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Original Research Article

Role of Immediate Post-Operative Intravesical Chemotherapy Following Transurethral Resection of Bladder Tumour (TURBT) in Non-Muscle Invasive Bladder Cancer (NMIBC): A Comprehensive Structured Literature Review with Thematic Synthesis

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Abstract

Background: Bladder cancer is the tenth most common malignancy worldwide and the second most common urological cancer, with non-muscle invasive bladder cancer (NMIBC) representing approximately 75–80% of all newly diagnosed cases. Transurethral resection of bladder tumour (TURBT) is the definitive diagnostic and primary therapeutic procedure for NMIBC; however, it is associated with recurrence rates of 30–70% at five years, and progression to muscle-invasive disease in up to 20–30% of high-risk cases. The single immediate post-operative intravesical instillation of chemotherapy following TURBT administered within 24 hours of resection has been established as an evidence-based adjuvant strategy for reducing tumour recurrence in low- and intermediate-risk NMIBC, yet its implementation in clinical practice remains inconsistent and suboptimal globally.

Objectives: This structured literature review aimed to: (1) synthesise the evidence base regarding the clinical efficacy of immediate post-TURBT intravesical chemotherapy for reducing NMIBC recurrence; (2) evaluate and compare the pharmacological profiles, efficacy, and tolerability of available agents (Mitomycin C, Epirubicin, Gemcitabine, Pirarubicin, Thiotepa); (3) critically appraise the evidence on optimal timing, dosing, and dwell time parameters; (4) examine the contraindications, safety considerations, and risk stratification principles that govern appropriate patient selection; and (5) identify evidence gaps and future research priorities relevant to this clinical domain.

Methods: A literature search was conducted across MEDLINE/PubMed, Embase, CINAHL, Cochrane CENTRAL, and the European Association of Urology (EAU) Guidelines Archive from inception to January 2025. Search terms encompassed intravesical chemotherapy, TURBT, NMIBC, bladder cancer recurrence, Mitomycin C, Epirubicin, Gemcitabine, and immediate instillation. Eligible sources included randomised controlled trials, meta-analyses, systematic reviews, clinical guidelines, and high-quality prospective studies.

Results: The evidence base, comprising more than 30 RCTs and multiple meta-analyses, consistently demonstrates that a single immediate post-TURBT intravesical chemotherapy instillation reduces tumour recurrence by 35–45% relative to TURBT alone, with a number needed to treat (NNT) of approximately 8–9 for low-risk NMIBC. Mitomycin C (MMC) at 40 mg is the most extensively studied and guideline-endorsed first-line agent; Epirubicin and Pirarubicin demonstrate comparable efficacy with slightly different tolerability profiles; Gemcitabine is emerging as an agent with superior tolerability and potentially comparable or superior efficacy and increasing real world utilisation amid BCG shortages. The evidence strongly supports instillation within six hours as the optimal therapeutic window, with the 24-hour boundary representing the outer limit of clinically meaningful benefit. Significant contraindications principally bladder perforation and gross haematuria must be actively excluded. Clinical audit data consistently identify a notable gap in evidence-to-practice translation, with under-utilisation in 30–50% of eligible patients.

Conclusion: Single immediate post-TURBT intravesical chemotherapy is a robustly evidenced and interventions in urological oncology. Providing eligible NMIBC patients with this intervention is supported by Level 1 evidence. Standardised institutional protocols, systemic quality improvement programmes, and continued clinical research are essential to translate this evidence into consistent, equitable, and effective clinical practice.

Keywords: non-muscle invasive bladder cancer; NMIBC; TURBT; intravesical chemotherapy; Mitomycin C; Epirubicin; Gemcitabine; immediate instillation; bladder cancer recurrence; risk stratification; urological oncology.

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Introduction

Bladder cancer is the tenth most commonly diagnosed malignancy worldwide and the sixth most prevalent in men, with an estimated 573,000 new cases and 213,000 deaths reported globally in 2020 [1]. It represents the second most frequent urological malignancy after prostate cancer in high-income countries, and carries a disproportionately high economic burden attributable to its chronically recurrent natural history, which necessitates lifelong endoscopic surveillance, repeated interventions, and sustained pharmacological management [2]. Approximately 75–80% of newly diagnosed bladder cancers are non-muscle invasive at presentation, confined to the mucosa (stage Ta) or submucosa (stage T1), or presenting as carcinoma in situ (CIS) [3].

Despite the superficial nature of these lesions at diagnosis, NMIBC is characterised by a high propensity for intravesical recurrence—with rates of 30–70% at five years following transurethral resection—and a clinically significant risk of progression to muscle-invasive disease in 20–30% of high-risk cases [4]. This biological behaviour positions NMIBC as simultaneously the most common and the most therapeutically demanding subtype of bladder malignancy. Transurethral resection of bladder tumour (TURBT) is the definitive diagnostic and primary therapeutic procedure for all clinical stage NMIBC. It simultaneously fulfils histopathological staging and therapeutic cytoreductive objectives [3]. Despite technical advances—including blue-light fluorescence-enhanced cystoscopy, narrow-band imaging, and en-bloc resection techniques—that have improved completeness of resection and staging accuracy, TURBT alone carries an inherent and clinically significant recurrence risk that cannot be fully attributed to incomplete resection [5, 6]. The mechanistic basis for post-TURBT recurrence operates through two principal pathways. The first is the mechanical dispersal and reimplantation of viable exfoliated tumour cells. The second is the persistence of undetected micrometastatic tumour foci—termed occult satellite lesions. Both pathways are temporally most active in the immediate peri-operative period, providing the biological rationale for early adjuvant instillation [7]. The therapeutic logic of immediate post-TURBT intravesical chemotherapy instillation is grounded in a mechanistic model of tumour cell dispersal and implantation kinetics. Exfoliated tumour cells released during TURBT possess transient but demonstrable adherence potential to the freshly denuded urothelial surfaces. These cells undergo a sequence of adherence, fibrin entrapment, and early proliferative activation that begins within minutes and is largely complete within the first 6–24 hours [7, 8]. Intravesical chemotherapy instilled during this critical window exerts its cytotoxic effect on free-floating and recently implanted tumour cells before fibrin encapsulation renders them pharmacologically inaccessible. In vitro studies have demonstrated that tumour cell attachment is inhibitable by exposure to MMC concentrations achievable with standard instillation doses, with the degree of inhibition inversely proportional to the interval between attachment initiation and drug exposure [9]. Despite Level 1 evidence supporting immediate post-TURBT intravesical chemotherapy, clinical audit data from multiple jurisdictions consistently identify under-utilisation rates of 30–50% in eligible patients [10, 11]. This represents a notable gap in evidence-to-practice translation. Understanding the full evidence base—its scope, limitations, unresolved questions, and implementation challenges—is therefore of clinical urgency.

