Urology Services Inquiry

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Dr Maria O'Kane
Chief Executive
Trust Headquarters
Craigavon Area Hospital
68 Lurgan Road
Portadown
Craigavon
BT63 5QQ

17 August 2022

Dear Dr O'Kane,

Re: Patient Safety Issue

As part of the Inquiry's investigation into the delivery of urology services in the Southern Trust ('the Trust') we have recently received evidence from a witness statement from Mr. David Connolly, FRCS. He is a consultant urologist who was employed by the Trust between September 2012 and March 2013. He is now employed by the Belfast Trust.

Mr Connolly has told the Inquiry that during his employment in the Trust he had opportunity to observe aspects of the practice of Mr Aidan O'Brien. He has explained that Mr O'Brien displayed what he has described as *"idiosyncrasies to his practice that he [Mr Connolly] did not understand."*

Mr Connolly has provided two examples to illustrate his concerns. The first example related to the practice of Mr O'Brien (and others) admitting patients with recurrent urinary tract infections to the Urology ward for 5 to 7 days, where they were treated with intravenous antibiotics and fluids. The Inquiry was already aware of that issue before Mr Connolly drew attention to it, and of the steps taken by the Trust in an effort to bring it to an end.

The second example of 'idiosyncratic practice' described by Mr Connolly relates to the treatment of high-risk bladder cancers. It is this issue which I wish to focus on.

Mr Connolly has described his experience as follows:

> "Similarly, he [Mr Aidan O'Brien] did not like using intravesical BCG therapy for high-risk non-muscle invasive bladder cancer and preferred Mitomycin therapy. I was informed (I do not recall if this was by Mr. O'Brien himself or someone else), that Mr. O'Brien had a patient soon after BCG was first introduced that developed a small capacity, poorly functioning bladder as a side effect of the BCG treatment and since that time, he did not like using BCG. I did not have this experience and continued to advise BCG for my patients."

Issued by the Urology Services Inquiry on 17/08/2022. Annotated by the Urology Services Inquiry.

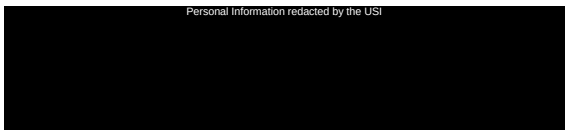
I am advised that BCG therapy is, in part, the treatment indicated for the management of high-risk non muscle-invasive bladder cancers. The use of BCG therapy in such cases is supported by NICE and NICAN. I am advised that the use of Mitomycin is likely to be a less effective treatment in such cases and would be regarded by practitioners as a potential under treatment of these cancers.

I am concerned that Mr Connolly's description appears to indicate that some patients have not received appropriate care for the treatment of high-risk bladder cancer. We have not sought further details of what he has described, although the point which he is making is very clear and specific.

This has the hallmarks of a patient safety issue and I am of the view that it is a matter which requires investigation by the Trust, quite apart from the Inquiry's interest in the matter. I know that the Trust has conducted SAI, Lookback and SCRR exercises which have examined a considerable number of Mr O'Brien's patients, and that aspects of those processes are ongoing. I am not aware of any findings concerning the misuse of Mitomycin therapy, but it is important that this issue is now looked at specifically having regard to what Mr Connolly has disclosed.

I look forward to hearing from you as a matter of urgency with an outline of the steps which the Trust proposes to take in response to this information.

Yours sincerely



Christine A Smith
Chair of the Urology Services Inquiry

Cc: Mr Connolly FRCS

From: chiefexecutiveoffice <Personal Information redacted by the USI>
Sent: 02 September 2022 15:56
To: OHagan, MargaretM
Subject: Patient Safety Issue - Letter to Ms Christine Smith from Dr Maria O'Kane
Attachments: 2022-08-17 Letter from CS to Dr OKane re Patient Safety Issue.pdf; Christine Smith QC Chair Urology Services Inquiry - Patient Safety Issue 30 August 2022 - signed version.pdf

Margaret – copy for your records.
Many thanks Elaine

From: chiefexecutiveoffice <Personal Information redacted by the USI>
Sent: 02 September 2022 15:34
To: info@usi.org.uk
Subject: Patient Safety Issue - Letter to Ms Christine Smith from Dr Maria O'Kane

Dear Celine

Further to your email below, please find attached response from Dr Maria O'Kane to Ms Christine Smith.

Many thanks.
Kind regards, Elaine

Elaine Wright
Manager – Office of the Chair & Chief Executive
Southern Health & Social Care Trust
Personal Information redacted by the USI
☎ (028) Personal Information redacted by the USI (Internal: Personal Information redacted by)

From: USI Info <info@usi.org.uk>
Sent: 17 August 2022 16:07
To: OKane, Maria <Personal Information redacted by the USI>; chiefexecutiveoffice <Personal Information redacted by the USI>
Subject: Re: Patient Safety Issue - Letter to Dr O'Kane from Ms Christine Smith

Received from the SHSCT on 02/09/2022. Annotated by the Urology Services Inquiry.

For the attention of Dr Maria O'Kane

Good afternoon Dr O'Kane

Please find attached correspondence from Ms Christine Smith for your information and attention.

Kind Regards

Celine

Urology Services Inquiry
Contact: info@usi.org.uk | Tel: 028 90251141 | Ext: 51141

Urology Services Inquiry

Received from the SHSCT on 02/09/2022. Annotated by the Urology Services Inquiry.

Southern Health
and Social Care Trust

Quality Care - for you, with you

Chair
Eileen Mullan

Chief Executive
Dr Maria O'Kane

30 August 2022

BY EMAIL - info@usi.org.uk

Ms Christine Smith
Chair of Urology Services Inquiry
Urology Services Inquiry Office
1 Bradford Court
Belfast
BT8 6RB

Dear Ms Smith

PATIENT SAFETY ISSUE

Thank you for your letter dated 17 August 2022 regarding a potential patient safety issue related to patients with high-risk, non-muscle invasive, bladder cancer under the care of Mr O'Brien.

I am very grateful that you have brought this to my attention as it provides us with an opportunity to investigate the situation fully and take appropriate action.

I can confirm the Trust will undertake an audit of the treatment received by all patients who had a diagnosis of high-risk, non-muscle invasive, bladder cancer within an identified time period. This time period will be clarified when the audit methodology, including the tool audit, is finalised.

Within the audit, the use, or not, of Bacillius Calmette-Guerin (BCG) or Mitomicin therapy will be specifically considered and conclusions made on whether clinical practice has resulted in harm to patients.

Trust Headquarters, Craigavon Area Hospital site, 68 Lurgan Road, Portadown, Craigavon BT63 5QQ
Tel: Personal Information redacted by the USI Email: Personal Information redacted by the USI

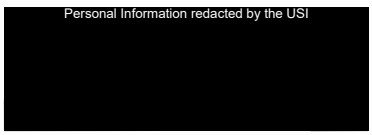
Received from SHSCT on 02/09/2022. Annotated by the Urology Services Inquiry.

I would like to assure you we will undertake this audit at pace and take immediate steps to address any shortcomings. We will be open and honest with patients if they have not received the correct treatment.

We will share the outcome of this work with the Urology Services Inquiry team.

Furthermore, we will make sure the GMC is aware of this allegation and will share the outcomes of the audit with them, as part of the ongoing regulatory process.

Yours sincerely



DR MARIA O'KANE
CHIEF EXECUTIVE

Southern Health and Social Care Trust

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BCG (Bacillus Calmette Guérin) Audit

With reference to the concern raised with regards to Mr O'Brien's use of intravesical BCG treatment for patients with high risk non-muscle invasive urothelial cancers of the bladder, the existing Lookback Review cases have been interrogated. A single case of high risk non muscle invasive bladder cancer was identified where BCG treatment was not offered. For this patient there was clinical justification for the decision to not offer BCG. Therefore, to date the Lookback Review has not identified any concerns regarding the offer of BCG treatment to patients with high risk non muscle invasive bladder cancer. As BCG treatment for high risk non muscle invasive bladder cancer is given after initial diagnosis (and re-resection TURBT) and that following retirement Mr O'Brien's patients' care has been continued by the remaining members of the Southern Trust urology team, we do not have any concern that there is an ongoing patient concern regarding this group of patients not currently receiving appropriate management.

Mr Connolly references the risk of functional side effects of BCG therapy, in particular in the longer term. Bladder function / symptoms factor into decision making for patients, and may be a clinical reason why BCG treatment is not offered – in order to receive BCG treatment patients need to retain the BCG in their bladder for up to 2 hours. Patients who are unable to do this either because of incontinence or severe urgency symptoms would not be suitable for the treatment. In addition, patients' bladder symptoms can become worse during the course of BCG treatment. Approximately 1/3 of patients do not complete 3-year maintenance BCG programmes with the majority of these being because of worsened bladder symptoms. Risk of persistent bladder pain '…sometimes leading to bladder removal' is quoted as 1:50 – 1:250 in the patient information leaflet produced by BAUS for patients receiving BCG treatment. Patients are counselled regarding these risks when their treatment options are discussed with them. Unfortunately, some patients do develop intractable bladder symptoms as described by Mr Connolly as a result of BCG treatment and may subsequently require surgery to remove their bladders to manage these symptoms.

We have considered the guidance for bladder cancer management which was available during the time which Mr Connolly was a consultant in Southern Trust, in order to ascertain if the assertion by Mr Connolly can be evidenced in the treatment patients received. At this time, NICE guidelines had not been published (they were first published in 2015). The available guidance for multidisciplinary teams at this time had been produced by BAUS (January 2013) which recommends 'Intravesical BCG + maintenance 1-3 years' (page 17 of BAUS MDT guidance for the management of bladder cancer 2013) and references the European Association of Urology guidelines for bladder cancer.

A significant factor which has occurred on a number of occasions over the past decade is disruption / unavailability of BCG supplies. This was an issue during the time period 2012 – 2013. This has been a worldwide problem and has meant that at times of unavailability of BCG patients were not able to be offered this treatment and delivery of maintenance BCG for patients has been interrupted and therefore sub-optimal. Supplies of BCG during periods of disruption have been intermittent and

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variable meaning we have not been able to clearly identify dates between which BCG was unavailable.

The BAUS guidance for MDMs summarises the evidence available at the time with regards to intravesical treatment for management of high risk non muscle invasive bladder cancer. Potential treatment benefits for patients are a reduction in the risk of recurrence and a reduction in the risk of progression (development of invasive disease). The overview highlights that at the time ***'…In studies and meta-analyses comparing BCG with intravesical chemotherapy in a combination of high-risk and intermediate-risk patients, contradictory results have been obtained with respect to the relative benefit of BCG on progression'***. The evidence summary for comparisons of these treatments is below;

BCG versus mitomycin C

- In an individual patient data meta-analysis of data from 9 clinical trials involving 2820 intermediate- and high-risk patients with Ta, T1 or CIS, TUR + BCG was compared with TUR + MMC. Median follow-up was 4.4 years (maximum 17.7 years).[59]
  - In the studies with BCG maintenance therapy (n=1324), a 32% reduction in the risk of recurrence was determined versus MMC (43.2% versus 57.9%; p<0.0001).
  - Notably, without maintenance BCG (n=1496), the risk of recurrence was increased versus MMC, by 28% (42.6% versus 31.8%; p=0.006).
  - There were no significant differences in progression, OS or DSS, irrespective if patients receiving BCG with maintenance were subanalysed.
- In a meta-analysis of data from 9 trials performed by Bohle & Bock (n=2410), median follow-up was 26 months (range, 11.5–50.4).[67]
  - When considering all treatment regimens, there was no significant difference between BCG and MMC in tumour progression (7.7% versus 9.4%; OR, 0.77; 95% CI, 0.57–1.03; p=0.081).
  - In the subgroup of patients receiving maintenance BCG therapy for at least 1 year, the risk of progression was significantly reduced compared with MMC (OR, 0.66; 95% CI, 0.47–0.94; p=0.02).
  - In patients not receiving maintenance BCG therapy, there were no differences between treatments in terms of disease progression (OR, 1.16; 95% CI, 0.65–2.07; p=0.61).
- In a meta-analysis involving 700 patients with CIS and where the overall median follow-up was 3.4 years, a reduction of 43% in the odds of treatment failure on BCG was shown provided BCG maintenance was given (OR, 0.57; p=0.04).[76]

As noted previously, supply of BCG at this time was intermittent, with periods of BCG unavailability. This would impact on the ability of services to provide maintenance BCG treatment. While the data available at this time demonstrates a reduced risk of recurrence with BCG compared to MMC, this is only when maintenance BCG is given. With regards to impact on progression, the evidence at the time, as summarised in the BAUS document, does not demonstrate a clear benefit of BCG over MMC, with differing studies showing no difference or a slight reduction in risk of progression. Again, this possible benefit was only demonstrated where maintenance BCG was given. In the context of limited, intermittent BCG supply, where optimal BCG maintenance treatment could not be provided the evidence at the time does not indicate that single induction (6 doses) of BCG is superior to 6 doses of MMC. A consensus statement from the European Association of Urology guidelines panel regarding the BCG shortages outlines recommended options available to urologists when faced with

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limited BCG supply. This document states, ***'References about the use of only an induction course (6 weekly instillations without maintenance) are controversial. A recently presented cohort study showed promising results, however meta-analyses have shown induction only BCG to have inferior efficacy compared to intravesical chemotherapy.'*** The recommendations for management of this group of patients when faced with limited BCG supply, as was the case during this time period, included a recommendation to deliver maintenance treatment for 1 year (not up to 3 years, recommendation 3), and recommendation 4 states, ***'In patients with Ta or T1 tumours at intermediate or high risk of recurrence and intermediate risk of progression, adjuvant BCG treatment can be replaced by intravesical chemotherapy which represents an alternative treatment option'.***

Despite the NICE guidelines not being published until 2015, in order to assess the care of patients with non muscle invasive bladder cancer treated in Southern Trust during the time period when Mr Connolly worked as a Consultant in Southern Trust we utilised the audit tool published alongside these guidelines. Unfortunately, the data output from this audit did not provide sufficient insight into the care provided to patients with high risk non muscle invasive bladder cancer to be able to assess Mr O'Brien's utilisation of BCG for patients with high risk non muscle invasive bladder cancer and the concern raised in Mr Connolly's statement.

This audit did enable us to identify those patients who were first diagnosed with high risk non muscle invasive bladder cancer in the 2012-13 and 2013-14 financial years and a subsequent review of all of these cases was undertaken with regards to the offer of intravesical treatment and the MDM recommendations given at the time.

A total of 38 patients were identified with a diagnosis of high risk non muscle invasive bladder cancer on their initial TURBT. Of these 7 patients were upstaged to muscle invasive disease on re-resection TURBT, and 1 patient was found to have metastatic disease on staging. A further 3 patients had severe significant co-morbidities and were managed with palliative intent.

The remaining 27 patients were potentially eligible for BCG treatment. A total of 9 consultants who worked in the Southern Trust urology department during this time period managed these patients. Mr O'Brien was recorded as managing 5 of these patients. The table below details the intravesical treatment offered to these patients.

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	All consultants	Mr O'Brien	All other consultants (excluding Mr O'Brien)
Offered BCG	10/27 = 37%	2/5 = 40%	8/22 = 36%
Offered MMC, BCG noted as unavailable	3/27 = 11%	0/5 = 0%	3/22 = 14%
Offered MMC, BCG availability not recorded	6 = 22%	1/5 = 20%	5/22 = 23%
Not offered intravesical treatment with clinical justification	3 = 11%	0/5 = 0%	3/22 = 14%
Not offered intravesical treatment, no clinical justification recorded	4 = 15%	1/5 = 20%	3/22 = 14%
DNA follow-up	1 = 4%	1/5 = 20%	0/22 = 0%

From the data collected over this time period there is therefore no evidence that patients under the care of Mr O'Brien during this time period were less likely to be offered BCG in the management of their high risk non muscle invasive bladder cancer than patients under the care of the rest of the urology team.

Review of the MDM recommendations made during this time period identifies that for 12 patients the MDM outcome specifically recommends BCG treatment (including availability issues for 3 patients), for 5 patients the outcome recommends MMC therapy alone, 1 outcome recommends 'Intravesical treatment' but does not specify MMC or BCG, 8 outcomes do not make any recommendation of intravesical treatment and for 1 patient no MDM record was identified (Consultant = Mr Brown). Mr O'Brien is listed as the chair of MDM for all of these MDM outcomes. While it is possible that Mr O'Brien expressed the view highlighted by Mr Connolly during MDM discussions, a greater proportion of MDM outcomes recommended BCG treatment than any alternative treatment. For those outcomes that recommended MMC, intravesical therapy or did not recommend any intravesical treatment, it is possible that the MDM discussion considered BCG treatment but that this was not recorded in the outcome detail. For those patients for whom the MDM outcome did not recommend any intravesical treatment, clinical records at the time indicate significant co-morbidity / frailty / co-existent pathology in 7 (of 8) patients. It is also possible that recommendations for MMC were made in the light of BCG supply problems but not referenced in these MDM outcomes.

With regards to current practice within the Southern Trust urology service, we are confident that BCG is being offered to patients with high-risk non muscle invasive bladder cancer as per NICE guidelines from 2015 and we are auditing current practice against the NICE 2015 standards as part of our current departmental audit plan. In addition, more recent EAU guidance has clearly identified sub-groups of high-risk patients who are at a very high risk of progression and in whom radical cystectomy is recommended. This is being utilised as part of MDM recommendations and patient counselling. Currently, supplies of BCG are satisfactory and therefore at present this is not a factor in treatment selection.

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Of note during the process of this review concern has been identified regarding the management of 1 patient (who is now deceased) with metastatic / muscle invasive disease and this has been flagged to the Trust lookback team for further assessment. This concern is not in relation to intravesical treatment.

Mark Haynes

Consultant Urologist

24 November 2023

Received from SHSCT 24/11/2023. Annotated by the Urology Services Inquiry.

TRU-320016

Multi-disciplinary Team (MDT) Guidance for Managing Bladder Cancer

2nd Edition (January 2013)

Produced by:

- **British Uro-oncology Group (BUG)**
- **British Association of Urological Surgeons (BAUS) Section of Oncology**
- **Action on Bladder Cancer (ABC)**

This guidance has been supported by unrestricted educational grants from:
Cambridge Laboratories (A Division of Alliance Pharmaceuticals Ltd)
ProStrakan Limited (part of the Kyowa Kirin group)
Pierre Fabre Ltd

The development and content of this guidance has not been influenced in any way by the supporting companies.

Date of preparation: January 2013

Received from SHSCT 24/11/2023. Annotated by the Urology Services Inquiry.

This guidance has been developed for healthcare professionals and multi-disciplinary teams with the following aims:

- To provide evidence-based guidance on the management options for superficial, muscle-invasive and advanced bladder cancer
- To ensure clarity on the role of the MDT on the management of superficial, muscle-invasive and advanced bladder cancer

Acknowledgements:

The Guidance has been compiled and edited from a multi-disciplinary panel with extensive experience in the management of patients with bladder cancer.

Particular recognition for work on this Guidance goes to:

Dr Alison Birtle, Consultant Clinical Oncologist, Preston;

Mr Leyshon Griffiths, Consultant Urologist, Leicester

Received from SHSCT 24/11/2023. Annotated by the Urology Services Inquiry.

Contents

Received from SHSCT 24/11/2023. Annotated by the Urology Services Inquiry.

Abbreviations

5-ALA: 5-aminolevulinic acid

BCG: bacillus Calmette-Guérin

BPT: bladder-preserving therapy

BSC: best supportive care

CI: confidence interval

CIS: carcinoma *in situ*

CR: complete response

CRT: chemoradiotherapy

CT: computed tomography

DC: docetaxel + cisplatin

DFS: disease-free survival

DRE: digital rectal examination

DSS: disease-specific survival

EAU: European Association of Urology

ECOG: Eastern Co-operative Oncology Group

EORTC: European Organization for the Research and Treatment of Cancer

GC: gemcitabine + cisplatin

GCb: gemcitabine + carboplatin

GCSF: granulocyte colony stimulating factor

GFR: glomerular filtration rate

HAL: hexaminolevulinic acid

HR: hazard ratio

IFN: interferon

LUTS: lower urinary tract symptoms

MDT: multi-disciplinary team

MMC: mitomycin C

MRC: Medical Research Council

MRI: magnetic resonance imaging

M-CAVI: methotrexate + vinblastine + carboplatin

M-VAC: methotrexate + vinblastine + cisplatin

NBI: narrow-band imaging

NMIBC: non-muscle invasive bladder cancer

OR: odds ratio

ORR: overall response rate

OS: overall survival

PDD: photodynamic diagnosis

PFS: progression-free survival

PR: partial response

PS: performance status

PSA: prostate-specific antigen

RCON: radiotherapy + carbogen + nicotinamide

RCP: Royal College of Pathologists

RCT: randomised controlled trial

RFS: recurrence-free survival

RR: relative risk

SD: stable disease

TB: tuberculosis

TCC: transitional cell carcinoma

TNM: tumour-node-metastasis

TTP: time to progression

TUR: transurethral resection

US: ultrasound

WHO: World Health Organization

Received from SHSCT 24/11/2023. Annotated by the Urology Services Inquiry.

Integrated Care and the Multi-disciplinary Team (MDT)

The provision of a consistent treatment strategy across a multi-disciplinary team (MDT), as well as the model of integrated care is increasingly being adapted as a valuable approach to overcome the fragmentation of patient management. In addition, an MDT provides an ideal framework to conduct audits and facilitate peer review.

The management strategies proposed for patients with non-muscle invasive bladder cancer (NMIBC), muscle invasive and advanced bladder cancer within the MDT can be successfully driven when the members of the MDT work together with ongoing support provided by the wider team (Table 1). The MDT can provide patients with treatment options that are specifically tailored to address their individual needs, such as disease state, co-morbid conditions and lifestyle. To ensure the success of the MDT approach, familiarity with the entire spectrum of management strategies is recommended.

Table 1: Proposed composition of the MDT in the non-muscle invasive, muscle invasive and advanced bladder cancer setting

• Urological surgeons	• Pathologists
• Clinical and medical oncologists*	• Urology and oncology nurse specialists
• MDT co-ordinator and administrative support	• Palliative care specialists
• Radiologists	

*Medical oncologist attendance is not necessary for low-risk superficial disease

The purpose of the treatment algorithms presented in this document is to provide a unique framework that can be adapted for the management of the three main types of bladder cancer: non-muscle invasive, muscle invasive and advanced transitional cell carcinoma (TCC) (Figure 1).[1] Management of the less common tumours such as squamous cell carcinomas or adenocarcinomas are not addressed within this document.

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Figure 1: Summary of the definition of urinary bladder cancer stages *(adapted from the American Joint Committee on Cancer staging manual 2010)*[1]

NON-MUSCLE INVASIVE TCC	MUSCLE INVASIVE TCC	ADVANCED TCC (METASTATIC)
pTa/pTis/T1 N0 M0	T2/T3/T4 Nx/N0/N1 M0	Any T N2/N3 M1

T – Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
pTa	Non-invasive papillary carcinoma
pTis	Carcinoma in situ: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
pT2a	Tumour invades superficial muscle (inner half)
pT2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate (direct stromal invasion), uterus, vagina, pelvic wall, abdominal wall
pT4a	Tumour invades prostate, uterus or vagina
pT4b	Tumour invades pelvic wall or abdominal wall

N – Regional lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Single positive node in primary drainage regions
N2	Multiple positive modes in primary drainage regions
N3	Common iliac node involvement

M – Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

is: *in situ*; M: metastases; N; node; p: pathological; TCC: transitional cell carcinoma

Received from SHSCT 24/11/2023. Annotated by the Urology Services Inquiry.

Approach within the MDT

Key questions for the MDT

- Grade (World Health Organization [WHO])
- Tumour size
- Tumour Node Metastasis (TMN) stage
- New/recurrent
- Single/multiple
- Risk group if NMIBC
- Previous tumours
- Previous response to intravesical therapy
- Bladder symptoms/function
- Bladder diverticula diagnosis
- Bowel symptoms
- Bilateral hip prosthesis
- Hydronephrosis
- Renal function
- Age
- Co-morbidities
- Life expectancy
- Availability of appropriate clinical trials

The MDT plays an essential role in non-muscle invasive, muscle invasive and advanced bladder cancer management. However, it is often difficult to know which patients warrant discussion; thus it is essential to ensure that individual patients' details together with their diagnosis are available, as well as a record of any decisions that may have resulted from meetings. It is crucial that in order to fully discuss a particular patients' treatment plan, a member of the MDT team should have already seen the patient. As the majority of patients are sourced through pathology, relapses are more difficult to identify and as such patient identification continues to be a problem.

To ensure that all professional groups and appropriate disciplines contribute to, and participate in, decisions on the clinical management of patients, MDTs have repeatedly been endorsed as the principal way to do this.

One of the key concepts of integrated care is to support the role of the MDT (working as a single unit) but it should not be forgotten that the MDT has the freedom to clinically tailor management strategies for the specific needs of an individual patient.

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Treatment strategies are influenced by the following:

- The stage of the bladder cancer, as well as the risk of disease progression, survival and patient characteristics, such as age and general fitness, influence the treatment strategy employed by the MDT. All these factors should be discussed to determine the most appropriate treatment modality for an individual patient. For example, age may be a restrictive factor in opting for surgery for some patients with bladder cancer.
- Patient preference should be discussed within the MDT and the MDT should ensure the involvement of the patient in determining the most appropriate treatment strategy.
- Patient case notes, pathology reports, laboratory test results and radiology data should be made available for discussion at the meeting.
- The inclusion of a patient in an appropriate clinical trial should also be considered.

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Approach to the patient

Key points for discussion with the patient

- Likelihood of recurrence
- Likelihood of disease progression
- Treatment options
- Ability to tolerate general anaesthetic
- Fitness for radical radiotherapy
- Fitness for cystectomy
- Fitness for chemotherapy
- Patient preference
- Local disease control
- Major symptoms
- Life expectancy
- Palliative care
- Treatment side-effects
- Impact of treatment on quality of life
- Occupational exposure and advice
- Smoking history and cessation advice
- Diabetes and pioglitazone treatment
- Clinical trials

Patient expectations

The patient has the right to discuss their treatment strategy with appropriately trained members of the MDT

The occurrence of any potential side-effects associated with each treatment modality and the implications for future lifestyle changes should be discussed with the patient by the healthcare professional when determining an appropriate management option.

To ensure the patient and his/her partner, family and/or carers can make an informed decision, based upon the treatment options that are offered, all the points detailed above should be addressed. For example, the choice between radical radiotherapy and radical cystectomy may be influenced by a patient's anticipated effect of treatment on quality of life.

The available treatment modalities and the potential adverse effects they may have on lifestyle and quality of life should be discussed with all patients.

The lack of guidance for how healthcare professionals should effectively exchange clinical evidence supporting various treatment options to patients facing decisions is acknowledged. However, if recommendations are largely based on appropriate clinical studies and expert opinion, it is possible to achieve the five communication tasks when framing and communicating clinical evidence (Table 2).

Received from SHSCT 24/11/2023. Annotated by the Urology Services Inquiry.

Table 2: Exchange of clinical evidence with patients

1. Understand the patient's experience, expectations and preferences
2. Build partnerships between the patient and carer
3. Provide evidence, including uncertainties, and discuss adverse events
4. Provide and present recommendations
5. Check for understanding and agreement

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Assessment and Diagnosis

Primary diagnosis

Symptoms

- Asymptomatic non-visible haematuria is generally the first sign of bladder cancer and is the most common finding in NMIBC.[2,3] It is microscopically present in almost all patients with cystoscopically detectable tumours.[4] However, it is an intermittent finding upon repeat testing.[5]
- Lower urinary tract symptoms (LUTS) such as urgency, increased urinary frequency and bladder pain may be associated with the presence of carcinoma *in situ* (CIS).[2,3]
- A key issue is the workup following presentation of haematuria or LUTS.

Screening

There is currently no evidence to support opportunistic screening for bladder cancer without a clinical reason.[6]

Urine cytology

- The diagnosis of a high-grade tumour or CIS can be made following cytological analysis of voided urine.[3]
- Urine cytology is highly specific (>90%) and has a reasonable sensitivity for detecting high-grade lesions /CIS (>60%).
- However, the sensitivity of urine cytology in detecting bladder cancers (especially low-grade NMIBC) in patients presenting with non-visible haematuria may be suboptimal; a negative test does not rule out malignancy. Urine cytology should therefore not be used as a diagnostic test in isolation.[7–9]

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Urinary molecular biomarker tests

- Routine application of these tests has not been established to date.[3]
- Currently available molecular urinary biomarkers approved by the US Food and Drug Administration are the qualitative point-of-care tests (NMP22 Bladder Chek; bladder tumour antigen stat) and the laboratory-based tests (BTA TRAK; ImmunoCyt ; UroVysion).
    - The sensitivities of NMP22, ImmunoCyt and UroVysion are significantly higher than that of urine cytology.
    - However, the higher sensitivity comes at a price of reduced specificity. All three novel biomarkers and cytology were better at detecting more aggressive higher-risk tumours than less aggressive lower-risk tumours.[10]
- The clinical value of a novel urinary biomarker depends not only on its performance metrics but also the clinical context in which it is to be used.
    - As an adjunct in the primary detection of bladder cancer, such as in the haematuria clinic environment, the concern is that the lower specificity (higher false positive rate) of currently available urinary biomarkers would lead to unnecessary anxiety, further costly and invasive investigations and the potential dilemma of discharging a patient with a positive urinary biomarker test but negative diagnostic investigations.
    - The most promising arena for the use of novel contemporary biomarkers is likely to be as part of surveillance protocols in patients with a previous history of low- or intermediate-risk NMIBC. However, surveillance protocols utilising novel urinary biomarkers have not been validated in large prospective studies. Moreover, the cost-effectiveness and patient acceptability of such approaches needs further study.

White light cystoscopy

- Cystoscopy, guided by white light, has been the gold standard technique for the detection and follow-up of bladder cancer. However, the use of white light can lead to missing lesions that are not visible.[3]

Photodynamic diagnosis-assisted cystoscopy

- Photodynamic (fluorescence) diagnosis-assisted (PDD) cystoscopy with 5-aminolevulinic acid (5-ALA) or hexaminolevulinic acid (HAL) improves the detection of bladder tumours compared with conventional white-light cystoscopy (WLC), especially with respect to CIS and results in more complete resections.
    - HAL is an ester-derivative of 5-ALA with better bioavailability and a shorter instillation time. Only HAL is currently registered for PDD in bladder cancer patients.
- There are conflicting data on the effects of PDD on longer term outcomes.
    - The true added value of PDD in reducing tumour recurrence in routine practice is difficult to assess as studies vary in the use of immediate single- dose intravesical chemotherapy post-transurethral resection (TUR) and choice of photosensitiser (5-ALA or HAL).
    - The effects of PDD on time to progression (TTP) or survival remain to be demonstrated.
- PDD is most useful for detection of CIS and guiding biopsies in patients with positive cytology or a history of high-grade NMIBC.[3]
- PDD may also have a role to play in patients who have positive urine cytology, but negative WLC and negative upper urinary tract imaging.

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Clinical evidence

- A systematic review and meta-analysis assessed the performance of PDD in 27 studies.[11] Most used 5-ALA (n=18) as the only photosensitising agent.
  - The median sensitivity for PDD was 92% (95% confidence interval [CI], 80–100) versus 71% (95% CI, 49–93) for WLC.
  - For higher-risk tumours, the median sensitivity of PDD was 89% (95% CI, 6–100) whereas for WLC it was 56% (95% CI, 0–100).
  - For lower-risk tumours, the median sensitivity of PDD and WLC were broadly similar; 92% (95% CI, 20–95) versus 95% (95% CI, 8–100), respectively.
  - However, the overall median specificity was less for PDD than for WLC; 57% (95% CI, 36–79) versus 72% (95% CI, 47–96).
  - In patient-based detection of bladder cancer across 4 studies using 5-ALA and 3 using HAL, the median (range) sensitivity and specificity for 5-ALA was 96% (64–100) and 52% (33–67) respectively, compared with 90% (53–96) sensitivity and 81% (43–100) specificity for HAL.
  - Four randomised controlled trials (RCTs) using 5-ALA reported clinical effectiveness. PDD at TUR resulted in fewer residual tumours at first check cystoscopy (relative risk [RR], 0.37; 95% CI, 0.20–0.69] and longer recurrence-free survival (RFS) (RR, 1.37; 95% CI, 1.18–1.59] than WLC.
- A meta-analysis of clinical studies has shown that an additional 20% of NMIBC (95% CI, 8–35) was detected using PDD compared with WLC, and an additional 39% of CIS cases (95% CI, 23–57).[12]
  - In addition, this analysis demonstrated improved RFS rates with PDD versus WLC (16–27% higher at 12 months and 12–15% higher at 24 months).
- More recently, 3 RCTs of PDD versus WLC have been published showing conflicting data on the clinical effectiveness of PDD.[13–15]
  - No benefit of PDD with 5-ALA was demonstrated for the detection of bladder tumours, recurrence rates or progression rates.[13]
  - Improved detection rates with 5-ALA assisted PDD did not translate into reduced recurrence rates at 12 months.[14]
  - PDD with HAL resulted in improved RFS at short-term follow-up (9 months) compared with WLC.[15]
    - This was a large trial (766 patients) in 28 centres in the USA, Canada and Europe. In this study, 16% of Ta and T1 tumours were detected solely with HAL-PDD.

Narrow-band imaging cystoscopy

- Narrow-band imaging (NBI) cystoscopy has been developed for use in both flexible and rigid cystoscopies. It increases contrast between normal and hypervascularised structures by filtering white light to 2 narrow bandwidths that are absorbed by haemoglobin.
- Several small non-randomised studies have shown promising results in terms of improved bladder tumour detection compared with WLC. More recently, NBI-assisted TUR was shown to reduce the residual tumour rate compared to a matched cohort.[16]
- However, the role of NBI cystoscopy as an aid to TUR and in surveillance needs further evaluation in RCTs.

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Biopsy

- European Association of Urology (EAU) guidance recommends that on visualisation of the urothelium, abnormal areas should be biopsied, using either 'cold-cup' or resection loop methods.[3]
- In patients with positive urine cytology but no visible tumour or non-papillary tumour, biopsies from the trigone, bladder dome and bladder walls should be performed.[3] In this scenario, PDD improves detection of bladder tumour and could facilitate more targeted biopsies.

