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Did the Scientific Innovations in the Management of Non-Muscle Invasive Bladder Cancer Patients Improve the Outcome during the Last 2 Decades?

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Abstract

Objectives: Previous reviews reported the outcome of each scientific modality in the management of T1 high-grade bladder cancer. The objective of this review is to assess and evaluate the available scientific modalities used during the last two decades and determine whether they were able to improve the clinical outcome. **Literature Search Methodology:** A systematic literature review was conducted from 2000-2020 using PubMed, Medline, Embase, and other database sites looking at randomized controlled trials (RCTs), clinical trials, research, review articles, and original articles addressing the different scientific modalities used to diagnose and manage patients with non-muscle invasive Bladder cancer (NMIBC)during the last 2 decades. More than 573 studies were retrieved following the preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and PICOS criteria (Population, Intervention, Comparators, Outcomes, and Study design). Only 85 articles were selected for review including 19 prospective trials, 44 RCTs, original articles, research articles, one review article, and clinical trials—Retrospective studies were excluded to limit bias as much as possible in the analysis. **Results:** Randomized controlled trials (RCTs) have become the gold standard for evaluating the efficacy of new treatments. They are considered the highest standard of evidence-based medicine and are the method of choice. Overall, we selected 85 studies for review, among them 63 prospective trials and RCTs, with a total of 21,895 patients, published between 2000 and 2020. Previously conducted studies have shown that identifying rare histological types with poor prognoses can help improve outcomes, mainly the plasmacytoid

type. Many articles addressed the role of biomarkers in the early identification of patients with NMIBC for recurrence and progression—P-cadherin expression and others were used to predict recurrence and/or progression with promising results. Despite the need for modifications, risk stratification is an important tool that should be used to improve the outcome of patients with NMIBC. Some found that fluorescence diagnostic cystoscopy (FDC) and Photodynamic diagnosis (PDD) improved recurrence-free survival but not progression and outcome. All authors agree that intravesical BCG is the most effective therapy that changes the course of high-grade T1 mainly progression. Re-TURBT has become one of the recommendations of international societies, but its potential effect on survival improvement is debatable. Most of the articles showed the advantages of early cystectomy in NMIBC but all agree that the selection criteria must be clearly defined. **Conclusions:** This review analyzed the outcomes provided by the scientific advances in the field of management of NMIBC patients in the last two decades. Patients with T1 bladder cancer have variable outcomes because of tumor heterogeneity and clinical staging. Despite the great development in the field of diagnosis, risk stratification, and management, further large studies are mostly needed to better elucidate this subset of patients and avoid over and under-treatment.

Keywords

Non-Muscle Invasive Bladder Cancer, Outcome, Early Cystectomy, Biomarkers, Intravesical Agents, Re-TURBT, Histology, Risk Stratification

1. Introduction & Background

In the US, bladder cancer is the fourth most frequent cancer in males, while it ranks eighth in the UK. Urothelial cancer is the most prevalent kind of bladder cancer, and between 70 and 80 percent of these cases are non-muscle invasive bladder cancers (NMIBCs), with the remaining 20 to 30 percent being muscle-invasive bladder cancers (MIBCs) [1].) NMIBC is very difficult for patients to treat because of its high recurrence rate (up to 50%) and progression to muscle invasion (10% - 30%). Patients with T1 tumors have varying clinical outcomes; 10 - 34 percent of them will pass away within five years of their diagnosis. [2]. Intravesical BCG, which was first used to treat patients with NMIBC in the early 1970s, is still among the most successful treatments and is advised by numerous worldwide standards. Although transurethral resection (TUR) followed by Bacillus Calmette-Guérin (BCG) is regarded as the gold standard therapy, questions about BCG's ability to slow the development of high-grade T1 persist. With satisfactory outcomes, other intravesical drugs including Mitomycin and Gemcitabine have been employed. For patients with non-muscle invasive bladder cancer, a variety of treatments and methods have been developed, including re-TURBT, radiochemotherapy, systemic immunotherapy, gene therapy, EMDA electromotive drug administration, early cystectomy, and diagnostic techniques

(biomarkers, gene expression mutation, Fluorescence cystoscopy). The results of each scientific technique in the treatment of T1 high-grade bladder cancer were documented in earlier reviews. To enhance the results of diagnostic, imaging tests, histology, biomarkers, intravesical agents, risk stratification, re-TURBT, and early cystectomy, several modalities have been utilized during the past 20 years in NMIBC patients.

2. Methods and Materials

To find pertinent papers, a search of the literature from 2000 to 2020 was carried out in May 2021 using PubMed, Medline, Embase, and other database sites. Using the Preferred Reporting Items for Systematic Review and Meta-analysis, the eligible publications were chosen (PRISMA). The search phrases and keywords were organized using the PICO model (patient/population, Intervention, Comparator, and Outcome) for the particular issue under study. We set out to perform a comprehensive review of the literature, including randomized controlled trials (RCTs), clinical trials, and original papers that addressed the many scientific approaches employed during the previous two decades to diagnose and treat patients with NMIBC. We only chose publications that discussed the results. Over 570 studies total were found. 44 RCTs were included in the 85 publications chosen for the assessment using PRISMA (Figure 1).