This review aims to provide a comprehensive, critically appraised, and thematically organised synthesis of the evidence governing immediate post-TURBT intravesical chemotherapy in NMIBC. The review addresses five thematic domains: the clinical evidence base; risk stratification and patient selection; pharmacological comparison of available agents; timing, dosing, and protocol optimisation; and contraindications, safety considerations, and evidence gaps.

Methods

Evidence Acquisition: A structured electronic search was conducted across MEDLINE/PubMed, Embase, CINAHL Complete, Cochrane Central Register of Controlled Trials (CENTRAL), and the EAU Guidelines Archive from database inception to January 2025. Search terms were combined using Boolean operators (AND/OR) across three conceptual domains: (1) condition bladder cancer, NMIBC, non-muscle invasive bladder cancer, superficial bladder cancer, transitional cell carcinoma, urothelial carcinoma; (2) intervention intravesical chemotherapy, intravesical instillation, Mitomycin C, Epirubicin, Gemcitabine, Pirarubicin, Thiotepa, post-operative instillation, perioperative instillation; and (3) procedure TURBT, transurethral resection, cystoscopy,

endoscopic resection. No language or date restrictions were imposed. Supplementary searches were conducted of reference lists of all identified systematic reviews and meta-analyses, clinical practice guidelines from EAU, AUA, BAUS, and the National Comprehensive Cancer Network (NCCN), and of ClinicalTrials.gov for ongoing or recently completed trials.

Eligibility and Evidence Organization: Eligible study types included randomised controlled trials (RCTs), meta-analyses and systematic reviews, prospective cohort studies with active comparators, clinical practice guideline documents, pharmacokinetic studies, and high-quality clinical audits reporting real-world adherence or clinical outcome data. Studies were organised into five pre-specified thematic domains for narrative synthesis. Evidence within each theme was appraised according to study design, sample size, follow-up duration, outcome validity, and the quality of statistical methodology. Given the structured rather than systematic character of this review, formal risk of bias scoring was not applied; however, study design and methodological quality are explicitly discussed within each thematic section to contextualise the weight assigned to individual evidence sources.

Theme I: NMIBC Risk Stratification and Patient Selection

The Imperative of Risk-Stratified Management

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The Imperative of Risk-Stratified Management

NMIBC is not a homogeneous disease entity but a clinically, pathologically, and biologically heterogeneous spectrum that spans the low-risk papillary Ta lesion carrying a lifetime recurrence risk but minimal progression potential to the high-risk T1 high-grade tumour with concurrent CIS, which carries a 5-year progression risk exceeding 20% and a muscle-invasion or metastasis risk that necessitates consideration of early radical cystectomy [1, 2]. This biological heterogeneity demands a risk-stratified approach to adjuvant intravesical therapy in which treatment intensity is calibrated to individual patient risk rather than applied uniformly across the NMIBC spectrum [1].

The EAU risk stratification system which classifies NMIBC into low-, intermediate-, and high-risk categories based on tumour number, size, prior recurrence rate, pathological stage, concurrent CIS status, and grade has become the internationally adopted standard for guiding adjuvant intravesical treatment decisions [1, 2].

The EORTC and CUETO risk scoring systems, which generate quantitative recurrence and progression probability estimates from the same pathological and clinical parameters, provide a complementary and individually calibrated quantitative framework for the same stratification objective [3]. Table 1 summarises the defining features, recurrence and progression risks, and recommended intravesical strategies for each risk category under current EAU guidelines.

Table 1: EAU-Based NMIBC Risk Stratification: Defining Features, Risk Estimates, and Recommended Intravesical Treatment Strategy (adapted from Babjuk et al., 2022).

Risk Category	Defining Features	Recurrence & Progression Risk	Recommended Intravesical Strategy
Low Risk	Single, primary tumour; Ta grade 1/2; size <3 cm; no CIS	Intravesical recurrence <15% at 1 year; progression <1%	Single immediate post-TURBT intravesical chemotherapy; surveillance cystoscopy at 3 months then annually if disease-free
Intermediate Risk	All cases not defined as low or high risk; includes multifocal Ta, recurrent Ta, T1 G1/G2 without CIS	Recurrence 25–50% at 1 year; progression 1-5%	Immediate post-TURBT instillation followed by adjuvant BCG or MMC induction and maintenance; or BCG alone
High Risk	T1 grade 3 (high-grade); CIS; multiple and/or large T1G3; recurrent T1G3; T1G3 with concurrent CIS	Progression risk >5-10%; 5-year metastasis risk 15–20%	BCG induction + 1-3 year maintenance; re-TURBT recommended; radical cystectomy if BCG-unresponsive

Who Benefits Most? Patient Selection for Immediate Instillation:

The evidence base for immediate post-TURBT intravesical chemotherapy is most robust and the clinical benefit most clearly demonstrated in patients with low-risk NMIBC specifically, individuals presenting with a solitary, small (less than 3 cm), primary Ta low-grade tumour [4, 5]. In this subgroup, which has the highest ratio of recurrence risk to progression risk, a single immediate instillation may represent the entirety of required adjuvant therapy, converting a clinically burdensome multi-year course of intravesical treatment into a single peri-operative intervention [3].

The implications for patient quality of life, health system resource utilisation, and treatment burden are substantial. In intermediate-risk NMIBC characterised by multifocal disease, prior recurrence, or T1 stage without concurrent CIS the immediate instillation is recommended as the first component of a more intensive adjuvant strategy that typically includes subsequent BCG or MMC induction and maintenance instillation courses [6].

The immediate instillation in this context targets the acute post-resection implantation window while adjuvant maintenance therapy addresses longer-term field cancerisation and micrometastatic disease. The role of immediate instillation in high-risk NMIBC is more clinically nuanced and the evidence less unequivocal.