Histopathology

- Sufficient muscle tissue from biopsies is required for correct assignment of a T category.[3]
- In order to limit the variability in classifying and grading Ta and T1 tumours, it is recommended that the pathologist review the histological findings together with the urologist, in order to provide a clinical context.[17–19]
- Histopathologists in the UK are currently recommended to continue reporting the 1973 World Health organization (WHO) classification alongside the 2004 WHO classification and that results are compared through prospective audit of patient outcomes.
- Further details can be obtained in the standards and databases for reporting cancers prepared by the Royal College of Pathologists (RCP) and a published comment.[20,21]

Ultrasonography

- Transabdominal ultrasound (US) is a useful tool for investigation of haematuria. It permits detection of renal masses, intraluminal bladder masses and hydronephrosis.[3]

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Computed tomography urography and Intravenous urography

- In many centres, computed tomography (CT) urography is now the investigation of choice compared with intravenous (IV) urography. However, the use of CT requires the exposure of the patient to an increased dose of radiation.
    - Urography is generally used to detect filling defects within the kidneys and ureters, which may indicate the presence of a tumour within the ureter.[22]
    - CT urography can also provide more comprehensive information including local tumour stage, the status of lymph nodes and neighbouring organs.
    - The diagnostic accuracy of CT urography has been estimated at around 90%; therefore, it should only be used in conjunction with cystoscopy and histology for the diagnosis of urinary tract cancers.[23,24]
- Routine urography is not advised in all patients at the time a primary bladder tumour has been detected.[25–29]
- Urography should, however, be considered in selected cases where the incidence of upper tract findings is higher, such as patients with trigonal tumours and those with high-risk or multifocal NMIBC.
    - The incidence of concomitant upper urinary tract TCC is low (1.8%), but in patients with trigonal tumours, the incidence is 7.5%.[30]
- The risk of upper urinary tract TCC recurrence during follow-up is more likely in patients with high-grade and multifocal NMIBC.[31]
    - In such patients, urography is also recommended during surveillance.[26,29,32,33]
    - Follow-up urography should only be considered in patients who are fit for upper tract intervention.
    - In such patients, the frequency of upper tract imaging surveillance has not been validated. There is no evidence to support annual imaging of the upper tract.
- Upper urinary tract CT or IV urography should be used as a surveillance tool in patients with high-risk NMIBC who have received bacillus Calmette Guérin (BCG), but the optimal frequency is unknown.

Functional tests and biochemistry

The following tests may be useful in the detection of advanced bladder cancer:

- Renal function test (glomerular filtration rate [GFR])
- Liver function test
- Full blood count
- Bone biochemistry

Determination of disease spread/staging

- Imaging modalities (CT and magnetic resonance imaging [MRI]) should be used for the staging of suspected muscle invasive bladder tumours, where this will influence treatment decisions.[24,34]

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Local staging of invasive bladder cancer

- Both CT and MRI may be used for local staging of bladder cancer, but neither technique can detect tumours that have microscopically invaded perivesicular fat, i.e. Stage T3a.[35] Therefore they are used to detect T3b and more advanced tumours.
    - MRI is superior to CT in evaluating the T stage of suspected muscle invasive bladder cancer.[36–38]

Nodal involvement

- The sensitivities of both CT and MRI in the detection of lymph node metastases are low.[24,35]

Distant metastases

- CT and MRI can be used to detect distant metastases within the lungs and liver.[34] Routine scanning of bone and brain is not recommended unless specific symptoms indicative of bone or brain metastases are present.[24]
- The use of US is not recommended in patients for whom a diagnosis of bladder cancer has already been established.
    - US may be used for the evaluation of metastases, in patients with contraindications to CT and/or MRI. However, its sensitivity compared with these other modalities is low.[39]

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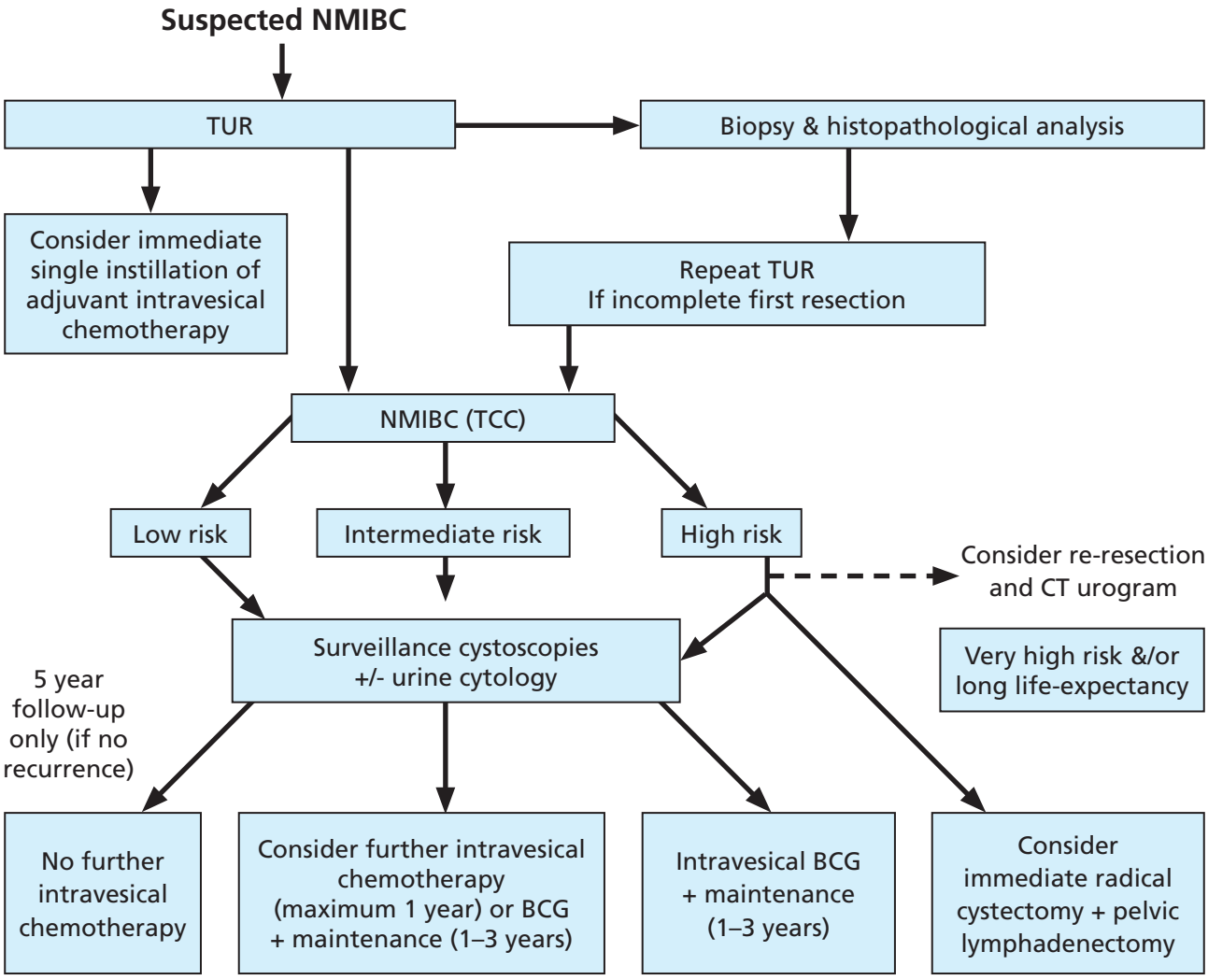
Non-muscle invasive bladder cancer: Management options

Figure 2: Algorithm for the primary management of non-muscle invasive bladder cancer *(adapted from Griffiths et al., 2012)*[40]



BCG: bacillus Calmette Guérin; NMIBC: non-muscle invasive bladder cancer; TCC: transitional cell carcinoma; TUR: transurethral resection

- The European Organization for the Research and Treatment of Cancer Genitourinary (EORTC GU) Group has carried out a large number of randomised trials in NMIBC patients, which has allowed the development of a risk assessment tool for recurrence and progression.[41]
- The annual risk of and cumulative risk of tumour recurrence and progression can be made using the EORTC scoring system, which combines data on previous tumour recurrence rate, number of tumours, tumour diameter, T stage, WHO grade and presence or absence of concomitant CIS.
- The web-based EORTC risk calculator can be downloaded from: http://www.eortc.be/tools/bladdercalculator/default.htm.
- It is recognised that the EORTC risk calculator may overestimate the risk of recurrence and progression in patients with high-risk NMIBC because in historical trials, re-resection was not standard practice, only 171 patients overall were treated with BCG and most of these patients had induction BCG without maintenance.
    - The Spanish Urological Club for Oncological Treatment (CUETO) has proposed a scoring model to stratify the risk of recurrence and progression in patients treated with BCG.[42]

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Transurethral resection – first resection

Overview

- Transurethral resection (TUR) is the gold standard for the initial diagnosis and treatment of newly-diagnosed, apparently NMIBC.
- The adequacy of the initial TUR and the skills and experience of the surgeon may have a substantial impact on the recurrence rate at the first follow-up cystoscopy.
- Small tumours (<1 cm) can be resected en bloc.
- Larger tumours (>1 cm) should be resected so that at least exophytic tumour and deep (tumour base) biopsies are submitted in separate fractions.

Patient selection

- Newly-diagnosed NMIBC

Adverse effects of treatment

- Bleeding
- Infection
- Perforation of the bladder wall
- Clot retention

Clinical evidence

- The basic technique for TUR is illustrated in Wiesner et al., 2010.[43] It can be accessed at: http://onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2010.09387.x/pdf.
- TUR is used to remove the tumour and to obtain a biopsy specimen, which is subject to histopathological analysis to determine the tumour type, stage and grade. The pathological report should contain information on the type of specimen, tumour histology, growth pattern, grade and depth of invasion and the involvement of adjacent urothelium. Further details can be obtained in the standards and databases for reporting cancers prepared by the RCP.[21]
- Brausi et al. highlighted that the quality of the initial TUR performed by the individual surgeon may have a substantial impact on the local recurrence rate at the first follow-up cystoscopy. An overall evaluation of 2410 patients who participated in 7 studies revealed that 316 (13.1%) patients had a recurrence at the first follow-up cystoscopy.
    - When the data were analysed by the number of institutions who enrolled a median of 30 patients with a single tumour, local recurrence rates at the first cystoscopy check-up ranged from 3.5% to 20.6%, which suggested that the quality of the initial TUR was highly variable.[44]
- Removal of adequate detrusor muscle tissue is associated with a reduced risk of disease recurrence after the first TUR.[45]
    - In a study of 356 patients, the absence of detrusor muscle in tumours following first TUR was associated with an RR of recurrence at first follow-up cystoscopy (at 3 months) of 44% compared with 22% for tumours including detrusor muscle (odds ratio [OR], 2.9; 95% CI, 1.6–5.4; p=0.002).[45]
    - The presence of negative muscle tissue indicates a complete resection.[46]

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Transurethral resection – second resection

Overview

- In many patients undergoing initial TUR, a subsequent second TUR performed 2–6 weeks later has demonstrated a high incidence of residual tumour.[46]
- Multiple tumours, poorly-defined tumours and CIS may contribute to an incomplete first resection.[46]
- Repeat TUR improves staging accuracy and can enhance treatment outcomes in NMIBC if all visible residual and suspected tumour is removed.[46]
- A second TUR should be performed when biopsies contain insufficient or no muscle tissue and/or inadequate separate exophytic tumour and tumour base fractions.
- For patients with pTa disease, if adequate biopsy samples have been obtained (i.e. muscle included) and macroscopic tumour clearance confirmed, a second TUR is generally unnecessary.
- For patients with pT1 disease, repeat TUR should also be considered, especially for high-grade tumours.

Adverse effects of treatment

- As per the first TUR.

Clinical evidence

- A prospective study randomised 210 patients with newly-diagnosed T1 bladder cancer to repeat TUR within 2–6 weeks of first TUR, or no repeat TUR. All patients received instillation of mitomycin C (MMC) within 24 hours of the first TUR.[47]
  - Second TUR resulted in a change of treatment strategy in 8 patients undergoing this procedure, due to changes in staging.
  - Presence of CIS or T2 tumour at second TUR was correlated with grade, size and numbers of the initial tumour.
  - Tumour-free status was confirmed histologically in 67% of this group of patients.
  - RFS was significantly higher in patients undergoing second TUR than in those not undergoing this procedure (5-year RFS, 59% versus 32%; p=0.0001).
- In an analysis of 1312 patients undergoing repeat TUR, around 50% of patients with low-grade tumours demonstrated residual disease.[46]
  - 25% of patients with T1 tumours following first TUR had residual disease on repeat TUR.
- Another analysis of 523 patients initially staged as T1, after repeat TUR 106 (20%) were upstaged to muscle invasive disease (T2).[48]
- In a separate study, 110 patients with newly-diagnosed NMIBC underwent repeat TUR.[49]
  - Cystoscopy prior to the second TUR was negative in 79 (78%) patients, but 14 of these were subsequently found to have residual disease.
  - Of the total 40 patients with residual disease at the second TUR, 22 had an identical stage to the first TUR, 9 had a lower stage and 9 had a higher stage of bladder tumour.
  - Of 76 patients with stage T1 cancer after the first TUR, 25 (33%) demonstrated residual disease at second TUR.

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Immediate, single instillation of adjuvant intravesical chemotherapy

Overview

- Based on clinical evidence, a single instillation of adjuvant intravesical chemotherapy after the first TUR should be considered the standard of care for all NMIBC patients.
- There is strong evidence for the use of single-dose intravesical chemotherapy at first TUR, with the greatest benefit observed with low-grade, low-risk tumours.
- A meta-analysis conducted by the EORTC demonstrated that a single instillation of adjuvant intravesical chemotherapy immediately after TUR reduces the RR of local recurrence by 39% in all risk groups.[50]
- The single instillation of chemotherapy is thought to eradicate any tumour left behind after an incomplete first TUR and to destroy any circulating tumour cells that could implant at the resection site to prevent recurrence.
- Evidence suggests that the first instillation of adjuvant intravesical chemotherapy should be administered on the same day as the TUR, and ideally within 6 hours of the procedure.[50]
- The chemotherapeutic agents MMC, epirubicin and doxorubicin are all considered to have similar efficacy.[50]
- An immediate single instillation of adjuvant intravesical chemotherapy should be avoided when it is obvious or even suspected that the bladder wall is perforated.[51]

Patient selection

- First or repeat TUR after diagnosis of any NMIBC, if clinically safe to do so and the bladder is clear of any macroscopic disease.

Adverse effects of treatment

- Irritative bladder symptoms, including dysuria and frequency
- Haematuria
- Allergic skin reactions with MMC[52]
- Irritative bladder symptoms with epirubicin

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Clinical evidence

- A meta-analysis of 7 RCTs (n=1476) compared one immediate post-operative instillation of adjuvant chemotherapy using MMC, epirubicin, doxorubicin or thiotepa, with TUR alone, to determine whether adjuvant chemotherapy decreased the risk of recurrence in patients with single and multiple Ta/T1 tumours.[50]
    - Recurrence data were available for 1476 patients at a median follow-up of 3.4 years.
    - Recurrence occurred in 48.4% of patients who had TUR alone and in 36.7% of patients receiving one post-operative instillation of chemotherapy. This was associated with a decreased risk of recurrence by 39% (OR, 0.61; 95% CI, 0.49–0.75; p<0.0001) versus TUR alone.
    - Patients with a single tumour (recurrence rate, 35.8%; OR, 0.61; 95% CI, 0.46–0.80; p=0.00050) or multiple tumours benefited (recurrence rate, 65.2%; OR 0.44; 95% CI, 0.18–1.02; p=0.06) from one immediate instillation of adjuvant chemotherapy compared with TUR alone.
    - However, in patients with multiple tumours, one instillation may be suboptimal and additional adjuvant treatment is necessary (discussed in more detail below).
    - For every 100 patients treated with a single instillation of adjuvant chemotherapy, 12 repeat TURs were avoided. Thus, 9 patients must be treated with a single instillation of adjuvant chemotherapy to prevent a recurrence. The cost of a TUR, anaesthesia and hospitalisation is probably more than 9 times that of one instillation of adjuvant chemotherapy.
- Kaasinen et al. found that the risk of recurrence doubled if the first instillation of MMC was not administered within 24 hours of TUR.[53]
- Bouffioux et al. demonstrated that when the first instillation of adjuvant chemotherapy was given within 24 hours after TUR with long-term maintenance chemotherapy, patients tended to have fewer recurrences than those who received treatment later than 24 hours.[54]

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Follow-up of patients with low-risk NMIBC (low risk of recurrence and progression)

Overview

- In patients at low risk of recurrence and progression (EORTC recurrence and progression scores = 0), the probability of recurrence and progression at 1 year is 15% and 0.2%, respectively.[41]
- Data on the optimal follow-up regimen for patients with low-risk NMIBC is limited.
- EAU guidelines recommend that all patients with low-risk TaT1 tumours should have a follow-up cystoscopy at 3 months after the first resection. If recurrence-free at 3 months, the next cystoscopy is advised at 9 months, and then yearly for 5 years.[3]

Clinical evidence

- Oge et al. retrospectively evaluated the recurrence and progression rates of 120 patients with pTaG1/G2 and small (<4 cm) TCC.[55]
  - The recurrence rate was 6.5% at 3 months, and 6.7% and 3.6% at 6 and 9 months, respectively.
  - When the first 3-month follow-up cystoscopy was clear, the 6-, 9- and 12-month cystoscopy recurrence rates were 4.3%, 2.7% and 8%, respectively.
  - The progression rate was <1% for the first year.
- In a Scottish study utilising a prospective database, patients with TaG1 were followed for up to 20 years after TUR.[56]
  - The authors concluded that tumour status at 3 months was the strongest predictor of recurrence.
  - Of patients who had not experienced recurrence at 5 years, 98.3% remained tumour-free for 20 years.

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Additional intravesical chemotherapy or BCG for patients with intermediate-risk NMIBC (intermediate or high risk of recurrence and intermediate risk of progression)

Overview

- The main priority in these patients is to reduce the risk of recurrence, although the risk of progression is not negligible.
- According to an analysis of 7 EORTC trials using the EORTC risk tables, the probability of recurrence at 1 and 5 years in patients with intermediate-risk TaT1 bladder cancer is 24–38% and 46–62%, respectively; the risk of progression to muscle invasive disease is estimated at 1–5% at 1 year and 6–17% at 5 years.[41]
- The prophylactic effect of a single instillation of chemotherapy after TUR lasts for 1–2 years.[52,57]
- The results of an EORTC and Medical Research Council (MRC) meta-analysis showed that adjuvant chemotherapy after TUR prevents disease recurrence; however, it has no apparent effect on disease progression.[58]
- The optimal duration and intensity of intravesical chemotherapy schedule is currently undefined.
- However, the available evidence does not support intravesical chemotherapy for more than 1 year.
- For prevention of recurrence, maintenance BCG is required to demonstrate superiority to MMC.[59]
- Current EAU guidelines recommend either a maximum of 1 year of intravesical chemotherapy or a minimum of 1 year of intravesical BCG.[3]
- The superior efficacy of BCG needs to be balanced against its increased toxicity.

Patient selection

- Recurrent pTaG1 TCC 2.
- pTaG1/G2 TCC and either >3 cm tumour diameter or multiple tumours.
- pT1G2 TCC and <3 cm tumour diameter and single tumour.

Adverse effects of treatment

- Irritative bladder symptoms. e.g. dysuria, urgency
- Haematuria
- Infection

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Clinical evidence

- A meta-analysis of 5 studies conducted by the Japanese Urological Cancer Research Group, which included 1732 patients with NMIBC, revealed that the prophylactic effect of a single instillation of intravesical chemotherapy after TUR continued for a period of 500 days.[57]
- Two parallel randomised studies conducted by the EORTC highlighted that 1-year of monthly (15 instillations) maintenance chemotherapy was no more effective than 6 months (9 instillations) of treatment in reducing the recurrence rate when the first instillation was given immediately after TUR.[54]
- More recently, a Japanese randomised study of 150 patients with TaT1 bladder cancer demonstrated that long-term epirubicin therapy was more effective than short-term treatment after TUR in preventing recurrence.[60]
    - At 3 years, the recurrence rate was 14.8% in the group who received 1 year of epirubicin (19 instillations) compared with 36.1% in those who received 3 months of epirubicin (9 instillations) after TUR.
- The MRC has shown that five doses of adjuvant MMC is not superior to a single dose and that the treatment effect of a single dose lasts for at least 7 years.[61]
- In a prospective randomised study, Serretta et al. demonstrated that 10 monthly instillations of chemotherapy following a 6-week induction cycle of treatment (a total of 16 instillations) was not superior to the 6-week chemotherapy cycle (6 instillations) alone in terms of the recurrence-free rate, in 482 patients with Ta/T1 tumours (single, multiple or recurrent).[62]
    - At a median follow-up of 48 months (range, 3–78), recurrence rates were 29.6% for 6 instillations of chemotherapy versus 29.2% for 16 instillations of chemotherapy (p=0.43).
- In an earlier study, 495 patients with intermediate- to high-risk primary or recurrent bladder cancer (pTaG1/2, pT1G1–3) were randomised to 6 weekly instillations of MMC, 6 weekly instillations of BCG, or 6 weekly instillations followed for monthly instillations of MMC for 3 years.[63]
    - At a median follow-up of 2.9 years (range: 0–6.6), recurrence rates were 10.4% in the long-term MMC arm, 25.1% for BCG and 25.7% for 6 weekly instillations of MMC.
    - Three-year recurrence rates were 65.5%, 68.6% and 86.1% for BCG (p=0.0005 versus long-term MMC), 6 weekly instillations of MMC (p=0.0006 versus long-term MMC) and long-term MMC, respectively.
- In an individual patient data meta-analysis comparing BCG with MMC (n=2820), maintenance BCG resulted in a significant (32%) reduction in the risk of recurrence compared with MMC. In contrast, in studies where maintenance BCG was not given, there was a significant (28%) increase in risk of recurrence.[59]
- In a large RCT, BCG with maintenance significantly reduced the risk of progression/distant metastases (hazard ratio [HR], 0.63), overall survival (OS) (HR, 0.76) and disease-specific survival (DSS) (HR, 0.47) compared with intravesical epirubicin.[64]
    - The observed treatment benefit was at least as large, if not larger, in the intermediate-risk patients as compared with the high-risk patients. In this trial, high-risk patients did not undergo re-resection.

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Follow-up of patients with intermediate-risk NMIBC

Overview

- Data on the optimal follow-up regimen for patients with intermediate-risk NMIBC is limited.
- EAU guidelines recommend that patients with TaT1 tumours at intermediate-risk of progression should have a follow-up schedule using cystoscopy and urinary cytology, which is dependent on the individual patient.[3]

Adjuvant BCG for high-risk NMIBC (high risk of recurrence or progression)

Overview

- The risk for tumour recurrence and progression to muscle invasive disease is high within this group of patients with NMIBC. According to an analysis of 7 EORTC trials using the EORTC risk tables, the probability of recurrence at 1 and 5 years in patients with high-risk TaT1 bladder cancer is 61% and 78%, respectively; the risk of progression to muscle invasive disease is estimated at 5–17% at 1 year and 17–45% at 5 years.[41]
- Patients who have multiple tumours at presentation and recurrence at 3 months have a 1-year risk of further recurrence of 90%.[65]
- Clinical evidence from a meta-analysis shows that when BCG is compared with a variety of strategies, the risk of progression from TaT1/CIS to muscle invasive disease is reduced provided maintenance instillations are given.[66] Similar findings were demonstrated for the subgroups of patients with CIS or papillary tumours.
- In studies and meta-analyses comparing BCG with intravesical chemotherapy in a combination of high-risk and intermediate-risk patients, contradictory results have been obtained with respect to the relative benefit of BCG on progression.[59,64,67]
- The optimum BCG maintenance regimen is not yet known. A commonly used schedule is that described by Lamm et al., who recommended 27 instillations over a 3-year period, i.e. administration once every 6 weeks.[68]
- Current EAU Guidelines for high-risk TaT1 TCC and also for CIS recommend at least 1 year of intravesical BCG.[3]
- The results of the Phase III trial EORTC 30962, which included intermediate-risk and selected high-risk (solitary tumour without CIS) patients, failed to demonstrate that 1 year of intravesical BCG was inferior to 3 years of intravesical BCG, or that 3 years of BCG was superior to 1 year of BCG.[69]
    - The best DFS was demonstrated in those patients who had received 3 years of BCG but this was not statistically significant.
    - A pragmatic approach should be therefore considered in these patients after 1 year of BCG, based on risk of progression and side-effects.

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Patient selection

- pT1G2 and either >3 cm tumour diameter or multiple tumours.
- pTa/T1G3.
- CIS.
- Immunocompetent (avoid patients with leukaemia/lymphoma, Human Immunodeficiency Virus infection, organ transplant, and active and previous GU tuberculosis [TB]).
- Caution if previous pelvic radiotherapy >40 Gy.

Adverse effects of treatment

- Haematuria has been reported in 31–35% of patients.[70,71]
- BCG-induced cystitis has been reported in 3–54% of patients.[67,70–72]
- Systemic side-effects such as fever, general malaise and skin rash have been reported in 15–39% of patients.[70,73]
- BCG therapy may provoke both local and systemic side-effects and these can be serious in approximately 5% of treated patients. Only the systemic side-effects can be serious and life-threatening and require early systemic therapy.
    - It is therefore important to prevent complications and BCG instillation should be avoided after traumatic catheterisation, when frank haematuria persists after bladder biopsy, during the first 14 days after TUR and when irritative voiding symptoms or systemic upset persist after previous instillations of BCG.
- It is expected that with repeated instillation, patients will develop short-lived bladder irritative symptoms lasting 48–72 hours, associated with mild fever, arthralgia and even frank haematuria. Persistence of these symptoms is a warning to defer the next instillation until they have settled. Reduction to one-third of the dose could also be considered.
- Granulomatous prostatitis occurs in the majority of treated men, but it is usually asymptomatic and requires no treatment. In the small percentage of patients where this is symptomatic, high-dose fluoroquinolone antibiotics are recommended, along with suspension of intravesical therapy.[74]
- Epididymitis can be due to either BCG infection or more usual uropathogens. Therefore initial treatment with a quinolone antibiotic is appropriate. Isoniazid 300 mg daily for 6 weeks should be considered.
- Generalised polyarthritis, often associated with conjunctivitis, does occur and there is an association with the HLA-B27 genotype. As it is generally an allergic reaction, treatment with systemic steroids and/or isoniazid may be required and no further BCG therapy should be given. Referral to an appropriate physician should be considered.
- Miliary BCG infection affecting lungs, liver, kidneys and brain may rarely occur as may BCG septicaemia. If clinically suspected then there should not be a delay before the administration of triple anti-TB chemotherapy and high-dose systemic steroids. Blood testing for TB can help with more rapid diagnosis. The recommended treatment regimen is isoniazid 300 mg daily for 3 months, rifampicin 600 mg daily and ethambutol 1200 mg daily for 6 weeks and prednisolone 40 mg daily or greater IV during the acute stages.[67,75]

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Clinical evidence

- A meta-analysis of 24 clinical trials with data relating to progression on 4863 patients was conducted by the EORTC. TUR + BCG was compared with either TUR alone or TUR + non-BCG treatment (control).[66]
  - At a median follow-up of 2.5 years (maximum of 15 years), 9.8% of patients receiving TUR + BCG progressed compared with 13.8% of control patients.
  - Overall, treatment with BCG was associated with a 27% reduction in tumour progression (OR, 0.73; 95% CI, 0.60–0.89; p=0.001).
  - Similar treatment effects were reported in the 2880 patients with only papillary tumours (OR, 0.68; 95% CI, 0.50–0.93; p=0.001) and in the 403 patients with CIS (OR, 0.65; 95% CI, 0.36–1.16; p=0.001).
  - Patients receiving maintenance BCG demonstrated a 37% reduction in tumour progression (OR, 0.63; 95% CI, 0.51–0.78; p=0.00004).
  - No reduction in tumour progression was reported in the 4 trials where maintenance BCG was not administered.
- The Phase III EORTC 30962 trial randomised 1355 patients to 1 year of full-dose BCG (1YFD), 3 years of full-dose BCG (3YFD), 1 year of one-third dose BCG (1Y3D) or 3 years of third-dose BCG (3Y3D).[69]
  - At a median follow-up of 7.1 years, 5-year DFS was 58.8% (1YFD), 54.5% (1Y3D), 64.2% (3YFD), and 62.6% (3Y3D).
  - The inferiority of the disease-free interval for 1Y3D versus 1YFD was not demonstrated.
  - FD BCG was not superior to one-third BCG (p=0.092).
  - 3 years of BCG was not superior to 1 year of BCG (p=0.059).
  - There were no differences between treatment groups for TTP or duration of survival.
- The South West Oncology Group 8507 study randomised 550 patients with recurrent Ta/T1 disease or CIS to induction + maintenance BCG therapy for 3 years (total 27 doses) or no maintenance (i.e. induction BCG therapy only).[68]
  - Median RFS was 76.8 months (95% CI, 64.3–93.2) with maintenance BCG versus 35.7 months (95% CI, 25.1–56.8) with no maintenance BCG (p<0.0001).
  - 5-year OS was 83% in the maintenance group compared with 78% in the no maintenance group.
- A meta-analysis of data from 9 trials involving 700 patients with CIS has demonstrated that BCG is associated with a superior response rate and reduction in disease recurrence when compared with chemotherapy (MMC, epirubicin, adriamycin).[76]
  - Complete response (CR) was achieved by 68.1% of patients receiving BCG versus 51.5% of patients receiving chemotherapy (OR, 0.53; p=0.0002).
  - Based on a median follow-up of 3.6 years, 161 of 345 patients receiving BCG (46.7%) had no evidence of disease compared with 93 of 355 patients on chemotherapy (26.2%), a reduction of 59% in the odds of treatment failure on BCG (OR, 0.41; p <0.0001).

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BCG versus mitomycin C

- In an individual patient data meta-analysis of data from 9 clinical trials involving 2820 intermediate- and high-risk patients with Ta, T1 or CIS, TUR + BCG was compared with TUR + MMC. Median follow-up was 4.4 years (maximum 17.7 years).[59]
    - In the studies with BCG maintenance therapy (n=1324), a 32% reduction in the risk of recurrence was determined versus MMC (43.2% versus 57.9%; p<0.0001).
    - Notably, without maintenance BCG (n=1496), the risk of recurrence was increased versus MMC, by 28% (42.6% versus 31.8%; p=0.006).
    - There were no significant differences in progression, OS or DSS, irrespective if patients receiving BCG with maintenance were subanalysed.
- In a meta-analysis of data from 9 trials performed by Bohle & Bock (n=2410), median follow-up was 26 months (range, 11.5–50.4).[67]
    - When considering all treatment regimens, there was no significant difference between BCG and MMC in tumour progression (7.7% versus 9.4%; OR, 0.77; 95% CI, 0.57–1.03; p=0.081).
    - In the subgroup of patients receiving maintenance BCG therapy for at least 1 year, the risk of progression was significantly reduced compared with MMC (OR, 0.66; 95% CI, 0.47–0.94; p=0.02).
    - In patients not receiving maintenance BCG therapy, there were no differences between treatments in terms of disease progression (OR, 1.16; 95% CI, 0.65–2.07; p=0.61).
- In a meta-analysis involving 700 patients with CIS and where the overall median follow-up was 3.4 years, a reduction of 43% in the odds of treatment failure on BCG was shown provided BCG maintenance was given (OR, 0.57; p=0.04).[76]

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BCG versus epirubicin

- In a large prospective RCT (837 eligible patients), intravesical epirubicin was compared with BCG alone and BCG + isoniazid in patients with intermediate- and high-risk Ta/T1 bladder cancer, following TUR. Patients received instillations of drug therapy immediately following TUR and 6 weekly doses, followed by 3 weekly instillations at months 3, 6, 12, 18, 24, 30 and 36 (27 in total). Median follow-up was 9.2 years.[64]
  - There were no differences between the two BCG groups for any outcome, so these data were combined.
  - BCG with maintenance significantly reduced the risk of progression/distant metastases (HR, 0.63), OS (HR, 0.76) and DSS (HR, 0.47) compared with intravesical epirubicin.[77]
  - In all patients the risk of recurrence was significantly reduced with BCG versus epirubicin (HR, 0.62; 95% CI, 0.50–0.76; p<0.001); similar results were achieved in intermediate-risk patients (n=497; HR, 0.59; 95% CI, 0.45–0.76; p<0.001). However, this was not true for the subgroup of high-risk patients (n=323; HR, 0.69; 95% CI, 0.48–1.05; p=0.09).
  - In all, intermediate- and high-risk patients, there were no significant differences between BCG and epirubicin for disease progression.
  - Disease-specific mortality was significantly reduced in intermediate-risk patients with BCG versus epirubicin (HR, 0.35; 95% CI, 0.14–0.86; p=0.02) but not in high-risk patients (HR, 0.60; 95% CI, 0.23–1.56; p=0.39).
- In a meta-analysis by the Cochrane Group, BCG was compared with epirubicin, using data from 5 clinical trials involving 1111 patients with TaT1 bladder cancer.[71] The meta-analysis did not include the large RCT described above.[64]
  - The incidence of recurrence was 35.5% with BCG versus 51.4% with epirubicin (RR, 0.69; 95% CI, 0.60–0.79; p<0.05)
  - There was no significant difference between treatments for the risk of disease progression. Progression to T2 or greater stage occurred in 8.02% of patients receiving BCG and 10.32% of patients receiving epirubicin (RR, 0.78; 95% CI, 0.54–1.13; p=0.19).
  - Results from only two trials were analysed for mortality data. There was no significant difference between BCG and epirubicin for overall mortality (RR, 0.86; 95% CI, 0.71–1.04), or for disease-specific mortality (RR, 0.94; 95% CI, 0.23–3.80).

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Follow-up of patients with high-risk NMIBC

Overview

- All patients with NMIBC at high-risk of progression and those with CIS should have cystoscopy at 3–4 months after TUR. If this is negative, it should be repeated every 3–4 months for 2 years, then every 6 months for 5 years. After this period, annual cystoscopy is recommended and annual urinary cytology should be considered.

Primary radical cystectomy for patients with high-risk NMIBC

Overview

- Immediate radical cystectomy may be offered to patients at highest risk of tumour progression according to the EORTC calculator.[3]
- Residual T1 disease on restaging TUR is associated with early progression following induction BCG.[78]
- Retrospective series suggest immediate radical cystectomy provides a survival benefit over delayed surgery in BCG failures. However, the benefit is heterogeneous, and so is likely to include selection bias.[79]
- Higher percentages of micropapillary variant within TCC correlate with increasing adverse outcomes, including relative inefficacy of BCG.[80,81]

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Patients failing to respond to adjuvant BCG therapy

Overview

- A change in approach should be undertaken for high-risk NMIBC patients who fail to respond to BCG within 6 months of initiating therapy.[82]
- Patients with refractory high-grade TCC, T1 TCC or CIS despite 2 induction courses of BCG (12 instillations) or 1 induction course followed by maintenance should be considered to have failed BCG treatment.
- Standard treatment should be radical cystectomy and delaying beyond this may lead to progression and advanced disease (discussed in more detail in the management options for muscle invasive bladder cancer).
- Radiotherapy has no place in the management of NMIBC that has failed to respond to BCG therapy.
- Some patients will be either unfit or unwilling to undergo cystectomy and could be offered other adjuvant therapies. The use of these is not well-established and therefore the risks need to be conveyed to the patient. These include:
- Device-assisted intravesical chemotherapy
    - microwave hyperthermia MMC (HT-MMC)
    - electromotive delivery of MMC (EMDA-MMC)
    - BCG combined with interferon-alpha (IFN-α)
    - Passive intravesical chemotherapy

Clinical evidence

HT-MMC

- Several single-arm proof-of-concept studies evaluating HT-MMC have included patients with disease recurrence after BCG induction therapy.
    - In the largest series to date, Nativ et al. used maintenance HT-MMC in 111 patients with NMIBC in whom BCG therapy had failed, including 77% with high-risk disease.[83]
    - This group reported recurrence-free rates of 85% and 56% at 12 and 24 months, respectively; 3% of the patients progressed to muscle invasive disease and 5% withdrew from treatment due to adverse events.

