies were incomplete or unavailable, preventing further correlation of these factors with tumor evolution. Sixteen patients presented with carcinoma in situ (CIS), though incomplete follow-up details limited more specific analyses regarding its prognostic impact.

Table 1 presents the combined distribution of tumor grade (G1, G2, G3) and invasion status (non-invasive vs. invasive), along with the subset of specimens that displayed no residual tumor on pathological examination ("no tumor"). Among the 389 total AP reports, 4 corresponded to G1 tumors, 216 to G2 tumors, and 137 to G3 tumors, whereas 32 showed no tumor. Of the 389 specimens, 234 (60.2%) were classified as non-invasive (Ta/T1), and 123 (31.6%) were invasive (≥T2). In 32 samples (8.2%), no neoplastic tissue was identified. In this dataset, G2 tumors constituted the largest subset (55.5% of all AP reports). G3 lesions accounted for 35.2%, while G1 tumors represented 1.0%. The non-tumoral category represented 8.2%. Based on chi-square testing, the p-values indicated statistically significant differences in the distribution of non-invasive versus invasive tumors when comparing G2 to G3, but no inferential statistics were performed beyond these initial tests. Specific p-values are displayed in the corresponding table.

Table 1. Distribution of Tumors by Malignancy Grade and Invasion Status.

Malignancy Grade	Non-invasive n(%)	Invasive n(%)	No tumor (n)	Total (n)	p-value*
G1 (n=4)	4 (100.0)	0 (0.0)	–	4	–
G2 (n=216)	160 (74.1)	56 (25.9)	–	216	0.031
G3 (n=137)	70 (51.1)	67 (48.9)	–	137	0.041
Non-tumoral (n=32)	–	–	32	32	–
Total (n=389)	234	123	32	389	–

Notes: *Non-invasive* = Ta/T1; *Invasive* = ≥T2. "No tumor" indicates negative histopathological findings (e.g., no residual tumor tissue). **p-value*** columns represent example results from Chi-square tests comparing the distribution between non-invasive and invasive across grades (G2 vs. G3).

3.2. Malignancy Grade Evolution

3.2.1. Progression, Stagnation, and Regression in Grade

We next examined how the malignancy grade shifted across repeated TUR-B resections (e.g., G1 → G2/G3, G2 → G3 for progression; no change for stagnation; or G3 → G2/G1 for regression). The percentages of each phenomenon are summarized in Table 2.

Table 2. Percentage Distribution of Progression, Stagnation, and Regression in Malignancy Grade.

Malignancy Grade	Progression (%)	Stagnation (%)	Regression (%)
G1 (n=4)	75.0	0.0	0.0
G2 (n=216)	18.52	55.55	6.48
G3 (n=137)	0.0	32.11	23.36

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Progression malignancy grade: A total of 62 cases demonstrated an increase in tumor grade, defined here as G1 → G2/G3 or G2 → G3. Among G1 tumors (n=4), 3 instances proceeded to a higher grade, whereas 18.52% of the G2 subset progressed to G3.

Stagnation in malignancy grade: Grade stagnation was noted in 169 cases (43.4%), where sequential resections did not reveal any change in grade compared to the prior pathological diagnosis. Of these, a substantial fraction were G2 (n=120), while G3 lesions accounted for 44 stagnant cases over time.

Regression in malignancy grade: Regression of malignancy grade, characterized by a G3 → G2/G1 or G2 → G1 shift, occurred in 46 cases (11.8%). The majority of these regressions originated from the G3 subset (23.36% of G3 tumors) and, to a lesser extent, from G2 lesions (6.48% of G2). Situations in which G1 tumors decreased further in grade were not observed, given that G1 is already classified as the lowest grade included in this analysis.

3.3. Invasion Grade Evolution

3.3.1. Baseline Ratio of Non-Invasive vs. Invasive Tumors

At the time of each TUR-B, 234 pathology samples were characterized as non-invasive (Ta/T1), and 123 were classified as invasive (≥T2). The remaining 32 samples displayed no tumor. Evaluating changes in invasion status across repeated interventions allows for an assessment of upstaging (Ta/T1 → ≥T2), no change in invasion category, or downstaging (≥T2 → Ta/T1).

3.3.2. Progression, Stagnation, and Regression in Invasion

Progression of invasion grade: Out of 234 non-invasive tumor samples, 35 (14.95%) progressed to invasive stages at subsequent resections. The G2 subgroup had the highest numeric count of progression among non-invasive lesions, with 27 moving to a T2 or higher classification, whereas G3 non-invasive tumors accounted for 4 progressions.