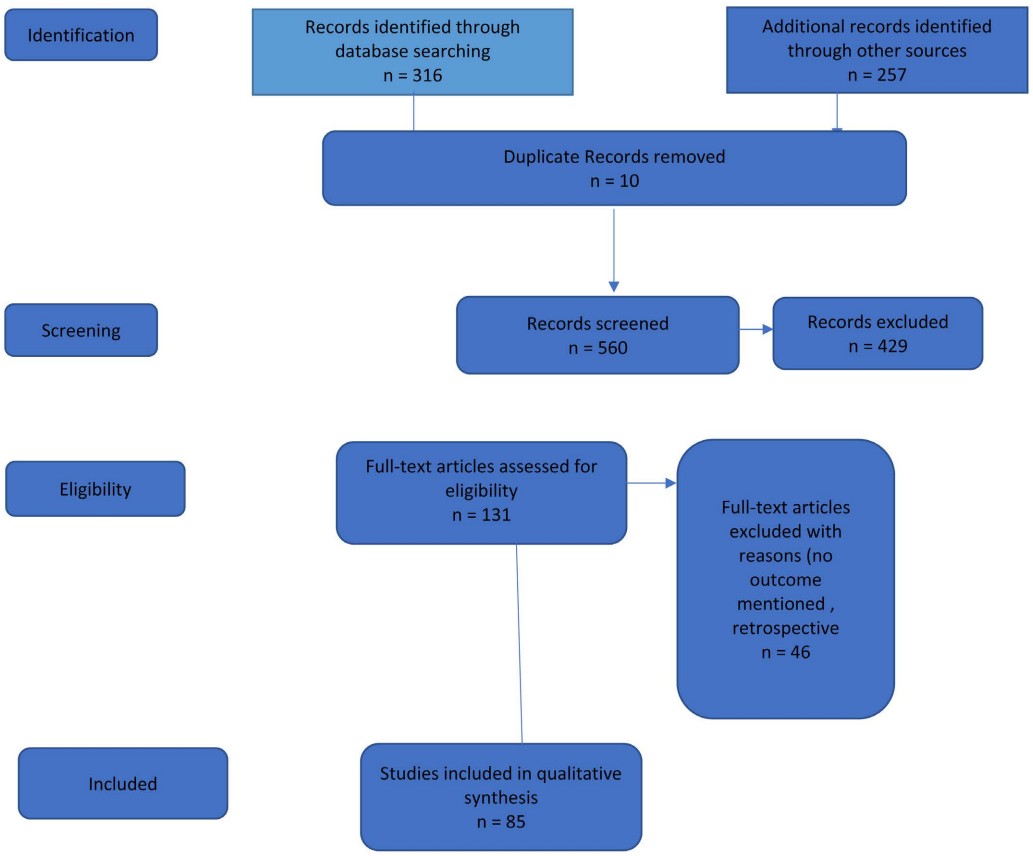

Figure 1. PRISMA flow diagram of NMIBC studies.

Inclusion and exclusion criteria:

Inclusion criteria: 1) patients must be older than 18 years old; 2) patients must have non-muscle-invasive bladder cancer; 3) the sample size must be greater than 30 patients and should preferably come from randomized control trials; 4) they must be written in English; 5) they must have been published within the past 20 years; and 6) they must have sufficient outcome data

Exclusion criteria:

Articles are excluded if: 1) patients had a history of muscle-invasive disease or upper tract Tumor; 2) outcome not mentioned as the primary objective; 3) unavailable full texts, case reports, systematic review studies, and retrospective studies.

3. Results

The standard treatment for patients with NMIBC is TURBT, which has a high 5-year survival rate, however, with the high recurrence and progression rates (31 - 78 percent and 1 - 45 percent, respectively), urologists were bound to search for factors that can prevent these failures. Among these factors were different histologies, biomarkers, diagnostic imaging, cystoscopy, risk stratifications, TURBT and re-TURBT, intravesical agents, and early cystectomy.

3.1. Histology and Outcome

Data on urothelial cancer histologic variations were presented in two papers. Variant histology refers to the presence of any bladder malignancy besides pure urothelial carcinomas, such as UC with aberrant differentiation and pure non-UC due to metaplasia, which makes up 10% - 25% of all BC [3].

13 distinct urothelial malignancies are listed in the most recent World Health Organization (WHO) classification of urothelial cancers. The description of molecular characteristics and clinical behavior of these variations have drawn increasing attention since the World Health Organization (WHO) 2004 classification defined many histologic subtypes of urothelial carcinomas. Patients with a poor prognosis are defined as having the plasmacytoid form of bladder cancer.

Following radical cystectomy and adjuvant cisplatin-based chemotherapy for 205 tumor samples of patients with locally advanced bladder cancer who were primarily treated in the randomized AUO-AB05/95 trial, 178 UC, 18 plasmacytoid (PUC), and 9 micropapillary (MPC) carcinomas of the bladder were identified. Compared to traditional UC and MPC of the bladder, which appeared to have the greatest clinical outcomes (27.4 months, 62.6 months, and 64.2 months, respectively; $p = 0.013$ by Kaplan Meier analysis), patients with PUC had the lowest clinical result in terms of overall survival. The authors of this paper concluded that finding these uncommon histological types carrying a bad prognosis can ameliorate the situation [4]. After BCG instillation, Prado *et al.* compared the recurrence rate in patients with variable histology and pure urothelial cancer. They discovered that NMIBC with variable histology treated with BCG had a

lower 2-year recurrence rate [5].

3.2. Biomarkers

Nine studies provided information on the use of biomarkers in patients with NMIBC. The primary mediators of cell-cell adhesion in epithelial tissues have been well-described as calcium-dependent transmembrane glycoprotein molecules called cadherins.

The extracellular, transmembrane, and cytoplasmic domains are all shared by the traditional cadherins E, N, and P-cadherin expression with prognostic significance in bladder cancer that is hardly ever studied.

P. Wang *et al.* examined samples from 110 individuals with NMIBC and P-cadherin protein underwent an immunohistochemistry test. The predictive usefulness of P-cadherin in non-muscle-invasive bladder tumors was demonstrated by Kaplan Meier's data revealing that patients with high P-cadherin expression had inferior progression-free survival but not recurrence-free survival (P: 0.133) [6].

To investigate the predictive value of Ki-67 expression and demonstrate if the combination of the European Organization for Research and Treatment of Cancer (EORTC) risk scores and Ki-67 staining status could improve risk stratification in patients with non-muscle-invasive bladder cancer, Ding Weihong *et al.* studied 332 patients with NMIBC (NMIBC). They concluded that Ki-67 positive is predictive for tumor recurrence and progression through their study of the prognosis function of EORTC risk ratings, Ki-67 staining, and their combination on tumor recurrence-free survival and progression-free survival (PFS).