BCG + IFN-α

- In a study involving 40 patients who had failed previous therapy with BCG, treatment with 1/3 dose (27 mg) BCG + 50 MU IFN-α2B was initiated.[84]
    - At 12 months, 63% of patients were disease-free; at 24 months this was 53%.
- In a post-hoc analysis of data from 467 BCG-refractory patients entered in a Phase II clinical trial, the combination of low-dose BCG and 50 MU IFN-α demonstrated a disease-free survival (DFS) rate of 34% at 24 months.[85]

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Passive intravesical chemotherapy

- A prospective randomised trial has compared intravesical gemcitabine and BCG in 80 patients with high-risk NMIBC who had previously failed 1 course of BCG therapy.[86] Treatment began 4–6 weeks after TUR, with either twice-weekly gemcitabine 2000 mg for 6 weeks, followed by weekly instillations for 3 weeks at months 3, 6 and 12 months; or BCG over a 6-week induction course and then weekly instillations for 3 weeks at months 3, 6 and 12 months.
    - At a median follow-up of around 15 months, 52.5% of patients receiving gemcitabine and 87.5% of patients receiving BCG experienced disease recurrence (p=0.002).
    - Disease progression was reported for 33% in the gemcitabine group and 37.5% of patients in the BCG group (p=0.12).
    - RFS at 24 months was significantly higher in the gemcitabine group than in the BCG group (19% versus 3%; HR, 0.15; 95% CI, 0.1–0.3; p<0.008).
- In a RCT comparing BCG with MMC, crossover treatment with MMC for BCG-refractory bladder cancer resulted in a 19% DFS at 24 months.[87]

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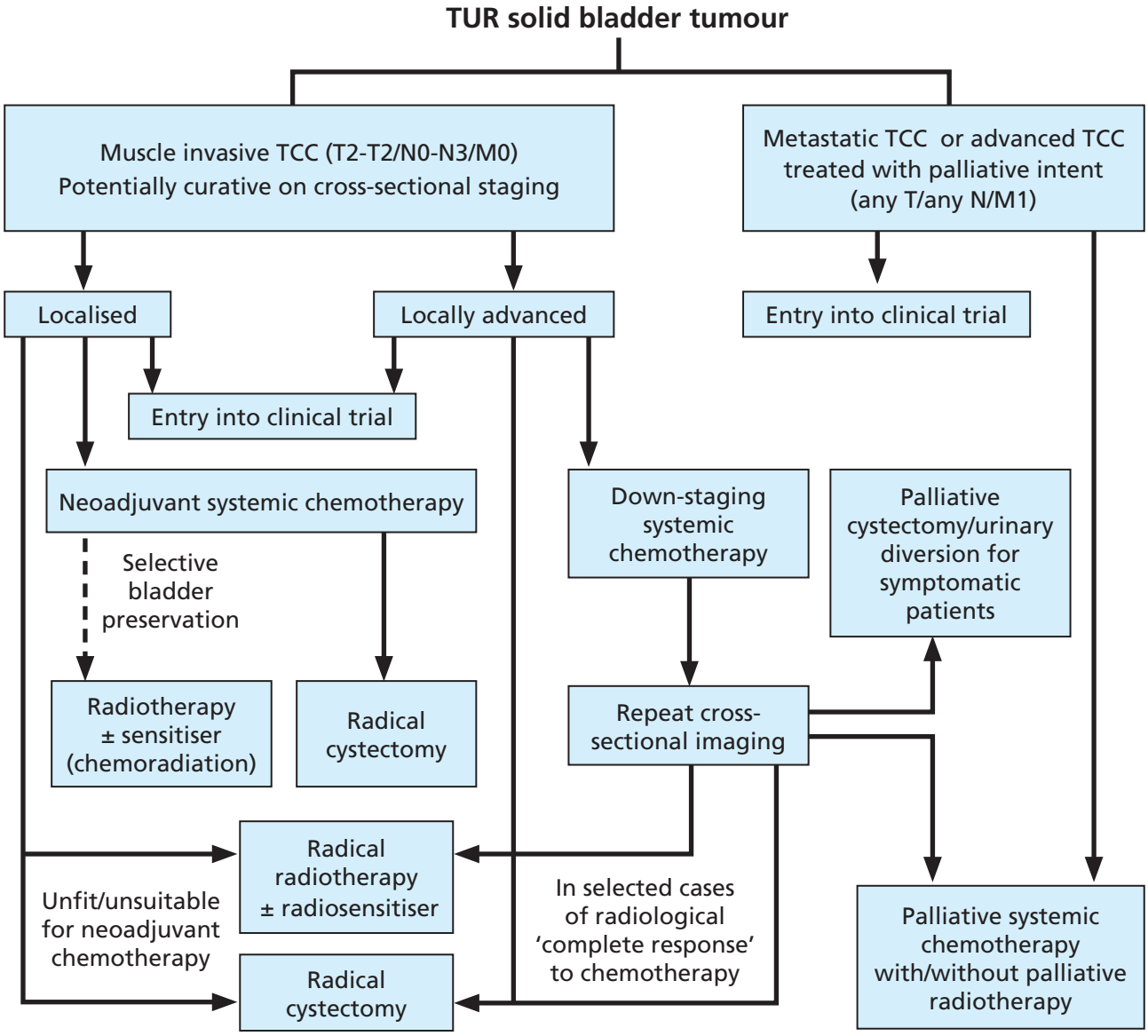
Muscle invasive bladder cancer: Management options

Figure 3: Treatment algorithm for muscle invasive or advanced/metastatic bladder cancer *(adapted from Griffiths et al., 2012)*[40]



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Radical treatments

Overview

- Chemotherapy may be used in a number of settings as part of a radical treatment plan for MIBC.
  - Neoadjuvant: the use of 3 cycles of cisplatin-based combination chemotherapy given **prior** to definitive local treatment with either radical cystectomy or radical radiotherapy to improve OS.
  - Down-staging: the use of 3–6 cycles of chemotherapy given to patients with locally advanced or node-positive, non-metastatic disease in an attempt to render the disease amenable to radical radiotherapy or cystectomy.
  - Synchronous chemoradiation: chemotherapy given **concurrently** with radical radiotherapy.
- There are no RCT data that support the superiority of radical cystectomy over radical radiotherapy, with respect to survival.
- When considering surgery, the morbidity associated with the procedure must be weighed against treatments that aim to preserve bladder and sexual function.
- There are concerns with using radical radiotherapy in muscle invasive bladder cancer: the disease may become inoperable, so that future surgery may be compromised, be more hazardous and at higher risk of complications and development of metastatic disease.
- It is therefore attractive to be able to identify at an early stage those patients in whom radiotherapy is likely to be successful, while offering immediate surgery to those patients in whom success is less likely.
- Patient preference and the presence or absence of co-morbidities should be considered when determining the appropriate treatment.
- In the BC2001 trial, synchronous chemoradiation was associated with a significantly prolonged RFS (but not OS) compared with radiotherapy alone.[88]

Patient selection

- A number of factors can result in the selection of either cystectomy or radical radiotherapy as the preferred treatment modality (Table 3). Where there are no clear medical indications for either treatment then patient choice becomes the dominant selection criteria.

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Table 3. Factors favouring surgery or radiotherapy

Favours surgery	Favours radiotherapy
• Poor bladder function, especially small capacity • Widespread CIS or CIS remote from muscle invasive tumour • Large volume tumours • Multifocal disease • Pre-existing hydronephrosis (unless treated with stenting or nephrostomy) • Previous pelvic radiotherapy • Active inflammatory bowel disease • Severe lower urinary tract symptoms	• Unifocal disease • Maximum TUR • Good bladder capacity • Minimal or moderate lower urinary tract symptoms • No CIS distant to primary tumour • Unfit for surgery due to comorbidities • Patient preference

Clinical evidence for radical cystectomy versus radical radiotherapy

- A Cochrane review has compared radical surgery and radical radiotherapy for muscle invasive bladder cancer, using data from 3 trials (n=439).[89] **However, it must be noted that these data should be viewed with caution as they are somewhat out of date.**
  - Mean OS at 3 years was 45% for radical cystectomy and 28% for radical radiotherapy (OR, 1.91; 95% CI, 1.30–2.82).
  - Mean OS at 5 years was 36% for radical cystectomy and 20% for radical radiotherapy (OR, 1.85; 95% CI, 1.22–2.82).
  - There were 143 recurrences within the thoracic region, with a median of 1.3 years (range: 0.1–16.9). The same significant predictive factors as were identified for abdominal/pelvic recurrences were identified for thoracic recurrence.
  - However, only three historical trials were available for analysis, the patient numbers were small and many patients did not receive the treatment to which they were randomised.
  - The difference in OS may be attributable to several confounding variables, including selection bias. For example, patients treated with cystectomy were likely to have been younger and fitter than those having radiotherapy. Secondly, post-surgical tumours were more likely to have been staged pathologically rather than clinically, which frequently results in an increase in assigned stage for some patients.
  - Therefore, the data for cystectomy in these studies may not be applicable to the general population and comparisons with radical radiotherapy need to be interpreted with caution.
  - In addition, over 25 years has elapsed since the last patient was treated in these studies and significant improvements in radiotherapeutic and surgical techniques have taken place; these data may therefore be irrelevant to contemporary practice.
  - Hence an RCT comparing modern bladder-sparing therapy with state-of-the-art surgical techniques is required.
  - Recruitment of patients to studies was difficult due to clinician bias towards radical cystectomy

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- In a series of 398 patients managed in Yorkshire (T2–T4, 96%), outcomes following radical cystectomy and radical radiotherapy were compared.[90]
  - 5-year OS was 36.5% (95% CI, 27.4–45.6) for radical cystectomy and 37.4% (95% CI, 32.3–42.6) for radical radiotherapy.
  - Following radical radiotherapy, 43.6% of patients experienced disease recurrence within the bladder and 18.8% underwent salvage cystectomy.
- In a UK series involving 169 patients treated between 1996–2000, there were no differences between radical radiotherapy and radical cystectomy for muscle invasive TCC in terms of OS, DSS and RFS at 5 years. This was despite the radiotherapy group being older (median age 75.3 years versus 68.2 years).[91]
  - In a more recent cohort (2002–2006), the median age of radiotherapy patients but not the cystectomy patients was higher than in the 1996–2000 cohort (78.4 years versus 75.3 years for radiotherapy and 67.9 years versus. 68.2 years for surgery).
  - The authors therefore concluded that although the patients undergoing radical cystectomy were significantly younger than the radiotherapy patients, treatment modality did not influence survival and radical radiotherapy is a viable treatment option.
- In a Swedish study, the adverse effects of radical radiotherapy and radical cystectomy in patients with muscle invasive bladder cancer were compared with each other and with healthy controls.[92]
  - The RR of urinary tract infections was significantly higher in the radiotherapy patients than in controls (22% versus 10%; RR, 2.0; 95% CI, 1.0–3.9).
  - The RR for night-time micturition with radiotherapy versus controls was 1.6 (95% CI, 1.2–2.0).
  - There were no differences between patients receiving radiotherapy and controls with respect to micturition urgency.
  - A total of 26% of patients receiving radiotherapy reported distress if their urinary symptoms persisted, compared with 13% of control subjects (RR, 1.9 (95% CI, 1.0–3.4).
  - There were no significant differences between radiotherapy and cystectomy in the frequencies of abdominal pain at least every month (22% versus 12%), diarrhoea at least once a month (35% versus 28%), faecal leakage at least once a month (17% versus 10%), and distress if gastrointestinal symptom-related problems persisted (32% versus 24%).
  - There were no significant differences between radiotherapy and cystectomy in the frequencies of sexual desire less than every month (68% versus 64%), erection difficulties (75% versus 92%), dissatisfaction with sex life (36% versus 67%), impairment to sex life due to urinary symptoms (19% versus 25%), and distress if urinary symptom-related sexual limitations persisted (32% versus 27%).

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Radical cystectomy

Overview

- Radical cystectomy with bilateral pelvic iliac lymph node dissection is the standard treatment for muscle invasive bladder cancers.
- Incidental prostate cancer is a common finding following radical cystoprostatectomy.
- The presence of positive soft tissue surgical margins following radical cystectomy is a strong predictor of disease recurrence and survival.
- The pT stage of bladder tumours is a predictive factor for the presence of lymph node involvement at radical cystectomy.[93–95]
- There is currently no consensus regarding the extent of lymphadenectomy required for successful outcomes. However, the available data suggest that removal of at least 11 lymph nodes may be associated with more favourable outcomes.
- It should be ensured that the lymph nodes associated with the obturator fossa and the external and internal iliac vessels should be removed, up to the common iliac bifurcation.
- There is little evidence to support a more extensive field for lymphadenectomy in most patients, with the exception of confirmed node-positive disease.
- Patients should be informed of the urinary diversion techniques performed after radical cystectomy, which include an ileal conduit, a bladder reconstruction or a continent diversion.

Patient selection

- T2–T4a/N0-Nx/M0 tumours.
- Extensive papillary disease that cannot be controlled by TUR and intravescial therapy alone.
- Fitness for anaesthesia.
- Performance status (PS).
- Male patients should have an assessment of their prostate-specific antigen (PSA) concentration prior to surgery.

Adverse effects of treatment

- High risk of infection (~40%) and bleeding (~60%).[96,97]
- Early complications reported in 12–30% of patients.[90,93,97]
- Common complications include gastrointestinal, cardiovascular and pulmonary disorders and venous thromboembolism.[90,96]
- 30-day mortality of 2–4%.[90,93,96,97]
- 90-day mortality rates increase with patient age: ≤69 years, 2%; 70–79 years, 5.4%; 80 years, 9.2%.[98]

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Clinical evidence

- In an analysis of data from 1388 patients undergoing radical cystectomy (T1–T3, 81%), a total of 493 patients (35.5%) had experienced at least 1 disease recurrence at a median follow-up of 14.3 years (range, 0.03–29.1).[99]
    - There were 67 disease recurrences within the upper urinary tract, at a median 3.1 years (range, 0.2–14.5) after surgery. A multivariate analysis of the data determined that pT4 tumours, positive ureteral margins, and multifocal tumours were significantly associated with upper urinary tract recurrences.
    - There were 388 disease recurrences within the abdomen/pelvis, at a median of 1.1 years (range, 0.1–17.3 years). A multivariate analysis of the data determined that pT3–T4 tumours, pNx, pN0 (+1–10 lymph nodes), pN1 + pN2, multifocal tumours and prostatic involvement were significantly associated with these recurrences.
- Stein et al. reported the long-term effects of radical cystectomy with pelvic lymph node dissection in 1054 patients with invasive bladder cancer.[93]
    - Overall, there were 27 (2.5%) perioperative deaths and 292 (28%) early complications.
    - RFS and OS at 5 years was 68% and 60%, respectively; and 66% and 43%, respectively, at 10 years.
    - Furthermore, in patients with muscle invasive (P2 and P3a), lymph node-negative tumours, 89% and 87%, and 78% and 76% had 5- and 10-year RFS rates, respectively.
- In a series of 432 patients undergoing radical cystectomy (pT2–T4, 64%; Grade 3, 95%), 27 (6%) developed a local recurrence and 78 (18%) developed a distant recurrence, with a mean time to recurrence of 13.6 months.[100]
    - 5-year DFS rates were: ≤pT1, 92%; pT2, 79%; pT3, 56%; pT4, 24%.
    - The mean number of lymph nodes removed was 10, and the mean number of positive lymph nodes was 3.8.
    - 5-year OS and DSS rates in node-positive patients were 22% and 40%, respectively. A positive lymph node percentage >30% was significantly associated with a worse prognosis (p=0.007).
- In a retrospective analysis of data from 4410 patients undergoing radical cystectomy with bilateral pelvic lymphadenectomy, positive soft tissue margins were identified in 278 cases (6.3%).[101]
    - 5-year RFS rates were 21.6% and 62.8% for patients with and without positive margins, respectively (p<0.001).
    - 5-year DSS rates were 26.4% and 69% for patients with and without positive margins, respectively (p<0.001).

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Cystoprostatectomy

- On analysis of tissue from a series of 235 men undergoing radical cystoprostatectomy at a single centre over a 3-year period, 158 had evidence of prostate cancer (67%).[102]
    - A multivariate analysis demonstrated that the presence of CIS in the bladder, or tumours within the trigone and bladder neck were significantly associated with the presence of prostate cancer.
- In a separate series including 204 men undergoing radical cystoprostatectomy, 58 (28%) were found to have prostate cancer that was not predicted by preoperative PSA or digital rectal examination (DRE).[103]
    - In 18 cases the prostate cancer was considered to be clinically significant.
- In a series of 95 men undergoing radical cystoprostatectomy for invasive bladder cancer, 26 (27.4%) had incidental prostate cancer; 19 of these were unsuspected, based on preoperative PSA measurements and DRE.[104]
    - Seven of these patients were considered to have clinically significant prostate cancer.

Lymph node dissection

- A German retrospective analysis of data has assessed 477 patients with node-positive tumours (pN1–N2, M0) who had undergone radical cystectomy.[105]
    - T3 or higher stage tumours were found in 73% of patients and pN2 in 61% of patients.
    - The median number of lymph nodes removed was 12 (range, 1–66), and the median number of positive lymph nodes was 2 (range, 1–25).
    - With a median follow-up of 28 months (range, 2–240), for the overall study population, the 1-, 3- and 5-year DFS rates were 73%, 49% and 39%, respectively.
    - Patients with a positive lymph node percentage of ≤20% demonstrated a 5-year DFS of 46%, compared with 31% for patients with a positive lymph node percentage of >20% ($p<0.001$).
    - In a multivariate analysis, the number of lymph nodes removed was a significant predictor for reduced DFS, as was a positive lymph node percentage >20%.
- In a series of 171 consecutive patients undergoing radical cystectomy, pathological lymph node disease was found in 25 patients (17.2%) and the mean number of lymph nodes removed from all patients was approximately 14.[106]
    - 3-year DFS rates were 71% for node-negative disease and 40% for node-positive disease ($p<0.0001$).
    - The number of lymph nodes removed did not significantly impact on DFS in patients with node-negative disease. However, in patients with node-positive disease, the removal of ≥13 lymph nodes was associated with a longer DFS compared with the removal of <13 lymph nodes ($p=0.002$). However, it should be noted that the sample size in this group was small.
- In another series of 637 patients with T2–T4/N0/M0 bladder cancer, Herr evaluated the effect on survival of removing pre-defined quartiles of lymph nodes.[94]
    - In patients with node-negative disease, survival was significantly improved if ≥11 lymph nodes were removed versus ≤10 ($p=0.0001$).
    - In patients with node-positive disease, survival was significantly improved if ≥13 lymph nodes were removed versus ≤12 ($p=0.001$).

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- In a previous study involving 302 patients undergoing radical cystectomy, at 5 years after surgery, 65% of patients who had ≥16 lymph nodes removed were alive and disease-free compared with 51% of patients who had ≤15 lymph nodes removed.[107]
    - For patients with stage pT1G3, pT2a and pT2b node-negative disease, 5-year DFS was 85% when ≥16 lymph nodes were removed versus 65% when ≤15 lymph nodes were removed (p<0.01).
    - In patients with pT3 or pT4 tumours, there was no effect on the number of lymph nodes removed on DFS.
- A prospective study in 400 consecutive patients with invasive bladder cancer randomised patients to either radical cystectomy with standard lymphadenectomy (up to the bifurcation of the common iliac vessels) or with extended lymphadenectomy (at the level of origin of the inferior mesenteric artery).[108]
    - A mean of 16 lymph nodes were removed with standard lymphadenectomy and 49 with extended lymphadenectomy.
    - 5-year DFS rates were 66.6% in the extended lymphadenectomy group versus 54.7% in the standard lymphadenectomy group (p=0.043).
    - In patients with node-positive disease (n=96), 5-year DFS rates were 48.0% in the extended lymphadenectomy group versus 28.2% in the standard lymphadenectomy group (p=0.029).
    - There were no differences between type of lymphadenectomy for 5-year DFS in node-negative patients.
- Another study has shown that in 117 patients with stage ≤pT3a tumours at radical cystectomy, extending lymph node dissection up to the bifurcation of the aorta was associated with an improved 5-year RFS rate versus lymph node dissection up to the bifurcation of the common iliac vessels (85% versus 64%; p<0.02). However, this was not the case for tumours >pT3.[109]

Urethrectomy

- EAU guidelines recommend that urethrectomy should be performed if positive surgical margins are present at the level of urethral dissection or within the bladder, the primary tumour is located at the bladder neck or in the urethra (in women), or if the tumour extensively infiltrates the prostate.[24]
- Factors predictive of urethral recurrence include the presence of distant CIS, high tumour stage and grade, multifocal recurrent tumours, trigonal or bladder neck invasion, prostatic urethral involvement and a positive urethral resection margin.[110]
- Factors that may protect against urethral recurrence include orthotopic bladder reconstruction and radical radiotherapy.

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Synchronous chemoradiation/selective bladder preservation

Overview

- Patients with a good response to neoadjuvant chemotherapy can be offered radiotherapy rather than cystectomy.
- Modern bladder-preserving strategies are multi-faceted, aimed at maintaining a functional bladder, while maintaining similar survival rates radical cystectomy, but maintaining a good quality of life with a functioning native bladder.
- The discrepancy between clinical staging and pathological staging is an important confounding factor when comparing results of radical cystectomy with results of bladder preservation, as clinical staging is more likely to underestimate disease extent.
    - In 156 patients who had undergone radical cystectomy, Ficarra et al. found only 23% of clinically-staged T2 tumours to be pT2 at cystectomy, and 74% to be pT3/4.[111] There is thus an outcome bias in favour of surgical series, which have pathological staging data.
- The key factors for successful selective bladder preservation are:
    - Careful selection of patients, to increase the number of complete responders.
    - Meticulous cystoscopic follow-up to identify recurrent or persistent muscle invasive disease and candidates for early salvage cystectomy.
    - It is important to aim to reduce the amount of normal tissue in the irradiated area, especially as the small bowel may be used for reconstruction in the event of cystectomy.
- An initial maximal TUR is required, followed by neoadjuvant chemotherapy in appropriately selected patients. Radiation therapy either given alone or with synchronous chemotherapy is subsequently given to neoadjuvant chemotherapy responders, with early cystectomy for non-responders.
    - If maximal TUR has been performed longer than 6–8 weeks prior to neoadjuvant chemotherapy or radiotherapy, a repeat and complete TUR is recommended.
    - The ability to completely resect visible tumour is a strong predictor of CR as well as OS in univariate and multivariate analyses.[112]
- It has been suggested that in patients receiving chemoradiotherapy (CRT) following TUR, if this is unsuccessful, the associated delay until cystectomy allows disease progression and a worse prognosis than undergoing immediate cystectomy.
    - A systematic review of the literature suggests that there is a window of opportunity of less than 12 weeks between diagnosis of invasive disease and radical cystectomy.[113]
- Response to neoadjuvant chemotherapy is a strong prognostic marker, as pathological downstaging to pT0 disease is significantly associated with improved survival.
- Hydronephrosis is in general a poor prognostic indicator for patients with muscle invasive bladder cancer, irrespective of type of local treatment. Patients with hydronephrosis are in general excluded from bladder preservation protocols.[114]
- The optimal CRT regimen appears to be as per BC2001.

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Patient selection

- T2–T4/N0–Nx/M0 tumours.
- Eastern Co-operative Oncology Group (ECOG) PS≤2.
- Absence of hydronephrosis.
- Unifocal disease (although not essential).
- Adequate renal function.
- Adequate white blood cell and platelet counts.
- Medical fitness for surgery/radiotherapy.
- Absence of extensive CIS.
- Node-negative disease on CT/MRI.

Adverse effects of treatment

- Acute side-effects include diarrhoea, tenesmus, proctitis, cystitis and lethargy.
- Late side-effects such as bladder fibrosis, second malignancies, haematuria and impotence.
- Platinum-associated toxicities, including myelosuppression and sepsis.
- Impaired sexual functioning has been reported in around 50% of men.[115]
- 40% of patients have concurrent BPH, which could have affect their urinary control after radiotherapy.
- A questionnaire-based study involved 29 patients who received bladder-preserving therapy (BPT), i.e. a combination of CRT and TUR, and 30 patients who had undergone radical cystectomy.[116]
    - Of the BPT group, 62% felt physically well, compared with 53% of the radical cystectomy group; 10% of the BPT group and 27% of the radical cystectomy group reported feeling ill.
    - A greater number of BPT patients were able to look after themselves compared with the cystectomy group.
    - Of the BPT patients, 28% were anxious and 24% were depressed; of the cystectomy patients, 57% were anxious and 47% were depressed.
    - The patients undergoing BPT reported dysuria (20%), daytime micturition frequency (44%), night-time micturition frequency (42%) and difficulty in controlling micturition (38%).
- In another study involving 32 patients with T2–T4a bladder cancer who had undergone TUR, chemotherapy and radiotherapy, at a median follow-up of 6.3 years (range, 1.6–14.9), 24 had normal bladder function.[115]
    - Urinary flow problems were reported by 6% of patients, urgency by 15%, problems with urinary control in 19%, and urinary leakage in 19%.
    - Post-void residual volume >100 ml was observed for 3 men and 1 woman.
    - Distress from urinary symptoms was reported by 50% of patients experiencing these.
    - Median bladder capacity was 400 ml in men.
    - Difficulty with bowel control occurred in 7 men and 3 women.
    - 59% of male subjects reported that they were satisfied with their sex life.
    - Physical functioning was comparable to US age-matched norms for men and women.

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- Late pelvic toxicity following BPT was assessed in 157 patients with T2–T4a bladder cancer.[117]
  - At a median follow-up of 5.4 years (range, 2.0–13.2), 34 patients (22%) experienced late grade 1 pelvic toxicity, 16 (10%) developed late grade 2 pelvic toxicity, and 11 patients (7%) developed late grade 3 pelvic toxicity. No patients developed late grade 4 pelvic toxicity and there were no treatment-related deaths.
  - Median time to late grade 2 pelvic toxicity was 31.2 months (range, 9.2–137.8), and median time to late grade 3 pelvic toxicity was 22.1 months (range, 8.0–98.8).

Clinical evidence

- In the Phase III open-label BC2001 trial, 360 patients with T2–T4a MIBC were randomised to radiotherapy with concurrent fluorouracil + mitomycin C, or radiotherapy alone.[88]
  - 2-year RFS was 67% (95% CI, 59–74) with CRT and 54% (95% CI, 46–62) with radiotherapy alone (HR, 0.68; 95% CI, 0.48–0.96; p=0.03).
  - 5-year OS was 48% (95% CI, 40–55) with CRT and 35% (95% CI, 28–43) with radiotherapy alone (HR, 0.82; 95% CI, 0.63–1.09; p=0.16).
- In a retrospective analysis (1982–2000), 415 patients with T2–T4 or high-risk T1 disease received TUR followed by radiotherapy or CRT.[112]
  - A CR after initial therapy was achieved in 288 patients (72%), and of this subgroup, 186 had developed no recurrence of bladder tumours. Twenty-six patients demonstrated a non-invasive recurrence, 15 demonstrated a T1 recurrent tumour, 32 patients had a muscle invasive recurrence and 10 patients had a pelvic recurrence.
  - Eighty-three patients (20%) underwent radical cystectomy: 41 of the 110 incomplete responders to initial therapy and 42 patients with an initial CR who experienced a local relapse.
  - For patients with a preserved bladder, 5-year OS was 42% and 10-year OS was 27%. This compared with 50% and 32% 5- and 10-year OS for all patients.
  - For all patients with muscle invasive disease (T2–T4; 79%), 5-year OS was 45% and 10-year OS was 29%.
- In another series of 333 patients with bladder cancer (high-risk T1 or muscle invasive), following TUR patients received radiotherapy alone or platinum-based CRT.[118]
  - CR rates were 57% for radiotherapy and 80% for CRT (p<0.05).
  - 5-year DSS rates were 40% for radiotherapy, 64% for CRT with cisplatin and 54% for CRT with carboplatin.

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- In a study involving 190 patients with T2–T4a bladder cancer, initial treatment was TUR plus CRT.[114]
  - A bladder preservation approach was utilised for those patients who demonstrated a CR following the induction phase of radiotherapy. This subgroup then received consolidation with additional concurrent chemotherapy and radiotherapy to a total dose of 65 Gy.
  - Patients with an incomplete response to TUR followed by chemotherapy and radiotherapy or progressive disease underwent radical cystectomy.
  - Sixty-six patients (35%) underwent radical cystectomy; 41 for an incomplete response and 25 as salvage therapy for invasive recurrent disease.
  - At a median follow-up of 6.7 years 5-year OS for patients with an intact bladder was 57% for T2 tumours and 35% for T3–T4 tumours (p=0.0008).
  - Ten-year OS for patients with an intact bladder was 50% for T2 tumours and 24% for T3–T4 tumours (p=0.0008).
  - For the 66 patients undergoing radical cystectomy, 5-year OS was 48% and 10-year OS was 41%
  - Of the patients demonstrating a CR after initial therapy, 60% developed no further bladder tumours, 24% developed a superficial recurrence and 16% developed an invasive tumour.
- In a phase II clinical study, patients with high-risk T1 or T2–T4 bladder cancer were treated with cisplatin-based CRT after TUR.[119]
  - At 6 months after completion of treatment, 79 patients (70%) achieved a CR and 21 patients demonstrated persistent or progressive disease; of these, 6 underwent salvage cystectomy.
  - Recurrence of invasive disease occurred in 11/79 patients with CR at 6 months (14%). Six of these underwent salvage cystectomy. Another 3 patients underwent cystectomy for persistent isolated NMIBC.
  - For the whole study population, 5-year RFS and DFS rates were 33% and 50%, respectively. In patients achieving a CR at 6 months, 5-year RFS and DFS rates were 44% and 68%, respectively.
  - The 5-year local control rate (free of both non-muscle invasive and muscle invasive recurrences) was 45% for all patients and 53% for those that achieved a CR at 6 months.
- In a phase II trial, 50 patients with T2–T3/N0/M0 bladder cancer received gemcitabine-based CRT following TUR.[120]
  - Of 47 patients undergoing post-treatment cystoscopy, 44 achieved a CR.
  - At a median follow-up of 36 months (range, 15–62), 36 patients were alive; 7 died as a result of metastatic bladder cancer, 5 died as a result of other diseases, and 2 died due to treatment-associated factors.
  - Four patients underwent salvage cystectomy.
  - The 3-year DSS rate was 82% and 3-year OS was 75%.
- In a study conducted in Canada, 340 patients with bladder cancer (T2–T4, 89%) received radical radiotherapy, cisplatin-based CRT, or neoadjuvant CRT.[121]
  - At a median follow-up of 7.9 years (range: 1.5 months–16.8 years), CR rate as assessed by cystoscopy was 64% for radical radiotherapy, 79% for CRT and 52% for neoadjuvant CRT.

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- Sternberg et al. treated 104 patients with T2–T4 TCC with 3 cycles of methotrexate + vinblastine + cisplatin (M-VAC) given as a 2-weekly schedule with granulocyte colony stimulating factor (GCSF) (i.e. accelerated M-VAC) followed by TUR.122 Dependent on the response to chemotherapy, patients underwent TUR and partial cystectomy (i.e. bladder preservation) or radical cystectomy.
    - At a median follow-up of 56 months, in patients undergoing M-VAC and TUR, with or without subsequent partial cystectomy (63%), 5-year OS was 67%.
    - In the 52 patients undergoing M-VAC and TUR without partial cystectomy, 37 (71%) achieved a CR. Of this subgroup, 13 patients experienced superficial disease recurrence, 5 patients developed invasive disease, 12 patients developed metastatic disease and 3 patients developed both invasive and metastatic disease. 5-year OS was 67%.
    - Thirty-nine patients not achieving a CR to M-VAC and TUR underwent radical cystectomy. At a median follow-up of 45 months, 14 patients developed metastatic disease. The 5-year OS in this subgroup was 46%.
    - A total of 83 patients were downstaged following repeat TUR, including 48 (46%) to T0, 6 to Ta, 8 to Cis, 17 (16%) to T1 and 4 to T2 disease.

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Radical radiotherapy

Overview

- Standard radiotherapy involves CT-planned external beam conformal radiotherapy using fractionation schedules such as 64 Gy in 32 fractions, over 6.5 weeks, or 55 Gy in 20 fractions over 4 weeks. The daily dose should be 1.8–2.0 Gy, with a maximum treatment duration of 6–7 weeks.[24]
- OS rates of 60% for T2 tumours, 45% for T3 tumours and 15% for T4 tumours have been reported with radical radiotherapy, similar to single institution series of radical cystectomy for MIBC.

Patient selection

- T2–T4/NX–N0 (N+ patients can be downstaged with adjuvant chemotherapy)/M0.
- Good bladder function.
- WHO PS ≤3.
- Maximal TUR.
- No hydronephrosis (unless treated).

Adverse effects of treatment

- Acute side-effects include diarrhoea, tenesmus, proctitis, cystitis and lethargy.
- Late side-effects such as bladder fibrosis, second malignancies, haematuria and impotence.
- Urinary complications occur in 5% of patients.[90]
- Increased risk of inoperable disease or more difficult and high-risk surgery.
- 30-day mortality of <1%.[90]
- Radiotherapy may impair the chance of bladder reconstruction.

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Clinical evidence

- In an Italian study, a series of 459 patients with T1–T4/N0-Nx/M0 bladder cancer received a minimal radiation dose of 50–70 Gy.[123]
  - Treatment failure (defined as absence of CR at first cystoscopy) was observed in 218 patients (47.5%).
- Bell et al. evaluated the efficacy and morbidity of definitive EBR (40–65 Gy, median fractions, 20) in 120 patients with T1–T4 bladder cancer, over an 8-year period in the UK.[124]
  - Local recurrence developed in 77 (59%) patients, which was invasive in 36 (30%) patients.
  - The overall mortality rate was 52%.
  - Median OS at 5 years was 67% for T1 tumours, 37% for T2 tumours and 22% for T3 tumours.
  - Thirty-three (27%) patients underwent a salvage cystectomy.
- In the BCON study, 333 patients with T1G3–T4a bladder cancer were randomised to either radiotherapy in combination with carbogen and nicotinamide (RCON) to reduce the risk of hypoxia, or radiotherapy alone.[125]
  - Median OS was 54 months with RCON and 30 months with radiotherapy alone (p=0.04).
  - 3-year OS was 59% with RCON versus 46% with radiotherapy alone (p=0.04).
  - 3-year RFS was 52% for RCON and 41% for radiotherapy alone (p=0.06).