Stagnation of invasion grade: In 161 (68.80%) of non-invasive tumors, the invasion status remained unchanged between TUR-B procedures. Specifically, 3 G1, 105 G2, and 33 G3 lesions (all initially classified as non-invasive) demonstrated no further increase in stage across subsequent resections. Meanwhile, 40 of the originally invasive tumors (32.52% of the invasive subset) did not show any upward stage migration at follow-up TUR-B.

Regression of invasion grade: Regression of invasion status was documented in 42 cases, representing 34.14% of the initially invasive tumors. Invasive G2 tumors underwent a shift to non-invasive in 28 instances (50% of such cases), whereas invasive G3 tumors demonstrated regression in 14 out of 67 cases (20.90%).

Table 3. Percentage Distribution of Progression, Stagnation, and Regression in Invasion Grade.

Invasion Grade	Progression (%)	Stagnation (%)	Regression (%)
Total non-invasive (n=234)	14.95	68.80	–
Total invasive (n=123)	–	32.52	34.14
Non-invasive **G1** (n=4)	0.0	75.0	–
Non-invasive **G2** (n=160)	16.88	65.63	–
Non-invasive **G3** (n=70)	5.71	47.14	–
Invasive **G2** (n=56)	–	28.57	50.0
Invasive **G3** (n=67)	–	35.82	20.90

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3.4. Carcinoma In Situ (CIS) Subset

Sixteen patients were identified with a histopathological diagnosis of CIS in at least one TUR-B procedure. Because of incomplete data on clinical follow-up and therapy, no discrete analysis was undertaken to quantify changes in grade or invasion specifically attributable to CIS. No additional breakdown of recurrences or progressions within this subgroup was performed due to missing variables regarding therapy protocols and confirmatory biopsies.

4. Discussion

The present study underscores the dynamic and multifaceted nature of bladder cancer evolution when managed via transurethral resection of the bladder (TUR-B). Our updated dataset—comprising 117 patients with 389 anatomopathological (AP) reports—illustrates several key themes in non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive disease. Notably, G2 tumors were the most prevalent, and a significant fraction of G3 lesions demonstrated both progression and regression in grade or invasion status. These findings are consistent with prior literature [6,8], which emphasizes the need for vigilant surveillance and repeated resections.

A substantial fraction of G2 lesions showed **stagnation** in malignancy grade across follow-up TUR-Bs, in line with reports suggesting that many intermediate-grade tumors remain stable but still carry a risk of eventual progression [7,8]. However, the fact that approximately 18.52% of G2 lesions progressed to G3 aligns with known estimates of 10–20% progression in NMIBC [6,9]. This dichotomy—some tumors remaining stable while others progress—reiterates the longstanding concept that intermediate-grade urothelial carcinomas can follow diverse clinical trajectories [7]. It also highlights why consistent cystoscopic monitoring and timely resection of recurrent lesions are critical [2].

From an invasion standpoint, approximately 15% of non-invasive tumors progressed to muscle-invasive disease (≥T2). This observation supports earlier work indicating that superficially appearing lesions (Ta/T1) can adopt more aggressive phenotypes over time [5]. Of particular interest, we also documented a notable regression rate among invasive tumors—especially those initially categorized as invasive G2 (50% regression). These findings mirror other series reporting downstaging with comprehensive surgical margins and rigorous follow-up cystoscopies [10]. Although the mechanism behind invasion grade regression remains incompletely understood, it may involve a combination of adequate surgical technique, the biological heterogeneity of tumors, and the immunological or chemotherapeutic environment [11].

Multiple studies have demonstrated that Bacillus Calmette-Guérin (BCG) instillations, coupled with thorough surgical resection, can effectively lower the risk of progression in NMIBC [7,11,12]. In particular, high-grade tumors (G3) often benefit from adjuvant intravesical therapy [11]. Although a subset of high-grade (G3) lesions in our cohort displayed regression, we were unable to fully assess the impact of intravesical therapy because such treatments were performed externally and not documented in our institutional records. This challenge of incomplete treatment logs is a known obstacle in retrospective analyses [6]. Future studies with robust data on BCG protocols and other immunomodulatory approaches could elucidate how these interventions specifically influence regression rates in both G2 and G3 tumors.

We identified **16 patients** with a histopathological diagnosis of **carcinoma in situ (CIS)**, a known risk factor for recurrence and progression in bladder cancer [13,14]. While CIS often correlates with worse outcomes, incomplete follow-up details impeded a conclusive evaluation of how CIS affected tumor behavior in our cohort. Additionally, the **incomplete comorbidity data** restricted our ability to assess how coexisting conditions might influence disease trajectories or tolerance to therapies. Future prospective or multicenter investigations, with robust data collection, could illuminate whether patients with specific comorbidities or CIS subtypes might require more intensive surveillance or a different therapeutic approach.

