North of Scotland Clinical Management Guideline (CMG):Bladder Cancer Last Updated 26/04/2023

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For symptoms of suspected urological cancers, please refer to the Scottish Referral Guidelines for Suspected Cancer

General Principles

- All patients must be discussed at MDT meeting throughout their patient journey as required.
- All patients referred with a suspicion of bladder cancer need to be treated equally whether referred as USC, Urgent or Routine by referral GP / HCP / other speciality.
- All patients referred for investigation of symptoms potentially indicative of bladder cancer should receive an appointment to a diagnostic urology outpatient clinic.
- Patients should be vetted in accordance with the Scottish Referral Guidelines for Suspected Cancer.
- Where possible a definitive diagnosis be made clinically (cystoscopy or imaging where appropriate) and pathological staging should be done prior to definitive treatment.
- Where available, clinical trials should be considered as the preferred option for all eligible patients and consideration can be given to referral to another NHS board / national referral.
- Patients must be involved in all decision-making relating to their care and informed consent is required for patients undergoing treatment.
- All patients should be referred to or made aware of the Urology Clinical Nurse Specialist services available in the North of Scotland, for assessment and ongoing advice, education, support and coordination.
- The wishes of the patients must influence decision-making with respect to treatment choices within this CMG.
- A list of SACT regimens is provided on Page 11.
- Full regional SACT Protocols will be developed and linked to from this document.

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North of Scotland Clinical Management Guideline (CMG): Non-Muscle Invasive Bladder Cancer (NMIBC) Risk

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Reference: European Association of Urology Guidelines on Non Muscle Invasive Bladder Cancer https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/

Low Risk

Low grade / Low Grade G2 Ta < 3cm

Any papillary urothelial neoplasm of low malignant potential (PUNLMP, low grade)

Intermediate Risk

Solitary low grade G2 Ta with diameter >3cm

Multifocal low grade G2 Ta

Solitary low grade G2 T1 <3cm (some may be regarded as high risk)

Any G2 Ta grade not further specified

Any low-risk non-muscle invasive bladder cancer with recurrence (no time limit)

High Risk

Urothelial cancer with any of:

- Solitary or multifocal high grade G2 / G3 Ta of any size
- Solitary or multifocal high grade G2 / G3 T1 of any size
- Solitary or multifocal high grade G2 / G3 Ta of any size + CIS
- Solitary or multifocal high grade G2 / G3 T1 of any size + CIS
- Primary CIS (Tis)
- Aggressive variants of urothelial carcinoma, for example micro papillary or nested variants

Very High Risk / Highest Risk

Any high risk tumour with any of the following characteristics:

- Solitary or multifocal high grade G2 / G3 T1 >3cm
- Solitary or multifocal high grade G2 / G3 T1 of any size + CIS
- Any high risk tumour in prostatic urethra
- Recurrent high grade tumour (note - this also includes BCG refractory / relapsed disease)
- Aggressive variants of urothelial carcinoma

Note: tumours in the diverticulum may be considered high risk.

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Initial Evaluation

- Patient history, examination and assess & record Performance Status
- Full Blood Count (FBC), Renal Function (RF) and Urea & Electrolytes (U&E) +/- Urine Dipstick
- Flexible Cystoscopy + CTU or Ultrasound
    - Urine dipstick suspected of UTI (nitrite/leucocyte) with no symptoms – consider flexible cystoscopy under antibiotic cover (IV or oral)
    - Urine dipstick suspected of UTI (nitrite/leucocyte) with LUTS – defer flexible cystoscopy + urine culture + antibiotic treatment + reappoint ASAP for flexible cystoscopy
- Request staging CT chest and CTU if suspect high risk / large volume / suspected MIBC

Initial Treatment / staging / pathological diagnosis

- Transurethral resection of a bladder tumour (TURBT – PDD optional) + EUA
- If appropriate; intravesical mitomycin C preferably within theatre after TURBT (if no contraindication). If not possible, consider within 24 hours of TURBT
- At MDT, confirm clinical and pathological diagnosis and staging CT-urogram (can be excluded for low grade UC or poor risk candidates with renal failure and choices are MRU or non-contrast CT, if appropriate)