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Neoadjuvant chemotherapy prior to definitive local treatment

Overview

- The use of neoadjuvant chemotherapy prior to radical radiotherapy or radical cystectomy in MIBC is associated with improvements in survival rates.[126]
- Neoadjuvant platinum-based combination chemotherapy is given prior to definitive local treatment with either radiotherapy or cystectomy in patients who have disease that is amenable to radical treatment. This is different to 'down-staging' chemotherapy, which may be given to reduce tumour bulk and nodal disease in patients who are not suitable for radical treatment initially but who may be rendered operable or encompassable in a radical radiotherapy field by the use of down-staging chemotherapy.

Patient selection

- T2–T4.
- NX/N0/N1.
- M0.
- PS 0–1.
- Creatinine clearance >50 ml/min.
- Fit for chemotherapy.
- Given the modest yet definite improvements in OS with neoadjuvant chemotherapy, patients aged >70 should be considered on a case-by-case basis.

Adverse effects of treatment

- Neuropathy
- Renal toxicity
- Tinnitus
- Anaemia
- Neutropenic sepsis
- Bleeding
- Nausea and vomiting
- Stomatitis
- Alopecia
- Fatigue

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Clinical evidence

- A meta-analysis of 11 neoadjuvant chemotherapy clinical trials with data from 3005 patients has been completed by the Advanced Bladder Cancer Meta-analysis Collaboration.[126]
    - For all included trials, the risk of death was significantly reduced with neoadjuvant chemotherapy versus local treatment alone (HR, 0.89; 95% CI, 0.81–0.98; p=0.022).
    - However, when considering the type of chemotherapy regimen, platinum-based combinations were also significantly superior to local treatment alone (HR, 0.86; 95% CI, 0.77–0.95; p=0.003), whereas single-agent platinum was not (HR, 1.15; 95% CI, 0.90–1.47; p=0.26).
- With combination platinum therapy, this equated to an OS of 50% at 5 years.
    - Similar results were obtained for DFS, with an HR of death from cancer of 0.81 (95% CI, 0.74–0.89; p<0.0001) for all chemotherapy regimens.
    - Platinum-based combination therapy was also significantly superior to local treatment alone (HR, 0.78; 95% CI, 0.71–0.86; p<0.0001), whereas single-agent platinum was not (HR, 1.14; 95% CI, 0.83–1.55; p=0.42).
- Another neoadjuvant chemotherapy trial randomised 976 patients with T2–T4a bladder cancer to curative cystectomy or EBR alone or 3 cycles of neoadjuvant M-VAC chemotherapy prior to radical cystectomy or radiotherapy.[127]
    - At a median follow-up of 8 years, the risk of death was reduced by 16% (HR, 0.86; 95% CI, 0.72–0.99; p=0.037) for neoadjuvant M-VAC versus no neoadjuvant chemotherapy.
- This equated to a 10-year OS of 36%.
- A smaller retrospective study conducted in the UK assessed 80 patients with T2–T4a bladder cancer who had received accelerated M-VAC (aM-VAC; 3 cycles of methotrexate + vinblastine + cisplatin given as a 2-weekly schedule with GCSF) as neoadjuvant chemotherapy prior to either radical cystectomy or radical radiotherapy.[128]
    - Following neoadjuvant aM-VAC, 43% of patients scheduled for radical cystectomy were pT0; 12% had residual disease (pT2 or pT3); none had pT4 disease.
    - 19% of the surgically-managed patients had 1 or more affected pelvic lymph nodes following neoadjuvant aM-VAC.
    - The radiological overall response rate (ORR) following neoadjuvant aM-VAC was 83% (rCR, 32%; rPR, 51%).
    - At a median follow-up of 27.5 months, 32% of assessable patients (25/78) had experienced disease recurrence (either loco-regional or metastatic).
    - 2-year RFS was 65% and predicted median DFS >60 months.
    - 2-year OS was 77% and predicted median OS >5 years.

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Neoadjuvant radiotherapy prior to radical cystectomy or radical radiotherapy

- The available evidence suggests that there is no benefit of neoadjuvant radiotherapy in patients with muscle invasive bladder cancer.
- The role of radiotherapy administered prior to cystectomy was compared with cystectomy alone in a meta-analysis of 5 RCTs.[129]
    - The authors calculated an OR of 0.94 (95% CI, 0.57–1.55), with no significant difference between treatments.

Adjuvant chemotherapy

- There are currently no data to support the use of adjuvant chemotherapy.
- A meta-analysis conducted by the Advanced Bladder Cancer Meta-analysis Collaboration evaluated data from 491 patients with T2–T4a bladder cancer included in six trials.[130]
    - When comparing adjuvant chemotherapy with no adjuvant treatment, there was a 25% relative reduction in the risk of death, equivalent to a 9% absolute improvement in survival (95% CI, 1–16; p=0.019) at 3 years.
    - When considering platinum-based chemotherapy versus no adjuvant therapy, there was a 29% relative reduction in the risk of death (HR, 0.71; 95% CI, 0.55–0.92; p=0.01).
    - However, these results are difficult to interpret, as there were multiple different regimens of chemotherapy used.

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Advanced/metastatic bladder cancer: Management options

An overview of the treatment approach for patients with advanced bladder cancer is presented in Figure 3.

First-line systemic chemotherapy

Overview

- The M-VAC regimen or gemcitabine + cisplatin (GC) combination can be used for the first-line management of advanced bladder cancer.
- However, GC is associated with less toxicity than M-VAC.
- Standard M-VAC or accelerated M-VAC (aM-VAC; 3 cycles of methotrexate + vinblastine + cisplatin given as a 2-weekly schedule with GCSF) may be used
- Carboplatin-based therapy may be an option for patients 'unfit' for cisplatin therapy, due to comorbidities or suboptimal renal function.

Patient selection

- Cisplatin-based therapy: PS 0–1, Adequate renal function, CrCl >50 ml/min, calculated from Cockroft-Gault or EDTA.
- Carboplatin-based therapy: PS 2–3, CrCl 30–50 ml/min.
- Cisplatin or carboplatin: adequate liver and haematological function.
- No other significant comorbidities that would interfere with chemotherapy administration.
- Adequate renal function (GFR ≥60 ml/min; creatinine clearance ≥50 ml/min).
- Adequate liver function (according to enzyme tests).

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Adverse effects of treatment

- GC has a better safety and tolerability profile than standard M-VAC, with a reduced frequency of grade 3/4 neutropenia, neutropenic fever, mucositis and alopecia occurring in GC-treated patients.
- M-VAC treatment is associated with substantial toxicity, including neutropenia, mucositis and toxic deaths.
- Side-effects may be problematic for older patients, who may also present with co-morbidities.
- The administration of granulocyte colony stimulating factor (GCSF) alongside M-VAC can improve its tolerability.
- Neuropathy
- Renal toxicity
- Tinnitus
- Anaemia
- Bleeding
- Nausea and vomiting
- Stomatitis
- Alopecia
- Fatigue

Clinical evidence

- In a randomised trial of 405 patients with advanced bladder cancer, after more than 5 years of follow-up, median OS was 15.2 months with M-VAC and 14.0 months with GC (HR, 1.09; 95% CI, 0.88–1.34; p=0.66).[131]
    - OS rates at 24 months (M-VAC, 31.0% versus GC, 25.0%), 48 months (M-VAC, 17.3% versus GC, 16.4%) and 60 months (M-VAC, 15.3% versus GC, 13.0%) were comparable.
    - There were no differences between treatments for PFS (HR, 1.09; 95% CI, 0.89–1.34; p=0.63) and median PFS was 8.3 months with M-VAC and 7.7 months with GC.
    - Toxicity with GC was substantially lower than with M-VAC. Grade 3/4 neutropenia, neutropenic fever, mucositis and alopecia occurred more frequently in patients who received M-VAC.
- The superiority of M-VAC compared with single-agent cisplatin has been demonstrated in a randomised trial of 269 patients with advanced bladder cancer.[132]
    - Median OS was 12.5 months for M-VAC versus 8.2 months for cisplatin (p=0.04).
    - However, M-VAC was associated with a greater toxicity, in particular leukopenia, mucositis and granulocytopenic fever.
    - Long-term follow-up confirmed that M-VAC was superior to single-agent cisplatin; however, at 6 years, only 3.7% of the patients randomised to M-VAC were alive and continuously disease-free.[133]

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- In a separate study, aM-VAC was administered in 263 patients with advanced bladder cancer.[134]
  - aM-VAC achieved higher response rates than standard M-VAC (62% versus 50%, respectively; p=0.06).
  - Progression-free survival (PFS) was also significantly better with aM-VAC compared with standard M-VAC (9.1 months versus 8.2 months, respectively; HR, 0.75; 95% CI, 0.58–0.98; p=0.037).
  - At the 7-year update of this study, the 2- and 5- year OS rates were 36.7% and 21.8% for aM-VAC compared with 26.2% and 13.5% for standard M-VAC.[135]
  - Median OS was 15.1 months with aM-VAC versus 14.9 months with standard M-VAC (HR for mortality, 0.76; 95% CI, 0.58–0.99).
- In a Phase III trial, 220 patients with inoperable, metastatic or recurrent bladder cancer were randomised to aM-VAC or docetaxel + cisplatin with GCSF (DC).[136]
  - Median OS was 14.2 months with accelerated M-VAC compared with 9.3 months for DC (HR, 1.52; 95% CI, 1.11–2.08; p=0.0255).
  - Two-year OS rates were 28.6% with accelerated M-VAC versus 18.9% with DC.
  - Median TTP was 9.4 months in patients receiving accelerated M-VAC compared with 6.1 months in patients receiving DC (HR, 1.73; 95% CI, 1.24–2.42; p=0.0029).

Patients unfit for M-VAC or GC

- In a randomised Phase II study involving 178 patients with advanced bladder cancer and WHO PS 2 and/or impaired renal function (GFR >30 but <60 ml/min), treatment was either gemcitabine + carboplatin (GCb) or methotrexate, vinblastine and carboplatin (M-CAVI).[137]
  - CR rates were 3.4% with GCb and 4.6%, but ORRs were 38% with GCb and 20% with M-CAVI.
  - ORRs were lower for patients with both PS 2 and GFR <60 ml/min versus those with either PS >2 or GFR <60 ml/min (26.1% versus 39.5%).
  - Severe acute toxicity was reported for 12 patients (13.6%) of patients receiving GCb and 20 patients (23.0%) receiving M-CAVI.
  - Death associated with treatment toxicity occurred in 2 patients receiving GCb and 4 patients receiving M-CAVI.
  - Severe acute toxicity was also more common in patients with both these factors (26.1% versus 15.5% for patients with either PS >2 or GFR <60 ml/min).
- In a retrospective analysis of data, patients (n=15) with Stage IV bladder cancer received GCb for up to 6 cycles.[138]
  - A CR was observed in 1 patient, PRs in 9 patients, and SD in 1 patient.
  - Median OS was 9 months (95% CI, 7.4–10.6).

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Second-line systemic therapy in metastatic disease

Overview

- There are no standard treatment regimens in this setting, but patients who have responded for 6 months to first-line treatment may be rechallenged with that regimen.
- Patients who received first-line GC can receive second-line M-VAC or aM-VAC.
- Clinical data also support the use of other agents, e.g. paclitaxel.
- A single RCT of vinflunine has shown a modest improvement compared with BSC; more clinical trials in this setting are needed.
- Ongoing studies are evaluating targeted therapies.

Patient selection

- PS 0–1.
- Life expectancy ≥12 weeks.
- Fit for further chemotherapy.
- Adequate haematological, renal and hepatic function (choice of agent dependent on renal function).

Adverse effects of treatment (as per first-line therapy)

- Haematological side-effects, including leukopenia, neutropenia, thrombocytopenia and anaemia
- Infusion-site reactions
- Alopecia
- Nausea, vomiting, constipation
- Stomatitis/mucositis
- Fatigue

Clinical evidence

- In a retrospective analysis, aM-VAC was evaluated in 45 patients with metastatic bladder cancer who had previously received gemcitabine + platinum chemotherapy (in the neoadjuvant, adjuvant or metastatic disease setting).[139]
    - In patients receiving gemcitabine + platinum in the metastatic setting (n=22), 1 achieved a CR, 9 achieved a PR and 6 demonstrated SD.
    - Median PFS in these patients was 4.0 months (95% CI, 2.9–5.2) and median OS was 5.7 months (95% CI, 2.8–8.7).
- Weekly paclitaxel has been evaluated in a Phase II trial involving 31 patients with recurrent or metastatic disease.[140]
    - PR was achieved by 3 patients (10%).
    - Median OS was 7.2 months and median TTP was 2.2 months.

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- Patients (n=31) with recurrent or metastatic disease who had previously received M-VAC were treated with weekly paclitaxel and carboplatin in a Japanese Phase II trial.[141]
  - ORR was 32% (CR, 6%).
  - Median OS was 7.9 months and median PFS was 3.7 months.
- In a Phase II study, 60 patients with locally advanced or metastatic bladder cancer, who had received ≤1 previous chemotherapy regimen, received paclitaxel + GCb in 21-day cycles.[142]
  - The ORR was 43%, with 12% of patients achieving a CR.
  - Median PFS was 7.4 months at a median follow-up of 31 months.
  - Median OS was 11 months; 1- and 2-year OS was 46% and 27%, respectively.
- In another Phase II trial, 24 patients with advanced bladder cancer previously treated with M-VAC received gemcitabine + paclitaxel in 21-day cycles.[143]
  - ORR was 42% (CR was 8%).
  - Median OS was 12.4 months (95% CI, 0.5–30.2); 1- and 2-year OS was 52% and 11%, respectively.
  - Median PFS was 6.1 months (95% CI, 0.5–23.9).
- In a Phase II study, 57 patients with advanced bladder cancer who had previously received one course of treatment with platinum-based chemotherapy were treated with vinflunine for 2 cycles. If disease had progressed at this stage, treatment was halted; patients with stable disease (SD) received another 2 cycles and were reassessed; patients with a response could receive vinflunine until disease progression or unacceptable toxicity.[144]
  - Nine patients achieved a partial response (PR) and another 25 demonstrated SD.
  - Median duration of response was 9.1 months (95% CI, 4.2–15.0).
  - Median OS was 6.6 months (95% CI, 4.8–7.6) and median PFS was 3.0 months (95% CI, 2.4–3.8).
- Another Phase II study included 151 patients with metastatic bladder cancer who had progressed following platinum-based first-line chemotherapy.[145]
  - PR was achieved by 22 patients (14.6%) and another 64 patients (42.4%) achieved SD.
  - Median OS was 8.2 months (95% CI, 6.8–9.6) and PFS was 2.8 months (95% CI, 2.6–3.8).
- A subsequent Phase III study compared vinflunine + best supportive care (BSC) with BSC alone, in 370 patients with locally advanced or metastatic bladder cancer.[146]
  - Median OS was 6.9 months for vinflunine + BSC versus 4.6 months for BSC alone (HR for risk of death, 0.88; 95% CI, 0.69–1.12; p=0.287).
  - In the eligible patient population (patients not violating study entry criteria, n=357), median OS was 6.9 months for vinflunine + BSC versus 4.3 months for BSC alone (HR for risk of death, 0.78; 95% CI, 0.61–0.99; p=0.04)
  - Median PFS for all patients was 3.0 months for vinflunine + BSC versus 1.5 months for BSC alone (p=0.0012).
  - Sixteen patients receiving vinflunine + BSC achieved a PR compared with no patients in the BSC alone arm. No patients in either group achieved a CR.
  - SD rates were 46.5% with vinflunine + BSC and 27.1% with BSC alone.

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Symptomatic/palliative treatments – patients unfit for chemotherapy

Overview

- In patients for whom a cure is not possible, a number of treatments are available that can alleviate pain and other symptoms such as haematuria, in order to improve quality of life.
- Quality of life is paramount – palliative radiotherapy offers good palliation of symptoms.
- Collaboration between MDT members and patients is paramount.

Clinical evidence

- The MRC trial BA09 compared the efficacy of 35 Gy in 10 fractions over 2 weeks with 21 Gy in 3 fractions over 10 days in 272 patients considered to be unsuitable for curative treatment due to disease stage or co-morbidity.[147]
    - The shorter, fractionated schedule of palliative radiotherapy (21 Gy in 3 fractions) was as effective as the 35 Gy in 10 fractions in providing overall symptomatic improvement (64% versus 71% respectively).
- In an earlier study, two regimens of radiotherapy were compared: (A) 1700 cGy in two fractions over 3 days and (B) 4500 cGy in 12 fractions over 26 days, in 41 patients with haematuria and localised pain.[148]
    - Resolution of haematuria was achieved by 59% of patients in Group A versus 16% in Group B.
    - Improvement in pain was achieved by 73% of patients in Group A compared with 37% in Group B.
    - However, median OS was 9.8 months in Group A and 14.5 months in Group B.
- In a retrospective analysis of data from 65 elderly patients (60–98 years) with symptomatic advanced bladder cancer, radiotherapy was administered in 6 Gy fractions, for a total dose of 30 or 36 Gy.[149]
    - At 1 month after completion of radiotherapy, 28 of 55 evaluable patients (51%) experienced complete symptom relief. An additional 7 patients achieved an improvement in their urinary symptoms.
- In a prospective clinical trial, 40 patients with bladder cancer and bony metastases underwent radiotherapy followed by randomisation to zoledronic acid or placebo, once a month, for 6 months.[150]
    - At the 1-year follow-up, the mean number of skeletal-related events (e.g. fractures, spinal compression) was 0.95 in the zoledronic acid group versus 2.05 in the placebo group (p=0.001).
    - Mean pain score was reduced with zoledronic acid versus placebo (mean score, 4.37 versus 2.95).
    - The 1-year OS was 36.3% for zoledronic acid compared with 0 for placebo.

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Ongoing Support

- Regular communication between the MDT and the primary care team are key to providing ongoing support, and may include the following:
  - Provision of detailed discharge or out-patient summaries in a timely manner.
  - Rationale why a particular treatment option has been chosen.
  - Details of the patient's response to the chosen treatment.
  - Exchange of protocols.
  - Electronic educational resources.
  - Agreement on prescribing policies.
  - Provision of contact details for information exchange.
- In addition to the MDT and primary care team, the local patient support network, such as a partner or family member, should be included in the exchange of information and/or education process which may include patient information material.
  - Local charities can provide support and educational materials
- Patients should be able to access information regarding clinical trials.
- Community palliative care should be discussed at the appropriate time.

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EAU Guidelines on

Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

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1. INTRODUCTION

1.1 Aim and scope

This overview represents the updated European Association of Urology (EAU) Guidelines for Non-muscle-invasive Bladder Cancer (NMIBC), TaT1 and carcinoma *in situ* (CIS). The information presented is limited to urothelial carcinoma (UC), unless specified otherwise. The aim is to provide practical recommendations on the clinical management of NMIBC with a focus on clinical presentation and recommendations. Separate EAU Guidelines are available addressing upper tract urothelial carcinoma (UTUC) [1], muscle-invasive and metastatic bladder cancer (MIBC) [2] and primary urethral carcinoma [3]. It must be emphasised that clinical guidelines present the best evidence available to the experts, but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and references/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a pathologist, and a statistician. Members of this Panel have been selected based on their expertise and to represent the professionals treating patients suspected of suffering from bladder cancer. In the course of 2021 two patient representatives have formally joined the NMIBC Panel. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available. This is an abridged version which may require consultation together with the full text version. Several scientific publications are available, the latest publication dating to 2022 [4], as are a number of translations of all versions of the EAU NMIBC Guidelines. All documents are accessible through the EAU website Uroweb: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/.

1.4 Publication history and summary of changes

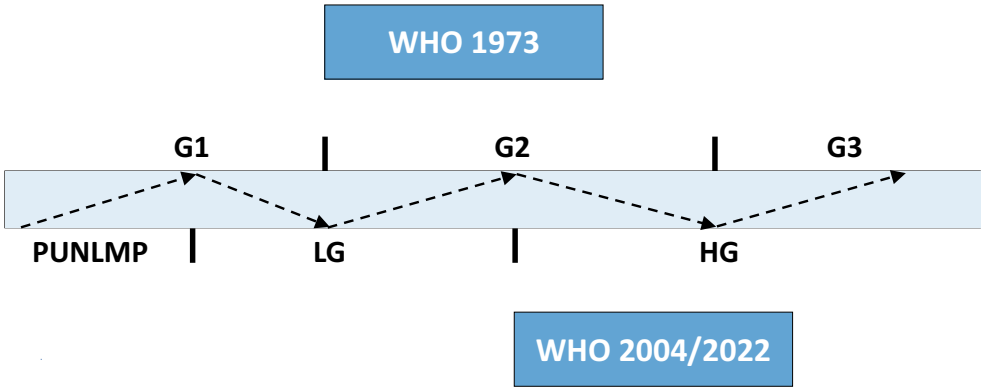
1.4.1 Publication history

The EAU Guidelines on Bladder Cancer were first published in 2000. This 2023 NMIBC Guidelines document presents a limited update of the 2022 publication.

1.4.2 Summary of changes

Additional data has been included throughout this document text. In particular in Chapters/Sections:

- Section 3.2 Aetiology, was restructured.
- Chapter 4 Pathological staging and classification systems, was significantly updated.
- The inclusion of the new WHO 2022 classification resulted in new Figure 4.1 Stratification of tumours according to grade in the WHO 1973 and 2004/2022 classifications;



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- Revision of Section 4.7 Subtypes of urothelial carcinoma.
- In Section 4.10 the following recommendation was revised:

Recommendations	Strength rating
2022 recommendation: Use both the 1973 and 2004/2022 WHO classification systems.	Strong
Revised 2023 recommendation: Use both the 1973 and 2004/2022 WHO classification systems, or a hybrid system.	Weak

- Section 5.1 Transurethral resection of TaT1 tumours has been revised and restructured, in particular 'New methods of tumour visualisation', the inclusion of Table 5.1 TURBT checklist, with changes to recommendations:

Recommendations	Strength rating
2022 recommendation: Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder carcinoma *in situ* is present or suspected, if there is positive cytology or urinary molecular marker test without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	Strong
Revised 2023 recommendation: Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if there is positive cytology or urinary molecular marker test without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be performed at the time of the second resection.	Strong
2022 recommendation: Take a prostatic urethral biopsy from the pre-collicular area (between the 5 and 7 o'clock position) using a resection loop. In case any abnormal-looking areas in the prostatic urethra are present at this time, these need to be biopsied as well.	Weak
Revised 2023 recommendation: Take a prostatic urethral biopsy from the pre-collicular area (between the 5 and 7 o'clock position) using a resection loop.	Weak
2022 recommendation: The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection.	Weak
Revised 2023 recommendation: The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, extent, macroscopic completeness of resection as well as any complications.	Strong

Table 5.1 TURBT checklist*

TURBT checklist - In the Operating Room	
Check the operating room setup	Instruments (sheath, resectoscope, loops, roller if needed, monopolar/ bipolar), camera, video, strainer, specimen container, catheter if needed
Decide irrigation fluid	Saline, Glycine, Water
Disease characteristics checklist	History of bladder cancer, tumour characteristics at cystoscopy if any, imaging results if any, first or second look, visual optimisation planned (PDD/NBI), risk classification
Cystoscopy/ TURBT	
Cystoscopy	Urethra/prostate (males)
	Ureteral orifices
	Diverticuli
	Tumour location, number, size, appearance (papillary/sessile), CIS (yes/no)
	White light/PDD/NBI/IMAGE1 S™
	Urine for cytology/bladder wash
TURBT	Resection technique (standard/*en bloc*/cold cup/roller ball cautery)
	Depth of resection
	Complete/incomplete resection
	Prostatic urethra biopsy if performed
	Any additional procedure, i.e. retrograde contrast study
	Estimated blood loss
	Intra-operative complications, if any
	Intravesical therapy if given or planned in recovery setting

**Adapted from Mostafid et al., and Suarez-Ibarrola et al. [5, 6].*

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- Chapter 7 Disease management; new Sections 7.2 Office-based fulguration and laser vaporisation; 7.3 Active Surveillance; 7.4.1 Post-operative irrigation; Conductive chemo-hyperthermia; 7.4.4.3 Sequential chemotherapy instillations; in Section 7.7 Primary treatment by disease type, Treatment of carcinoma *in situ* was added; and a new Section 7.8 Multidisciplinary tumour board, resulting in changes to recommendations:

Recommendations	Strength rating
2022 recommendation: Counsel smokers with confirmed non-muscle-invasive bladder cancer (NMIBC) to stop smoking.	Strong
Revised 2023 recommendation: Counsel smokers to stop smoking.	Strong
2022 recommendation: In patients with tumours presumed to be at low risk and in those with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB, offer one immediate chemotherapy instillation.	Strong
Revised 2023 recommendation: In patients with tumours presumed to be at low risk and in those with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB, offer one immediate single chemotherapy instillation.	Strong
New 2023 recommendation: Offer post-operative saline or water continuous irrigation of the bladder to patients who cannot receive a single instillation of chemotherapy.	Strong
New 2023 recommendation: Patients with small recurrent low grade Ta tumours can be effectively and safely offered office fulguration.	Strong
New 2023 recommendation: Only offer active surveillance to selected patients with presumed low-risk tumours not amendable to endoscopic ablation.	Strong
2022 recommendation: In patients with intermediate-risk tumours (with or without immediate instillation), offer one-year full- dose Bacillus Calmette- Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year. The final choice should be made in a shared decision-making process with the patient, reflecting his/her risk of recurrence and progression, as well as the efficacy and side effects of each treatment modality.	Strong
Revised 2023 recommendation: In patients with intermediate-risk tumours (with or without immediate instillation), one-year full- dose Bacillus Calmette- Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality, in a shared decision-making process with the patient.	Strong
2022 recommendation: In patients with high-risk tumours, full-dose intravesical BCG for one to 3 years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and problems connected with BCG shortages. Immediate radical cystectomy (RC) may also be discussed with the patient.	Strong
Revised 2023 recommendation: In patients with high-risk tumours, full-dose intravesical BCG for one to 3 years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and access to BCG. Immediate radical cystectomy (RC) may also be discussed with the patient.	Strong
2022 recommendation: In patients with very high-risk tumours discuss immediate RC. Offer intravesical full-dose BCG instillations for one to 3 years to those who refuse or are unfit for RC.	Strong
Revised 2023 recommendation: In patients with very high-risk tumours offer immediate RC. Discuss intravesical full-dose BCG instillations for one to 3 years and discuss clinical trials with those who refuse or are unfit for RC.	Strong
New 2023 recommendation: Cautiously offer quinolones to treat BCG-related side effects*.	Weak
Recommendations - technical aspects for treatment	
BCG intravesical immunotherapy	
New 2023 recommendation: Discuss high-risk and very high-risk patients within a multidisciplinary board, when possible.	Weak

**The side-effect profile of quinolones and fluoroquinolones resulted in the adoption of European regulation restricting their use [7].*

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- Chapter 8 Follow-up of patients with NMIBC, significant marker data in the follow-up setting has been included, as well as a new table 8.1 Urinary markers in the surveillance setting, resulting in the deletion of one recommendation:

Recommendation	Strength rating
In patients initially diagnosed with Ta LG/G1–2 bladder cancer, use ultrasound of the bladder during surveillance in case cystoscopy is not possible or refused by the patient.	Weak

Table 8.1: Urinary markers in the surveillance setting*

Marker	Sensitivity overall	HG	Specificity overall	HG	PPV overall	HG	NPV overall	HG	N studies/ patients
XPERT BC® MONITOR	0.72	0.88	0.76	0.75	0.43	0.18	0.92	0.99	10/> 2000
EpiCheck™	0.74	0.91	0.84	0.81	0.48	0.43	0.94	0.98	5/1600
ADX Bladder™	0.57	0.71	0.62	0.76	0.29	0.37	0.82	0.93	3/1600
CX BLADDER	0.91	-	0.61	-	0.16	-	0.98	-	2/1000
FDFGR3+TERT	0.93	-	0.79	-	0.67	-	0.96	-	2/250

**Data extracted from a pooled analyses of systematic review [8].*

HG = high grade; NMIBC = non-muscle-invasive bladder cancer; PPV = positive predictive value; NPV = negative predictive value; n = number.

2. METHODS

2.1 Data Identification

For the 2022 NMIBC Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature.

A broad and comprehensive scoping exercise covering all areas of the NMIBC Guidelines was performed. Excluded from the search were basic research studies, case series, reports, and editorial comments. Only articles published in the English language, addressing adults, were included. The search was restricted to articles published between June 3rd 2021 and May 4th 2022. Databases covered by the search included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 825 unique records were identified, retrieved, and screened for relevance.

A total of 72 new references were added to the 2023 NMIBC Guidelines. A detailed search strategy is available online: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=appendicespublications.

For Chapters 3 through 6 (Epidemiology, Aetiology and Pathology, Staging and Classification systems, Diagnosis, Predicting disease recurrence and progression) the references used in this text were assessed according to their level of evidence (LE) based on the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence [9]. For the Disease Management and Follow-up chapters (Chapters 7 and 8) a system modified from the 2009 CEBM levels of evidence was used [9].

For each recommendation within the guidelines there is an accompanying online strength rating form which includes the assessment of the benefit to harms ratio and patients‘ preferences for each recommendation. The strength rating forms draws on the guiding principles of the GRADE methodology but do not purport to be GRADE [10, 11]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation [9];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

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These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [12]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The 2021 publication was peer reviewed prior to print.

2.3 Future goals

The findings of the ongoing 'Individual Patient Data Validation of the Definition of bacillus Calmette-Guérin (BCG) Failure/BCG Unresponsive in Patients with Non-muscle Invasive Urothelial Carcinoma of the Bladder: an international multicentre retrospective study' will be included in the future update of the NMIBC Guidelines.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, and it is the tenth when both genders are considered [13]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 in men and 2.4 in women [13]. In the European Union, the age-standardised incidence rate is 20 in men and 4.6 in women [13].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) is 3.3 for men vs. 0.86 for women [13]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and variations in access to, and delivery of, healthcare. Additionally, epidemiological variations have been attributed to differing methodologies and the quality of data from individual datasets [14]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative factors [15].

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1); in younger patients (< 40 years of age) this percentage is even higher [16]. Patients with TaT1 and CIS have a high disease prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality compared to patients with T2-4 disease [13, 14].

3.2 Aetiology

*3.2.1 **Main risk factors***

3.2.1.1 Tobacco

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [14, 15, 17-19] (LE: 3). The aromatic amines and polycyclic aromatic hydrocarbons within the tobacco smoke, which undergo renal excretion, are linked to the development of BC. The risk of BC increases with smoking duration and intensity [18]. Low-tar cigarettes are not associated with a lower risk of developing BC [18]. The risk associated with electronic cigarettes has not been adequately assessed; however, carcinogens have been identified in the urine with electronic cigarettes [20]. 'Second-hand' exposure to tobacco smoke is also associated with an increased risk of BC [14].

3.2.1.2 Occupational exposure

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases. This type of occupational exposure occurs mainly in industrial plants which process paint, dye, metal, and petroleum products [14, 15, 21, 22]. In developed industrial settings these risks have been reduced by work-safety guidelines; therefore, chemical workers no longer have a higher incidence of BC compared to the general population [14, 21, 22]. Recently, greater occupational exposure to diesel exhaust has been suggested as a significant risk factor (odds ratio [OR]: 1.61; 95% confidence interval [CI]: 1.08–2.40) [23].

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3.2.2 *Genetic*

Family history seems to have little impact [24]. To date, no clinically relevant genetic alteration has been linked to BC. Genetic predisposition may lead to a higher susceptibility to other risk factors, and thereby explain the familiar clustering of BC in first- and second-degree relatives (hazard ratio [HR]: 1.69; 95% CI: 1.47–1.95) [14, 25-30] that has been confirmed more recently [31]. A recent study identified three single nucleotide polymorphisms related to the development of aggressive NMIBC [32]. Currently, there is insufficient evidence to support genetic screening for BC.

3.2.3 *Dietary habits*

Dietary habits seem to have limited impact on the risk of developing BC. A protective impact of flavonoids has been suggested. The Mediterranean diet, characterised by a high consumption of vegetables and non-saturated fat (olive oil) with moderate consumption of protein, has been linked to some reduction of BC risk (HR: 0.85, 95% CI: 0.77–0.93) [33-38]. Western diet (high in saturated fats) and organ meat has been shown to increase the risk of BC in a recent meta-analysis [39, 40]. The impact of an increased consumption of fruits has been suggested to reduce the risk of BC. This effect has been demonstrated to be significant in women only (HR: 0.92, 95% CI: 0.85–0.99) [41]. Higher consumption of tea has been associated with a reduction in risk of BC but only among men with also an interaction with tobacco smoking, thus making the protective effect of this compound questionable [42].

3.2.4 *Environmental exposure*

Although the impact of drinking habits remains uncertain, the chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic. Additionally, exposure to arsenic in drinking water has been suggested to increase the risk of BC [14, 43] (LE: 3). Arsenic intake and smoking have a combined effect [44]. However, chronic exposure to nitrate in drinking water does not seem to be associated with increased risk of BC [45].

The association between personal hair dye use and risk of BC remains uncertain; an increased risk has been suggested in users of permanent hair dyes with a slow *NAT2* acetylation phenotype [14] but a large prospective cohort study could not identify an association between hair dye and risk of cancer and cancer-related mortality [46].

3.2.5 *Other*

The impact of metabolic factors (body mass index, blood pressure, plasma glucose, cholesterol, and triglycerides) remains uncertain [47]. However, data suggest that high circulating levels of vitamin D are associated with a reduction in the risk of BC [48]. Schistosomiasis, which is an infection caused by a parasitic trematode, can lead to BC [14] (LE: 3).

Exposure to pelvic ionizing radiation is associated with an increased risk of BC [49]. In a retrospective analysis of patients with localised prostate cancer, external beam radiotherapy was independently associated with the risk to develop a second primary BC [49]. A weak association was also suggested for cyclophosphamide and pioglitazone [14, 43, 50] (LE: 3).

3.3 Pathology

The information presented in this text is limited to UC, unless otherwise specified.