The classification of the risks for both recurrence and progression in NMIBC may be improved by combining EORTC risk ratings with Ki-67 expression [7].

Targeted sequencing was performed to find the mutations in 82 NMIBC tumor tissue DNA and plasma ctDNA based on 861 gene panels.

Following TURBT, they discovered 165 somatic variants in ctDNA from 54 patients (65.85%) and 476 somatic variations in tumor DNA from 82 NMIBC patients (100%).

The disease-free survival was considerably shorter in patients with high tumor DNA heterogeneity compared to those with moderate heterogeneity. In the plasma of 43 individuals, some changes came from the tumor (52.44 percent). Patients with T1 stage and tumors less than 3 cm had greater somatic variation concordance between tumor DNA and plasma ctDNA ($p = 0.0001$) and $p = 0.0002$ respectively. Larger tumor size was positively linked ($p = 0.0020$) with the molecular tumor burden index (mTBI) in ctDNA. It can assist in predicting the return of an illness [8].

A randomized trial was conducted by Ying-Li Lin to evaluate the clinical significance of protocadherin Re8 (PCDH8) methylation in NMIBC—PCDH8 is a novel tumor suppressor gene frequently inactivated by promotor methylation in human cancer—They noted that PCDH8 methylation is a frequent event in

NMIBC is correlated with high grade, advanced stage, large tumor size, tumor recurrence, and progression.

They found that PCDH8 methylation is related to tumor growth and poor prognosis and might be utilized as a possible biomarker to predict the prognosis of NMIBC patients [9].

Some investigators went further and studied the role of urinary metabolomics in the diagnosis and prediction of survival. Jin *et al.* compared the urine metabolites of 138 patients with BC to 121 control subjects. Their differentiation model detected BC with 91.3% sensitivity and 92.5% specificity, respectively. According to multivariate regression, the metabolomic profile correlates with cancer-specific survival time [10].

Chade D *et al.* conducted a prospective study to evaluate the predictive value of CEA, CA 19-9, and CA125 on disease recurrence and progression of NMIBC patients. These blood-based biomarkers were taken from 328 patients before TURBT. They found that CEA and CA 19-9 levels were significantly higher in patients who had a recurrence and/or progression compared to those who had no recurrence-CA125 did not differ between the two groups after a mean follow-up of 4.9 years [11]. The authors concluded that further larger future studies should consider including these biomarkers in a predictive model.

3.3. Diagnostic Imaging and Cystoscopy

Twelve studies discussed the role of innovation in the field of imaging and diagnostic cystoscopy to improve outcomes since White light imaging cystoscopy was missing some bladder tumors, many researchers conducted studies to find better techniques to identify the tumors during cystoscopy. Among these was the use of narrow-banding imaging (NBI). Yi-Jun Shen *et al.* conducted a prospective study on 78 patients with suspected bladder cancer. White Light imaging, followed by narrow-band imaging was used during cystoscopy for each patient. Biopsies were taken from suspicious areas. Thirty-six tumors in 13 patients (17%) were detected by NBI and only four tumors (1.9%) in 3 patients were found by WLI. NBI had higher sensitivity than WLI (92.9% v/s 77.7%) and lower specificity than WLI (73.5% v/s 82.7%).

The authors concluded that the "second look" with NBI did show superiority over standard WLI flexible cystoscopy for detecting primary NMIBC including CIS lesions [12].

Naselli *et al.* randomized 148 subjects to undergo either NBI TUR or white light TUR—The 1-year recurrence risk was 32.9% in the NBI versus 51.4% in the WL group [13].

The same Italian group explored the role of NBI in identifying high-grade malignant tumors overlooked by white light during second transurethral resection. They enrolled 47 patients who were willing to undergo a second look TUR—Using white light TUR, ten patients were diagnosed with having residual urothelial bladder cancer, including one patient with muscle-invasive—NBI biopsies detected six more patients with high-grade cancerous tissue.

The authors concluded that taking NBI biopsies at the second look of TUR will improve the identification of the urothelial cancers otherwise missed on white light TUR [14].

These results were not supported by another research group from Germany that used NBI to evaluate the diagnostic accuracy of this technique in the follow-up of patients with NIMBC as compared to White light cystoscopy—Six hundred patients were randomized to either NBI or white Light cystoscopy for the follow-up—The cancer recurrence detection was 26% using NBI cystoscopy and 23% using White light cystoscopy ($p = 0.507$).

This study showed no differences in tumor detection between these two techniques [15].

Mukherjee *et al.* conducted a prospective, blinded sequential randomized controlled trial—Patients were randomized into two arms: group A underwent resection using the white light and then used the NBI for the second look, while the other group B, used the NBI for the resection, used the white light for the second resection—The additional lesions detected in both groups were analyzed. In group A, additional lesions were detected in 37% versus 9% in Group B—The authors concluded that NBI is superior to WL in the detection of tumors thus allowing a more complete resection [16].

In addition, on Re-TURBT, residual tumors rates were significantly lower for the NBI group—The recurrence rate at 1 year was lower for the NBI group (7.2% vs.18.3%).

Another technique that has emerged to improve bladder tumor detection rates compared to the white light cystoscopy is the use of Fluorescence endoscopy with 5-aminolevulinic acid (ALA).

Riedl *et al.* conducted a prospective randomized study on 102 patients that underwent transurethral resection of bladder tumors using either white light or ALA fluorescence-assisted endoscopy. A second look at TUR was performed with ALA fluorescence 6 weeks after the initial resection to assess the recurrence [17]. Recurrence was detected in 39% of the patients in the white light group versus 16% in the ALA fluorescence group (0.005).