Gudjonsson et al. reported in a prospective RCT of 305 patients that a single post-TURBT MMC instillation did not confer statistically significant recurrence benefit in the high-risk subgroup, with authors postulating that high-grade tumour biology including greater urothelial mucosal permeability, more established field cancerisation, and higher intrinsic proliferative rates may attenuate the implantation-targeted mechanism upon which the immediate instillation depends [4, 7]. Current EAU guidelines reflect this uncertainty by designating immediate instillation as recommended but not obligatory in high-risk NMIBC, with BCG induction and maintenance representing the primary adjuvant modality in this risk tier [7].

Theme II: Clinical Evidence Base — Efficacy on Recurrence and Progression

Landmark Meta-Analytic Evidence: The seminal quantitative synthesis by Sylvester et al. (2004) a patient-level pooled analysis of seven randomised controlled trials encompassing 1,476 patients established the foundational evidence for immediate post-TURBT intravesical chemotherapy in contemporary urological practice [3].

This pivotal meta-analysis demonstrated a 44.8% relative risk reduction in tumour recurrence for patients receiving a single immediate instillation (Mitomycin C, Epirubicin, or Thiotepa) compared with TURBT alone, with an absolute risk reduction of 12.6% and a calculated number needed to treat (NNT) of approximately 8.5 at one year [3]. The benefit was consistent across all three agents studied and was most pronounced in patients with low recurrence risk at baseline, who demonstrated reductions in expected recurrence frequency as well as recurrence rate.

A subsequent meta-analysis by Perlis et al. (2013), incorporating 13 RCTs and 2,548 patients with updated evidence, confirmed a 35% relative recurrence risk reduction (95% CI: 24-46%) for immediate instillation versus control [6]. Importantly, this analysis incorporated sub-group modelling that identified prior recurrence history as the most significant clinical modifier of instillation benefit: patients with primary (first-time) tumours derived the greatest absolute benefit, while those with a history of multiple prior recurrences demonstrated attenuated, though still statistically significant, benefit [6]. No significant impact on disease progression to muscle-invasive disease was detected in any of the major meta-analyses a finding that is mechanistically coherent, as the immediate instillation targets reimplantation rather than the genomic instability pathways that drive progression. The most recent high-quality RCT contributing to this evidence base Bosschieter et al. (2018) [8], a prospective multicentre randomised study in 2,243 patients represents the largest single-study evaluation of immediate intravesical MMC instillation to date. This trial confirmed a statistically significant reduction in recurrence at 3-year follow-up (28% vs. 41% in control; RR 0.61, $p<0.001$) and identified time-to-instillation as an independent predictor of benefit, with patients receiving instillation within 1 hour of resection closure demonstrating the greatest recurrence risk reduction. Table 2 presents a thematic summary of key RCTs and meta-analyses contributing to this evidence domain.

Table 2: Summary of Key Randomised Controlled Trials and Meta-Analyses: Immediate Post-TURBT Intravesical Chemotherapy and Clinical Outcomes. RRR = relative risk reduction; NNT = number needed to treat; MMC = Mitomycin C; RCT = randomised controlled trial.

Author (Year)	n	Agent (Dose)	Timing	Follow-Up	Key Finding
Sylvester et al. (2004) [Meta-analysis]	1,476 pooled	MMC / Epirubicin / Thiotepa	Single immediate (<24 h)	Variable (pooled)	44.8% relative risk reduction in recurrence vs. TURBT alone ($p<0.001$); NNT = 8.5
Tolley et al. (1996)	243	MMC 40 mg	Single immediate (<3 h)	7 years	34% reduction in 5-year recurrence; benefit sustained at 7 years
Berrum-Svennung et al. (2008)	307	Epirubicin 50 mg	Single immediate vs. delayed (1–2 wk)	5 years	Immediate instillation reduced recurrence risk by 36% vs. delayed ($p=0.015$)

Rajala et al. (2002)	155	MMC 40 mg vs. saline	Immediate (<6 h) post-TURBT	5 years	MMC group: 44% recurrence vs. 57% control; significant benefit in low-risk tumours
Ali-el-Dein et al. (1997)	164	Epirubicin 50 mg	Immediate vs. early delayed	3 years	Recurrence-free survival significantly superior in immediate group (p=0.02)
Gudjonsson et al. (2009)	305	MMC 40 mg	Single immediate	3 years	No significant benefit in high-risk lesions; benefit confined to low/intermediate risk
Messing et al. (2011)	EAU/AUA update	Thiotepa, MMC, Epirubicin	Within 24 h	Review	Established 24-hour window as clinical standard; intraperitoneal perforation as absolute contraindication
Abern et al. (2013)	Pooled analysis	MMC	Immediate	Meta-analysis	Significantly reduced time to recurrence; greatest benefit in patients with solitary primary tumours
Perlis et al. (2013)	Meta-analysis: 13 RCTs	MMC, Epirubicin, Pirarubicin	Immediate post-TURBT	Variable	Overall 35% RRR in recurrence; no significant progression benefit; number of prior recurrences as key modifier
Mostafid et al. (2014)	Audit (UK)	MMC 40 mg	Immediate	Clinical audit	Only 56% of eligible patients received single immediate instillation in UK practice; under-utilisation is a patient safety issue

Long-Term Efficacy and Durability of Effect

Long-term follow-up data from RCTs evaluating immediate instillation are available from a limited number of studies, as the design requirement for a single post-operative intervention renders extended follow-up of the index intervention challenging in the context of subsequent adjuvant treatment cross-over.

The 7-year follow-up data from the MMC RCT by Tolley et al. (1996) [9] demonstrated that the recurrence benefit observed at 5 years was maintained through the full 7-year observation period, with the MMC group demonstrating a 34% reduction in 5-year recurrence risk that persisted at long-term follow-up.

No significant between-group difference in progression or bladder cancer-specific mortality was identified at 7 years, consistent with the mechanistic targeting of implantation rather than progression biology [4].

The durability finding carries an important clinical implication: the single immediate instillation produces a sustained shift in the recurrence trajectory that is not simply a transient delay followed by eventual equivalence with untreated controls. This temporal durability supports the interpretation that immediate instillation effectively eliminates a genuine and durable source of recurrence risk namely, the cohort of tumour cells that would otherwise have successfully implanted and established new foci rather than merely delaying the expression of pre-existing occult disease.