3.4 Summary of evidence for epidemiology, aetiology, and pathology

Summary of evidence	LE
Worldwide, bladder cancer (BC) is the tenth most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of BC diagnosis have been identified.	3
Tobacco smoking is the most important risk factor for BC.	3

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4. PATHOLOGICAL STAGING AND CLASSIFICATION SYSTEMS

4.1 Definition of non-muscle-invasive bladder cancer

Tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively, according to the Tumour, Node, Metastasis (TNM) classification system [51]. Intra-epithelial, high-grade (HG) tumours confined to the mucosa are classified as CIS (Tis). All of these tumours can be treated by transurethral resection of the bladder (TURB), eventually in combination with intravesical instillations and are therefore grouped under the heading of NMIBC for therapeutic purposes. The term 'Non-muscle-invasive BC' represents a group definition and all tumours should be characterised according to their stage, grade, and further pathological characteristics (see Sections 4.5 and 4.7 and the International Collaboration on Cancer Reporting website: http://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/bladder. The term 'superficial BC' should no longer be used as it is incorrect.

4.2 Tumour, Node, Metastasis Classification (TNM)

The latest TNM classification approved by the Union International Contre le Cancer (UICC) (8th Edn.) is referred to (Table 4.1) [51].

Table 4.1: 2017 TNM classification of urinary bladder cancer

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma *in situ*: 'flat tumour'	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
	T2a	Tumour invades superficial muscle (inner half)
	T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

4.3 T1 subclassification

The depth and extent of invasion into the lamina propria (T1 sub-staging) has been demonstrated to be of prognostic value in retrospective cohort studies [51, 52] (LE: 3). Its use is recommended by the most recent 2022 World Health Organization (WHO) classification [53, 54]. T1 sub-staging methods are based either on micrometric (T1e and T1m) or histo-anatomic (T1a and T1b) principles; the optimal classification system, however, remains to be defined [55, 56].

4.4 Lymphovascular invasion

The presence of lymphovascular invasion (LVI) in TURB specimens is associated with an increased risk of pathological upstaging and worse prognosis [57-61] (LE: 3). Immunohistochemistry for confirmation is not mandatory [56].

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4.5 Histological grading of non-muscle-invasive bladder urothelial carcinomas

4.5.1 Types of histological grading systems

In 2004 the WHO published a histological classification system for UCs including papillary urothelial neoplasm of low malignant potential (PUNLMP), non-invasive papillary carcinoma low grade (LG) and HG. This system was also taken into the updated 2016/2022 WHO classifications [53, 54]. It provides a different patient stratification between individual categories compared to the older 1973 WHO classification, which distinguished between grade 1 (G1), grade 2 (G2) and grade 3 (G3) categories [55, 62].

There is a significant shift of patients between the categories of the WHO 1973 and the WHO 2004/2022 systems (see Figure 4.1), for example an increase in the number of HG patients (WHO 2004/2022) due to inclusion of a subset of G2 patients with a more favourable prognosis compared to the G3 category (WHO 1973) [63]. According to a multi-institutional individual patient data analysis, the proportion of tumours classified as PUNLMP (WHO 2004/2016) has decreased to very low levels in the last decade [64].

4.5.2 Prognostic value of histological grading

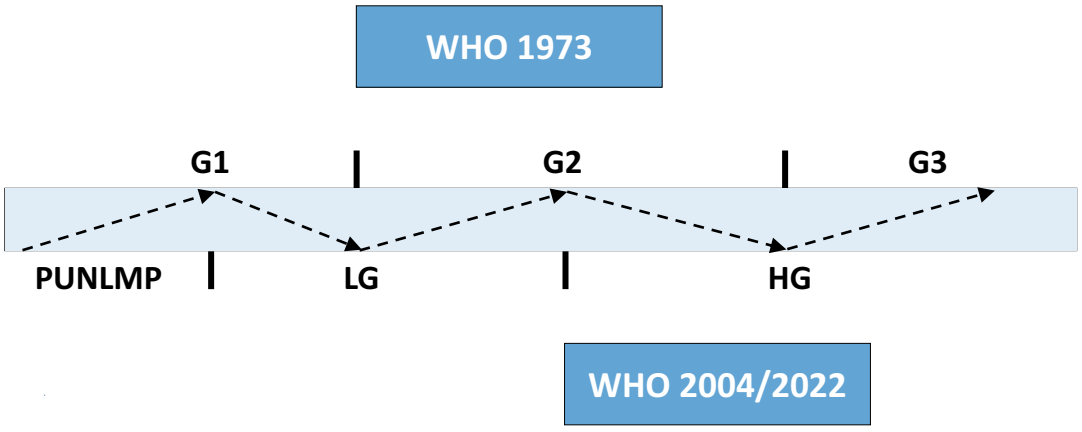
A systematic review and meta-analysis did not show that the 2004/2016 classification outperforms the 1973 classification in prediction of recurrence and progression [63] (LE: 2a).

To compare the prognostic value of both WHO classifications, an individual patient data analysis of 5,145 primary TaT1 NMIBC patients from 16 centres throughout Europe and one in Canada was conducted. Patients had a transurethral resection of bladder tumour (TURBT) followed by intravesical instillations at the physician's discretion. In this large study, the WHO 1973 and the WHO 2004/2016 were both prognostic for progression but not for recurrence. When compared, the WHO 1973 was a stronger prognosticator of progression in TaT1 NMIBC than the WHO 2004/2016. However, a 4-tier combination LG/G1, LG/G2, HG/G2 and HG/G3) of both classification systems proved to be superior to either classification system alone, as it divides the large group of G2 patients into two subgroups (LG/HG) with different prognoses [65]. In a subgroup of 3,311 patients with primary Ta bladder tumours, a similar prognosis was found for PUNLMP and Ta LG carcinomas [65].

4.5.3 Clinical application of histological grading systems

- The WHO 2002/2022 classification system is currently supported by the WHO for clinical application. Nevertheless, the WHO 1973 is still being used.
- The most important parameters, which must be considered for clinical application of any grading system are its inter-observer reproducibility and prognostic value (see Sections 4.5.1 and 4.6).
- These guidelines provide recommendations for tumours classified by both classification systems.

Figure 4.1: Stratification of tumours according to grade in the WHO 1973 and 2004/2022 classifications [65]*



**Grade shifts from the WHO1973 (G1–G3) to the WHO2004/2016 (LG and HG) classification for Ta/T1 bladder tumours are displayed with dotted lines and arrows. Along the dotted lines, both the degree of anaplasia and the 5-year progression rates increased in LG/G1, LG/G2, HG/G2, and HG/G3 patients.*
Figure reproduced with permission from Elsevier from [65].

4.6 Carcinoma *in situ* and its classification

Carcinoma *in situ* is an intra-epithelial, HG, non-invasive UC. It can be missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied. Carcinoma *in situ* is often multifocal and can occur in the bladder, but also in the upper urinary tract (UUT), prostatic ducts and urethra [66].

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From a clinical point of view, CIS may be classified as [67]:

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS;
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

4.7 Inter- and intra-observer variability in staging and grading

There is significant variability among pathologists for the diagnosis of CIS, for which agreement is achieved in only 70–78% of cases [68] (LE: 2a). There is also inter-observer variability in the classification of stage T1 vs. Ta tumours and tumour grading in both the 1973 and 2022 classifications. The general conformity between pathologists in staging and grading is 50–60% [69-72] (LE: 2a). The WHO 2004/2016 classification provides slightly better reproducibility than the 1973 classification [63].

4.8 Subtypes of urothelial carcinoma

Currently the following differentiations of UC are used [73, 74]:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular or divergent differentiation;
3. micropapillary UC;
4. nested/microcystic variant;
5. large nested variant;
6. microtubular UC;
7. plasmacytoid, signet ring
8. lymphoepithelioma-like;
9. giant cell, diffuse, undifferentiated;
10. sarcomatoid UC;
11. some UCs with other rare differentiations;
12. urothelial carcinomas with partial NE (neuroendocrine differentiation, % to be given);
13. pure neuroendocrine carcinoma (including small and large cell neuroendocrine carcinomas [Chapter NE carcinomas in the genitourinary tract]).

In the new WHO 2022 all subtypes are considered HG [54]. The percentage of subtype in the specimen should be reported since it has been shown to be of prognostic value [75]. The majority are MIBC which is pure HG UC, and no more than 15–30% are non-muscle invasive [2, 75-82] (LE: 3).

4.9 Tumour markers and molecular classification

Tumour markers and their prognostic role have been investigated [83-87]. These methods, in particular complex approaches such as the stratification of patients based on molecular classification, are promising but have not yet been recommended by any pathological organisation and are therefore not suitable for routine application [56, 88, 89].

4.10 Summary of evidence and guidelines for bladder cancer classification

Summary of evidence	LE
The depth of invasion (staging) is classified according to the TNM classification.	2a
Tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis).	2a
Histological grading of urothelial NMIBC is classified according to the WHO 1973 (G1–G3) and/or the WHO 2004/2016 (PUNLMP, LG/HG) systems.	2a
Both the WHO 1973 and the 2004/2016 classification systems are prognostic for progression, but not for recurrence.	2a
The WHO 1973 is a stronger prognosticator of progression in TaT1 NMIBC than the WHO 2004/2022. However, a 3-tier hybrid (LG/G1-G2, HG/G2 & HG/G3) or a 4-tier hybrid LG/G1, LG/G2, HG/G2 and HG/G3) combination of both classification systems proved to be superior to either classification system alone.	2a
The WHO 2004/2022 classification provides better reproducibility than the 1973 classification.	2a
PUNLMP lesions have the same prognosis as Ta LG carcinomas.	2a

Recommendations	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Use both the 1973 and 2004/2022 WHO classification systems, or a hybrid system.	Weak
Do not use the term ‘superficial’ bladder cancer.	Strong

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5. DIAGNOSIS

5.1 Patient history

A focused patient history is mandatory.

5.2 Signs and symptoms

Haematuria is the most common finding in NMIBC. Visible haematuria was found to be associated with higher stage at diagnosis disease compared to nonvisible haematuria [90]. Carcinoma *in situ* might be suspected in patients with lower urinary tract symptoms, especially irritative voiding symptoms.

5.3 Physical examination

A focused urological examination is mandatory although it does not reveal NMIBC.

5.4 Imaging

*5.4.1 **Computed tomography urography and intravenous urography***

Computed tomography (CT) urography is used to detect papillary tumours in the urinary tract, indicated by filling defects and/or hydronephrosis [91].

Intravenous urography (IVU) is an alternative if CT is not available [92] (LE: 2b), but particularly in muscle-invasive tumours of the bladder and in UTUCs, CT urography provides more information (including status of lymph nodes and neighbouring organs).

The necessity to perform a baseline CT urography once a bladder tumour has been detected is questionable due to the low incidence of significant findings which can be obtained [93-95] (LE: 2b). The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [94] (LE: 2b). The risk of UTUC during follow-up increases in patients with multiple and high-risk tumours [96] (LE: 2b).

*5.4.2 **Ultrasound***

Ultrasound (US) may be performed as an adjunct to physical examination as it has moderate sensitivity to a wide range of abnormalities in the upper- and lower urinary tract. It permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder, but cannot rule out all potential causes of haematuria [97, 98] (LE: 3). It cannot reliably exclude the presence of UTUC and cannot replace CT urography.

*5.4.3 **Multi-parametric magnetic resonance imaging***

The role of multi-parametric magnetic resonance imaging (mpMRI) has not yet been established in BC diagnosis and staging. A standardised methodology of MRI reporting (Vesical Imaging-Reporting and Data System [VI-RADS]) in patients with BC has recently been published and requires further validation [99]. A first systematic review of 8 studies showed that the VI-RADS scoring system can accurately differentiate NMIBC from MIBC with high inter-observer agreement rates [100].

A diagnosis of CIS cannot be made with imaging methods alone (CT urography, IVU, US or MRI) (LE: 4).

5.5 Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in HG and G3 tumours (84%), but low sensitivity in LG/G1 tumours (16%) [101]. The sensitivity in CIS detection is 28–100% [102] (LE: 1b). Cytology is useful, particularly as an adjunct to cystoscopy, in patients with HG/G3 tumours; it is not designed to detect LG tumours. Positive voided urinary cytology can indicate an UC anywhere in the urinary tract; negative cytology, however, does not exclude its presence.

Cytological interpretation is user-dependent [103, 104] and evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations: although in experienced hands specificity exceeds 90% [103] (LE: 2b). Artificial intelligence algorithms combined with digital image processing (VisioCyt test) improved the sensitivity of cytology for HG tumours up to 92% [105].

A standardised reporting system known as The Paris System published in 2022 (2nd Edn.) redefined urinary cytology diagnostic categories as follows [106]:

- No adequate diagnosis possible (No diagnosis);
- Negative for UC (Negative);
- Atypical urothelial cells (Atypia);
- Suspicious for HG UC (Suspicious);
- High-grade/G3 UC (Malignant).

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The principle of the system and its terminology underlines the role of urinary cytology in detection of G3 and HG tumours. The Paris system for reporting urinary cytology has been validated in several retrospective studies [107, 108].

Urine collection should respect the recommendation provided in Section 5.9. One cytospin slide from the sample is usually sufficient [109]. In patients with suspicious cytology repeat investigation is advised [110] (LE: 2b).

5.6 Urinary molecular marker tests

Driven by the low sensitivity of urine cytology in LG/G1 tumours, numerous urinary tests have been developed [111]. None of these markers have been accepted as routine practice by any clinical guidelines for diagnosis or follow-up.

The following conclusions can be drawn regarding the existing tests:

- Sensitivity is usually higher at the cost of lower specificity compared to urine cytology [112-117] (LE: 3).
- Benign conditions and previous BCG instillations may influence the results of many urinary marker tests [112-114] (LE: 1b).
- Requirements for sensitivity and specificity of a urinary marker test largely depend on the clinical context of the patient (screening, primary detection, follow-up [high-risk, low/intermediate-risk]) [113, 114] (LE: 3).
- The wide range in performance of the markers and low reproducibility may be explained by patient selection and complicated laboratory methods required [114, 115, 118-125].
- Positive results of cytology, UroVysion™ (FISH), Nuclear Matrix Protein (NMP)22®, *Fibroblast Growth Factor Receptor (FGFR)3/Telomerase Reverse Transcriptase (TERT)* and microsatellite analysis in patients with negative cystoscopy and upper tract work-up, may identify patients more likely to experience disease recurrence and possibly progression [118, 121, 124-129] (LE: 2b).
- Promising novel urinary biomarkers, assessing multiple targets, have been tested in prospective multicentre studies [119, 120, 124, 130-133]. Four of the promising and commercially available urine biomarkers, Cx-Bladder [119, 133], ADX-Bladder™ [134, 135], Xpert Bladder® [136, 137] and EpiCheck™ [132], although not tested in RCTs, have such high sensitivities and negative predictive values in the referenced studies for HG disease that these biomarkers may approach the sensitivity of cystoscopy. These 4 tests might be used to replace and/or postpone cystoscopy as they may identify the rare HG recurrences occurring in low/intermediate NMIBC.

5.7 Potential application of urinary cytology and markers

The following objectives of urinary cytology or molecular tests must be considered.

*5.7.1 **Screening of the population at risk of bladder cancer***

The application of haematuria dipstick, followed by *FGFR3*, NMP22® or UroVysion™ tests if dipstick is positive has been reported in BC screening in high-risk populations [138, 139]. However, the low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness of BC screening [127, 139]. Thus, routine screening for BC is not recommended [127, 138, 139].

*5.7.2 **Exploration of patients after haematuria or other symptoms suggestive of bladder cancer (primary detection)***

IIt is generally accepted that none of the currently available tests can replace cystoscopy. However, urinary cytology or biomarkers can be used as an adjunct to cystoscopy to detect missed tumours, particularly CIS. In this setting, specificity is particularly important. Recently, CellDetect® and UroVysion™ have shown similar performance to detect BC and were both superior to cytology [140]. In addition, Xpert Bladder® had higher sensitivity and negative-predictive value than both cytology or UroVysion™ for the detection of BC in patients with haematuria [141].

*5.7.3 **Surveillance of non-muscle-invasive bladder cancer***

Research has been carried out into the usefulness of urinary cytology vs. markers in the follow-up of NMIBC [118, 119, 131, 132, 142]. A recent systematic review and network meta-analysis showed high accuracy of novel urinary biomarkers supporting their utility in the NMIBC surveillance setting [8].

5.7.3.1 Follow-up of high-risk non-muscle-invasive bladder cancer

High-risk tumours should be detected early in follow-up and the percentage of tumours missed should be as low as possible. Therefore, the best surveillance strategy for these patients will continue to include cystoscopy and cytology (see Chapter 8).

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5.7.3.2 Follow-up of low/intermediate-risk non-muscle-invasive bladder cancer

To reduce the number of cystoscopy procedures, urinary markers should be able to detect a recurrence before the tumours are large, numerous and/or muscle invasive. The limitation of urinary cytology and current urinary markers is their low sensitivity for LG recurrences [113, 118] (LE: 1b).

According to current knowledge, no urinary marker can replace cystoscopy during follow-up or lower cystoscopy frequency in a routine fashion. One prospective randomised study (RCT) found that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [143] (LE: 1b), supporting the adjunctive role of a non-invasive urine test performed prior to follow-up cystoscopy [143] (see Section 8.1).

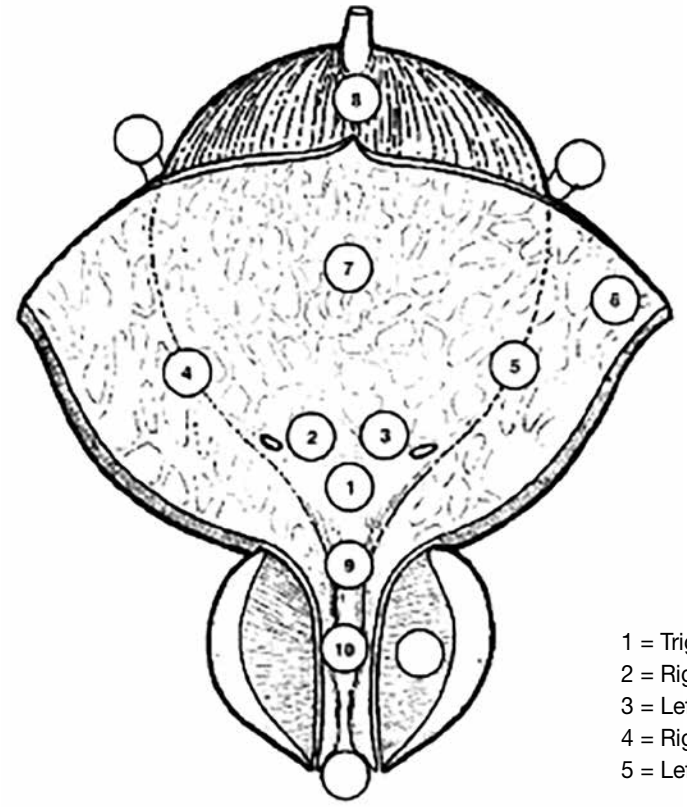
5.8 Cystoscopy

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of sampled tissue by either cold-cup biopsy or resection. Carcinoma *in situ* can be suspected through cystoscopy and urine cytology and confirmed by histological evaluation of multiple bladder biopsies [144].

Cystoscopy is initially performed as an outpatient procedure. A flexible instrument with topical intraurethral anaesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men [145, 146] (LE: 1b).

To temporary increase the urethral pressure by irrigation 'bag squeeze' when passing membranous and prostatic urethra with a flexible cystoscope in males also decreases pain during the procedure [147, 148].

Figure 5.1: Bladder diagram



1 = Trigone
2 = Right ureteral orifice
3 = Left ureteral orifice
4 = Right wall
5 = Left wall
6 = Anterior wall
7 = Posterior wall
8 = Dome
9 = Neck
10 = Posterior urethra

5.9 Summary of evidence and guidelines for the primary assessment of non-muscle-invasive bladder cancer

Summary of evidence	LE
Cystoscopy is necessary for the diagnosis of BC.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	2b

Recommendations	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography-intravenous urography (CT-IVU) during the initial work-up in patients with haematuria.	Strong

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Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
In men, use a flexible cystoscope, if available, and apply irrigation 'bag squeeze' to decrease procedural pain when passing the proximal urethra.	Strong
Describe all macroscopic features of the tumour (site, size, number, and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram (Figure 5.1).	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong
Perform cytology on at least 25 mL fresh urine or urine with adequate fixation. First morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris System 2nd Edn. for cytology reporting.	Strong

5.10 Transurethral resection of TaT1 bladder tumours

*5.10.1 **Strategy of the procedure***

The goals of TURB in TaT1 BC is to establish accurate pathological diagnosis/staging and completely remove all visible lesions. It is a crucial procedure in the management of BC. Transurethral resection of the bladder tumours should be performed systematically in individual steps [6, 149] (see Section 5.14).

The operative steps necessary to achieve a successful TURB include identifying the factors required to assign disease risk (number of tumours, size, architecture, location, concern for the presence of CIS, recurrent vs. primary tumour), clinical stage (bimanual examination under anaesthesia, assignment of clinical tumour stage), adequacy of the resection (visually complete resection, visualisation of muscle at the resection base), visualisation of tumour in the distal ureter and presence of complications (assessment for perforation) [6, 150]. To measure the size of the largest tumour, one can use the end of the cutting loop, which is approximately 1 cm wide, as a reference. Tumour architecture can be sessile, nodular, papillary, mixed papillary/solid or flat.

*5.10.2 **Surgical and technical aspects of tumour resection***

5.10.2.1 Surgical strategy of resection (piecemeal/separate resection, en-bloc resection)

A complete resection, performed by either fractioned or *en-bloc* technique, is essential to achieve a good prognosis [149, 151].

- Piecemeal resection in fractions (separate resection of the exophytic part of the tumour, the underlying bladder wall and the edges of the resection area) provides good information about the vertical and horizontal extent of the tumour [152] (LE: 2b). Whilst this technique is carried out using a loop with diathermy (monopolar or bipolar), the Thulium-YAG laser is potentially a feasible alternative [153].
- *En-bloc* resection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG or KTP-Green Light lasers is feasible in selected exophytic tumours. It provides high-quality resected specimens with the presence of detrusor muscle in 96–100% of cases [149, 154-160] (LE: 3). Respect of tumour architecture increases the accuracy of T1 staging and the possibility of sub-staging while potentially reducing the risk of bladder perforation [154, 159, 160] (LE: 1b).

The technique selected is dependent on the size and location of the tumour and experience of the surgeon. With better detection of tumours and abnormal margins, methods of optical enhancement are expected to improve complete resection (see Section 5.11). A recent RCT [161] did not confirm a higher rate of detrusor muscle retrieval in *en-bloc*- compared to piecemeal resection [162].

5.10.2.2 Evaluation of resection quality

The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence, and tumour under-staging [163] (LE: 1b). The presence of detrusor muscle in the specimen is considered as a surrogate criterion of the resection quality [163] and is required (except in Ta LG/G1 tumours). Surgical checklists and quality performance indicator programmes have shown to increase surgical quality (accurate documentation of factors required to assign risk and sample detrusor muscle) and decrease recurrence rates [6, 150, 164, 165]. The Panel have included a sample TURBT checklist in Table 5.1 (modified and adapted from [5] and [6]).

It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [163, 166]. Virtual training on simulators is an emerging approach [167]. Its role in the teaching process still needs to be established [6]. Surgical experience and/or volume has been associated with risk of complications [168], recurrence [169] and survival [170] in retrospective studies (LE: 3).

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5.10.2.3 Monopolar and bipolar resection

Compared to monopolar resection, bipolar resection has been introduced to reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) and to produce better specimens. Currently, the results remain controversial [171-173], with significant inherent limitations due to selection bias, heterogeneity of surgical approach or inability to qualify surgeon experience. A systematic review of 13 RCTs (2,379 patients) showed no benefit of bipolar vs. monopolar TURB for efficacy and safety [173] while one meta-analysis of RCTs (n = 2,099) suggests a lower fall in haemoglobin and shorter hospital stay with bipolar resections [171] and another systematic review of RCTs and observational studies (n = 19,927) suggests lesser thermal artifacts in the specimen [172].

5.10.2.4 Resection of small papillary bladder tumours at the time of transurethral resection of the prostate (TURP)

It is not uncommon to incidentally detect bladder tumours during TURP in men with benign prostatic hyperplasia. Provided these tumours are papillary, rather small and not extensively multifocal, it seems feasible to resect these tumours and continue with the resection of the prostate [174, 175]. Simultaneous TURB and TURP does not appear to lead to any increased risk of tumour recurrence or progression [176] (LE: 3).

5.11 Endoscopic biopsies

*5.11.1 **Bladder biopsies***

Carcinoma *in situ* can present as a velvet-like, reddish area, indistinguishable from inflammation, or it may not be visible at all. For this reason, biopsies from suspicious urothelium should be taken. In patients with positive urine cytology (see Section 5.5), and normal-looking mucosa at cystoscopy, mapping biopsies are recommended [177, 178]. To obtain representative mapping of the bladder mucosa, biopsies should be taken from the trigone, bladder dome, right, left, anterior and posterior bladder wall [177, 178]. If the equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy.

*5.11.2 **Prostatic urethral biopsies***

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou *et al.*, showed that in 128 men with T1G3 UC, the incidence of CIS in the prostatic urethra was 11.7% [179] (LE: 2b). The risk of prostatic urethra or duct involvement is higher if the tumour is located at the trigone or bladder neck, in the presence of bladder CIS and multiple tumours [180] (LE: 3b). Based on this observation, a biopsy from the prostatic urethra is necessary in some cases (see recommendation in Section 5.14) [179, 181, 182].

5.12 New methods of tumour visualisation

As a standard procedure, cystoscopy and TURB are performed using white light (WL). However, the use of WL alone can lead to missing lesions that are present but not visible, which is why new technologies are being developed.

*5.12.1 **Photodynamic diagnosis (fluorescence cystoscopy or blue light cystoscopy)***

Photodynamic diagnosis is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL).

5.12.1.1 Impact on bladder cancer detection

It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for the detection of malignant tumours, particularly CIS [183, 184] (LE: 1a). In a systematic review and meta-analysis, PDD had higher sensitivity than WL endoscopy in the pooled estimates for analyses at both the patient-level (92% vs. 71%) and biopsy-level (93% vs. 65%) [184]. A prospective RCT did not confirm a higher detection rate in patients with known positive cytology before TURB [185].

Photodynamic diagnosis had lower specificity than WL endoscopy (63% vs. 81%) [184]. False-positivity can be induced by inflammation or recent TURB and during the first 3 months after BCG instillation [186, 187] (LE: 1a).

5.12.1.2 Impact on bladder cancer recurrence

The beneficial effect of ALA or HAL fluorescence cystoscopy on recurrence rate in patients with TURB was evaluated. A systematic review and analysis of 14 RCTs including 2,906 patients, 6 using 5-ALA and 9 HAL, demonstrated a decreased risk of BC recurrence in the short and long term. There were, however, no differences in progression and mortality rates. The analysis demonstrated inconsistency between trials and potential susceptibility to performance and publication bias [188] (LE: 1a). While a recent systematic review and meta-analysis of 12 RCTs (n = 2,288) revealed lower risk of recurrence and improved time to recurrence (at least in the first 2 years and possibly up to 5 years) with PDD [189] (LE: 1a), the most recent Cochrane systematic review and meta-analysis of 16 RCTs (n = 4,325) demonstrated that PDD-assisted TURBT may

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prolong not only recurrence over time but also risk of progression, albeit supported only by low certainty evidence [190].

A recent RCT showed that PDD-guided TURBT did not reduce recurrence rates, nor was it cost-effective compared with WL cystoscopy at 3 years [191]. The study was considered underpowered, potentially having captured a diluted effect of PDD at 3 years (as opposed to the positive trend in time to recurrence seen within the first 18 months) [192-194].

*5.12.2 **Narrow-band imaging***

In narrow-band imaging (NBI), the contrast between normal urothelium and hyper-vascular cancer tissue is enhanced. Improved cancer detection has been demonstrated by NBI flexible cystoscopy and NBI-guided biopsies and resection [195-198] (LE: 3b). Two RCTs assessed the reduction of recurrence rates if NBI is used during TURB [198, 199]. Although the overall results were negative, a benefit after 3 and 12 months was observed for low-risk tumours (pTa LG, < 30 mm, no CIS) [199].

A systematic review and meta-analysis by Russo *et al.*, (17 RCTs and non-RCTs) demonstrated improved detection (diagnostic accuracy) of bladder tumours with either PDD or NBI over WL cystoscopy [200], while another one (including 5,217 patients) showed improved RFS with either enhancement technique [201] (LE: 1a). Conversely, a systematic review and network meta-analysis that took into account the use of single post-operative instillation of chemotherapy, concluded that there was a lower likelihood of recurrence at one year only following PDD-guided TURB (with or without single instillation) but not with NBI-guided surgery [202] (LE: 1a).

*5.12.3 **IMAGE1 S™, and other technologies***

IMAGE1 S™ (formerly named SPIES) is an image enhancement system based on a computerized processing of different colour components that uses specific light filters. Limited evidence has been produced so far in an attempt to validate the 4 different light spectra modalities, suggesting an improvement in the diagnostic accuracy of WL [203, 204]. Early (18 months) follow-up data of an RCT failed to show an advantage in recurrence rate in the IMAGE1 S™ arm over WL, except in a subgroup of primary low intermediate-risk NMIBCs [205].

Confocal laser micro-endoscopy is a high-resolution imaging probe designed to provide endoscopic histological grading in real time but requires further validation [206].

5.13 Second resection (second TURB)

*5.13.1 **Detection of residual disease and tumour upstaging***

The significant risk of residual tumour after initial TURB of TaT1 lesions has been demonstrated [151] (LE: 1b). This residual cancer has the potential to worsen oncological outcomes and therefore further emphasises the importance of an effective initial TURB. As patients with an initial incomplete TURB (either from extensive tumour or intra-operative complications) will require a second completion resection, documentation of resection completeness at the time of the initial TURB is essential.

A systematic review analysing data of 8,409 patients with Ta or T1 HG UC demonstrated a 51% risk of persistence and an 8% risk of under-staging in T1 tumours. The analysis also showed a high risk of residual disease in Ta tumours, but this observation was based only on a limited number of cases. Most of the residual lesions were detected at the original tumour location [207] (LE: 1a).

Another systematic review and meta-analysis of 3,556 patients with T1 tumours showed that the prevalence rate of residual tumours and upstaging to invasive disease after TURB remained high even in a subgroup with detrusor muscle sampled at the initial TURB. In the subgroup of 1,565 T1 tumours with detrusor muscle present, persistent tumour was found in 58% and under-staging occurred in 11% of cases [208].

Prospective trials suggest that post-operative positive urine cytology [209] and Xpert Bladder® (urine mRNA test) [210] are independently associated with residual disease at second resection and risk of future recurrences, respectively (LE: 2b). These data, however, need to be confirmed in further studies.

*5.13.2 **The impact of second resection on treatment outcomes***

A second TURB can increase recurrence-free survival (RFS) [211, 212] (LE: 2a), improve outcomes after BCG treatment [213] (LE: 3) and provide prognostic information [214-217] (LE: 3).

In a retrospective evaluation of a large multi-institutional cohort of 2,451 patients with BCG-treated T1 G3/HG tumours (a second resection was performed in 935 patients), the second resection improved RFS, progression-free survival (PFS) and overall survival (OS) only in patients without detrusor muscle in the initial resection specimen [218] (LE: 3). In a retrospective analysis of 7,666 patients diagnosed with T1 cancer in Ontario, 2,162 underwent a second resection; after adjusting for the effects of confounding variables, only OS

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(and not CSS) was better in patients who underwent second resection [170] (LE: 3). This apparent improved survival could also be the result of selection bias with fitter patients undergoing second resections. High-level evidence is required to identify specific sub-groups of patients with high-grade cancer who are most likely to benefit from a second resection.

*5.13.3 **Timing of second resection***

Retrospective evaluation showed that a second resection performed 14–42 days after initial resection provides longer RFS and PFS compared to second resection performed after 43–90 days [219] (LE: 3). Based on this currently available evidence, a second TURB is recommended in selected cases 2 to 6 weeks after initial resection [219] (for recommendations on patient selection, see Section 5.14).

*5.13.4 **Recording of results***

The results of the second resection (residual tumours and under-staging) reflect the quality and effectiveness of the initial TURB. As the goal is to improve the quality of the initial TURB, the results of the second resection should be recorded.

5.14 Pathology report

Pathological investigation of the specimen(s) obtained by TURB and biopsies is an essential step in the decision-making process for BC [220]. Close co-operation between urologists and pathologists is required. Clinical information and high quality of resected and submitted tissue is essential for correct pathological assessment. To obtain all relevant information, the specimen collection, handling and evaluation, should respect the recommendations provided below (see Section 5.14) [221]. In difficult cases, an additional review by an experienced genitourinary pathologist can be considered.

Table 5.1 TURBT checklist*

TURBT checklist - In the Operating Room	
Check the operating room setup	Instruments (sheath, resectoscope, loops, roller if needed, monopolar/ bipolar), camera, video, strainer, specimen container, catheter if needed
Decide irrigation fluid	Saline, Glycine, Water
Disease characteristics checklist	History of bladder cancer, tumour characteristics at cystoscopy if any, imaging results if any, first or second look, visual optimisation planned (PDD/NBI), risk classification
Cystoscopy/ TURBT	
Cystoscopy	Urethra/prostate (males)
	Ureteral orifices
	Diverticuli
	Tumour location, number, size, appearance (papillary/sessile), CIS (yes/no)
	White light/PDD/NBI/IMAGE1 S™
	Urine for cytology/bladder wash
TURBT	Resection technique (standard/*en bloc*/cold cup/roller ball cautery)
	Depth of resection
	Complete/incomplete resection
	Prostatic urethra biopsy if performed
	Any additional procedure, i.e. retrograde contrast study
	Estimated blood loss
	Intra-operative complications, if any
	Intravesical therapy if given or planned in recovery setting

**Adapted from Mostafid et al., and Suarez-Ibarrola et al. [5, 6].*
NBI = narrow-band imaging; PDD = photodynamic diagnosis; TURBT = transurethral resection of bladder tumour.

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5.15 Summary of evidence and guidelines for transurethral resection of the bladder, biopsies and pathology report

Summary of evidence	LE
Transurethral resection of the bladder tumour (TURB) followed by pathology investigation of the obtained specimen(s) is an essential step in the management of NMIBC.	1
The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and tumour under-staging (with the exception of Ta LG/G1 tumours).	2b
A second TURB can detect residual tumours and tumour under-staging, increase recurrence-free survival, improve outcomes after BCG treatment and provide prognostic information.	2

Recommendations	Strength rating
In patients suspected of having bladder cancer, perform a transurethral resection of the bladder tumour (TURB) followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	Strong
Perform TURB systematically in individual steps: • bimanual palpation under anaesthesia; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from the prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • recording of findings in the surgery report/record; • precise description of the specimen(s) for pathology evaluation.	Strong
Performance of individual steps	
Perform *en-bloc* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area).	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended if cytology or urinary molecular marker test is positive. If the equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if there is positive cytology or urinary molecular marker test without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be performed at the time of the second resection.	Strong
Take a prostatic urethral biopsy from the pre-collicular area (between the 5 and 7 o'clock position) using a resection loop.	Weak
Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers.	Weak
The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, extent, macroscopic completeness of resection as well as any complications.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong
Perform a second TURB in the following situations: • after incomplete initial TURB, or in case of doubt about completeness of a TURB; • if there is no detrusor muscle in the specimen after initial resection, with the exception of Ta LG/G1 tumours and primary CIS; • in T1 tumours.	Strong
If indicated, perform a second TURB within 2–6 weeks after the initial resection. This second TURB should include resection of the primary tumour site.	Weak
Register the pathology results of a second TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
The pathological report should specify tumour location, tumour grade and stage, lympho-vascular invasion, subtypes of urothelial carcinoma, presence of CIS and detrusor muscle.	Strong

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6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 TaT1 tumours

Treatment should take into account a patient's prognosis. In order to predict the risk of disease recurrence and/or progression, several prognostic models for specified patient populations have been introduced.