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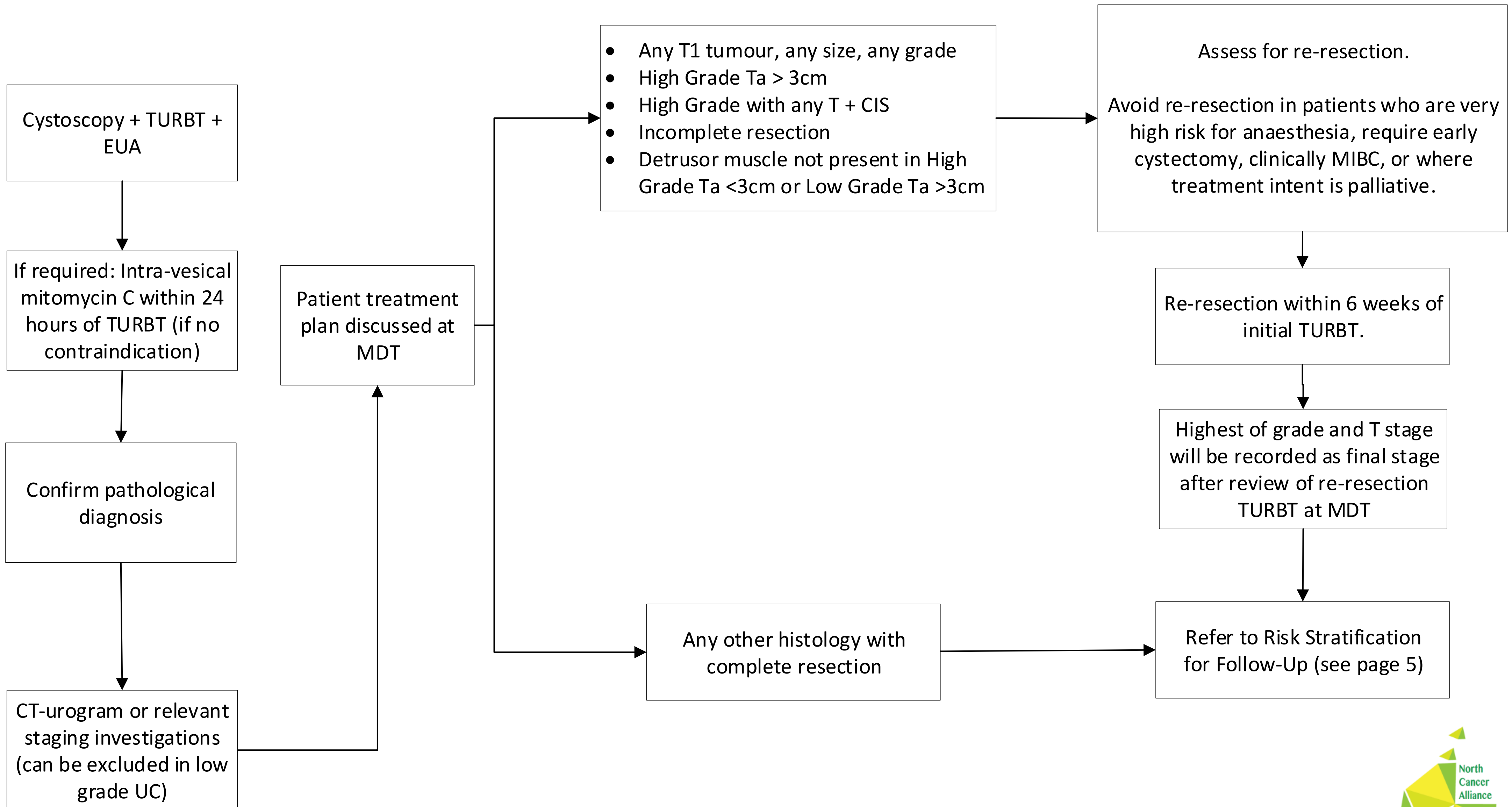
North of Scotland Clinical Management Guideline (CMG): NMIBC Treatment Last Updated 26/04/2023

Evaluation & Initial Treatment	Histology Evaluation at MDT meeting	Additional treatment



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Low risk →

Check flexible cystoscopy at 3 months & 12 months, then consider endoscopy for up to 5 years at 12-24 monthly intervals.
Consider discharge after 5 years of disease-free follow-up.