Hexvix Photodynamic diagnosis-assisted (PDD) transurethral resection has emerged as a new diagnostic tool to reduce the recurrence rate. A prospective controlled study was conducted by Mariappan *et al.* on 808 patients to compare the early recurrence rate using this technique with the conventional technique—The PDD group had a 13.6% early recurrence rate versus 30.9% for the White Light Group [18].

3.4. Risk Stratification and Outcome

Eight studies provided data on the role of risk stratification models for better selection of patients to improve the outcome. The European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Urological Club for Oncological Treatment (CUETO) are two important risk assessment models for predicting the risk of NMIBC recurrence. Among them, EORTC is most com-

monly used worldwide for risk stratification. But these methods have their limitations and were criticized by many authors.

Since NMIBC tends to progress with a worse prognosis than primary invasive bladder cancer, there is a strong need to improve risk stratification so we can manage the high-risk cases earlier. Some studies developed other stratification methods based on clinicopathological characteristics, urine biomarkers, and life-history traits. Wang *et al.* [19] developed novel recurrence risk stratification based on ten prognostic factors [bladder cancer-specific nuclear matrix protein 4 (BLCA-4), bladder tumor antigen (BTA), nuclear matrix protein 22 (NMP22), carcinoembryonic antigen (CEA), body mass index, smoking, family history of bladder cancer, occupational exposure to aromatic amine chemicals, number of tumors, bladder instillation of chemotherapeutic agents] to predict tumor recurrence

A group from Japan proposed another novel risk stratification model, the Japanese NIshinihon uro-oncology Extensive collaboration group (J-NICE), consisting of seven factors to predict recurrence, progression, and cancer—specific death after stratification of their patients according to the score—All these novel new models needs further external validation to strengthen its clinical impact [20].

Another group from Japan analyzed 1085 patients with NMIBC at six hospitals to investigate whether the EORTC risk stratification system is useful to predict recurrence and progression in Japanese patients. In addition, they developed a novel risk classification system for recurrence using four independent prognostic factors (tumor size, tumor number, BCG instillation, and Intravesical chemotherapy) and compared it to the EORTC risk classification—Using the latter system, there was no significant difference in RFS and PFS—According to the novel system, there was a significant difference in 5 y RFS rate between the low (68.4%) intermediate (45.8%), and high (33.7%) ($p < 0.001$) -The authors concluded that the EORTC risk group stratification may not apply to Asian patients [21]. Fernandez-Gomez *et al.* from Spain conducted a study to evaluate the external validity of the EORTC risk tables in NMIBC patients treated with BCG. They concluded that the EORTC model successfully stratified recurrence and progression risks in their cohort. However, the discriminative ability of the EORTC tables decreased in their patients for progression. Moreover, these tables overestimated the risks of recurrence and progression after BCG therapy [22].

Ki-67 is a well-established cell proliferation marker that is present during the G1, S, G2, and M phases of the cell cycle. A large multicenter study has confirmed the role of Ki-67 as an independent factor associated with disease recurrence and overall survival in patients treated with radical cystectomy [23]. But only a few trials used the Ki-67 to study its role in predicting recurrence and progression in patients with NMIBC.

3.5. TURBT and Outcomes

Thirteen RCTs provided data on the role of innovation and modification in

TURBT to improve outcomes. Worldwide, most TURBTs are performed using monopolar cautery. Bipolar cautery was introduced in early 2000 and initial studies showed some advantages over monopolar cautery. Since then, many studies were conducted to compare these modalities. Venkatramani *et al.* conducted a randomized controlled trial to compare the efficacy and safety of bipolar TURBT and monopolar resection [24]. After exclusion, 147 patients were randomized including 75 in the monopolar arm and 72 in the bipolar arm. The authors concluded that bipolar transurethral resection of the bladder tumor was not superior to monopolar resection concerning obturator jerk, bladder perforation, and hemostasis. The only advantage was pathological, resulting in a significantly lower incidence of severe cautery artifact in the bipolar arm (25% vs 46.7%).

Similar conclusions were observed with Murugavaithianathan *et al.* in their randomized controlled trial [25]. Others compared the safety and efficacy of plasma kinetic bipolar versus conventional monopolar TURBT. One hundred thirty-two patients were randomized into two groups using one of the two modalities [26].

The operative time was shorter for the bipolar group compared to the monopolar group, with shorter catheterization time, and more bladder perforation occurring in the Monopolar group.

Other authors compared the Detrusor muscle sampling rate in monopolar and bipolar TURBT in a randomized trial and found that using bipolar cautery will provide a better sampling rate for pathologists [27].

In one of the largest comparative studies done in Japan, the authors analyzed 19,953 Monopolar TURBT to 8188 Bipolar TURBT and found that B-TUBT was associated with a lower incidence of severe bladder injury as compared to M-TURBT [28].

Bolat *et al.* conducted an RCT to compare the perioperative outcomes and complications of monopolar and bipolar TURBT in patients with coronary artery disease (CAD). Both systems were safe and effective during TURBT in CAD patients with more Obturator jerk seen with monopolar resection [29].

Pathologists complain of the inability and difficulty to make an accurate pathological assessment on the tissue sampling provided by the conventional monopolar electrocautery technique. For this reason, resection using the Laser technique has been introduced to perform TURBT. Chen *et al.* conducted an RCT involving 142 patients with NMIBC who were randomly assigned to either monopolar resection or 2-micron Laser treatment. Obturator jerk was observed more frequently with the conventional technique. There was no statistical difference in the rate of recurrence during the follow-up better and clear base samples were provided with laser treatment allowing for the pathologists to better report [30].

Others used Potassium-Titanyl-Phosphate (KTP) Laser Vaporization and compared it with conventional monopolar electro-resection in a randomized control trial. No difference in operative time and recurrence rate was noted between the two groups, with the laser group having fewer perioperative complica-

tions, shorter catheterization time, and hospitalization duration [31].