*6.1.1 **Scoring models using the WHO 1973 classification system***

6.1.1.1 The 2006 European Organisation for Research and Treatment of Cancer (EORTC) scoring model

To be able to predict both the short- and long-term risks of disease recurrence and progression in individual patients, the EORTC Genito-Urinary Cancer Group (GUCG) published a scoring system and risk tables based on the WHO 1973 classification in 2006 [222]. The scoring system is based on the 6 most significant clinical and pathological factors in patients mainly treated by intravesical chemotherapy:

- Number of tumours;
- Tumour diameter;
- Prior recurrence rate;
- T category;
- Concurrent CIS;
- WHO 1973 tumour grade.

Using the 2006 EORTC scoring model, individual probabilities of recurrence and progression at 1 and 5 years may be calculated (https://www.omnicalculator.com/health/eortc-bladder-cancer).

6.1.1.2 The model for patients with Ta G1/G2 (WHO 1973) tumours treated with chemotherapy

Patients with Ta G1/G2 tumours receiving chemotherapy were stratified into 3 risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade (WHO 1973), number of tumours and adjuvant chemotherapy [223].

6.1.1.3 Club Urologico Español de Tratamiento Oncologico (CUETO) scoring model for BCG-treated patients

A model that predicts the risk of recurrence and progression, based on 12 doses of intravesical BCG over a 5 to 6 months period following TURB, has been published by the CUETO (Spanish Urological Oncology Group). It is based on an analysis of 1,062 patients from 4 CUETO trials that compared different intravesical BCG treatments. No immediate post-operative instillation or second TURB was performed in these patients. The scoring system is based on the evaluation of seven prognostic factors:

- gender;
- age;
- prior recurrence status;
- number of tumours;
- T category;
- associated CIS;
- WHO 1973 tumour grade.

Using this model, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients [224] (LE: 2a). The lower risks in the CUETO tables may be attributed to the use of BCG in this study. The prognostic value of the EORTC scoring system has been confirmed by data from the CUETO patients treated with BCG [225] and by long-term follow-up in another patient population [226] (LE: 2a).

6.1.1.4 The 2016 EORTC scoring model for patients treated with maintenance BCG

In 1,812 intermediate- and high-risk patients without CIS treated with 1 to 3 years of maintenance BCG, the EORTC found that the prior disease-recurrence rate and number of tumours were the most important prognostic factors for disease recurrence, stage and WHO 1973 grade for disease progression and disease-specific survival, while age and WHO 1973 grade were the most important prognostic factors for OS. T1 G3 patients did poorly, with 1- and 5-year disease-progression rates of 11.4% and 19.8%, respectively. Using these data, EORTC risk groups and nomograms for BCG-treated patients were developed [227] (LE: 2a).

*6.1.2 **Scoring model using the WHO 2004/2016 and WHO 1973 classification systems***

6.1.2.1 EAU NMIBC 2021 scoring model

To update the risk of disease progression and create new prognostic factor risk groups using both the WHO 1973 and WHO 2004/2016 classification systems (without central pathology review), individual patient data

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from 3,401 primary patients treated from 1990 to 2018 were used [65] (see Section 4.5). Only patients treated with TURB ± intravesical chemotherapy were included, those treated with adjuvant intravesical BCG were excluded because BCG may reduce the risk of disease progression. From the multivariate analyses, tumour stage, WHO 1973 grade, WHO 2004/2022 grade, concomitant CIS, number of tumours, tumour size and age were independent predictors of disease progression [65].

This is the only available model where the WHO 2004/2022 classification system is included as one of the parameters to calculate an individual patient's risk group and probability of progression. As the WHO 2004/2022 classification system is the main grading classification system used by pathologists, the Guidelines Panel recommends to use the 2021 EAU NMIBC scoring model for risk groups definition (see Section 6.3).

The 2021 EAU NMIBC scoring model determines the risk of tumour progression, but not recurrence; therefore any of the models mentioned in Section 6.1.1 may be used for calculation of an individual's risk of disease recurrence.

*6.1.3 **Further prognostic factors***

Further prognostic factors have been described in selected patient populations:

- In T1 HG/G3 tumours, important prognostic factors were female sex, CIS in the prostatic urethra in men treated with an induction course of BCG, and age, tumour size and concurrent CIS in BCG-treated patients (62% with an induction course only) [179, 228] (LE: 2b).
- Attention must be given to patients with T1 HG/G3 tumours in bladder (pseudo) diverticulum because of the absence of muscle layer in the diverticular wall [229] (LE: 3).
- In patients with T1 tumours, the finding of residual T1 disease at second TURB is an unfavourable prognostic factor [215-217] (LE: 3).
- In patients with T1G2 tumours treated with TURB, recurrence at 3 months was the most important predictor of progression [230] (LE: 2b).
- The prognostic value of pathological factors has been discussed elsewhere (see Section 4.6). More research is needed to determine the role of molecular markers in improving the predictive accuracy of currently available risk tables [226, 231].

6.2 Carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [232] (LE: 3). There are no reliable prognostic factors, but some studies, however, have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [233, 234], in extended CIS [235] and in CIS in the prostatic urethra [179] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [224, 225, 230]. Approximately 10 to 20% of complete responders eventually experience disease progression to muscle-invasive disease, compared with 66% of non-responders [236, 237] (LE: 2a).

6.3 Patient stratification into risk groups

To be able to facilitate treatment recommendations, the Guidelines Panel recommends the stratification of patients into risk groups based on their probability of progression to muscle-invasive disease. The new risk group definitions provided in these EAU Guidelines are based on an individual patient data analysis in primary patients and the calculation of their progression scores (2021 EAU NMIBC scoring model) as presented in Sections 4.5 and 6.1.2) [65].

For calculation of the risk group in individual patients, either one, or both, of the WHO 1973 and WHO 2004/2016 classification systems may be used. The probability of progression at 5 years varies from less than 1% to more than 40% between the risk groups.

For factors where individual patient data were not collected such as subtypes of UC, LVI, primary CIS and CIS in the prostatic urethra; literature data have been used to classify patients into risk groups.

The clinical compositions of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or WHO 1973 classification systems are provided in Table 6.1. Apps for the web (www.nmibc.net), iOS and Android (iOS / https://apps.apple.com/us/app/eau-nmibc-risk-calculator/id1578482687 and Android / https://play.google.com/store/apps/details?id=net.ydeal.nmibc) have been developed to facilitate determining a patient's risk group in daily clinical practice. The individual probability of disease progression at 1, 5 and 10 years for the new EAU NMIBC risk groups is presented in Table 6.2. A single-centre study validated the EAU NMIBC 2021 scoring model in 529 patients who received BCG [238]. The authors found that the progression risk for the EAU 2021 high- and very high-risk groups were significantly lower in BCG-treated patients than that in Table 6.2 [65]. These lower risks may be attributed to the use of BCG.

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Table 6.1: Clinical composition of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or the WHO 1973 grading classification systems [65]

- Only one of the two classification systems (WHO 1973 or WHO 2004/2016) is required to use this table.
- If both classification systems are available in an individual patient, the Panel recommends using the risk group calculation based on the WHO 1973 as it has better prognostic value.
- The category of LG tumours (WHO 2004/2016) also includes patients with tumours classified as PUNLMP.
- Additional clinical risk factors are:
    - age > 70;
    - multiple papillary tumours;
    - tumour diameter > 3 cm.

Risk group	
Low Risk	• A primary, single, TaT1 LG/G1 tumour < 3 cm in diameter without CIS in a patient ≤ 70 years
	• A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors
Intermediate Risk	Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High Risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group • All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: • Ta LG/G2 or T1G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1G2 no CIS with at least 1 risk factor
Very High Risk	**Stage, grade with additional clinical risk factors:** • Ta HG/G3 and CIS with all 3 risk factors • T1G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

The scoring model is based on individual patient data, but does not consider patients with primary CIS (high risk) or with recurrent tumours, as well as some pathologic parameters like subtypes of UC (see Section 4.7) and LVI. Nevertheless:

- Based on data from the literature, all patients with CIS in the prostatic urethra, with subtypes of UC (see Section 4.8) or with LVI should be included in the very high-risk group.
- Patients with recurrent tumours should be included in the intermediate-, high-, or very high-risk groups according to their other prognostic factors.

Table 6.2: Probabilities of disease progression in 1, 5 and 10 year(s) for the new EAU NMIBC risk groups [65]*

Risk group	***Probability of Progression and 95% Confidence Interval (CI)***		
	1 Year	5 Years	10 Years
New Risk Groups with WHO 2004/2016			
Low	0.06% (CI: 0.01%–0.43%)	0.93% (CI: 0.49%–1.7%)	3.7% (CI: 2.3%–5.9%)
Intermediate	1.0% (CI: 0.50%–2.0%)	4.9% (CI: 3.4%–7.0%)	8.5% (CI: 5.6%–13%)
High	3.5% (CI: 2.4%–5.2%)	9.6% (CI: 7.4%–12%)	14% (CI: 11%–18%)
Very High	16% (CI: 10%–26%)	40% (CI: 29%–54%)	53% (CI: 36%–73%)
New Risk Groups with WHO 1973			
Low	0.12% (CI: 0.02%–0.82%)	0.57% (CI: 0.21%–1.5%)	3.0% (CI: 1.5%–6.3%)
Intermediate	0.65% (CI: 0.36%–1.2%)	3.6% (CI: 2.7%–4.9%)	7.4% (CI: 5.5%–10%)
High	3.8% (CI: 2.6%–5.7%)	11% (CI: 8.1%–14%)	14% (CI: 10%–19%)
Very High	20% (CI: 12%–32%)	44% (CI: 30%–61%)	59% (CI: 39%–79%)

WHO = World Health Organization.

**Table 6.2 does not include patients with subtypes of urothelial carcinoma (variant histologies), LVI, CIS in the prostatic urethra, primary CIS or recurrent patients.*

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6.4 Summary of evidence and guidelines for stratification of non-muscle-invasive bladder cancer

Summary of evidence	LE
The EAU NMIBC 2021 scoring model and risk tables predict the short- and long-term risks of disease progression in individual patients with primary NMIBC using either the WHO 1973 or the WHO 2022 classification system (see Section 6.1.2.1).	2b
The 2006 EORTC scoring model and risk tables predict the short- and long-term risks of disease recurrence and progression in individual patients with NMIBC using the WHO 1973 classification system (see Section 6.1.1.1).	1b
Patients with Ta G1/G2 tumours receiving chemotherapy have been further stratified into 3 risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade (WHO 1973), number of tumours and adjuvant chemotherapy (see Section 6.1.1.2).	2b
In patients treated with 5 to 6 months of BCG, the CUETO scoring model predicts the short- and long-term risks of disease recurrence and progression using the WHO 1973 classification system (see Section 6.1.1.3).	1b
In patients receiving at least 1 year of BCG maintenance; prior recurrence rate and number of tumours are the most important prognostic factors for disease recurrence. Stage and grade are the most important prognostic factors for disease progression and disease-specific survival; patient age and grade (WHO 1973) are the most important prognostic factors for OS (see Section 6.1.1.4).	1b

Recommendations	Strength rating
Stratify patients into 4 risk groups to predict progression, according to Table 6.1. A patient's risk group can be determined using the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
For information about the risk of disease progression in a patient with primary TaT1 tumours, not treated with bacillus Calmette-Guérin (BCG), use the data from Table 6.2.	Strong
Use the 2006 EORTC scoring model to predict the risk of tumour recurrence in individual patients not treated with BCG.	Strong
Use the 2016 EORTC scoring model or the CUETO risk scoring model to predict the risk of tumour recurrence in individual patients treated with BCG intravesical immunotherapy (the 2016 EORTC model is calculated for 1 to 3 years of maintenance, the CUETO model for 5 to 6 months).	Strong

7. DISEASE MANAGEMENT

7.1 Counselling of smoking cessation

It has been confirmed that smoking increases the risk of tumour recurrence and progression in NMIBC patients [239, 240] (LE: 3). While it is still controversial whether smoking cessation in BC will favourably influence the outcome of BC treatment, patients should be counselled to stop smoking due to the general health risks associated with tobacco smoking [229, 241-243] (LE: 3).

7.2 Office-based fulguration and laser vaporisation

In patients with a history of small Ta LG/G1 tumours, fulguration, or laser vaporisation of small papillary recurrences on an outpatient basis can reduce the therapeutic burden [244, 245] (LE: 3). In a prospective RCT, laser photocoagulation with intravesical lidocaine in an outpatient setting proved non inferior to standard TURB under general anaesthesia for the 4 months recurrence rate. Notably, the laser fulguration procedure resulted in only a modest pain score (2.4) and was preferred by 98% of patients [246] (LE: 1b).

7.3 Active Surveillance

With recurrence in LG(G1)Ta tumours being more likely low grade and non-invasive [247-249] the risk of progression to a higher grade or stage is infrequent to rare [250-252]. Expectant management or active surveillance (AS), offer an alternative to TURB and office-based fulguration. Observing no progression to MIBC, Soloway *et al.*, first recommended this approach in 2003 [253] and Miyake *et al.*, subsequently proposed an algorithm for AS using changes in size and multifocality as triggers for intervention [254]. However, from a review undertaken by the EAU Young Academic Urology group [255], it appears that the level of evidence in

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favour of AS is low, with observational studies having heterogenous selection criteria, triggers for intervention and surveillance tools. The multicentre prospective Bladder Cancer Italian Active Surveillance (BIAS) project, conversely, demonstrated that AS is feasible in selected patients [256, 257]; however, additional evidence from quality clinical trials is required.

7.4 Adjuvant intravesical treatment

Although TURB by itself can eradicate a TaT1 tumour completely, these tumours commonly recur and can progress to MIBC. The high variability in the 3-month recurrence rate indicates that the TURB was incomplete or provokes recurrences in a high percentage of patients [151]. It is therefore necessary to consider adjuvant therapy in all patients.

*7.4.1 **Post-operative irrigation***

Two systematic reviews [258, 259] and one meta-analysis [260] suggest efficacy of continuous irrigation in the prevention of early recurrences. In case intravesical chemotherapy is not feasible, irrigation of the bladder might be considered.

*7.4.2 **Intravesical chemotherapy***

7.4.2.1 A single, immediate, post-operative intravesical instillation of chemotherapy

Immediate single instillation (SI) has been shown to act by destroying circulating tumour cells after TURB, and by an ablative effect on residual tumour cells at the resection site and on small overlooked tumours [261-264] (LE: 3).

Four large meta-analyses comprising 1,476 to 3,103 patients have consistently shown that after TURB, SI significantly reduces the recurrence rate compared to TURB alone [265-268] (LE: 1a). In a systematic review and individual patient data meta-analysis of 2,278 eligible patients [265], SI reduced the 5-year recurrence rate by 14%, from 59% to 45%. Only patients with primary tumours or intermediate-risk recurrent tumours with a prior recurrence rate of < 1 recurrence/year and those with a 2006 EORTC recurrence score < 5 benefited from SI. In patients with a 2006 EORTC recurrence score > 5 and/or patients with a prior recurrence rate of > 1 recurrence per year, SI was not effective as a single adjuvant treatment. No randomised comparisons of individual drugs have been conducted [265-268].

Single instillation with mitomycin C (MMC), epirubicin or pirarubicin [265], as well as gemcitabine [268], have all shown to lower the intravesical recurrence rate. Single instillation with gemcitabine was superior to saline in a RCT with approximately 200 patients per arm with remarkably low toxicity rates [269]. These findings are in contrast with a previous study, which, however, used a shorter instillation time [270]. In the Böhle *et al.*, study, continuous saline irrigation was used for 24 hours post-operatively in both arms, which could explain the low recurrence rate in the control arm [270].

Prevention of tumour cell implantation should be initiated within the first few hours after TURB. After that, tumour cells are firmly implanted and are covered by the extracellular matrix [261, 271-273] (LE: 3). In all SI studies, the instillation was administered within 24 hours. Two RCTs found no overall impact of SI with apaziquone; in contrast, a *post-hoc* analysis did find a reduction of recurrence risk in patients receiving apaziquone within 90 minutes following TURB [274].

To maximise the efficacy of SI, one should devise flexible practices that allow the instillation to be given as soon as possible after TURB, preferably within the first two hours in the recovery room or even in the operating theatre. As severe complications have been reported in patients with drug extravasation, safety measures should be maintained (see Section 7.7) [275, 276]. To allow for optimal compliance with this Level 1 evidence, clinical teams are encouraged to explore barriers and facilitators within their practice [277].

7.4.2.2 Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 6.1 and 6.2), a SI reduces the risk of recurrence and is considered to be the standard and complete treatment [265, 266] (LE: 1a). For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 6.1 and 6.2). Efficacy data for the following comparisons of application schemes were published.

Single installation only vs. SI and further repeat instillations

In one study, further chemotherapy instillations after SI improved RFS in intermediate-risk patients [278] (LE: 2a).

Repeat chemotherapy instillations vs. no adjuvant treatment

A large meta-analysis of 3,703 patients from 11 RCTs showed a highly significant (44%) reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [279]. This corresponds to an absolute

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difference of 13–14% in the proportion of patients with recurrence. Contrary to these findings, two meta-analyses have demonstrated that BCG therapy may also reduce the risk of tumour progression [280, 281] (see Section 7.2.2.1) (LE: 1a). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [282-284] (see Section 7.2.2.1) (LE: 1a). However, BCG causes significantly more side effects than chemotherapy [284] (LE: 1a).

Single instillation + further repeat instillations vs. later repeat instillations only

There is evidence from several studies in intermediate-risk patients that SI might have an impact on recurrence even when further adjuvant instillations are given [285-288]. A RCT including 2,243 NMIBC patients, which compared SI of MMC with an instillation of MMC delayed two weeks after TURB (followed by further repeat instillations in both treatment arms), showed a significant reduction of 9% in the risk of recurrence at 3 years in favour of SI, from 36% to 27%. The effect was significant in the intermediate- and high-risk groups of patients receiving additional adjuvant MMC instillations [285] (LE: 2a). Since the author's definition of the risk groups differed significantly in the initial publication, they adapted their patient stratification in the second analysis and consistently showed improved efficacy of SI followed by repeat MMC instillations [289]. The results of this study should be considered with caution since some patients did not receive adequate therapy. Another RCT found no impact of SI with epirubicin followed by further chemotherapy or BCG instillations in a cohort of predominant HR BC patients [290].

The optimal schedule of intravesical chemotherapy instillations

The length and frequency of repeat chemotherapy instillations is still controversial; however, it should not exceed one year [288] (LE: 3).

7.4.2.3 Options for improving efficacy of intravesical chemotherapy

7.4.2.3.1 Adjustment of pH, duration of instillation, and drug concentration

Two prospective RCTs showed that optimized intravesical administration of MMC reduced recurrence rates, either by a combination of measures (higher MMC-dose, peroral sodium bicarbonate, and refraining from drinking) [291] and by adding cytosine arabinoside [292], respectively (LE: 1b). The value of these measures in addition to alternative maintenance schedules is not known. Another trial reported that duration of a one-hour instillation of MMC was more effective compared to a 30-minute instillation, but no efficacy comparisons are available for one- vs. two-hour durations of instillation [293] (LE: 3). Another RCT using epirubicin has documented that concentration is more important than treatment duration [294] (LE: 1b). In view of these data, instructions are provided (see Section 7.7).

7.4.2.3.2 Device-assisted intravesical chemotherapy

Hyperthermic intravesical chemotherapy

Different technologies which increase the temperature of instilled MMC are available. A recent systematic review and meta-analysis including 4 RCTs suggests similar toxicity as for BCG with maintenance schedule [295].

Microwave-induced hyperthermia effect (RITE)

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [296]. In one RCT comparing one year of BCG with one year MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk BC, increased RFS at 24 months in the MMC group was demonstrated [297] (LE: 1b).

Conductive chemohyperthermia

In an open-label phase II RCT including 259 patients, HIVEC chemo-hyperthermia failed to demonstrate an improvement in DFS at 24 months over standard adjuvant intravesical chemotherapy in intermediate-risk NMIBC (61% vs. 60%), with a higher risk of treatment discontinuation (59% vs. 89% of completed planned treatments) [298].

In a pilot phase II RCT on 50 high-risk NMIBCs, HIVEC™ MMC showed early outcomes comparable to BCG (24 months RFS, 86.5% with HIVEC™ and 71.8% with BCG, p = 0.184) [299]. These data needs to be corroborated by further studies.

Electromotive drug administration

The efficacy of MMC using electromotive drug administration (EMDA) sequentially combined with BCG in patients with high-risk tumours has been demonstrated in one small RCT [300]. The definitive conclusion, however, needs further confirmation. For application of device-assisted instillations in patients recurring after BCG treatment, see Section 7.9.3.

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7.4.2.4 Summary of evidence - intravesical chemotherapy

Summary of evidence	LE
In patients with low-risk NMIBC and in those with a small Ta LG/G1 recurrence detected more than one year after previous TURB, a SI significantly reduces the recurrence rate compared to TURB alone.	1a
Single instillation might have an impact on recurrence even when further adjuvant chemotherapy instillations are given.	3
Repeat chemotherapy instillations (with or without previous SI) improve RFS in intermediate-risk patients.	2a

7.4.3 ***Intravesical bacillus Calmette-Guérin (BCG) immunotherapy***

7.4.3.1 Efficacy of BCG

7.4.3.1.1 Recurrence rate

Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB plus chemotherapy for preventing the recurrence of NMIBC [282, 301-304] (LE: 1a). Three RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin and interferon (INF) [305], MMC [306], or epirubicin alone [283] and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long lasting [283, 306] and was also observed in a separate analysis of patients with intermediate-risk tumours [283]. One meta-analysis [282] has evaluated the individual data from 2,820 patients enrolled in 9 RCTs that have compared MMC vs. BCG. In the trials with BCG maintenance, there was a 32% reduction in the risk of recurrence for BCG compared to MMC, but a 28% increase in the risk of recurrence for patients treated with BCG in the trials without BCG maintenance. A Cochrane systematic review confirmed that BCG is more effective in reducing the recurrence rate over MMC [307].

7.4.3.1.2 Progression rate

Two meta-analyses have demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [280, 281, 304] (LE: 1a). A meta-analysis carried out by the EORTC GUCG has evaluated data from 4,863 patients enrolled in 24 RCTs. In 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 years, tumours progressed in 9.8% of the patients treated with BCG compared to 13.8% in the control groups (TURB alone, TURB and intravesical chemotherapy, or TURB with the addition of other immunotherapy). This shows a reduction of 27% in the odds of progression with BCG maintenance treatment. The size of the reduction was similar in patients with TaT1 papillary tumours and in those with CIS [281]. A RCT with long-term follow-up has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin [283] (LE: 1b). In contrast, an individual patient data meta-analysis and Cochrane review were not able to confirm any statistically significant difference between MMC and BCG for progression, survival, and cause of death [282, 307].

The conflicting results in the outcomes of these studies can be explained by different patient characteristics, duration of follow-up, methodology and statistical power. However, most studies showed a reduction in the risk of progression in high-and intermediate-risk tumours if a BCG maintenance schedule was applied.

7.4.3.1.3 Influence of further factors

Two other meta-analyses have suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [308]. In the individual patient data meta-analysis, however, BCG maintenance was more effective than MMC in reduction of recurrence rate, both in patients previously treated and not previously treated with chemotherapy [282] (LE: 1a). It was demonstrated that BCG was less effective in patients > 70 years of age, but still more effective than epirubicin in a cohort of elderly patients [309] (LE: 1a). According to a cohort analysis, the risk of tumour recurrence after BCG was shown to be higher in patients with a previous history of UTUC [310].

7.4.3.2 BCG strain

Although smaller studies without maintenance demonstrated some differences between strains [310-312], a network meta-analysis identified ten different BCG strains used for intravesical treatment in the published literature but was not able to confirm superiority of any BCG strain over another [313].

Similarly, a published meta-analysis of prospective RCTs [281], published data from a prospective registry [314] as well as from a *post-hoc* analysis of a large phase II prospective trial assessing BCG and INF-α in both BCG-naive and BCG-failure patients did not suggest any clear difference in efficacy between the different BCG strains [315] (LE: 2a). The quality of data, however, does not allow definitive conclusions.

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7.4.3.3 BCG toxicity

Bacillus Calmette-Guérin intravesical treatment is associated with more side effects compared to intravesical chemotherapy [281, 307] (LE: 1a). However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [316] (LE: 1b). The incidence of BCG infections after BCG instillations was 1% in a registry-based cohort analysis [317]. It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [316]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [318]. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [319] (LE: 2a). No significant difference in toxicity between different BCG strains was demonstrated [314]. Symptoms may be the result of side effects of the BCG treatment or caused by bladder disease (widespread CIS) itself. Consequently, the burden of symptoms is reduced after completion of the treatment in a significant number of patients [320].

Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected (see Section 7.9). The presence of leukocyturia, nonvisible haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [121, 321] (LE: 3). Three RCTs suggest reduced side effects by administering different quinolones in conjunction with the BCG-instillations [322-324]. The latter, by using two doses of levofloxacin in conjunction with each BCG-instillation, reduced the proportion of patients with high-grade side effects, both local (pollakisuria) and systemic (fever), and additionally displayed improved PFS in the experimental arm [324] (LE: 1b).

Bacillus Calmette-Guérin should be used with caution in immunocompromised patients; e.g., immunosuppression, human immunodeficiency virus (HIV) infection poses relative contraindications [325], although some small studies have shown similar efficacy and no increase in complications compared to non-immunocompromised patients. The role of prophylactic anti-tuberculosis medication in these patients remains unclear [326-328] (LE: 3). The management of side effects after BCG should reflect their type and grade according to the recommendations provided by the International Bladder Cancer Group (IBCG) and by a Spanish group [329, 330] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical BCG [330-333]

Management options for local side effects (modified from International Bladder Cancer Group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or non-steroidal anti-inflammatory drugs (NSAIDs).
	If symptoms improve within a few days: continue instillations.
	If symptoms persist or worsen: a. Postpone the instillation b. Perform a urine culture c. Start empirical antibiotic treatment
	If symptoms persist even with antibiotic treatment: a. With positive culture: adjust antibiotic treatment according to sensitivity b. With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary) [331].
	If symptoms persist: anti-tuberculosis drugs + corticosteroids.
	If no response to treatment and/or contracted bladder: radical cystectomy.
Haematuria	Perform urine culture to exclude haemorrhagic cystitis if other symptoms present.
	If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
Symptomatic granulomatous prostatitis	Symptoms rarely present: perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for 3 months.
	Cessation of intravesical therapy.
Epididymo-orchitis [332]	Perform urine culture and administer quinolones.
	Cessation of intravesical therapy.
	Orchidectomy if abscess or no response to treatment.

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Management options for systemic side effects	
General malaise, fever	Generally resolve within 48 hours, with or without antipyretics.
Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Reactive arthritis: NSAIDs.
	If no/partial response, proceed to corticosteroids, high-dose quinolones or antituberculosis drugs [333].
Persistent high-grade fever (> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with more than two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post-transurethral resection of the bladder (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: • High-dose quinolones or isoniazid, rifampicin, and ethambutol 1.2 g daily for 6 months. • Early, high-dose corticosteroids as long as symptoms persist. • Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or *Enterococcus.*
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

** Persistent severe cystitis symptoms associated with BCG use have a high risk to underlie a complicated UTI (even in the absence of a positive culture) and thus no restriction applies to the empirical use of quinolones by the Pharmacovigilance Risk Assessment Committee of the EMA (see also Section 3.7 Complicated UTI and 3.7.4.1- Choice of antimicrobials of the EAU Guidelines on Urological Infection 2022) [7, 334].*

7.4.3.4 Optimal BCG schedule

Induction BCG instillations are given according to the empirical 6-weekly schedule introduced by Morales *et al.*, [335]. For optimal efficacy, BCG must be given in a maintenance schedule [280-282, 304] (LE: 1a). Many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 to 27 weeks over 3 years [336].

7.4.3.4.1 Optimal number of induction instillations and frequency of instillations during maintenance

The optimal number of induction instillations and frequency of maintenance instillations were evaluated by NIMBUS, a prospective phase III RCT. Safety analysis after 345 randomised patients demonstrated that a reduced number of instillations (3 instillations in induction and 2 instillations at 3, 6 and 12 months) proved inferior to the standard schedule (6 instillation in induction and 3 instillations at 3, 6 and 12 months) regarding the time to first recurrence [337] (LE: 1b). In a RCT including 397 patients CUETO showed that in high-risk tumours a maintenance schedule with only one instillation every 3 months for 3 years was not superior to induction therapy only, which suggested that one instillation may be suboptimal to 3 instillations in each maintenance cycle [338] (LE: 1b).

7.4.3.4.2 Optimal length of maintenance

In their meta-analysis, Böhle *et al.*, concluded that at least one year of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [280] (LE: 1a).

In a RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, 3 years' maintenance (3-weekly instillations 3, 6, 12, 18, 24, 30 and 36 months) reduces the recurrence rate compared to one year in high- but not in intermediate-risk patients. There were no differences in progression or OS. In the 3-year arm, however, 36.1% of patients did not complete the 3-year schedule [339] (LE: 1b). The main reason why these patients stopped treatment was treatment inefficacy, not toxicity.

7.4.3.5 Optimal dose of BCG

To reduce BCG toxicity, instillation of a reduced dose was proposed. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours [340, 341] (LE: 1b). The CUETO study compared one-third dose to full-dose BCG and found no overall difference in efficacy. One-third of the standard dose of BCG might be the minimum effective dose for intermediate-risk tumours. A further reduction to one-sixth dose resulted in a

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decrease in efficacy with no decrease in toxicity [342] (LE: 1b). The EORTC did not find any difference in toxicity between one-third and full-dose BCG, but one-third dose BCG was associated with a higher recurrence rate, especially when it was given only for one year [318, 339] (LE: 1b). In a recent meta-analysis of 9 RCTs, patients who received less than half of the standard BCG dose experienced less adverse events as compared to patients receiving the full dose, but suffered more recurrences [343].

7.4.3.6 BCG shortage

A statement by the Panel on BCG shortage can be accessed online:
https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/publications-appendices.

7.4.3.7 Summary of evidence - BCG treatment

Summary of evidence	LE
In patients with intermediate- and high-risk tumours, intravesical BCG after TURB reduces the risk of tumour recurrence; it is more effective than TURB alone or TURB and intravesical chemotherapy.	1a
For optimal efficacy, BCG must be given in a maintenance schedule.	1a
Three-year maintenance is more effective than one year to prevent recurrence in patients with high-risk tumours, but not in patients with intermediate-risk tumours.	1a

7.4.4 ***Combination therapy***

7.4.4.1 Intravesical BCG plus chemotherapy versus BCG alone

In one RCT, a combination of MMC and BCG was shown to be more effective in reducing the risk of disease recurrence while increasing toxicity compared to BCG monotherapy (LE: 1b). Using similar BCG schedules in both groups, each BCG instillation in the combination group was preceded a day before by an added MMC instillation [344]. In a RCT using MMC with EMDA, a combination of BCG and MMC with EMDA showed an improved recurrence-free interval and reduced progression rate compared to BCG monotherapy [300, 345] (LE: 2). Two meta-analyses demonstrated improved disease-free survival (DFS), but no benefit in PFS in patients treated with combination treatment comparing to BCG monotherapy [345, 346].

7.4.4.2 Combination treatment using interferon

In a Cochrane meta-analysis of 4 RCTs, a combination of BCG and IFN-2α did not show a clear difference in recurrence and progression over BCG alone [347]. In one study, weekly MMC followed by monthly BCG alternating with IFN-2α showed a higher probability of recurrence compared to MMC followed by BCG alone [348]. Additionally, a RCT in a similar population of NMIBC comparing BCG monotherapy with a combination of epirubicin and INF for up to two years showed the latter was significantly inferior to BCG monotherapy in preventing recurrence [349] (LE: 1b).

7.4.4.3 Sequential chemotherapy instillations

Preclinical data suggest that the efficacy of intravesical chemotherapy instillations can be improved by combinations compared to the administration of single agents only [350]. Sequential (immediate) instillations of gemcitabine and docetaxel was initially reported in 2015 in the wake of BCG-shortage but also at times of limited access to mitomycin [351]. Subsequently other sequential chemotherapy combinations such as valrubicin and docetaxel have been suggested [352]. Over time, additional retrospective data have accumulated where sequential gemcitabine and docetaxel instillations were used in patients recurring after induction BCG and BCG-unresponsive disease [353]; in patients with recurrence after BCG-induction but not fulfilling the criteria for BCG-unresponsive disease [354]; and also in BCG-naïve high-risk patients [355]. Thus, in patients with BCG-unresponsive disease when the treatment standard (radical cystectomy) is not feasible due to age and/or comorbidity or when patients are unwilling to accept radical surgery, sequential instillations with gemcitabine and docetaxel is an emerging treatment concept awaiting further prospective scientific evaluation.

7.4.5 ***Specific aspects of treatment of carcinoma in situ***

7.4.5.1 Treatment strategy

The detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumours [222, 224]. In this case further treatment according to the criteria summarised in Sections 7.4.2, 7.4.3 and 7.9 is mandatory. Carcinoma *in situ* cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or RC (LE: 4). Tumour-specific survival rates after immediate RC for CIS are excellent, but a large proportion of patients might be over-treated [232] (LE: 3).

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7.4.5.2 Cohort studies on intravesical BCG or chemotherapy

In retrospective evaluations of patients with CIS, a complete response rate of 48% was achieved with intravesical chemotherapy and 72–93% with BCG [232-235, 356] (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [235, 273, 336, 356] (LE: 3).

7.4.5.3 Prospective randomised trials on intravesical BCG or chemotherapy

Unfortunately, there have been few RCTs in patients with CIS only. A meta-analysis of clinical trials comparing intravesical BCG to intravesical chemotherapy in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [357] (LE: 1a).

In an EORTC-GUCG meta-analysis of tumour progression, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or immunotherapy [281] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [358]. In summary, compared to chemotherapy, BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression (LE: 1b).