→ Recurrent single / multiple tumours →

TURBT (consider immediate mitomycin – see page 6) and discuss histology at MDT
Consider Flexible cystoscopy and diathermy under LA if <10mm lesion, very poor risk for anaesthesia (ASA3/4). Staged flexible cystoscopy and diathermy can be considered for very poor risk candidates for larger or multifocal tumours

Intermediate risk →

Check cystoscopy at a minimum of 3, 9 and 18 months then yearly for five years.
No upper tract imaging required unless tumour at ureteric orifice (options CTU / USS / MRU)
Consider discharge after 5 years of disease-free follow-up.

→ Recurrent single / multiple tumours →

- TURBT (consider immediate mitomycin – see page 6) and discuss histology at MDT
- Low grade recurrence - surveillance for intermediate risk category (from date of latest TURBT)
- Multiple recurrence in <12 months - discuss mitomycin-C course (maintenance of MMC optional – see page 6)
- If further recurrence, discuss BCG
- High grade recurrence - re-resection (if appropriate) and follow High Risk pathway
- Multiple recurrences not responding to MMC course or BCG, or not suitable for endoscopic management (large volume disease) then discuss radical surgery

High risk →

Very High Risk? (see page 3)

Yes →

Discuss radical surgery
If not suitable for radical surgery, or patient preference, then follow the High Risk pathway, except post-induction BCG, provide maintenance BCG for three years.

No ↓

Discuss BCG / endoscopic surveillance / radical cystectomy (significant LUTS / BCG contraindicated / patient preference)

→

- Check flexible cystoscopy + urine cytology (if appropriate)
  - Years 1-2: 3monthly
  - Years 3-4: 6monthly
  - Years 5-10+: annually
- Offer BCG (if suitable)
- Induction BCG followed by flexible cystoscopy + urine cytology (no need for GA cystoscopy + biopsies) + maintenance BCG for one year
  - If urine cytology malignant, or significant redness in the bladder, consider GA cystoscopy + bladder biopsies + prostatic urethral biopsies
- Consider CTU surveillance in high risk patients / upper tract cancer patients (timelines can vary per local board arrangements)

Mitomycin-C (MMC) standard

Post TURBT single dose 40mg intravesically for 60-80 mins.

Induction doses 40mg intravesically for 60-80 mins every week for 6 weeks.

Where indicated, consider maintenance doses 40mg intravesically 3weekly dose every 3 months for 1 year

BCG

Induction course

Maintenance – 1 dose every week for 3 weeks, follow schedule as per high / very high risk patients

Note: Where Mitomycin-C (MMC) may be unavailable in future (manufacturing issues), intravesical treatment with Gemcitabine or epirubicin are suggested options by UK Medicines information, Specialist Pharmacy Service and NICE.

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North of Scotland Clinical Management Guideline (CMG): Muscle Invasive Bladder Cancer (MIBC) Treatment

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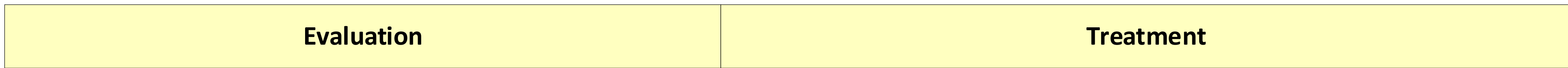

T2-4a, N0-2, M0

Assess fitness for NACT, radical surgery and radical radiotherapy

Not Fit

Consider palliative treatment

Fit

Check indications for urgent cystectomy (see page 8)

No

Fit for NACT? (see page 8)

Yes

Discuss NACT

Opted for NACT

Gemcitabine + Cisplatin x3 and staging CT

Response - Yes

Consider 4th cycle and proceed with patient choice of radical surgery or radical (chemo)radiotherapy

Response - No

Recommendation for surgery if fit

Declined

Not Fit or contra-indicated

Discuss radical surgery & radiotherapy

Proceed to Radical Radiotherapy

Yes

Fit for Radical Surgery?