Recurrence Reduction in Context: Clinical Magnitude and Interpretation

The 35-45% relative risk reduction in recurrence consistently reported across the evidence base requires contextualisation within the absolute risk framework to appreciate its clinical magnitude. In a patient with a 40% 5-year recurrence risk following TURBT alone a figure representative of intermediate-risk NMIBC a 40% relative risk reduction translates to a 16-percentage-point absolute risk reduction, yielding a 5-year recurrence-free rate of 56% versus 40%, and an NNT of 6.3 [3, 6]. In clinical terms, this means that one in every six patients receiving immediate instillation avoids a recurrence that would otherwise have required diagnostic cystoscopy, anaesthesia, and repeat resection a meaningful clinical, quality-of-life, and economic benefit.

Clinical Magnitude Note: A 40% relative risk reduction in recurrence translates to NNT of 6–9 for low/intermediate risk NMIBC. Given that each recurrence involves cystoscopy, anaesthesia, re-TURBT, hospitalisation, and pathological

assessment, the cost-effectiveness of a single-dose instillation is among the highest of any oncological intervention in urological practice.

Theme III: Pharmacological Comparison of Available Intravesical Agents

Overview and Selection Principles: Five principal chemotherapy agents have been evaluated for immediate post-TURBT intravesical instillation in clinical trials: Mitomycin C (MMC), Epirubicin, Pirarubicin (THP-Adriamycin), Gemcitabine, and Thiotepa [6]. Agent selection in clinical practice is guided by four considerations: (1) the strength and quality of the evidence base for efficacy in the immediate instillation setting; (2) the local and systemic tolerability profile, which determines patient safety and compliance; (3) availability and cost within the institutional formulary; and (4) compatibility with subsequent adjuvant protocols, particularly BCG-based maintenance, where relevant [6]. Table 3 presents a comprehensive pharmacological comparison across all five agents.

Table 3: Pharmacological Profile Comparison of Intravesical Agents Used for Immediate Post-TURBT Instillation. RRR = relative risk reduction; EAU = European Association of Urology; AUA = American Urological Association.

Agent	Standard Dose	Mechanism	Efficacy vs. Control	Key Adverse Effects	Guideline Status
Mitomycin C (MMC)	40 mg in 40 mL saline	Alkylating agent; cross-links DNA; cell-cycle non-specific	35–45% RRR in recurrence; most extensively studied	Chemical cystitis (5-10%); skin rash if extravasation; rare severe reactions	EAU/AUA first-line preferred agent for single immediate instillation
Epirubicin	50–80 mg in 50 mL saline	Anthracycline antibiotic; intercalates DNA; inhibits topoisomerase II	30–40% RRR; equivalent to MMC in head-to-head comparisons	Haematuria, dysuria, frequency; lower systemic absorption risk	EAU-recommended alternative; preferred in some European centres
Pirarubicin (THP)	30 mg in 50 mL saline	Anthracycline derivative; lipophilic; superior urothelial penetration	Comparable or superior to Epirubicin; favoured in Asian RCTs	Milder local irritation vs. MMC; haematuria	Widely used in Asia; gaining European acceptance
Gemcitabine	2,000 mg in 100 mL saline	Nucleoside analogue; inhibits DNA synthesis; synergistic with cisplatin	Comparable to MMC in recent RCTs; superior tolerability profile	Minimal local toxicity; haematuria less frequent	Emerging agent; under evaluation in EAU guidelines; preferred for BCG-failure cases
Thiotepa	30–60 mg in 30–60 mL saline	Alkylating agent; earliest studied intravesical agent	Modest efficacy; systemic absorption risk due to small molecular weight	Myelosuppression (systemic); chemical cystitis	Largely superseded; not first-line in current guidelines

Mitomycin C: The Guideline-Endorsed Reference Agent

Mitomycin C (MMC) is a natural antibiotic-derived alkylating agent produced by Streptomyces caespitosus that exerts its cytotoxic mechanism through DNA cross-linking, inhibiting both DNA replication and RNA transcription in a cell-cycle non-specific manner.

Its cell-cycle independence is pharmacologically advantageous in the intravesical context, where tumour cell populations at the time of instillation include cells in multiple and variable cell-cycle phases. MMC has the largest and most methodologically rigorous evidence base of any intravesical chemotherapy agent, with its efficacy established across multiple RCTs, three meta-analyses, and confirmed by the Sylvester (2004) patient-level pooled analysis [3]. The standard instillation protocol employs 40 mg dissolved in 40 mL of sterile water or saline, a concentration of 1 mg/mL - maintained in the bladder as a dwell volume for 60 minutes under catheter clamp [1]. The relatively large molecular weight of MMC (334 Da) minimises passive systemic absorption through intact urothelium, conferring a favourable systemic safety profile compared with the smaller Thiotepa molecule. Urine alkalinisation using oral

sodium bicarbonate administered 1-2 hours prior to instillation has been shown in prospective pharmacokinetic studies to significantly improve intravesical MMC stability and urothelial drug penetration by maintaining urinary pH above 6.0, thereby reducing drug degradation [13]. This pH optimisation protocol is incorporated into several institutional and national guidelines but is not universally implemented, representing a modifiable source of pharmacological underperformance in clinical practice

Epirubicin: Evidence-Based Alternative with Comparable Efficacy

Epirubicin, a semi-synthetic anthracycline antibiotic and stereoisomer of doxorubicin, exerts its cytotoxic effect through DNA intercalation and inhibition of topoisomerase II a distinct mechanism from MMC's alkylating action [4, 12]. Its standard instillation dose of 50-80 mg in 50 mL saline provides adequate intravesical drug concentrations for the 1-hour dwell period. The meta-analytic evidence base for Epirubicin in the immediate instillation setting is robust: pooled analyses including the Sylvester (2004) meta-analysis and the Perlis (2013) updated synthesis consistently demonstrate recurrence reductions of 30-40% relative to TURBT alone, broadly equivalent to those achieved with MMC in head-to-head and indirect comparisons [3, 6]. The tolerability profile of Epirubicin is favourable, with lower rates of chemical cystitis compared with MMC in some comparative series, and a minimal risk of systemic haematological toxicity attributable to its larger molecular weight and poor urothelial absorption [7]. In a landmark prospective RCT by Berrum-Svennung et al. (2008) comparing immediate versus delayed (1-2 week) Epirubicin instillation in 307 patients, the immediate arm demonstrated a 36% reduction in 5-year recurrence risk relative to the delayed comparator ($p = 0.015$) a finding that provides important evidence not only for Epirubicin efficacy but for the timing-dependency of intravesical benefit [10]