Throughout the last decade, certain institutions have adopted fluorescence cystoscopy to improve the diagnostic effectiveness of endoscopy and raise bladder tumor detection rates. The initial fluorescence endoscopy ingredient was ALA (5-aminolevulinic acid), which has been chemically changed to increase the rate of urothelial resorption and the duration of activity. Various forms of ALA are available (Spectrila®, Alasens®, and Hexvix®).

Daniltchenko *et al.* compared in a prospective randomized trial the 5-year outcome data of 115 patients who underwent TURBT under white light or using 5-aminolevulinic acid (ALA) induced fluorescence. The standard group had a 25% recurrence-free survival rate, whereas the ALA group had a 41% recurrence-free survival rate. The total number of recurrences was 82 in the standard group and 61 in the ALA group [32].

Another group from Germany studied 191 patients with superficial bladder tumors in a randomized fashion. They evaluated whether fluorescence diagnosis (FD) increases recurrence-free survival (RFS) or reduces progression to muscle-invasive stages [33]. The RFS at 4 and 8 years was 69% and 52% in the White light (WL), and 91% and 80% in the D group, respectively. In the WL group, three (12%), and the FD group four (19%) patients progressed to muscle-invasive. The authors concluded that FD was better for the RFS than WL but did not reduce the progression to muscle-invasive disease.

3.6. Second Look at TURBT and Outcome

Seven studies reported the role of re-TURBT in the better restaging of NMIBC patients. Many studies have reported that around 50% of the patients undergoing re-TURBT were found to have residual tumors and between 10% - 25% were found to have a muscle-invasive disease. For these reasons, many guidelines recommend a re-TURBT within 6 weeks in patients with newly diagnosed high-risk non-muscle invasive.

Kim *et al.* evaluated in a randomized trial the diagnostic accuracy of immediate second resection of the tumor bed during the initial TUR and compared the results to the standard technique.

The second resection was repeated until muscularis propria was identified in the specimen and the depth of tumor invasion was inspected. The recurrence and progression rates were compared in the two groups.

Among the 94 patients who followed up, those in the immediate second resection group had a significantly higher 2-year recurrence-free survival rate (77.0% vs 45.8%, $p = 0.025$), but there was no difference in progression-free survival rate [34].

Many studies have been conducted to identify the subgroup of patients with high-risk NMIBC who can avoid routine re-TURBT.

Among them, a prospective observational study was conducted by Gahlawat *et al.* on 270 patients with NMIBC.

They were divided into two groups according to the presence or absence of muscle in the TURBT specimen. They were further divided based on the presence or absence of residual tissue at the time of re-TURBT. In the data analysis, they found that only three factors can be associated with the risk of upstage re-TURBT: tumor size of more than 3 cm, absence of deep muscle in the primary TURBT specimen, and the presence of regrowth on re-TURBT. They concluded that re-TURBT can be avoided if the tumor is less than 3 cm, the muscle is present in the primary TURBT specimen, and there is an absence of regrowth in the re-TURBT [35].

This was consistent with the results of a large retrospective multicenter European—North America study including 2451 patients with NIMBC, which also found that re-section could be avoided if the muscle was present in the specimen [36].

Gill *et al.* conducted a prospective interventional study to identify the category of patients with NMIBC who may benefit from re-TURBT. They concluded that Re-TURBT may be recommended for high-grade and T1 tumors and tumors with a solid/sessile appearance on primary TURBT, especially when the deep muscle was absent on the primary specimen [37].

Gordon *et al.* compared the outcomes of 932 patients with high-grade non-muscle invasive BC who did or did not undergo re-resection following their initial treatment. Patients who had re-resection were more likely to have muscle invasion (126 [27%] vs 49 [11%]), chi-square p = 0.001. A total of 207 individuals died from BC, with 46 (22%) undergoing re-resection and 161 (78%) not. Patients who had re-resection within 3 months had significantly better disease-specific (log-rank p = 0.009) and overall survival (p = 0.001) than those who did not [38].

A prospective study from Taiwan also showed that re-resection identified 18% of residual tumors [39].

Another prospective study from Italy compared patients with completely resected high-grade T1 BC who did and did not undergo re-TURBT. The authors evaluated the impact of re-TURBT on recurrence-free survival, progression-free survival, and cancer-specific survival. After a follow-up of 60 months, they noted no difference in RFS, PFS, and CSS between patients who had or had not re-TUR [40].

Ali *et al.* performed an analytic prospective cohort study on 91 patients with stage T 1 or Ta bladder tumor—All the patients underwent a re-TURBT within 2 to 6 weeks following the initial resection—No tumor was noted in 41.7%. Upstaging had changed treatment strategy in 22 patients (24.2%). The authors concluded that re-TURBT is a valuable procedure and indicated in T1, high grade, large size > 3 cm, and nodular tumors [41].

3.7. BCG and Outcomes

Fifteen studies reported on BCG's role in modifying patient outcomes. Adjuvant

immunotherapy using intravesical Bacillus Calmette Guerin (BCG) was regarded as the gold standard of care in the treatment of non-muscle invasive bladder cancer for over fifty years.

Is there a difference in the efficacy of the different BCG strains?

A randomized phase III research comparing the two most regularly used strains in Europe and the United States (Tice v/s Connaught) was conducted, with the primary endpoint being recurrence-free survival—One forty-nine patients were randomized to either receive oncoTice or immunize BCG intravesical on weekly basis for six weeks—After a median of 24 months, the five-year recurrence-free survival rate for Connaught and Tice treated patients was 75% and 46%, respectively. The median recurrence-free survival for Connaught patients was 28 months (range: 0.6 - 136) and 22 months (range: 0.3 - 122) for Tice patients. The two strains had comparable progression-free and total survival rates.

The authors found that the BCG strain influences treatment results, and that Connaught is preferable to Tice in treating NMIBC [42].

Similar conclusions were presented from another prospective study conducted by Rentsh *et al.* [43] confirming the superiority of the BCG Connaught over BCG Tice in its ability to reduce the recurrence rate.