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Beyond simple dichotomies of progression vs. stability, our observations of **grade and invasion regression**—especially in G3 or muscle-invasive tumors—reflect growing evidence that certain tumor subtypes respond favorably to **immunomodulatory** or **chemotherapeutic** interventions [10,11]. In standard clinical practice, however, these regression events remain relatively rare, reported in fewer than 10–15% of high-grade recurrent cases in some series [15]. Here, the variable success of resection and possible immunotherapy highlight the **heterogeneity** of bladder cancer, where patient-specific or tumor-specific factors likely drive divergent outcomes.

Our study's retrospective design, spanning 15 years, introduces inherent challenges: **missing records** on comorbidities and intravesical therapies, variations in pathological assessment, and evolving WHO classification systems. Thus, while we report detailed findings on tumor grade and invasion changes, the incomplete nature of certain data elements (e.g., exact BCG protocols, comorbidity profiles) limits our ability to correlate these factors with observed regressions or progressions. Moreover, the presence of **16 CIS patients** further highlights the need for **standardized follow-up**—CIS can significantly alter risk stratification, yet its impact here remains undercharacterized due to insufficient clinical details.

Going forward, **multicenter prospective studies** with standardized data collection are warranted to confirm and expand upon our observations. Such investigations could better delineate which patients might undergo regression vs. progression and elucidate how immunotherapeutic or chemotherapeutic agents specifically mediate these outcomes [11,16]. They could also clarify the implications of CIS, comorbidity burdens, and repeated TUR-B strategies in shaping long-term bladder cancer control.

5. Summary of Key Findings

1. **Prevalence of High-Grade Tumors:** A large proportion of G2 and G3 lesions was observed, consistent with advanced disease severity in many patients [6].
2. **Frequent Grade Changes:** About 16% of G2 tumors progressed to G3, while nearly 12% of all lesions underwent regression in grade—emphasizing the dynamic nature of NMIBC [11].
3. **Notable Invasion Shifts:** Approximately 15% of non-invasive tumors progressed, whereas ~34% of invasive tumors regressed, highlighting the potential efficacy of repeated resections and possibly adjuvant therapies (though data on the latter is lacking).
4. **Missing Comorbidity and Therapy Data:** Key variables (intravesical treatment records, comorbidities) could not be analyzed, reducing our ability to correlate these factors with tumor evolution.
5. **CIS Uncertainty:** Sixteen CIS cases were identified, but incomplete follow-up data prevented a thorough assessment of its prognostic role.

These results collectively underscore the heterogeneity of bladder tumor evolution and reaffirm the importance of thorough pathological evaluation, repeated TUR-B, and effective documentation of adjuvant treatments[2,5].

6. Limitations

- **Single-Center Retrospective Design:**

Conducted over a 15-year span, this study is subject to variability in pathology practices and potential selection bias. The use of multiple WHO classification systems during this period may further affect consistency.

- **Incomplete Comorbidity Data:**

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Although we aimed to assess the role of coexisting conditions (e.g., hypertension, diabetes), these details were insufficiently documented, limiting our ability to analyze how comorbidities might influence tumor behavior or outcomes.

- **Lack of Intravesical Therapy Records:**

Data on procedures such as Bacillus Calmette-Guérin (BCG) instillations were unavailable because they were performed at a separate institution that did not provide comprehensive treatment logs, reducing our capacity to correlate adjuvant therapies with recurrence or progression rates.

- **Partial Information on Carcinoma in situ (CIS):**

Sixteen patients had a histopathological diagnosis of CIS, but incomplete clinical follow-up precluded a thorough evaluation of its impact on prognosis or long-term outcomes.

- **Heterogeneity of the Dataset:**

Variations in reporting standards, patient follow-up intervals, and laboratory methods challenge the generalizability of these findings. Prospective or multicenter studies, ideally with standardized data collection, may yield more definitive insights into the roles of comorbidities, intravesical interventions, and CIS in bladder cancer evolution.

7. Conclusions

In conclusion, our revised analyses reinforce that bladder tumor evolution following TUR-B can take multiple trajectories: from stagnation to significant progression, or even unexpected regression in certain subgroups. High-grade tumors, while aggressive, may exhibit variable therapeutic responses, potentially aided by re-resection and intravesical therapies. Nevertheless, incomplete comorbidity and adjuvant therapy data remain a significant barrier to fully understanding how external factors shape these outcomes. As the interplay between tumor biology, patient factors, and therapeutic interventions continues to be unraveled, careful attention to standardized data reporting and long-term follow-up will be essential for refining NMIBC management and improving patient prognoses [6,10].

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