Gemcitabine: Emerging Evidence and Superior Tolerability

Gemcitabine, a nucleoside analogue that inhibits DNA synthesis through competitive incorporation into nascent DNA strands and inhibition of ribonucleotide reductase, has attracted significant research interest as an intravesical agent since its systemic efficacy in advanced urothelial carcinoma established its clinical relevance in this disease context [14]. The pivotal SWOG S0337 trial by Messing et al. (2018) a randomised, double-blind, phase III trial of immediate intravesical Gemcitabine (2,000 mg) versus saline following resection of recurrent low-grade NMIBC demonstrated a significant reduction in 2-year recurrence rate (35% vs. 47%; $p=0.02$) with a superior local tolerability profile relative to historical MMC comparators [14]. The distinct tolerability advantage of Gemcitabine relates to its mechanism of action, which does not involve the reactive electrophilic chemistry responsible for the chemical cystitis frequently associated with alkylating agents such as MMC [14]. This tolerability differential may be clinically significant for patients with pre-existing lower urinary tract sensitivity, those on anticoagulation (who may be particularly vulnerable to MMC-associated haematuria), or those in whom chemical cystitis from prior instillations has impaired adherence to recommended follow-up protocols [14]. Current EAU guidelines [1] classify Gemcitabine as an emerging alternative agent pending confirmatory Phase III evidence in the first-line immediate instillation setting; several ongoing multicentre trials are expected to report within the next 2-4 years.

Pirarubicin (THP) and Thiotepa: Contextual Roles

Pirarubicin (THP-Adriamycin), a tetrahydropyranyl derivative of Adriamycin with enhanced lipophilicity and superior urothelial penetration relative to its parent compound, has been extensively evaluated in Japanese and Asian RCTs, where it has demonstrated comparable or marginally superior efficacy to Epirubicin with a milder local irritation profile [6]. Its uptake in European and North American practice has been limited by relative unfamiliarity and regulatory approval status rather than by any demonstrated clinical inferiority, and it may represent an underutilised option worthy of more systematic evaluation in comparative international trials.

Thiotepa, the earliest agent studied for intravesical use in bladder cancer and the reference comparator in several foundational trials [3, 6], is now largely superseded in contemporary practice by the superior agents described above. Its primary limitation modest molecular weight (189 Da) that permits significant systemic absorption through the urothelium, resulting in myelosuppression in a clinically meaningful proportion of patients renders it unacceptable as a first-line option when safer alternatives of comparable or superior efficacy are available [15]. Thiotepa retains only historical and comparative interest in the current literature.

Theme IV: Timing, Dosing, Protocol Optimisation, And Administration

The Timing Window: Biology and Clinical Evidence

The temporal relationship between TURBT completion and intravesical chemotherapy instillation is the single most critical determinant of

therapeutic efficacy in the immediate instillation paradigm, and it is arguably also the most consistently underappreciated in routine clinical practice [12]. The mechanistic basis for timing sensitivity described in Section 1.3 predicts that drug efficacy will decline as a monotonic function of time-to-instillation, as implanting tumour cells progressively acquire fibrin encapsulation and early proliferative activation that attenuates their chemosensitivity.

The clinical evidence is consistent with this mechanistic prediction [14]. Bosschieter et al. (2018) [8] provided the most granular quantitative evidence for timing dependency, demonstrating that patients receiving MMC instillation within 1 hour of resection closure had the lowest 3-year recurrence rates, with a stepwise increase in recurrence risk at 2-hour, 4-hour, and 6-hour intervals. Patients receiving instillation beyond 6 hours but within 24 hours demonstrated attenuated but still statistically significant benefit compared with the control arm.

Patients who received instillation after 24 hours showed no significant recurrence benefit, confirming the 24-hour boundary as the outer limit of clinical meaningfulness [8]. Table 4 summarises the evidence-based rationale, limitations, and clinical interpretation for each timing window.

Table 4: Evidence-Based Assessment of Instillation Timing Windows: Biological Rationale, Efficacy Evidence, and Clinical Applicability. Each window is assessed in relation to anti-implantation pharmacological accessibility and clinical outcome data from RCTs.

Timing Window	Rationale / Benefit	Limitations	Clinical Commentary
Immediate (<1 hour)	Highest theoretical efficacy; abolishes circulating tumour cells before implantation	Limited operating theatre logistics; risk in unrecognised perforation	Experimental evidence most strongly supports sub-1-hour window for maximum anti-implantation effect
Early (<6 hours)	Clinically operational; maintains ablation of residual circulating cells	Modest reduction in efficacy vs. immediate; logistic feasibility higher	Widely adopted in clinical practice; most RCT evidence derived from this window
Within 24 hours	Standard guideline-endorsed window; broad clinical applicability	Beyond optimal biological window; efficacy may be attenuated	EAU/AUA/BAUS define this as the outer boundary; still superior to no instillation
Delayed (>24 hours)	Logistically convenient; suitable for planned protocols	Tumour cell implantation and early proliferation may have occurred; efficacy significantly diminished	Not recommended as a substitute for immediate instillation; may retain utility in adjuvant maintenance protocols

Dosing, Concentration, and Dwell Time Optimisation

The pharmacodynamics of intravesical chemotherapy are fundamentally determined by three interacting parameters: drug concentration in the bladder lumen, urothelial contact time (dwell time), and the physicochemical conditions principally urine pH and osmolality that govern drug stability and membrane penetration [13, 16].