A French group, Pfister *et al.* investigated BCG maintenance and dosage modifications to reduce side effects while maintaining efficacy. They conducted an RCT to assess the maintenance treatment schedule for NMIBC at 2 years using one-third of the full dose and fewer instillations every 3 months or 6 months. For three years, the patients received either three weekly instillations of one-third of the dosage every six months (group I) or two weekly instillations every three months (group II). At 2 years, no significant difference was observed between the two groups concerning recurrence, progression, and tolerance. The authors noted that the use of leukocyturia or PSA levels to predict BCG toxicity is not justified [44].

The efficacy, safety, and optimal schedule of maintenance therapy with intravesical instillation of Bacillus-

Calmette Guérin in patients with NMIBC compared to induction only was investigated by a Japanese researcher in an RCT. Maintenance therapy was scheduled to be given in 3-week cycles at 6, 12, 18, 24 and 36 months after the induction therapy. A significant difference was noted between the induction group and the maintenance group in terms of 5-year recurrence-free survival (72.4% vs. 62%) as well as in the 5-year progression-free survival (100 vs. 69.3%), hence the authors concluded that maintenance therapy is necessary to obtain the best results [45].

Another group from Japan conducted a prospective study with the same primary endpoint to check the noninferiority of the half dose compared to a full dose. Their study did not confirm the noninferiority of the half dose, but fewer local side effects were observed [46].

To reduce the toxicity of intravesical BCG, Kandeel *et al.* randomized 80 patients into two groups receiving either regular dose or half dose intravesical BCG

[47]. After a follow-up of 12 months, there was no significant difference between the two groups relating to the recurrence rate (38% vs 40%) or progression rate (20% each). Significant differences were noted in the toxicity between the two groups (grade 2, 18% vs 7.5%; grade 3, 2.5% in the full dose group only).

To reduce the adverse effects, researchers from Spain compared the efficacy of modified 3-yr BCG maintenance using one instillation every 3 months for 3 years versus BCG induction only with no maintenance. Primary endpoints were disease-free intervals and time to progression. DFI and TTP were similar between the treatment arms with a progression rate at 5 years between 16% and 19.5% [48].

Tapazio *et al.* conducted a pilot study using Hyaluronic acid to reduce BCG local side effects with promising results [49].

The European Association of Urology Research Foundation "NIMBUS" conducted a randomized multicenter European study on 345 patients with high-grade NMIBC was done to determine if a decreased number of standard dosage BCG instillations and maintenance was non-inferior to the standard number and dose administered in a normal context [50].

The usual BCG program consisted of six weeks of induction followed by three weeks of maintenance at three, six, and twelve months (15 installations). The reduced frequency BCG plan consisted of induction at weeks 1, 2, and 6, followed by 2 weeks of maintenance (weeks 1 and 3) at 3, 6, and 12 months (nine installations).

After a follow-up of 12 months, the reduced frequency group showed more recurrence than the standard frequency group (46 vs. 21).

To confirm the efficacy and safety of the maintenance of BCG, Hinotsu *et al.* randomized 115 patients into three groups: maintenance group, non-maintenance group, and epirubicin group. After a median follow-up, the recurrence—free survival in the maintenance, non-maintenance, and epirubicin groups were 84.6%, 65.4%, and 27.7% respectively, confirming the superiority of the maintenance strategy [51].

Some authors have used urinary interleukin (IL)-8 to predict recurrence after BCG induction. They measured the IL-8 immediately before and after 4 hours of BCG instillation after a follow-up of 21 ± 13.8 months.

They noted that those who experienced recurrence had a major change in the IL-8 level between the pre-and the post instillation and choose the cutoff as 112 pg/ml with a positive predictive value of 72.7%, and negative predictive value of 76.7%.

This cutoff appears to be a good predictor of successful outcomes in BCG treatment following TUR [52].

3.8. Combination of Intravesical BCG/Chemotherapy and Outcomes

Eighteen studies reported data on the use of intravesical chemotherapy or combination therapy in modifying the outcome. Some investigators have used intra-

vesical chemotherapy after the failure of BCG, while others have used a sequential schedule combining BCG and chemotherapy.

Lorenzo *et al.* randomized 80 patients, after the failure of one course of BCG therapy, into two groups either receiving Gemcitabine twice weekly for 6 weeks then weekly for 3 weeks at 3, 6, and 12 months (Group A) or weekly for 6 weeks and each week for 3 weeks at 3, 6, and 12 months. (Group B)

Recurrence was noted in 52.5% in Group A versus 87.5% in group B. Disease progression was noted in 33% of group A and 37.5% in Group B. The authors concluded that Gemcitabine can be considered a good second-line option after the failure of BCG [53].

Some investigators compared a new method of administration of intravesical chemotherapy called Chemo hyperthermia (CHT)—Arends *et al.* conducted a prospective randomized trial on 190 patients with intermediate and high-risk NMIBC comparing 1-yr CHT (six weeks and six maintenance) using mitomycin to 1-yr BCG (six weekly induction and three weekly maintenance)—After 24 months of follow-up, the authors noted that the recurrence-free survival (RFS) was 87.1% in the CHT group compared to 64.8% in the BCG group – Progression was similar (less than 2%), side effects were similar, CHT appears to be safe and has less recurrence than BCG [54].

Di Stasi *et al.* randomly assigned 212 patients with high-risk NMIBC to either BCG weekly for six weeks or BCG weekly for two weeks, followed by electromotive mitomycin once a month for 2 months. They noted that the sequential group had better disease-free intervals (76 months vs 26 months) and better disease-specific mortality (9% vs 23%) [55].

In a randomized trial, others compared the sequential combination of mitomycin C plus BCG vs BCG alone. The authors noted in the sequential group a reduction in the disease relapse rate (33.9% to 20.65%) and an increase in the disease-free interval [56].