7.4.5.4 Treatment of CIS in the prostatic urethra and upper urinary tract

Patients with CIS are at high risk of extravesical involvement in the UUT and in the prostatic urethra. Solsona *et al.*, found that 63% of 138 patients with CIS developed extravesical involvement initially or during follow-up [359]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [359] (LE: 3). In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [360]. These situations should be distinguished from tumour invasion into the prostatic stroma (stage T4a in bladder tumours) and for which immediate radical cystoprostatectomy is mandatory. Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. Transurethral resection of the prostate can improve contact of BCG with the prostatic urethra [146, 361] (LE: 3). However, potential spread of CIS has to be considered; no suprapubic trocar-placed catheter should be used.

In patients with prostatic duct involvement there are promising results of BCG, but only from small series. The data are insufficient to provide clear treatment recommendations and radical surgery should be considered [361, 362] (LE: 3).

7.4.5.5 Summary of evidence - treatment of carcinoma in situ

Summary of evidence	**LE**
Carcinoma *in situ* cannot be cured by an endoscopic procedure alone.	4
Compared to intravesical chemotherapy, intravesical BCG maintenance instillations increase the complete response rate, the overall percentage of patients who remain disease free, and reduce the risk of tumour progression.	1b

7.5 Intravesical chemoablation and neoadjuvant treatment

Older marker lesion studies have shown that chemoablation with a single intravesical chemotherapy instillation can achieve a complete response in a proportion of patients [363]. In addition, hypothesis-generating findings from an older RCT comparing immediate pre-operative device-assisted (EMDA) MMC with post-operative SI with MMC and TURB only, showed improved long-term RFS among patients treated prior to TURB [364], and thus even suggest a long-term effect after neoadjuvant instillations. While this has not been reproduced by other groups, additional neoadjuvant clinical trials were recently published. In recurrent low-risk [365] and recurrent Ta tumours [366], 4 and 6 intravesical MMC instillations achieved complete response in 37% and 57% of the patients, respectively. The former study prematurely stopped recruitment as the anticipated 45% complete response after chemoablation was not achieved. Compared to TURB, less dysuria and incontinence occurred in the intervention arm of the trial. Before routine clinical application, additional high-level evidence with RFS as an outcome measure is required.

7.6 Radical cystectomy for non-muscle-invasive bladder cancer

There are several reasons to consider immediate RC for selected patients with NMIBC:

- The staging accuracy for T1 tumours by TURB is low with 27–51% of patients being upstaged to muscle-invasive tumour at RC [182, 367-371] (LE: 3).
- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).
- Patients who experience disease progression to muscle-invasive stage have a worse prognosis than those who present with ‘primary’ muscle-invasive disease [372, 373].

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The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life (QoL) and discussed with patients, in a shared decision-making process. It is reasonable to propose immediate RC in those patients with NMIBC who are at very high risk of disease progression (see Section 6.3 and Tables 6.1 and 6.2) [75, 179, 222, 224, 374] (LE: 3).

Early RC is strongly recommended in patients with BCG-unresponsive tumours and should be considered in BCG relapsing HG tumours as mentioned in Section 7.9 and Table 7.3. A delay in RC may lead to decreased disease-specific survival [375] (LE: 3).

In patients in whom RC is performed before progression to MIBC, the 5-year DFS rate exceeds 80% [376-378] (LE: 3).

7.7 Primary treatment by disease type

The type of further therapy after TURB should be based on the risk groups shown in Section 6.3 and Table 6.1. The stratification and treatment recommendations are based on the risk of disease progression. In particular in intermediate-risk tumours, the 2006 EORTC scoring model may be used (Section 6.1.1.1) to determine a patient's individual risk of disease recurrence as the basis to decide further treatment on.

- Treatment of low-risk disease
  Patients in the low-risk group have a negligible risk of disease progression. The single post-operative instillation of chemotherapy reduces the risk of recurrence and is considered as sufficient treatment in these patients.

- Treatment of intermediate-risk disease
  Patients in the intermediate-risk group have a low risk of disease progression (7.4 and 8.5% after 10 years according to the 2021 EAU NMIBC scoring model). In these patients one-year full-dose BCG treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year, is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.

- Treatment of high-risk disease
  Patients in the high-risk group have a high risk of disease progression (14.1 and 14.2% after 10 years according to the 2021 EAU NMIBC scoring model). In these patients full-dose intravesical BCG for one to 3 years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and problems associated with BCG shortage. Because of the high risk of progression, immediate RC may also be discussed with the patient. Radical cystectomy is the safest approach from an oncological point of view, it is, however, associated with the risk of complications and QoL impairment and represents over-treatment in some patients.

- Treatment of very high-risk disease
  Patients in the very high-risk group have an extremely high risk of tumour progression (53.1 and 58.6% after 10 years according to the 2021 EAU NMIBC scoring model). Immediate RC should be discussed with these patients. In case RC is not feasible or refused by the patient, full-dose intravesical BCG for one to 3 years should be offered.

- Treatment of carcinoma *in situ*
  Patients with carcinoma *in situ* cannot be managed by an endoscopic procedure alone and should be offered either intravesical BCG instillations or RC (LE: 4). BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression (LE: 1b). In comparison, immediate RC for CIS results in excellent tumour-specific survival rates although a large proportion of patients might be over-treated [232] (LE: 3).

7.8 Multidisciplinary tumour board

A multidisciplinary tumour board (MDT) approach including reassessment of radiology and pathology is associated with a changed treatment plan in up to 44% of BC patients [379], such as refraining from or recommending cystectomy in 7% of stage T1 patients [380-382], often as a result of the pathologic review [70, 381]. Thus, patients with high-risk and very high-risk NMIBC will especially benefit from MDT discussion and such an approach is recommended for these patients.

Figure 7.1 presents a treatment flow chart based on risk category, which may guide management of an individual patient.

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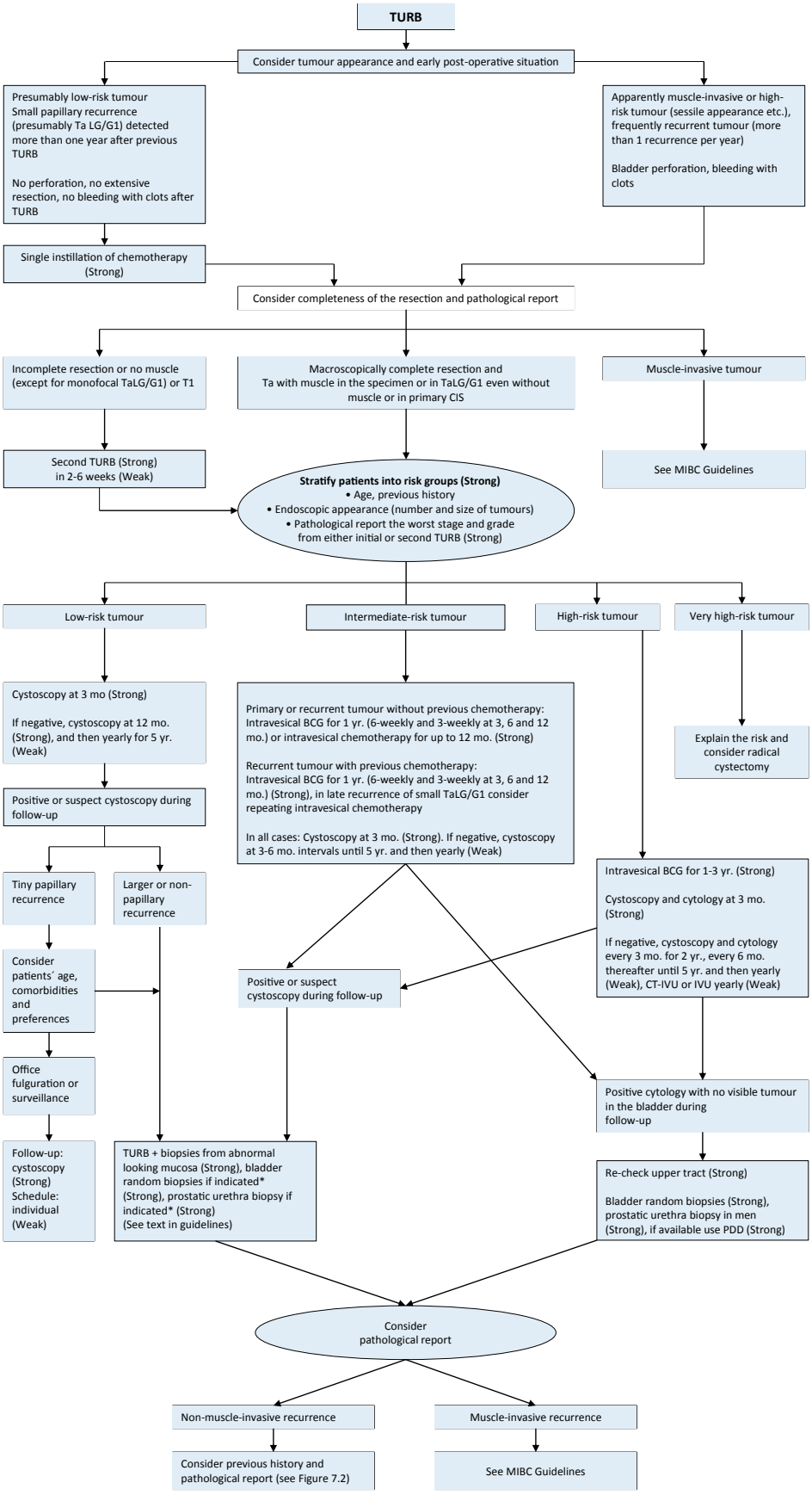
Figure 7.1: Treatment strategy in primary or recurrent tumour(s) without previous BCG*



** For details and explanations see the text of the guidelines.*
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CT = computed tomography; IVU = intravenous urography; MIBC = muscle-invasive bladder cancer; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

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7.9 Treatment of failure of intravesical therapy

7.9.1 Recurrence during or after intravesical chemotherapy

Patients with NMIBC recurrence during or after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillations [282] (LE: 1a).

7.9.2 Treatment failure after intravesical BCG immunotherapy

Several categories of BCG failures, broadly defined as any HG disease occurring during or after BCG therapy, have been proposed (see Table 7.2). Non-muscle-invasive BC may not respond at all (BCG refractory) or may relapse after initial response (BCG relapsing). Some evidence suggests that patients with BCG relapse have better outcomes than BCG refractory patients [383].

To be able to specify the subgroup of patients where additional BCG is unlikely to provide benefit, the category of BCG-unresponsive tumour was defined. Further BCG instillations in these patients are associated with an increased risk of progression [236, 384]. The category of BCG-unresponsive tumours comprises BCG-refractory and some of BCG-relapsing tumours (see Table 7.2) [385]. The definition was developed in consultation with the U.S. Food and Drug Administration (FDA), in particular to promote single-arm trials to provide primary evidence of effectiveness in this setting [386]. Non-HG recurrence after BCG is not considered as BCG failure.

Table 7.2: Categories of high-grade recurrence during or after BCG

Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1 HG/G3 tumour is present at 3 months [236, 384, 387] (LE: 3). 2. If Ta HG/G3 tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance [360] (LE: 4). 3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [67, 356, 360] (LE: 1b). 4. If HG tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour
Recurrence of HG/G3) tumour after completion of BCG maintenance, despite an initial response [388] (LE: 3).
BCG-unresponsive tumour
BCG-unresponsive tumours include all BCG refractory tumours and those who develop T1/Ta HG recurrence within 6 months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure [385] (LE: 4).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [330].

** Patients with LG recurrence during or after BCG treatment are not considered to be a BCG failure.*

*** Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.*

7.9.3 Treatment of BCG-unresponsive tumours, late BCG-relapsing tumours, LG recurrences after BCG treatment and patients with BCG intolerance

Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy; RC is therefore the standard and preferred option. Currently, several bladder preservation strategies are being investigated such as cytotoxic intravesical therapies [389-392], device assisted instillations [393-395], intravesical immunotherapy [396, 397], systemic immunotherapy [398] or gene therapy [399-401].

A phase III RCT including predominantly high-risk NMIBC patients failing at least a previous induction course of BCG, MMC combined with microwave-induced hyperthermia provided 35% overall DFS at 2 years as compared to 41% in the control arm (treated with either BCG, MMC or MMC and electromotive drug administration at the discretion of the investigator). In the pre-planned sub-analysis, MMC and microwave-induced thermotherapy showed lower response rates in CIS recurrences but higher DFS in non-CIS papillary tumours (53% vs. 24%) [395].

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Promising data on BCG-unresponsive cohorts of patients with CIS alone or concomitant to papillary tumours were recently reported following new immunotherapies. Systemic pembrolizumab achieved a 40% complete response rate in a prospective phase II study which was maintained in 48% of patients for up to 12 months (n = 101), resulting in FDA approval of the study drug for this patient population [402]. Promising data from a phase III multicentre RCT with intravesical nadofaragene firadenovec showed a complete response in 53.4% of patients with BCG-unresponsive CIS [403]. A secondary analysis indicates that a combination of post-treatment titres of serum anti–human adenovirus type-5 antibody and fold change from baseline can predict treatment efficacy [404].

A systematic review and meta-analysis including 4 RCTs and 24 single-arm studies (all currently available prospective studies) assessed bladder-sparing treatments following BCG failure [405]. The significant heterogeneity of both trial designs and patient characteristics included in these studies, the different definitions of BCG failures used, and missing information on prior BCG courses may account for the variability in efficacy for the different compounds assessed across different trials. A higher number of previous BCG courses, BCG refractory/unresponsive or CIS predicted lower response rates. The pooled 12-month response rates were 24% for trials with > 2 prior BCG courses and 36% for those with > 1 BCG courses. Initial response rate did not predict durable responses highlighting the need for longer-term follow-up. More recently, a systematic review assessing 42 prospective trials on bladder-preserving treatments after BCG showed that patients with papillary-only recurrences appeared more effectively treated (median recurrence free rate of 44% at 1 year, median progression-free rate of 89% at a median follow-up of 19 months) than CIS-containing tumours (median complete response rate of 17% at 1 year with a median progression-free rate of 95% at a median follow-up of 12 months), highlighting potential biological differences between these two tumour entities which should be analysed separately when reporting results of clinical trials [406].

At the present time, treatments other than RC are considered oncologically inferior in patients with BCG-unresponsive disease [236, 384, 387] (LE: 3). Various studies suggest that repeat-BCG therapy is appropriate for non-HG and even for some HG recurrent tumours; namely those relapsing beyond one year after BCG exposure (cases which do not meet the criteria of BCG-unresponsive disease) [407, 408] (LE: 3).

Treatment decisions in LG recurrences after BCG (which are not considered as any category of BCG failure) should be individualised according to tumour characteristics. Little is known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance.

*7.9.4 **Summary of evidence - treatment failure of intravesical therapy***

Summary of evidence	**LE**
Prior intravesical chemotherapy has no impact on the effect of BCG instillation.	1a
Treatments other than RC must be considered oncologically inferior in patients with BCG-unresponsive tumours.	3

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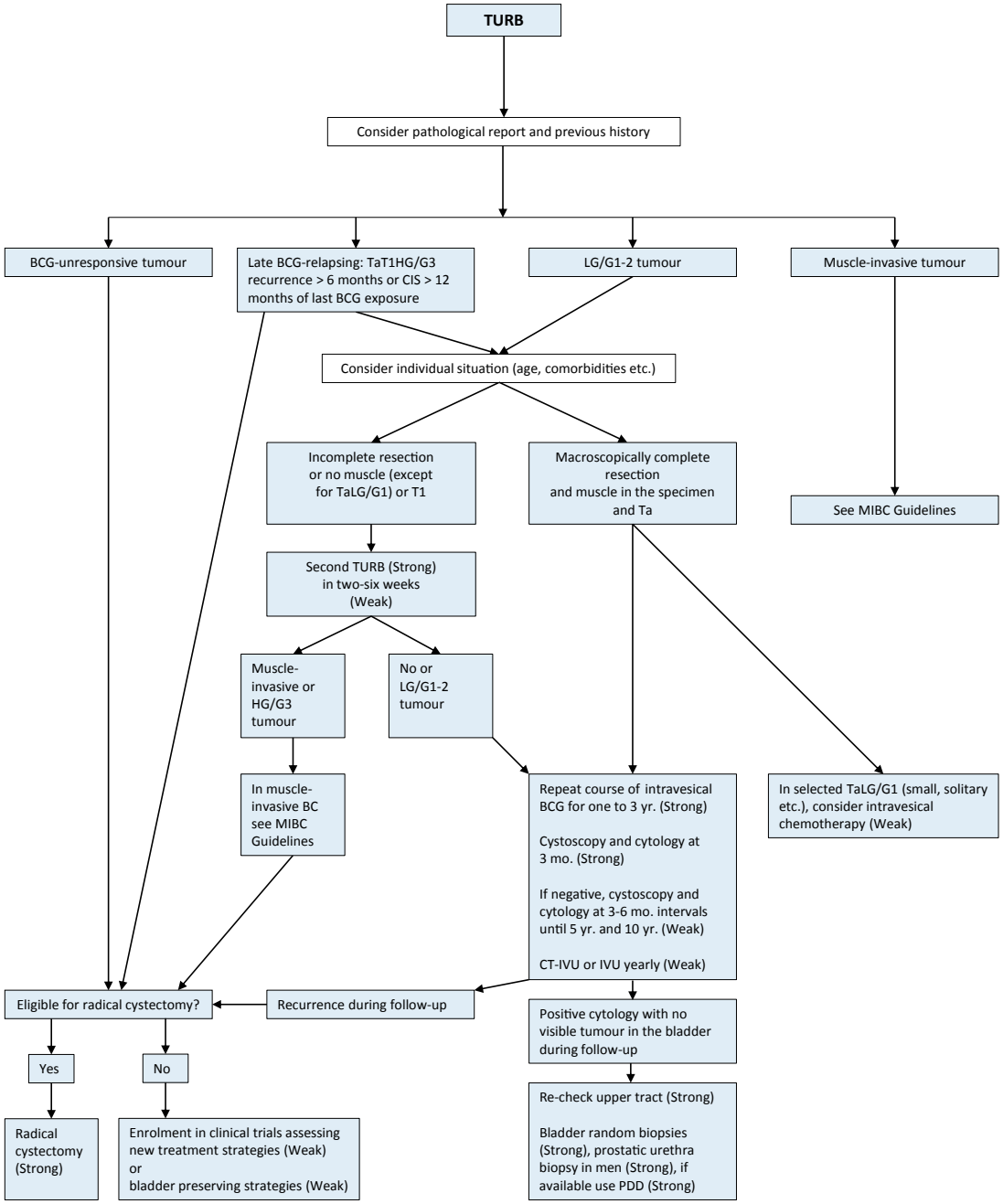
Figure 7.2: Treatment strategy in recurrence during or after intravesical BCG



BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high-grade; IVU = intravenous urography; LG = low-grade; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.10 Guidelines for adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*

General recommendations	Strength rating
Counsel smokers to stop smoking.	Strong
The type of further therapy after transurethral resection of the bladder (TURB) should be based on the risk groups shown in Section 6.3 and Table 6.1. For determination of a patient's risk group use the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
In patients with tumours presumed to be at low risk and in those with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB, offer one immediate single chemotherapy instillation.	Strong
Offer post-operative saline or water continuous irrigation of the bladder to patients who cannot receive a single instillation of chemotherapy.	Strong

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Patients with small recurrent low-grade Ta tumours can be effectively and safely offered office fulguration.	Strong
Only offer active surveillance to selected patients with presumed low-risk tumours not amendable to endoscopic ablation.	Weak
In patients with intermediate-risk tumours (with or without immediate instillation), offer one-year full-dose Bacillus Calmette-Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year. The final choice should be made in a shared decision-making process with the patient, reflecting his/her risk of recurrence and progression, as well as the efficacy and side effects of each treatment modality.	Strong
In patients with high-risk tumours, full-dose intravesical BCG for one to 3 years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and access to BCG. Immediate radical cystectomy (RC) may also be discussed with the patient.	Strong
In patients with very high-risk tumours offer immediate RC. Discuss intravesical full-dose BCG instillations for one to 3 years and discuss clinical trials with those who refuse or are unfit for RC.	Strong
Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra.	Weak
Cautiously offer quinolones to treat BCG-related side effects*.	Weak
The definition of 'BCG-unresponsive' should be respected as it most precisely defines the patients who are unlikely to respond to further BCG instillations.	Strong
Offer a RC to patients with BCG-unresponsive tumours.	Strong
Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak
Discuss high-risk and very high-risk patients within a multidisciplinary board, when possible.	Weak
Recommendations - technical aspects for treatment	
Intravesical chemotherapy	
If given, administer a single immediate instillation of chemotherapy within 24 hours after TURB.	Weak
Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	Strong
The optimal schedule and duration of further intravesical chemotherapy instillation is not defined; however, it should not exceed one year.	Weak
If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation.	Strong
The length of individual instillation should be a minimum of one, and up to two hours.	Weak
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	Strong

**The side-effect profile of quinolones and fluoroquinolones resulted in the adoption of European regulation restricting their use [7].*

7.11 Guidelines for the treatment of TaT1 tumours and carcinoma *in situ* according to risk stratification

Recommendations	Strength rating
EAU risk group: Low	
Offer one immediate instillation of intravesical chemotherapy after transurethral resection of the bladder (TURB).	Strong

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EAU Risk Group: Intermediate	
In all patients either one-year full-dose Bacillus Calmette-Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality. Offer one immediate chemotherapy instillation to patients with small papillary recurrences detected more than one year after previous TURB.	Strong
EAU risk group: High	
Offer intravesical full-dose BCG instillations for one to 3 years but discuss immediate radical cystectomy (RC).	Strong
EAU risk group: Very High	
Offer RC or intravesical full-dose BCG instillations for one to 3 years to those who refuse or are unfit for RC.	Strong

Table 7.3: Treatment options for the various categories of BCG failure

Category	Treatment options
BCG-unresponsive	1. Radical cystectomy (RC).
	2. Enrolment in clinical trials assessing new treatment strategies.
	3. Bladder-preserving strategies in patients unsuitable or refusing RC.
Late BCG relapsing: TaT1 HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to a patient's individual situation.
	2. Bladder-preserving strategies.
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy.
	2. Radical cystectomy.

8. FOLLOW-UP OF PATIENTS WITH NMIBC

As a result of the risk of recurrence and progression, patients with NMIBC need surveillance following therapy. However, the frequency and duration of cystoscopy and imaging follow-up should reflect the individual patient's degree of risk. Using the EAU NMIBC prognostic factor risk groups (see Section 6.3, Tables 6.1 and 6.2) or further prognostic models for specific patient populations (see Chapter 6), the short- and long-term risks of recurrence and progression in individual patients may be predicted and the follow-up schedule adapted accordingly (see Section 8.1) [222, 224]. However, recommendations for follow-up are mainly based on retrospective data and there is a lack of RCTs investigating the possibility of safely reducing the frequency of follow-up cystoscopy.

When planning the follow-up schedule and methods, the following aspects should be considered:

- The prompt detection of muscle-invasive and HG/G3 non-muscle-invasive recurrence is crucial and the percentage of tumours missed should be as low as possible because a delay in diagnosis and therapy can be life-threatening. Therefore, the best surveillance strategy for these patients will continue to include frequent cystoscopy and cytology.
- Tumour recurrence in the low-risk group is nearly always low stage and LG/G1. Small, Ta LG/G1 papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy [250, 409] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be safe [410] and comparable to conventional TURB (LE: 1b). Multiple authors have suggested active surveillance in selected cases [411-413] (LE: 3/2a). However, repeated TURBs before entry, as well as presence of more than one lesion at entry, were significantly associated with AS failure [256].
- The first cystoscopy after TURB at 3 months is an important prognostic indicator for recurrence and progression [230, 235, 248, 251, 414] (LE: 1a). Therefore, the first cystoscopy should always be performed 3 months after TURB in all patients with TaT1 tumours and CIS.
- In tumours at low risk, the risk of recurrence after 5 recurrence-free years is low [251] (LE: 3). Therefore, in low-risk tumours, after 5 years of follow-up, discontinuation of cystoscopy or its replacement with less invasive methods can be considered [414].

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- In tumours originally intermediate-, high risk, or very high risk treated conservatively, recurrences after ten years tumour-free are not unusual [415] (LE: 3). Therefore, life-long follow-up is recommended [414].
- The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT in both genders).
- The risk of UUT recurrence increases in patients with multiple- and high-risk tumours [96] (LE: 3).
- There may be a role for newer methods of tumour visualisation in follow-up cystoscopy. In two prospective studies of blue light flexible cystoscopy (BLFC) for surveillance of NMIBC, BLFC allowed identification of 4 to 5.7 % of recurrences that would have been missed in case of WL cystoscopy alone [416, 417]. On the other hand, a prospective study of NBI for NMIBC surveillance failed to show any benefit for NBI over WL cystoscopy alone [418].
- The current status of urine cytology and urinary molecular marker tests is discussed in detail in Sections 5.5, 5.6 and 5.7. Non-muscle-invasive BC follow-up strategies include urine cytology and urinary molecular marker tests as adjunct (or companion) tests to improve detection at the time of flexible cystoscopy or as replacement tests to reduce the number of flexible cystoscopies.
- The role of urinary cytology or urinary molecular markers as an adjunct to cystoscopy (companion test) in the follow-up of NMIBC has been investigated [118, 119, 131, 132, 142]. One prospective RCT found that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [143] (LE: 1b), supporting the adjunctive role of a non-invasive urine test performed prior to follow-up cystoscopy [143] (see Section 5.7.3).

  In order to reduce or replace cystoscopy altogether, urinary markers should be able to detect recurrence in all risk groups. However the previously reported low sensitivity for LG recurrences limits their utility in this group [113, 118] (LE: 1b) although more recent studies have shown reasonable sensitivity in low grade recurrences (sensitivity of 40–65% [136, 419] and only a 5.8% risk of missed recurrences using repeated molecular testing in a cohort of patients undergoing active surveillance for low-grade NMIBC [420].
- In patients initially diagnosed with Ta LG/G1–2 BC, US of the bladder or a urinary marker may be a mode of surveillance in case cystoscopy is not possible or refused by the patient [139, 142, 421].
- According to current knowledge, no urinary marker can replace cystoscopy during follow-up or lower cystoscopy frequency in a routine fashion. Nonetheless, some urinary markers have shown fairly high sensitivities to detect tumour recurrence, particularly in HG disease, along with very high NPVs to make the premises for their future implementation in follow-up [135, 419, 420, 422] (Table 8.1).

Table 8.1: Urinary markers in the surveillance setting*

Marker	Sensitivity overall	HG	Specificity overall	HG	PPV overall	HG	NPV overall	HG	N studies/ patients
XPERT BC® MONITOR	0.72	0.88	0.76	0.75	0.43	0.18	0.92	0.99	10/> 2000
EpiCheck™	0.74	0.91	0.84	0.81	0.48	0.43	0.94	0.98	5/1600
ADX Bladder™	0.57	0.71	0.62	0.76	0.29	0.37	0.82	0.93	3/1600
CX BLADDER	0.91	-	0.61	-	0.16	-	0.98	-	2/1000
FDFGR3+TERT	0.93	-	0.79	-	0.67	-	0.96	-	2/250

**Data extracted from a pooled analyses of systematic review [8].*
HG = high grade; NMIBC = non-muscle-invasive bladder cancer; PPV = positive predictive value; NPV = negative predictive value; n = number.

8.1 Summary of evidence and guidelines for follow-up of patients after transurethral resection of the bladder for non-muscle-invasive bladder cancer

Summary of evidence	LE
The first cystoscopy after transurethral resection of the bladder at 3 months is an important prognostic indicator for recurrence and progression.	1a
The risk of upper urinary tract recurrence increases in patients with multiple- and high-risk tumours.	3

Recommendations	Strength rating
Base follow-up of TaT1 tumours and carcinoma *in situ* (CIS) on regular cystoscopy.	Strong
Patients with low-risk Ta tumours should undergo cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years.	Weak

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Patients with high-risk and those with very high-risk tumours treated conservatively should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	Weak
Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy.	Weak
Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk and very high-risk tumours.	Weak
Perform endoscopy under anaesthesia and bladder biopsies when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong
During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong

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10. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is open access available on the European Association of Urology website: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=panel.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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Statement concerning the shortage of BCG vaccine from the EAU Guidelines Panel on non-muscle invasive bladder cancer

Panel members: M. Babjuk (chairman), A. Böhle, M. Burger, E. Compérat, E. Kaasinen, J. Palou Redorta, B. van Rhijn, M. Rouprêt, S. Shariat, R. Sylvester, R. Zigeuner

The current situation

The company Sanofi Pasteur has announced a suspension of the production of the BCG Connaught strain in June 2012. Because of the ongoing renovation of its manufacturing facility, production is not expected to resume before the end of 2013. As the Connaught strain supplies a significant segment of the world market, the suspension of its production may result in a global shortage of BCG in the treatment of non-muscle invasive bladder cancer. Although the situation is different in individual countries depending on the BCG strain on the market, it represents potential danger for patients and requires the attention of urologists.

Each urologist has an obligation to provide optimal treatment according to the current evidence for individual patients with non-muscle invasive bladder cancer. This statement summarizes information which can help the urologist with treatment decisions in the absence of BCG Connaught or with a suboptimal supply of BCG on the market.

Current role of BCG in the treatment of non-muscle invasive bladder cancer and EAU guidelines recommendations

BCG intravesical immunotherapy is the most effective conservative management for bladder carcinoma *in situ* (CIS) and for Ta T1 tumours at intermediate and high risk of recurrence and progression (EORTC risk calculator) after complete TURB (transurethral resection of the bladder), where it significantly reduces the recurrence rate and has an impact on the early progression rate.

According to EAU guidelines on non-muscle invasive bladder cancer, BCG intravesical instillations are indicated in patients with bladder CIS and in patients with Ta T1 tumours at intermediate and high risk of recurrence and/or progression. For optimal efficacy, the induction course (6 weekly instillations) should be followed by at least one year of maintenance.

Is the efficacy of different BCG strains comparable?

Only a small number of published studies have compared different BCG strains when used as induction treatment. The publication of a prospective randomized comparison of induction BCG Connaught and induction BCG TICE is expected soon. No head-to-head comparisons of the clinical efficacy of different BCG strains when used as maintenance therapy have been published in the literature.

The published meta-analysis of prospective randomized trials did not suggest any difference in efficacy of the BCG strains (Pasteur, Frappier, Connaught, TICE, RIVM).

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There are no data which provide information on whether switching from one BCG strain to another during the treatment schedule can have an impact on antitumor efficacy.

How long should the optimal BCG schedule be? When can BCG instillations be terminated without compromising efficacy?

For optimal efficacy, BCG should be given with a maintenance schedule. Many maintenance schedules have been used with a maximum of 27 instillations over 3 years. The optimal length of maintenance is, however, not known. According to meta-analyses, BCG should be given for at least one year to be superior to intravesical chemotherapy. With the current BCG shortage, instillations can be safely terminated when the patient has completed one year of BCG treatment.

References about the use of only an induction course (6 weekly instillations without maintenance) are controversial. A recently presented cohort study showed promising results, however meta-analyses have shown induction only BCG to have inferior efficacy compared to intravesical chemotherapy.

Can be BCG instillations be replaced by another treatment?

In patients with Ta and T1 tumours at intermediate or high risk of recurrence and intermediate risk of progression, intravesical chemotherapy (multiple instillations for up to 12 months) represents an alternative treatment option to BCG immunotherapy. It has a higher risk of recurrence but a lower risk of side effects.

In Ta and T1 tumours at high risk of progression and in CIS, EAU guidelines provide two treatment options, intravesical BCG immunotherapy and radical cystectomy. Cystectomy represents an oncologically safe but more invasive treatment which should be discussed, particularly with younger and fit patients.

Some promising data have been presented about device assisted chemotherapy (Synergo or EMDA) which might replace BCG instillations in patients with high risk tumors who are not fit for cystectomy. The current evidence however is limited and this treatment is considered to be experimental.

Conclusions and recommendations:

1. The efficacy of different BCG strains seems to be comparable
2. There is no information about the consequences of switching from one BCG strain to another. This seems, however, to be a reasonable solution during the first year of maintenance in the situation where BCG Connaught is no longer available, but another strain can be obtained.
3. In the current situation of BCG shortages, instillations can be safely terminated when the patient has completed one year of BCG.

4. In patients with Ta and T1 tumours at intermediate or high risk of recurrence and intermediate risk of progression, adjuvant BCG treatment can be replaced by intravesical chemotherapy, which represents an alternative treatment option.

5. In younger and fit patients with Ta T1 tumours at high risk of progression and with CIS, an immediate radical cystectomy should always be considered. This should be underlined, particularly in the current situation with BCG shortages.

6. In patients with Ta T1 tumours at high risk of progression or with CIS who are unfit to or unwilling to undergo a cystectomy, there is no scientifically proven alternative to BCG treatment. Thus every effort should be made to obtain an available BCG strain. As an alternative, device assisted chemotherapy seems to provide promising results and could be considered. Passive intravesical chemotherapy can achieve some responses in CIS, influence the recurrence rate in TaT1 tumours and thus provide some benefit for the patient. Urologists should not forget, however, that the effect of passive intravesical chemotherapy on tumour progression has never been confirmed.

7. It should be emphasized that the most important modality in the treatment of non-muscle invasive bladder cancer remains a complete and precisely performed TURB, independent of the availability of BCG on the market.

NICE National Institute for Health and Care Excellence

NICE guideline

Bladder cancer: diagnosis and management

NICE guideline
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Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guideline is the basis of QS106.

Overview

This guideline covers diagnosing and managing bladder cancer in people 18 and above referred from primary care with suspected bladder cancer, and those with newly diagnosed or recurrent bladder (urothelial carcinoma, adenocarcinoma, squamous-cell carcinoma or small-cell carcinoma) or urethral cancer.

Who is it for?

- Healthcare professionals
- Commissioners and providers
- Adults with bladder cancer and their families and carers

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Introduction

Bladder cancer is the seventh most common cancer in the UK. It is 3 to 4 times more common in men than in women. In the UK in 2011, it was the fourth most common cancer in men and the thirteenth most common in women. There were 10,399 people diagnosed with bladder cancer and 5081 deaths from bladder cancer in 2011. The majority of cases occur in people aged over 60. The main risk factor for bladder cancer is increasing age, but smoking and exposure to some industrial chemicals also increase risk.

Bladder cancer is usually identified on the basis of visible blood in the urine or blood found on urine testing, but emergency admission is a common way for bladder cancer to present, and is often associated with a poor prognosis.

Most bladder cancers (75 to 80%) do not involve the muscle wall of the bladder and are usually treated by telescopic removal of the cancer (transurethral resection of bladder tumour [TURBT]). This is often followed by instillation of chemotherapy or vaccine-based therapy into the bladder, with prolonged telescopic checking of the bladder (cystoscopy) as follow-up. Some people in this group who are at higher risk are treated with major surgery to remove the bladder (cystectomy). People with cancer in or through the bladder muscle wall may be treated with intent to cure using chemotherapy, cystectomy or radiotherapy, and those who have cancer too advanced to cure may have radiotherapy and chemotherapy.