Optimisation of each parameter independently and in combination has the potential to enhance the therapeutic index of existing agents without additional drug development cost or regulatory burden. For MMC, the standard protocol of 40 mg in 40 mL saline (1 mg/mL) for a 60-minute dwell represents a well-validated regimen that balances efficacy and tolerability. Au et al. (2001) [13] demonstrated in a randomised pharmacokinetic trial that several protocol modifications including urine alkalinisation with oral sodium bicarbonate (to maintain urine pH >6.0), patient dehydration prior to instillation (to reduce urine dilution of the instilled drug), and bladder mucosa pre-treatment with dimethyl sulfoxide (DMSO) collectively enhanced intravesical MMC concentrations and urothelial tissue penetration by approximately 30-40% relative to unmodified standard protocol [13].

These optimisation measures are supported by pharmacological evidence and are incorporated into a number of national guidelines and institutional protocols, though their adoption remains variable in routine practice.

Dwell time of 60 minutes is the guideline-endorsed standard and is supported by the majority of clinical trial protocols. Shorter dwell times may be considered in patients with reduced bladder capacity or severe lower urinary tract symptoms; pharmacokinetic modelling suggests that the minimum clinically meaningful dwell time for MMC at standard concentrations is approximately 30 minutes, below which urothelial tissue drug levels may fall below the therapeutic threshold

[13]. Longer dwell times (>90 minutes) do not appear to offer additional clinical benefit and may increase local toxicity without proportionate efficacy gain.

Practical Administration Protocol: A Standardised Framework: The safe and effective delivery of immediate post-TURBT intravesical chemotherapy requires a standardised institutional protocol that addresses pre-instillation safety checks, drug preparation, catheter insertion, dwell management, and post-void documentation [12]. The following evidence-informed framework reflects current guideline recommendations and established institutional practice standards:

- Confirm TURBT completion and haemostasis. Visually assess irrigant clarity; instillation is contraindicated if perforation is suspected or irrigant remains grossly haemorrhagic.
- Perform a systematic perforation risk assessment. Intraoperative findings, operative notes, and clinical assessment should be reviewed; any suspicion of bladder wall breach warrants deferral regardless of irrigant appearance.
- Prepare chemotherapy under pharmaceutical aseptic conditions. For MMC: 40 mg dissolved in 40 mL sterile water; for Epirubicin: 50-80 mg in 50 mL saline. Pre-labelled unit-dose preparations reduce preparation error and delay.
- Ensure urethral catheter patency and position. If the resection catheter is to be retained post-operatively, it is used for instillation; if removed at surgery closure, a new catheter should be inserted with minimal trauma.
- Instil chemotherapy by gravity drainage. The catheter bag is clamped immediately after instillation. The patient should be instructed to lie still; positional rotation (supine, left lateral, right lateral, prone) every 15 minutes is recommended by some authorities to maximise mucosal contact.
- Maintain 60-minute dwell time under catheter clamp. Time of instillation and catheter release are documented in the operative record.
- Release catheter clamp and allow voiding at 60 minutes. Advise adequate post-void hydration. Document instillation in operative notes, pharmacy records, and nursing care plan.

Institutional Protocol Imperative: Clinical audit data consistently attribute a substantial proportion of instillation failures to systemic organisational deficiencies including unavailability of pre-prepared drug, lack of a standing order pathway, and absence of a nursing checklist rather than clinical contraindications or clinician reluctance.

Standardised institutional protocols with pre-prepared unit-dose pharmacies and standing order sets are the single most impactful quality improvement intervention available for closing the evidence-to-practice gap.

Theme V: Contraindications, Safety Considerations, and Adverse Effects

Contraindications: Absolute and Relative: The most critical patient safety obligation in the perioperative management of intravesical chemotherapy instillation is the active exclusion of contraindications prior to drug administration [1, 12]. Unlike most pharmaceutical interventions contraindications are assessed at prescribing and dispensing stages the instillation of intravesical chemotherapy occurs in the acute post-operative setting, in which clinical assessment may be compromised by the transition between operating theatre and recovery environments, by documentation gaps, and by the involvement of multiple clinicians and nursing staff across different care settings. The primacy of a pre-instillation safety checklist in clinical governance cannot be overstated [12]. Table 5 systematically catalogues the principal contraindications with mechanistic basis and clinical guidance.

Table 5: Contraindications to Immediate Post-TURBT Intravesical Chemotherapy: Absolute and Relative Classification with Mechanistic Basis and Clinical Guidance.

Contraindication	Mechanistic Basis	Clinical Guidance
Suspected or confirmed bladder perforation	Intraperitoneal or extraperitoneal perforation during TURBT allows chemotherapy access to peritoneum or pelvic space	Absolute contraindication; instillation is permanently deferred regardless of perforation grade; systemic toxicity and chemical peritonitis reported with MMC and Epirubicin
Visible haematuria / grossly bloody urine	Heavy haematuria at conclusion of TURBT dilutes agent and may indicate mucosal disruption with enhanced systemic absorption	Relative to absolute contraindication depending on severity; clinical judgement required; instillation deferred in most guidelines until haematuria resolves
Traumatic catheterisation	False passage or significant urethral trauma increases extravasation risk and systemic absorption	Relative contraindication; defer instillation; clinical reassessment at first post-TURBT outpatient visit
Obstructed or	Vesicoureteric reflux or ureteric	Relative contraindication; pre-instillation

compromised upper urinary tract	obstruction risks retrograde chemotherapy exposure to the renal pelvis and calyx	imaging to assess upper tract status recommended in high-risk or complex cases
Known hypersensitivity to agent	Prior documented allergic or severe local reaction to the intended agent	Absolute contraindication to that agent; alternative chemotherapy agent may be used
Reduced bladder capacity or active UTI	Active infection or severely reduced bladder capacity reduces dwell time and increases mucosal permeability	Defer until infection resolved; bladder capacity <100 mL is relative contraindication; clinical case-by-case assessment recommended

Bladder Perforation: The Critical Absolute Contraindication

Bladder perforation during TURBT represents the absolute contraindication of highest clinical priority and the one most frequently invoked in serious adverse event reports associated with post-TURBT instillation [12]. Perforation occurs in approximately 1-5% of TURBT procedures, with the posterior bladder wall and dome representing the highest-risk anatomical sites given their proximity to peritoneal structures and susceptibility to diathermy-related thermal injury during tumour resection [17]. The distinction between intraperitoneal perforation a surgical emergency requiring open or laparoscopic repair and extraperitoneal perforation typically manageable with catheter drainage alone is clinically important but does not alter the absolute contraindication to intravesical instillation in either context.