To compare the efficacy of intravesical BCG with mitomycin C (MMC) in patients with NIMBC, Mangiarotti *et al.* randomly assigned their patients to either one of the treatments. Both MMC and BCG showed no difference in the recurrence or progression during the follow-up period, but more adverse events were noted in the MMC group [57].

Does long-term intravesical MMC further reduce the recurrence rate compared to short-term chemo and BCG?

Friedrich *et al.* conducted an RCT on 495 patients who were randomly assigned to BCG for 6 weeks, MMC for 6 weeks, and MMC for 6 weeks, followed by monthly instillations for 3 years. The 3 years recurrence rates were 65.5% for short-term BCG, 68.6% for short-term MMC and 86.1% for MMC long-term therapy [58].

Many researchers have used different regimens using MMC, BCG, and interferon alpha 2b in patients with promising results [59].

Immediate instillation of intravesical mitomycin C after TURBT has been approved in many trials as well as many international guidelines [60].

Bohle *et al.* conducted a randomized, placebo-controlled study on 355 patients with NIMBC – Immediate instillation of Gemcitabine, which was compared to placebo after TURBT, was found not to be superior [61].

In SWOG S0337, Messing *et al.* showed the superiority of immediate instillation of intravesical gemcitabine in reducing the risk of recurrence over a median of 4.0 years when compared to saline [62].

Several research studies used a combination of epirubicin and interferon-alpha2 and found a reduction in recurrence but BCG showed superiority over the combination [63].

3.9. Early Cystectomy and Outcomes

Only two comparative studies reported on the effect of early cystectomy in patients with high-grade NMIBC.

All other studies were retrospective. Many studies have reported that delaying the cystectomy for NMIBC leads to a worse prognosis compared to early surgery. Others showed controversial results. Most of these were retrospective studies. One study was RCT "BRAVO", but the results were not included because it was published in 2021—The aim was to include more than 400 patients but faced recruitment difficulties and was able to randomize only 50 patients [64].

Herr and Sogani compared 90 patients with high-risk NMIBC who underwent cystectomy during a follow-up of 15 to 20 years—Multivariate analysis showed that early cystectomy improved survival when compared to the delayed one [65].

Hautmann *et al.* compared two groups of patients with NMIBC who underwent either early (114 patients) v/s delayed cystectomy (260 patients). The objective of this comparative study was to review the understating rate and compare early to deferred cystectom—they concluded that the 10 years of cancer-specific survival was 78.7% for early versus 64.5% for delayed radical cystectomy [66].

Martin-Doyle *et al.* published a meta-analysis on more than 15,000 patients trying to improve the selection criteria for early cystectomy in high-grade T1 bladder cancer—this large analysis showed that deep lamina propria invasion had the largest impact and can be considered as a selection criterion for early cystectomy in HGT1 bladder cancer [67].

More recently, Wan performed a systematic review of the literature for studies published from 1946 to 2013 comparing the survival outcomes of patients with high-grade NMIBC who underwent early v/s deferred cystectomy.

After analysis of the 10 included studies, the author found only one prospective observational study with no level 1 evidence. The absence of randomized trial trials can introduce selection bias. Some of these studies included patients who concomitant Carcinoma in situ which can have a worse outcome.

The authors noted that the review did not have a clear definition of "early cystectomy" or deferred/delayed cystectomy. The cut-off time varied between 90 days and 2 years. In addition, the rate of understaging in the included studies

ranged between 20% and 50% which increased the degree of heterogenicity in the cohorts affecting the survival outcome

Although this review showed clearly the improvement of 5 to 10 y cancer-specific survival for patients who underwent the early cystectomy compared to delayed cystectomy, the authors recommended not performing immediate cystectomy before trying conservative management first with very close monitoring for many reasons [68] (**Table 1**).

4. Discussion

NMIBC remains a treatment challenge to all urologists, despite the advancement in the management of this entity during the last two decades.

The fact that this disease has different presentations and courses, progressing sometimes rapidly from indolent to aggressive in little time, has intrigued us to review the innovative scientific research and efforts made to improve clinical outcomes in the last two decades, hoping to answer the question concerning the best approach for the optimal outcome when treating patients with T1 high-grade bladder cancer. Whether these scientific treatment options had improved the results, and to what extent our understanding of the pathophysiology of this disease positively affected outcomes, was our review's goal.

We conducted a survey of the literature focused mostly on RCTs on PubMed, Medline, and Embrace to determine the influence of scientific advances over the previous two decades. This review's concentration on prospective trials and RCTs (38 out of 71) is one of its strongest points.

However, the lack of results from retrospective studies included in this review which can also help ascertain these findings might be a weak point to reconsider in the future, *i.e.*, including patients with muscle-invasive bladder cancer on presentation who were retrospectively reviewed for risk factors and aggressive features. In addition to that, the outcome being our primary objective makes this review a valuable asset to improve the decision-making capacities of urologists around the world who were compelled to look for novel methods to foretell failure because of the high recurrence rate of up to 78% and the high progression rates of up to 45%.

TURBT has been the treatment modality and has emerged as the most useful diagnostic tool when treating patients. Bipolar resection and re-TURBT after 2 - 6 weeks have improved sampling provided for pathologic reading and detection rate (10% - 25%) respectively, thus it should be used as advised by several guidelines if no muscle was discovered in the material, the tumor is more than 3 cm, it is T1, and it is high grade. It is usually offered after an initial cystoscopy that evolved into the application of novel imaging techniques such as narrow-band-imaging, ALA fluorescent cystoscopy, or photodynamic diagnosis-assisted (PDD) with Hexvix which has positively affected both the diagnosis and outcome. Among the diagnostic utility of TURBT, including re-TURBT, is the post-resection step involving the detection of histological variants significantly

Table 1. Summary of clinical outcomes.