The involvement of the urogenital tract and the nature of the treatments give this cancer a strong psychological impact, in addition to the physical impact of the disease and its treatments, which is often profound. The prevalence of the condition and the nature of its management make bladder cancer one of the most expensive cancers for the NHS.

There is thought to be considerable variation across the NHS in the diagnosis and management of bladder cancer and the provision of care to people who have it. There is evidence that the patient experience for people with bladder cancer is worse than that for people with other cancers.

This guideline covers adults (18 years and older) referred from primary care with suspected bladder cancer and those with newly diagnosed or recurrent bladder (urothelial carcinoma, adenocarcinoma, squamous-cell carcinoma or small-cell carcinoma) or urethral cancer. There was insufficient high-quality evidence on which to make specific

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recommendations for non-urothelial bladder cancer (adenocarcinoma, squamous-cell carcinoma or small-cell carcinoma).

It does not cover people aged under 18 or adults with bladder sarcoma, urothelial cancer of the upper urinary tract, or secondary bladder or urethral cancer (for example, bowel or cervix cancer spreading into the bladder).

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Key priorities for implementation

The following recommendations have been identified as priorities for implementation. The full list of recommendations is in section 1.

Information and support for people with bladder cancer

- Use a holistic needs assessment to identify an individualised package of information and support for people with bladder cancer and, if they wish, their partners, families or carers, at key points in their care such as:
  - when they are first diagnosed
  - after they have had their first treatment
  - if their bladder cancer recurs or progresses
  - if their treatment is changed
  - if palliative or end of life care is being discussed.

Diagnosing and staging bladder cancer

Diagnosis

- Consider CT or MRI staging before transurethral resection of bladder tumour (TURBT) if muscle-invasive bladder cancer is suspected at cystoscopy.
- Offer white-light-guided TURBT with one of photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker test (such as UroVysion using fluorescence in-situ hybridization [FISH], ImmunoCyt or a nuclear matrix protein 22 [NMP22] test) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT.
- Offer people with suspected bladder cancer a single dose of intravesical mitomycin C given at the same time as the first TURBT.

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Treating non-muscle-invasive bladder cancer

Prognostic markers and risk classification

- Ensure that for people with non-muscle-invasive bladder cancer all of the following are recorded and used to guide discussions, both within multidisciplinary team meetings and with the person, about prognosis and treatment options:
  - recurrence history
  - size and number of cancers
  - histological type, grade, stage and presence (or absence) of flat urothelium, detrusor muscle (muscularis propria), and carcinoma in situ
  - the risk category of the person's cancer (see the section on risk classification in non-muscle-invasive bladder cancer)
  - predicted risk of recurrence and progression, estimated using a risk prediction tool.

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High-risk non-muscle-invasive bladder cancer

- Offer the choice of intravesical BCG (Bacille Calmette-Guérin) or radical cystectomy to people with high-risk non-muscle-invasive bladder cancer (see the section on risk classification in non-muscle-invasive bladder cancer), and base the choice on a full discussion with the person, the clinical nurse specialist and a urologist who performs both intravesical BCG and radical cystectomy. Include in your discussion:
  - the type, stage and grade of the cancer, the presence of carcinoma in situ, the presence of variant pathology, prostatic urethral or bladder neck status and the number of tumours
  - risk of progression to muscle invasion, metastases and death
  - risk of understaging
  - benefits of both treatments, including survival rates and the likelihood of further treatment
  - risks of both treatments
  - factors that affect outcomes (for example, comorbidities and life expectancy)
  - impact on quality of life, body image, and sexual and urinary function.

Follow-up after treatment for non-muscle-invasive bladder cancer

Low-risk non-muscle-invasive bladder cancer

- Discharge to primary care people who have had low-risk non-muscle-invasive bladder cancer (see the section on risk classification in non-muscle-invasive bladder cancer) and who have no recurrence of the bladder cancer within 12 months.

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Intermediate-risk non-muscle-invasive bladder cancer

- Offer people with intermediate-risk non-muscle-invasive bladder cancer (see the section on risk classification in non-muscle-invasive bladder cancer) non-muscle-invasive bladder cancer cystoscopic follow-up at 3, 9 and 18 months, and once a year thereafter.

Treating muscle-invasive bladder cancer

Neoadjuvant chemotherapy for newly diagnosed muscle-invasive urothelial bladder cancer

- Offer neoadjuvant chemotherapy using a cisplatin combination regimen before radical cystectomy or radical radiotherapy to people with newly diagnosed muscle-invasive urothelial bladder cancer for whom cisplatin-based chemotherapy is suitable. Ensure that they have an opportunity to discuss the risks and benefits with an oncologist who treats bladder cancer.

Radical therapy for muscle-invasive urothelial bladder cancer

- Offer a choice of radical cystectomy or radiotherapy with a radiosensitiser to people with muscle-invasive urothelial bladder cancer for whom radical therapy is suitable. Ensure that the choice is based on a full discussion between the person and a urologist who performs radical cystectomy, a clinical oncologist and a clinical nurse specialist. Include in the discussion:
  - the prognosis with or without treatment
  - the limited evidence about whether surgery or radiotherapy with a radiosensitiser is the most effective cancer treatment
  - the benefits and risks of surgery and radiotherapy with a radiosensitiser, including the impact on sexual and bowel function and the risk of death as a result of the treatment.

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1 Recommendations

The following guidance is based on the best available evidence. The full guideline gives details of the methods and the evidence used to develop the guidance.

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Information and support for people with bladder cancer

1.1.1 Follow the recommendations on communication and patient-centred care in NICE's guideline on patient experience in adult NHS services and the advice in NICE's guidelines on improving outcomes in urological cancers and improving supportive and palliative care for adults with cancer throughout the person's care.

1.1.2 Offer clinical nurse specialist support to people with bladder cancer and give them the clinical nurse specialist's contact details.

1.1.3 Ensure that the clinical nurse specialist:

- acts as the key worker to address the person's information and care needs
- has experience and training in bladder cancer care.

1.1.4 Use a holistic needs assessment to identify an individualised package of information and support for people with bladder cancer and, if they wish, their partners, families or carers, at key points in their care such as:

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- when they are first diagnosed
- after they have had their first treatment
- if their bladder cancer recurs or progresses
- if their treatment is changed
- if palliative or end of life care is being discussed.

1.1.5 When carrying out a holistic needs assessment, recognise that many of the symptoms, investigations and treatments for bladder cancer affect the urogenital organs and may be distressing and intrusive. Discuss with the person:

- the type, stage and grade of their cancer and likely prognosis
- treatment and follow-up options
- the potential complications of intrusive procedures, including urinary retention, urinary infection, pain, bleeding or need for a catheter
- the impact of treatment on their sexual health and body image, including how to find support and information relevant to their gender
- diet and lifestyle, including physical activity
- smoking cessation for people who smoke
- how to find information about bladder cancer, for example through information prescriptions, sources of written information, websites or DVDs
- how to find support groups and survivorship programmes
- how to find information about returning to work after treatment for cancer
- how to find information about financial support (such as free prescriptions and industrial compensation schemes).

1.1.6 Offer smoking cessation support to all people with bladder cancer who smoke, in line with NICE's guideline on Tobacco: preventing uptake, promoting quitting and treating dependence.

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1.1.7 Offer people with bladder cancer and, if they wish, their partners, families or carers, opportunities to have discussions at any stage during their treatment and care with:

- a range of specialist healthcare professionals, including those who can provide psychological support
- other people with bladder cancer who have had similar treatments.

1.1.8 Clinicians caring for people with bladder cancer should ensure that there is close liaison between secondary and primary care with respect to ongoing and community-based support.

1.1.9 Trusts should consider conducting annual bladder cancer patient satisfaction surveys developed by their urology multidisciplinary team and people with bladder cancer, and use the results to guide a programme of quality improvement.

1.2 Diagnosing and staging bladder cancer

Diagnosis

1.2.1 Do not substitute urinary biomarkers for cystoscopy to investigate suspected bladder cancer or for follow-up after treatment for bladder cancer, except in the context of a clinical research study.

1.2.2 Consider CT or MRI staging before transurethral resection of bladder tumour (TURBT) if muscle-invasive bladder cancer is suspected at cystoscopy.

1.2.3 Offer white-light-guided TURBT with one of photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker test (such as UroVysion using fluorescence in-situ hybridization [FISH], ImmunoCyt or a nuclear matrix protein 22 [NMP22] test) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT.

1.2.4 Obtain detrusor muscle during TURBT.

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1.2.5 Do not take random biopsies of normal-looking urothelium during TURBT unless there is a specific clinical indication (for example, investigation of positive cytology not otherwise explained).

1.2.6 Record the size and number of tumours during TURBT.

1.2.7 Offer people with suspected bladder cancer a single dose of intravesical mitomycin C given at the same time as the first TURBT.

Staging

1.2.8 Consider further TURBT within 6 weeks if the first specimen does not include detrusor muscle.

1.2.9 Offer CT or MRI staging to people diagnosed with muscle-invasive bladder cancer or high-risk non-muscle-invasive bladder cancer (see the section on risk classification in non-muscle-invasive bladder cancer) that is being assessed for radical treatment.

1.2.10 Consider CT urography, carried out with other planned CT imaging if possible, to detect upper tract involvement in people with new or recurrent high-risk non-muscle-invasive or muscle-invasive bladder cancer.

1.2.11 Consider CT of the thorax, carried out with other planned CT imaging if possible, to detect thoracic malignancy in people with muscle-invasive bladder cancer.

1.2.12 Consider fluorodeoxyglucose positron emission tomography (FDG PET)-CT for people with muscle-invasive bladder cancer or high-risk non-muscle-invasive bladder cancer before radical treatment if there are indeterminate findings on CT or MRI, or a high risk of metastatic disease (for example, T3b disease).

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1.3 Treating non-muscle-invasive bladder cancer

Risk classification in non-muscle-invasive bladder cancer

There is no widely accepted classification of risk in non-muscle-invasive bladder cancer. To make clear recommendations for management, the Guideline Development Group developed the consensus classification in table 1, based on the evidence reviewed and clinical opinion.

Table 1 Risk categories in non-muscle-invasive bladder cancer

Low risk	Urothelial cancer with any of: • solitary pTaG1 with a diameter of less than 3 cm • solitary pTaG2 (low grade) with a diameter of less than 3 cm • any papillary urothelial neoplasm of low malignant potential
Intermediate risk	Urothelial cancer that is not low risk or high risk, including: • solitary pTaG1 with a diameter of more than 3 cm • multifocal pTaG1 • solitary pTaG2 (low grade) with a diameter of more than 3 cm • multifocal pTaG2 (low grade) • pTaG2 (high grade) • any pTaG2 (grade not further specified) • any low-risk non-muscle-invasive bladder cancer recurring within 12 months of last tumour occurrence

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High risk	Urothelial cancer with any of: • pTaG3 • pT1G2 • pT1G3 • pTis (Cis) • aggressive variants of urothelial carcinoma, for example micropapillary or nested variants

Prognostic markers and risk classification

1.3.1 Ensure that for people with non-muscle-invasive bladder cancer all of the following are recorded and used to guide discussions, both within multidisciplinary team meetings and with the person, about prognosis and treatment options:

- recurrence history
- size and number of cancers
- histological type, grade, stage and presence (or absence) of flat urothelium, detrusor muscle (muscularis propria), and carcinoma in situ
- the risk category of the person's cancer
- predicted risk of recurrence and progression, estimated using a risk prediction tool.

Low-risk non-muscle-invasive bladder cancer

1.3.2 For the treatment of low-risk non-muscle-invasive bladder cancer, see recommendations 1.2.3 to 1.2.8.

Intermediate-risk non-muscle-invasive bladder cancer

1.3.3 Offer people with newly diagnosed intermediate-risk

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non-muscle-invasive bladder cancer a course of at least 6 doses of intravesical mitomycin C.

1.3.4 If intermediate-risk non-muscle-invasive bladder cancer recurs after a course of intravesical mitomycin C, refer the person's care to a specialist urology multidisciplinary team.

High-risk non-muscle-invasive bladder cancer

1.3.5 If the first TURBT shows high-risk non-muscle-invasive bladder cancer, offer another TURBT as soon as possible and no later than 6 weeks after the first resection.

1.3.6 Offer the choice of intravesical BCG (Bacille Calmette-Guérin) or radical cystectomy to people with high-risk non-muscle-invasive bladder cancer, and base the choice on a full discussion with the person, the clinical nurse specialist and a urologist who performs both intravesical BCG and radical cystectomy. Include in your discussion:

- the type, stage and grade of the cancer, the presence of carcinoma in situ, the presence of variant pathology, prostatic urethral or bladder neck status and the number of tumours
- risk of progression to muscle invasion, metastases and death
- risk of understaging
- benefits of both treatments, including survival rates and the likelihood of further treatment
- risks of both treatments
- factors that affect outcomes (for example, comorbidities and life expectancy)
- impact on quality of life, body image, and sexual and urinary function.

Intravesical BCG

1.3.7 Offer induction and maintenance intravesical BCG to people having treatment with intravesical BCG.

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1.3.8 If induction BCG fails (because it is not tolerated, or bladder cancer persists or recurs after treatment with BCG), refer the person's care to a specialist urology multidisciplinary team.

1.3.9 For people in whom induction BCG has failed, the specialist urology multidisciplinary team should assess the suitability of radical cystectomy, or further intravesical therapy if radical cystectomy is unsuitable or declined by the person, or if the bladder cancer that recurs is intermediate- or low-risk.

Radical cystectomy

1.3.10 See recommendations 1.5.4 to 1.5.7 for people who have chosen radical cystectomy.

Recurrent non-muscle-invasive bladder cancer

1.3.11 Consider fulguration without biopsy for people with recurrent non-muscle-invasive bladder cancer if they have all of the following:

- no previous bladder cancer that was intermediate- or high-risk
- a disease-free interval of at least 6 months
- solitary papillary recurrence
- a tumour diameter of 3 mm or less.

Managing side effects of treatment

1.3.12 Do not offer primary prophylaxis to prevent BCG-related bladder toxicity except as part of a clinical trial.

1.3.13 Seek advice from a specialist urology multidisciplinary team if symptoms of bladder toxicity after BCG cannot be controlled with antispasmodics or non-opiate analgesia and other causes have been excluded by cystoscopy.

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1.4 Follow-up after treatment for non-muscle-invasive bladder cancer

1.4.1 Refer people urgently to urological services if they have haematuria or other urinary symptoms and a history of non-muscle-invasive bladder cancer.

1.4.2 See recommendation 1.2.1 on the use of urinary biomarkers for follow up after treatment for bladder cancer.

Low-risk non-muscle-invasive bladder cancer

1.4.3 Offer people with low-risk non-muscle-invasive bladder cancer (see the section on risk classification in non-muscle-invasive bladder cancer) cystoscopic follow-up 3 months and 12 months after diagnosis.

1.4.4 Do not use urinary biomarkers or cytology in addition to cystoscopy for follow-up after treatment for low-risk bladder cancer.

1.4.5 Discharge to primary care people who have had low-risk non-muscle-invasive bladder cancer and who have no recurrence of the bladder cancer within 12 months.

1.4.6 Do not offer routine urinary cytology or prolonged cystoscopic follow-up after 12 months for people with low-risk non-muscle-invasive bladder cancer.

Intermediate-risk non-muscle-invasive bladder cancer

1.4.7 Offer people with intermediate-risk non-muscle-invasive bladder cancer (see the section on risk classification in non-muscle-invasive bladder cancer) cystoscopic follow-up at 3, 9 and 18 months, and once a year thereafter.

1.4.8 Consider discharging people who have had intermediate-risk non-muscle-invasive bladder cancer to primary care after 5 years of disease-free follow-up.

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High-risk non-muscle-invasive bladder cancer

1.4.9 Offer people with high-risk non-muscle-invasive bladder cancer (see the section on risk classification in non-muscle-invasive bladder cancer) cystoscopic follow-up:

- every 3 months for the first 2 years **then**
- every 6 months for the next 2 years **then**
- once a year thereafter.

1.4.10 For people who have had radical cystectomy for high-risk non-muscle-invasive bladder cancer, see recommendations 1.6.1 and 1.6.2.

1.5 Treating muscle-invasive bladder cancer

1.5.1 Ensure that a specialist urology multidisciplinary team reviews all cases of muscle-invasive bladder cancer, including adenocarcinoma, squamous cell carcinoma and neuroendocrine carcinoma, and that the review includes histopathology, imaging and discussion of treatment options.

Neoadjuvant chemotherapy for newly diagnosed muscle-invasive urothelial bladder cancer

1.5.2 Offer neoadjuvant chemotherapy using a cisplatin combination regimen before radical cystectomy or radical radiotherapy to people with newly diagnosed muscle-invasive urothelial bladder cancer for whom cisplatin-based chemotherapy is suitable. Ensure that they have an opportunity to discuss the risks and benefits with an oncologist who treats bladder cancer.

Radical therapy for muscle-invasive urothelial bladder cancer

1.5.3 Offer a choice of radical cystectomy or radiotherapy with a radiosensitiser to people with muscle-invasive urothelial bladder cancer for whom radical therapy is suitable. Ensure that the choice is based on a

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full discussion between the person and a urologist who performs radical cystectomy, a clinical oncologist and a clinical nurse specialist. Include in the discussion:

- the prognosis with or without treatment
- the limited evidence about whether surgery or radiotherapy with a radiosensitiser is the most effective cancer treatment
- the benefits and risks of surgery and radiotherapy with a radiosensitiser, including the impact on sexual and bowel function and the risk of death as a result of the treatment.

Radical cystectomy

1.5.4 Offer people who have chosen radical cystectomy a urinary stoma, or a continent urinary diversion (bladder substitution or a catheterisable reservoir) if there are no strong contraindications to continent urinary diversion such as cognitive impairment, impaired renal function or significant bowel disease.

1.5.5 Members of the specialist urology multidisciplinary team (including the bladder cancer specialist urological surgeon, stoma care nurse and clinical nurse specialist) should discuss with the person whether to have a urinary stoma or continent urinary diversion, and provide opportunities for the person to talk with people who have had these procedures.

1.5.6 Offer people with bladder cancer and, if they wish, their partners, families or carers, opportunities to have discussions with a stoma care nurse before and after radical cystectomy as needed.

Adjuvant chemotherapy after radical cystectomy for muscle-invasive or lymph-node-positive urothelial bladder cancer

1.5.7 Consider adjuvant cisplatin combination chemotherapy after radical cystectomy for people with a diagnosis of muscle-invasive or lymph-node-positive urothelial bladder cancer for whom neoadjuvant chemotherapy was not suitable (because muscle invasion was not shown on biopsies before cystectomy). Ensure that the person has an

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opportunity to discuss the risks and benefits with an oncologist who treats bladder cancer.

Radical radiotherapy

1.5.8 Use a radiosensitiser (such as mitomycin in combination with fluorouracil [5-FU] or carbogen in combination with nicotinamide) when giving radical radiotherapy (for example, 64 Gy in 32 fractions over 6.5 weeks or 55 Gy in 20 fractions over 4 weeks) for muscle-invasive urothelial bladder cancer.

In February 2015, this was an off-label use of mitomycin in combination with fluorouracil and carbogen in combination with nicotinamide. See NICE's information on prescribing medicines.

Managing side effects of treatment

1.5.9 Seek advice from a specialist urology multidisciplinary team if symptoms of bladder toxicity after radiotherapy cannot be controlled with antispasmodics or non-opiate analgesia and other causes have been excluded by cystoscopy.

1.6 Follow-up after treatment for muscle-invasive bladder cancer

1.6.1 Offer follow-up after radical cystectomy or radical radiotherapy.

1.6.2 After radical cystectomy consider using a follow-up protocol that consists of:

- monitoring of the upper tracts for hydronephrosis, stones and cancer using imaging and glomerular filtration rate (GFR) estimation at least annually **and**
- monitoring for local and distant recurrence using CT of the abdomen, pelvis and chest, carried out together with other planned CT imaging if possible, 6, 12 and 24 months after radical cystectomy **and**

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- monitoring for metabolic acidosis and B12 and folate deficiency at least annually **and**
- for men with a defunctioned urethra, urethral washing for cytology and/or urethroscopy annually for 5 years to detect urethral recurrence.

1.6.3 After radical radiotherapy consider using a follow-up protocol that includes all of the following:

- rigid cystoscopy 3 months after radiotherapy has been completed, followed by either rigid or flexible cystoscopy:
  - every 3 months for the first 2 years **then**
  - every 6 months for the next 2 years **then**
  - every year thereafter, according to clinical judgement and the person's preference
- upper-tract imaging every year for 5 years
- monitoring for local and distant recurrence using CT of the abdomen, pelvis and chest, carried out with other planned CT imaging if possible, 6, 12 and 24 months after radical radiotherapy has finished.

1.6.4 See recommendation 1.2.1 on the use of urinary biomarkers for follow up after treatment for bladder cancer.

1.7 Managing locally advanced or metastatic muscle-invasive bladder cancer

First-line chemotherapy

1.7.1 Discuss the role of first-line chemotherapy with people who have locally advanced or metastatic bladder cancer. Include in your discussion:

- prognosis of their cancer **and**
- advantages and disadvantages of the treatment options, including best supportive care.

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1.7.2 Offer a cisplatin-based chemotherapy regimen (such as cisplatin in combination with gemcitabine, or accelerated [high-dose] methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] in combination with granulocyte-colony stimulating factor [G-CSF]) to people with locally advanced or metastatic urothelial bladder cancer who are otherwise physically fit (have an Eastern Cooperative Oncology Group [ECOG] performance status of 0 or 1) and have adequate renal function (typically defined as a glomerular filtration rate [GFR] of 60 ml/min/1.73 m^2 or more).

1.7.3 Offer carboplatin in combination with gemcitabine to people with locally advanced or metastatic urothelial bladder cancer with an ECOG performance status of 0 to 2 if a cisplatin-based chemotherapy regimen is unsuitable, for example, because of ECOG performance status, inadequate renal function (typically defined as a GFR of less than 60 ml/min/1.73 m^2) or comorbidity. Assess and discuss the risks and benefits with the person.

In February 2015 this was an off-label use of carboplatin in combination with gemcitabine. See NICE's information on prescribing medicines.

1.7.4 For people having first-line chemotherapy for locally advanced or metastatic bladder cancer:

- carry out regular clinical and radiological monitoring **and**
- actively manage symptoms of disease and treatment-related toxicity **and**
- stop first-line chemotherapy if there is excessive toxicity or disease progression.

Second-line chemotherapy

1.7.5 Discuss second-line chemotherapy with people who have locally advanced or metastatic bladder cancer. Include in your discussion:

- the prognosis of their cancer

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- advantages and disadvantages of treatment options, including best supportive care.

1.7.6 Consider second-line chemotherapy with gemcitabine in combination with cisplatin, or accelerated (high-dose) MVAC in combination with G-CSF for people with incurable locally advanced or metastatic urothelial bladder cancer whose condition has progressed after first-line chemotherapy if:

- their renal function is adequate (typically defined as a GFR of 60 ml/min/1.73 m^2 or more) **and**
- they are otherwise physically fit (have an ECOG performance status of 0 or 1).

1.7.7 Consider second-line chemotherapy with carboplatin in combination with paclitaxel or gemcitabine in combination with paclitaxel for people with incurable locally advanced or metastatic urothelial bladder cancer for whom cisplatin-based chemotherapy is not suitable, or who choose not to have it. (Also see the NICE topic page on bladder cancer for all our technology appraisal guidance on this topic.)

In February 2015, this was an off-licence use of carboplatin in combination with gemcitabine and gemcitabine in combination with paclitaxel. See NICE's information on prescribing medicines.

1.7.8 For recommendations on vinflunine as second-line chemotherapy for people with incurable locally advanced or metastatic urothelial bladder cancer, see NICE's technology appraisal guidance on vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract.

1.7.9 For people having second-line chemotherapy for locally advanced or metastatic bladder cancer:

- carry out regular clinical and radiological monitoring **and**
- actively manage symptoms of disease and treatment-related toxicity **and**
- stop second-line chemotherapy if there is excessive toxicity or disease progression.

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Genomic biomarker-based treatment

The point at which to use genomic biomarker-based therapy in solid tumour treatment pathways is uncertain. See the NICE topic page on genomic biomarker-based cancer treatments.

Managing symptoms of locally advanced or metastatic bladder cancer

Bladder symptoms

1.7.10 Offer palliative hypofractionated radiotherapy to people with symptoms of haematuria, dysuria, urinary frequency or nocturia caused by advanced bladder cancer that is unsuitable for potentially curative treatment.

Loin pain and symptoms of renal failure

1.7.11 Discuss treatment options with people who have locally advanced or metastatic bladder cancer with ureteric obstruction. Include in your discussion:

- prognosis of their cancer **and**
- advantages and disadvantages of the treatment options, including best supportive care.

1.7.12 Consider percutaneous nephrostomy or retrograde stenting (if technically feasible) for people with locally advanced or metastatic bladder cancer and ureteric obstruction who need treatment to relieve pain, treat acute kidney injury or improve renal function before further treatment.

1.7.13 If facilities for percutaneous nephrostomy or retrograde stenting are not available at the local hospital, or if these procedures are unsuccessful, discuss the options with a specialist urology multidisciplinary team for people with bladder cancer and ureteric obstruction.

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Intractable bleeding

1.7.14 Evaluate the cause of intractable bleeding with the local urology team.

1.7.15 Consider hypofractionated radiotherapy or embolisation for people with intractable bleeding caused by incurable bladder cancer.

1.7.16 If a person has intractable bleeding caused by bladder cancer and radiotherapy or embolisation are not suitable treatments, discuss further management with a specialist urology multidisciplinary team.

Pelvic pain

1.7.17 Evaluate the cause of pelvic pain with the local urology team.

1.7.18 Consider, in addition to best supportive care, 1 or more of the following to treat pelvic pain caused by incurable bladder cancer:

- hypofractionated radiotherapy if the person has not had pelvic radiotherapy
- nerve block
- palliative chemotherapy.

1.8 Specialist palliative care for people with incurable bladder cancer

1.8.1 A member of the treating team should offer people with incurable bladder cancer a sensitive explanation that their disease cannot be cured and refer them to the urology multidisciplinary team.

1.8.2 Tell the primary care team that the person has been given a diagnosis of incurable bladder cancer within 24 hours of telling the person.

1.8.3 A member of the urology multidisciplinary team should discuss the prognosis and management options with people with incurable bladder cancer.

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1.8.4 Discuss palliative care services with people with incurable bladder cancer and, if needed and they agree, refer them to a specialist palliative care team (for more information, see recommendation 1.1.4 on holistic needs assessment and NICE's guidelines on improving supportive and palliative care for adults with cancer and improving outcomes in urological cancers).

1.8.5 Offer people with symptomatic incurable bladder cancer access to a urological team with the full range of options for managing symptoms.

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2 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The Guideline Development Group's full set of research recommendations is detailed in the full guideline.

2.1 Patient satisfaction

What are the causative and contributory factors underlying the persistently very low levels of reported patient satisfaction for bladder cancer?

Why this is important

The urological cancers grouping (which includes bladder cancer but excludes prostate cancer) has consistently appeared near the bottom of the table of patient satisfaction comparisons of all cancer types in national patient experience surveys. Prostate cancer (which is also managed in urological services) is recorded separately and has continued to appear near the top of the tables.

It is uncertain why this is the case, except that there is now an accepted link between the level of clinical nurse specialist allocation, information and support provision and patient satisfaction. The urological cancers grouping has the lowest level of clinical nurse specialist allocation in comparison with all other cancer types or groupings (including prostate cancer). The prolonged pattern of intrusive procedures that dominate investigation, treatment and follow-up regimens for bladder cancer may also contribute to this position. Additionally, there is concern that people with bladder cancer at or near the end of life, who are by that stage often quite frail and elderly, may not always have access to the full range of palliative and urological support and may, at times, be treated in general wards in hospital and experience significant symptoms of pain and bleeding (haematuria).

To explore this research question bladder cancer patients need to be identified separately from the generic group of urological cancer patients in nationally collected data sets.

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2.2 BCG or primary cystectomy in high-risk non-muscle-invasive bladder cancer

Is primary radical cystectomy more effective than primary intravesical BCG in high-risk non-muscle-invasive bladder cancer (see the section on risk classification in non-muscle-invasive bladder cancer), in terms of quality of life and cancer-specific outcomes?

Why this is important

Options for people with high-risk non-muscle-invasive bladder cancer include cystoscopy surveillance, BCG immunotherapy or radical surgery. To date, these have not been directly compared across the same population to understand their relative benefits.

Bladder-sparing approaches avoid major surgery, but have a greater risk of cancer progression. The potential advantage of bladder-sparing approaches compared with cystectomy in maintaining quality of life may be offset by continuing concern about cancer progression and morbidity from treatment. Primary cystectomy may improve survival; however, it has high short-term risks and life-changing consequences. It will be overtreatment for those people whose cancer would not have progressed.

2.3 Follow-up of high-risk non-muscle-invasive bladder cancer

In people with high-risk non-muscle-invasive bladder cancer, are these follow-up regimens equally effective in terms of identification of progression, cost effectiveness and health-related quality of life?

- Cystoscopic follow-up at 3, 6, 12, 18, 24, 36 and 48 months, and then annually, interspersed with non-invasive urinary tests.
- Cystoscopic follow-up at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42 and 48 months, and then annually thereafter.

Why this is important

Cystoscopy is currently the standard of care for follow-up of people with high-risk non-muscle-invasive bladder cancer. Regular cystoscopy may be associated with anxiety,

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procedural discomfort to the person and significant costs to the NHS.

Urine tests based on a variety of technologies (including cytology, fluorescence in-situ hybridization [FISH] and proteomic platforms) can detect high-grade recurrence, raising the possibility that 1 or more of these tests could be used to reduce the frequency of cystoscopy. This could improve acceptability to patients and reduce costs to the NHS without increasing the risk of disease progression.

There is a lack of evidence on the optimal frequency of follow-up and whether the frequency of cystoscopy follow-up can safely be reduced by substitution of urinary tests.

2.4 Biomarkers for treatment selection

In patients with muscle-invasive bladder cancer suitable for radical treatment, does the use of biomarkers enable patients to select more effective treatment, and improve their outcomes, compared with treatment selected without biomarkers?

Why this is important

Response to surgery or radiotherapy is difficult to predict for individuals. There is variation not only in the cure rates for patients with muscle-invasive bladder cancer treated with either surgery or radiotherapy, but also in the side effects experienced during and after treatment. The usefulness of current biomarkers in predicting treatment outcomes for individual patients has not been clearly established. Currently treatment decisions are based on patient-related factors, and patient and clinician preference. Research into biomarkers that can predict the response of the patient's muscle-invasive bladder cancer to either radiotherapy or surgery could help individual patients and clinicians decide which treatment is more suitable and is considered an important step toward individualised treatment.

2.5 Follow-up after radical treatment for organ-confined muscle-invasive bladder cancer

Is symptom-based review as effective as scheduled follow-up for people treated with radical cystectomy or radical radiotherapy for organ-confined, muscle-invasive bladder cancer? Outcomes of interest are overall survival, health-related quality of life, resource use and cost.

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Why this is important

Standard care after treatment for organ-confined, muscle-invasive bladder cancer is scheduled follow-up at intervals set out by the treating team. Although this can be reassuring for both the patient and the treating team, it is not known whether scheduled follow-up offers clinical benefit compared with symptom-based review, which is increasingly used for people with other cancers. Moreover, there are significant costs associated with follow-up. The current evidence about follow-up is confined to cystectomy. There is no evidence concerning follow-up after radiotherapy. In addition, the evidence on radiological follow-up uses mainly outdated imaging techniques.

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Finding more information and committee details

NICE guidance on related topics, including guidance in development, see the NICE webpage on bladder cancer.

For full details of the evidence and the guideline committee's discussions, see the full guideline and evidence review. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put NICE guidance into practice.

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Update information

Minor changes since publication

January 2022: Minor changes to redirect NICE Pathways links.

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		and conformance to standards for penile cancer management at the time, in order to pass comment specifically regarding Mr O'Brien's case volume, treatment offered (vs guidance) and quality of surgery provided, an audit of penile cancer treatment is required. I regret that I have not been able to initiate such an audit due to the various continuing workload pressure on myself and the team. As recognised within this response, nephron sparing surgery also continued to be provided in CAH and a similar audit is required for this. It is the case that Mr O'Brien would have been trained to perform the procedures undertaken on Patient 3 and as acknowledged he would have continued to maintain a practice (albeit limited numbers as it is a rare cancer) until the Western Trust service commenced in December 2019. The audit will inform the annual case load of surgery provided by Mr O'Brien (and colleagues) in CAH and the quality of surgery received by these patients. ***Mr Mark Haynes has responded to both elements b and c in a*** ***b. Within the Trust correspondence dated 27 November 2020, reference is made to an audit of a patient's prescribed bicalutamide out with its licensed indications. Is there an official audit document? If so, can you please provide a copy?*** ***and*** ***c. Can you please provide the outcome of the subsequent audit in respect of patient's receiving 150mg Bicalutamide? Please also confirm whether any patients identified were provided with alternative or amended treatment in terms of the prescribing.*** As per comment to answer 2 above there is no official audit document. The 'Bicalutamide audit' was a rapid review of patients receiving

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		Bicalutamide in the management of their prostate cancer in order to identify those patients potentially requiring a change to their prostate cancer management. It was conducted as a rapid review of records following identification of a patient safety risk during the SAI process for other patients in whom prostate cancer management concerns had been identified, and which were characterised by the use of low dose Bicalutamide. This patient record review was performed at speed with the NIECR review being conducted by me alone conducting a rapid NIECR review of the prostate cancer management of 764 patients, in my own time (while on leave), with considerable external pressure for haste. This took place in October 2020 when the second wave of the COVID pandemic was also escalating with resultant multi-directional pulls on my time and so my follow-through on formalising the findings was hampered significantly. I have not subsequently re-reviewed these patients' records and not all of these patients' care has been subject to a lookback review as many were under the care of both urology and oncology teams / consultants across multiple trusts while lookback reviews have been done only on patients managed by Mr O'Brien. No prior approval was sought for my review of records for patients managed in other trusts / teams from the other trusts governance teams nor was it registered prospectively with the Southern Trust governance / audit team. Concerns had been identified regarding patients whose prostate cancer management was not to standard and that this was characterised by the prescribing of a low dose (50mg) of Bicalutamide. These cases were subject to an SAI / investigation which was ongoing, but it was felt that there was a significant risk of additional patients also having been managed in the same manner was significant and that any such patients required identification as their treatment may require changing. It was also recognised that patients may have been initially commenced on the low dose of

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