Intraperitoneal instillation of MMC has been associated with severe and potentially fatal chemical peritonitis characterised by diffuse peritoneal inflammation, bowel ileus, and systemic inflammatory response. Published case reports and adverse event registries document deaths attributable to inadvertent intraperitoneal MMC instillation following unrecognised perforation, underscoring that this contraindication is not merely theoretical but a genuine and preventable patient safety hazard [12]. Clinical protocols must include explicit pre-instillation documentation of perforation status, with instillation deferred as the default position in any case of doubt.

Adverse Effects and Tolerability Profile: Immediate post-TURBT intravesical chemotherapy is generally well tolerated, with the large majority of adverse effects being localised and self-limiting [1, 6]. The most common adverse effects associated with MMC instillation are chemical cystitis characterised by dysuria, urinary frequency, and suprapubic discomfort occurring in 5-15% of patients, and allergic contact dermatitis affecting the genitalia, perineum, or palms in approximately 2-8% of patients [13]. The dermatitis is attributable to residual drug contact following voiding and is effectively prevented by thorough genital washing with soap and water immediately after voiding the instillate [13]. Severe systemic reactions including anaphylaxis, haematological toxicity, or renal impairment are rare with MMC given its large molecular weight and limited systemic absorption through intact urothelium, but have been reported in the context of inadvertent systemic exposure following perforation or traumatic catheterisation [12]. Epirubicin shares a broadly similar local tolerability profile, with chemical cystitis occurring in a comparable frequency range.

The absence of significant systemic absorption renders haematological toxicity a recognised concern with the small-molecule Thiotepa effectively absent with both MMC and Epirubicin at standard instillation doses [6, 7]. Gemcitabine demonstrates the most favourable local tolerability profile of the evaluated agents, with chemical cystitis rates substantially lower than those reported for MMC, representing a clinically relevant differentiating attribute in patients with pre-existing lower urinary tract sensitivity [14].

Theme VI: Guideline Concordance, Under-Utilisation, and Implementation Challenges

International Guideline Landscape: Single immediate post-TURBT intravesical chemotherapy instillation is endorsed as a standard of care recommendation by all major international urological guidelines. The EAU Guidelines on NMIBC (Babjuk et al., 2022) assign a Level of Evidence 1a and Grade A Recommendation to immediate intravesical chemotherapy instillation following complete TURBT in patients without contraindications, defining it as recommended for all low-risk patients and as the initial component of adjuvant treatment in intermediate-risk patients [1].

The AUA/SUO Guideline on Non-Muscle Invasive Bladder Cancer (Chang et al., 2016) issues a strong, Index Patient recommendation for a single immediate instillation in patients with low-grade Ta tumours, explicitly noting that adherence to this recommendation has been identified as a quality-of-care indicator [18]. The BAUS consensus statement on NMIBC management equivalently endorses immediate instillation and has identified its non-delivery in eligible patients as a reportable clinical governance indicator.

The Evidence-Practice Gap: Scale and Consequences

Despite the highest level of guideline endorsement, clinical audit data from multiple jurisdictions reveal a persistent and substantial discordance between recommended and actual practice. Mostafid et al. (2014) conducted a national audit across 30 UK urology units and identified that only 56% of eligible NMIBC patients received the guideline-recommended immediate instillation, representing a 44% under-utilisation rate in a high-income health system with comprehensive urological infrastructure [12]. Comparable audits from the United States, Germany, the Netherlands, and Canada report under-utilisation rates of 30-60%, with no consistent improvement in adherence rates over time despite repeated guideline reinforcement [12, 18]. The consequences of this evidence-practice failure are quantifiable and clinically significant. Extrapolating from published NNT data to population-level analysis, the under-treatment of 40-50% of eligible NMIBC patients is estimated to generate thousands of preventable recurrences annually in high-income countries alone each requiring diagnostic cystoscopy, general or regional anaesthesia, TURBT, pathological analysis, and post-operative recovery with associated morbidity, anxiety, quality-of-life impairment, and direct healthcare costs [12, 18]. The economic case for systematic quality improvement programmes targeting immediate instillation adherence is therefore compelling on both clinical and health economic grounds.

Barriers to Implementation and Quality Improvement Strategies: Qualitative and audit research has identified a consistent set of organisational, logistical, and educational barriers contributing to immediate instillation under-utilisation:

- Absence of a standardised institutional protocol or pre-prepared unit-dose pharmacy pathway, resulting in drug unavailability at the time of instillation need
- Inadequate pre-operative identification of eligible patients and failure to include instillation in the operative plan prior to theatre admission
- Uncertainty among junior surgical staff or nursing personnel regarding contraindication assessment, leading to conservative deferral in ambiguous clinical scenarios
- Lack of a formal post-operative nursing checklist that positions instillation as an expected standard rather than an optional add-on
- Insufficient institutional audit and feedback mechanisms to identify, quantify, and address under-utilisation at the unit level [12,18].

Effective quality improvement interventions demonstrated to significantly increase immediate instillation rates include: pre-listing of intravesical chemotherapy in the operative plan for all NMIBC-listed cases; unit-dose pre-prepared pharmacy pathways with theatre-level drug availability; nurse-delivered instillation protocols understanding medical order sets; and institutional audit and public reporting of adherence rates as a quality indicator [12].

The integration of immediate instillation into national surgical safety checklists or equivalent audit frameworks has been proposed as a systemic intervention capable of driving consistent practice improvement across institutions and jurisdictions.

Evidence Gaps and Future Research Priorities: Despite the robust foundational evidence supporting immediate post-TURBT intravesical chemotherapy, the literature reveals a structured set of knowledge deficits that limit the precision, completeness, and equity of current clinical recommendations. Table 6 systematically maps these gaps with their rationale and recommended research approaches.

Table 6: Identified Evidence Gaps, Clinical Rationale, and Recommended Future Research Directions for Immediate Post-TURBT Intravesical Chemotherapy in NMIBC.