Factor	Clinical outcome	Reference
Histology	• Patients with Variant Histology fared the worst (PUS associated with decreased OS). • Lower 2-year RR post BCG in patients with Variable Histology.	[4] [5]
Biomarkers	• Helpful for stratification. • Needs further studies to be included in predictive models.	[7] [11]
Imaging	• NBI > WLI in detecting NMIBC including CIS allowing more complete resection. • NBI has a higher sensitivity and lower specificity compared to WLI. • Fluorescent endoscopy + ALA > WLI in detecting recurrence (39% vs 16%). • Hexvix PDD-assisted TUR decrease RR compared to traditional technique (13.6% vs 30%).	[12] [13] [17] [18]
Risk stratification	• EORTC and CUETO are the two most important risk assessment models • Combining EORTC + Ki-67 expression enhance risk stratification for recurrence and progression.	[19] [23]
TUR	• Monopolar vs bipolar :pathological advantage, better sampling rate, less operative time • Monopolar vs laser resection (no difference in RR). • Monopolar vs KTP (no difference in operative time and RR).	[24] [30] [31]
Re-TUR	• 7 studies reported the role of Re-TUR in restaging (50% residual tumor among them 10% - 25% MIBC). • Higher 2-year RFS (77% vs 45.8% p: 0.025; No effect on PFS). • Some studies showed the possibility of emitting Re-TUR if + muscle on initial resection. • Valuable if T1, high grade, more than 3 cm, absence of muscle • The effect on survival improvement is debatable.	[34] [35] [37] [40]
Intravesical agents	• BCG maintenance vs induction only : decreased RR and PR • Gemcitabine as a 2nd line option after BCG. • (Gem + BCG) vs BCG alone associated in decreased RR (33.9% vs 20%). • MMC vs BCG same efficacy w more SE.	[51] [53] [58]

(PUC: Plasmacytoid urothelial cance; OS: Overall survival; RR: Recurrence rate; RFS: Recurrence-free survival; BCG: Bacillus Calmette-Guérin; MMC: Mitomycin C; Gem: Gemcitabine; Hexvix-PDD: Hexvix Photodynamic diagnostic; EORTC: The European Organization for Research and Treatment of Cancer; CUETO: The Spanish Urological club for oncological treatment; KTP: Potassium-Titanyl-Phosphate).

contributing to better results. According to certain studies, patients with plasmacytoid variations fared worse in terms of overall survival than those with micropapillary and Nested variants. Close collaboration with pathologists is needed to discover these uncommon histologic types that could enhance results. This literature analysis proved that the ideal regimens for treating these variations are currently unknown but need bigger multicentric multinational prospective trials to be designed.

Several biomarkers were also reported in bladder cancer to examine their prognostic influence on recurrence and progression, such as methylation, protocadherin re8, and Ki67 expression which can be used to predict tumor growth and recurrence. Some researchers discovered that patients with recurrence and/or progression have greater levels of blood-based biomarkers including CA 19-9 and CEA. Numerous research has looked at circulating tumor DNA to establish its prognostic usefulness.

Additional data concerning these biomarkers are required to incorporate them in the risk stratification as sought by many authors.

It is evident that risk stratification models, such as the European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Urological Club for Oncological Treatment (CUETO), are crucial tools for assisting urologists in stratifying their patients with high-grade NMIBC, enabling the early diagnosis of progression, although they might not be applicable everywhere, *i.e.*, Asian patients, as seen by some authors.

Concerning treatment modalities of high-grade bladder cancer, intravesical BCG is still regarded as the gold standard of therapy for individuals with non-muscle invasive bladder cancer in combination with TURBT. Intravesical BCG, mitomycin C, and gemcitabine are the most studied intravesical agents. The effect on recurrence and progression of maintaining a BCG regimen rather than induction alone revealed a superior result. Studies comparing the noninferiority of reduced dosage BCG to full dose concurred that side events are lessened, but not recurrences. No difference between mitomycin and BCG was observed except for fewer side effects for BCG. Following the failure of BCG, gemcitabine is a viable alternative.

At this point, an important question should be asked about whether intravesical agents are the ultimate initial treatment option available and the role of early radical cystectomy as a subsequent treatment modality for patients with high-grade non-muscle invasive bladder cancer following re-TURBT.

The findings were conflicting as seen in a pioneering RCT comparing outcomes of early radical cystectomy vs BCG mainly because of recruitment issues, whereas the other studies were retrospectively either favoring an early radical cystectomy enhanced survival rates or advising against it before a conservative treatment trial to prevent overtreatment by taking a bladder preservation approach which in term might be convenient for the patient's quality of life.

While BCG therapy may affect survival by postponing final therapy in patients

with a high risk of advancement, cystectomy may constitute overtreatment and irreparably harm the quality of life in those with a high-grade low risk of progression.

Limitations

Major drawbacks are the various methods used to classify the patients as high risk which contributed to the heterogeneity in the reported outcomes; some will consider T1 High grade as high-risk others will include other criteria such as Ta high grade, Ta low grade large or multifocal tumors.

We noted that the number of studies included in each modality is variable which might contribute to bias

In our search, we included only three databases sites (PubMed, Medline, and Embase) which can explain some missing data.

We focused only on full-text articles prospective and RCT which can contribute to bias analysis.

5. Conclusions

Patients with high-grade T1 bladder cancer show diverse clinical courses, with some highly associated with poor prognosis. This paper reviewed all the scientific innovations during the last two decades and showed clearly that major improvements in the diagnosis and management of patients with NMIBC were responsible for improving the outcomes in many fields, such as histology, stratifications, re-TURBT, and intravesical agents. No clear conclusions could be withdrawn from biomarkers and early cystectomy trials, whereas new TURBT techniques, and new diagnostic imaging during cystoscopy (NBI, ALA, PDD) trials showed some promising results in reducing the recurrence rate, not the progression rate.

The current evidence suggests that clinicopathological and molecular risk classifiers together may help select the optimal management course for each high-grade T1 patient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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