Evidence Gap	Rationale	Recommended Research Approach
Head-to-head agent comparison RCTs	Existing evidence compares individual agents vs. control; direct comparative RCTs (MMC vs. Gemcitabine, Epirubicin vs. Pirarubicin) in the immediate instillation setting are sparse	Multi-arm, adequately powered RCTs directly comparing available agents with standardised dosing, dwell time, and pH optimisation across matched NMIBC risk strata
Optimal timing window within 24 hours	Current guidelines define a 24-hour window but provide limited mechanistic data on the sub-window (1 h vs. 6 h vs. 24 h) efficacy gradient	Prospective, time-stratified RCTs with pre-specified sub-group analyses comparing recurrence outcomes by time-to-instillation in 1-hour increments
Role of urine alkalinisation and pH optimisation	MMC efficacy is pH-dependent; pre-instillation sodium bicarbonate administration improves drug stability and urothelial penetration, but this protocol is	RCTs and pharmacokinetic studies examining urine pH-optimised immediate MMC instillation vs. standard-pH instillation on recurrence endpoints

	not universally adopted	
Gemcitabine as first-line alternative	Gemcitabine demonstrates superior tolerability and comparable or superior efficacy to MMC in Phase II data; Phase III head-to-head confirmation in the immediate instillation setting is lacking	Multicentre Phase III RCT comparing immediate Gemcitabine vs. MMC for low- and intermediate-risk NMIBC with recurrence-free survival as primary endpoint
Biomarker-guided patient selection	No validated molecular or pathological biomarker currently stratifies patients for maximal benefit from immediate instillation vs. those for whom benefit is marginal or absent	Prospective translational studies integrating tumour molecular profiling (FGFR3, TP53, CDKN2A) with clinical trial enrolment to define predictive biomarker signatures
Long-term follow-up and progression outcomes	The majority of RCTs demonstrate recurrence benefit but are underpowered or under-followed to detect meaningful differences in disease progression or bladder cancer-specific mortality	Long-term registry-based or trial extension studies with minimum 10-year follow-up incorporating progression, cystectomy rate, and overall survival as co-primary endpoints
Under-utilisation in clinical practice	Audit data from UK, US, and Europe indicate that 30–50% of eligible patients do not receive immediate instillation despite guideline recommendations; systemic implementation gaps persist	Health systems research and quality improvement studies identifying organisational, pharmacological, and clinician-level barriers to instillation; development and evaluation of standardised institutional protocols

Among the most clinically urgent research priorities is the head-to-head comparison of Gemcitabine versus MMC in an adequately powered, Phase III multicentre RCT in the immediate instillation setting. The existing evidence base for each agent derives primarily from placebo-controlled trials rather than direct comparative studies, and the indirect comparison evidence while suggestive of comparable or superior Gemcitabine efficacy with a superior tolerability profile is insufficient to support a guideline-level recommendation of one agent over the other [14].

A definitive comparative trial in this setting would have immediate and substantial clinical impact on agent selection, formulary decisions, and patient counselling globally. The biomarker-guided selection agenda represents a longer-term but transformatively important research priority. Current risk stratification systems are built upon clinical and pathological variables that carry meaningful but imperfect predictive accuracy for individual patient outcomes [18]. The integration of molecular tumour profiling encompassing FGFR3 mutation status, TP53 pathway integrity, CDKN2A deletion, and urothelial molecular subtype classification with clinical risk parameters has the potential to identify patient subpopulations in whom immediate instillation provides maximal benefit, and conversely, those for whom the intervention adds minimal incremental value to surveillance alone [17, 18]. Prospective translational studies embedding molecular profiling within RCT frameworks are needed to develop and validate such predictive biomarker signatures. Finally, the health systems research agenda encompassing the evaluation of implementation interventions, digital reminder systems, pharmacy integration models, and professional education programmes is essential for closing the persistent evidence-to-practice gap that renders the immediate instillation evidence base clinically ineffective for a substantial proportion of eligible patients [12]. High-quality implementation science research in this domain has the potential to generate patient benefit comparable in magnitude to the development of new pharmacological agents, at a fraction of the cost and regulatory complexity.

Conclusion

Single immediate post-operative intravesical chemotherapy instillation following TURBT in NMIBC represents one of the most robustly evidenced, guideline-endorsed, cost-effective, and persistently underutilised interventions in urological oncology. This structured literature review, encompassing the full range of relevant evidence from foundational meta-analyses to contemporary pharmacological trials and implementation audits, supports the following principal conclusions:

- The evidence base comprising more than 30 RCTs and multiple pooled analyses provides Level 1a evidence for a 35–45% relative reduction in tumour recurrence following a single immediate post-TURBT intravesical chemotherapy instillation compared with TURBT alone, with an NNT of 6–9 in low- and intermediate-risk NMIBC populations.
- The clinical benefit is maximal in low-risk primary NMIBC patients, where a single immediate instillation may represent the

entirety of required adjuvant therapy, and is attenuated but still present in intermediate-risk patients where it forms the initial component of a broader adjuvant programme.

- Mitomycin C (40 mg) is the guideline-endorsed first-line agent with the largest and most robust evidence base; Epirubicin and Pirarubicin are evidence-based alternatives with comparable efficacy and distinct tolerability profiles; Gemcitabine is an emerging agent with superior tolerability and promising efficacy that merits Phase III confirmation.
- Instillation timing is a critical determinant of efficacy: the sub-6-hour window is optimal; the 24-hour boundary represents the outer limit of clinical meaningfulness; instillation beyond 24 hours provides no demonstrable benefit over TURBT alone.
- Bladder perforation is the critical absolute contraindication requiring active exclusion before every instillation; a structured pre-instillation safety checklist is a clinical governance imperative.
- Under-utilisation of immediate instillation in 30–50% of eligible patients across high-income health systems represents a major and preventable patient safety failure; standardised institutional protocols, pharmacy integration, and audit feedback are the most impactful quality improvement interventions.
- Key evidence gaps including direct agent comparisons, biomarker-guided patient selection, sub-hour timing trials, and implementation science research define the research agenda for the next decade in this field.

The clinical responsibility to offer eligible NMIBC patients this simple, safe, and highly effective single-dose intervention is supported by the highest quality of evidence available in surgical oncology. Closing the evidence-to-practice gap through systematic institutional quality improvement, combined with the research agenda outlined herein, represents a dual obligation for the urological oncology community to both current patients whose recurrences are currently preventable, and to future patients whose care will be shaped by the trials we design and conduct today.

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