Yes

Discuss Radical Surgery

Proceed to Radical Surgery

No

Not Opted

Consider other management options as per need or Radiotherapy

Surgery patients

- ≤ T2 N0M0 clear margins: follow post-surgery follow-up (see page 10)
- T3-T4a or any T N1-2 M0: oncology to review to discuss adjuvant chemotherapy (if not had or declined NACT)
- Positive margins or extracapuslar nodal disease, consider adjuvant chemotherapy / radiotherapy

Radiotherapy patients

See page 11 for follow-up

North of Scotland Clinical Management Guideline (CMG): Muscle Invasive Bladder Cancer (MIBC) Contraindications

Last Updated 26/04/2023

Table 1 – Contraindications to NACT

- Not fit for Cisplatin
- Obstructive nephropathy not likely to be reversed sufficiently by nephrostomy / stent

Table 2 – Contraindications to Radiotherapy

- Inflammatory bowel disease
- Extensive CIS / involvement of ureteric orifices

Table 3 – Indications for Urgent Cystectomy

- Recurrent haematuria, not responding to endoscopic management
- Small capacity bladder with severe LUTS (not tolerant to catheter)
- Bladder perforation with bladder tumour (MIBC)
- Bilateral or unilateral hydronephrosis with renal failure
- Associated urethral tumour
- Associated upper tract tumour (UTUC) with bladder cancer
- Patients with previous radiotherapy to pelvis (prostate cancer/ rectal cancer etc)
- Significant OAB symptoms
- Non urothelial bladder cancer (except Small cell cancer) - adenocarcinoma/ SCC
- Variant urothelial cell carcinoma
- Compression from large volume bladder cancer (rectal/ colonic obstruction)
- Colovesical fistula with bladder cancer

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North of Scotland Clinical Management Guideline (CMG): MIBC NACT and Chemotherapy Last Updated 26/04/2023

Evaluation	Treatment

T3-T4a N3 M0 → Consider radical or palliative treatments
- → Radical treatment (see page 7)
- → Palliative chemotherapy

AnyT AnyN M1 → Assess suitability for palliative chemotherapy
- → Not suitable for any form of Chemotherapy → Best Supportive Care
- → Suitable and opted for Chemotherapy → Gemcitabine + Cisplatin x 4-6 (Re-stage after 3 and 6 cycles) → Assess response
- Suitable and opted for Chemotherapy → Not suitable for Cisplatin – consider Gemcitabine + Carboplatin → Gemcitabine + Carboplatin x 4-6 (Re-stage after 3 and 6 cycles) → Assess response

Assess response
- → Good response/stable disease – maintenance Avelumab → **Recurrence:** rechallenge with Gemcitabine + Cisplatin or consider Pembrolizumab
- → No response – Pembrolizumab

NOTE: Consider Carboplatin + Etoposide for small cell bladder cancer

North of Scotland Clinical Management Guideline (CMG): MIBC Follow-Up Last Updated 26/04/2023

Radical Surgery

Imaging
CT Chest Abdomen Pelvis
MRU +/- Non Contrast CT
(if appropriate)

minimum every 6-12 months for 2-3 years and then yearly for 5 years (as per EAU & NICE guidelines)

Bloods prior to imaging
FBC, renal function and PSA (if required)

Bicarbonate and Chloride in addition to above in patients with orthotopic bladder reconstruction

After 12 months or when patient becomes anaemic then check Vitamin B12, Folic acid, Iron

Flexible urethroscopy
(males with Ileal conduit)
yearly till 5 years

Flexible cystoscopy
(Orthotopic bladder reconstruction)
6 monthly for 5 years and then yearly till 10 years (minimum)

Radical Radiotherapy

Flexible cystoscopy
6 monthly for 5 years

GA Cystoscopy
Bladder Biopsies/ TURBT
for suspected recurrence

Reference: European Association of Urology Guidelines on Muscle Invasive & Metastatic Bladder Cancer
https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/

Notes

1. Extensive Follow-up as suggested above in patients with good performance status and can be considered for chemotherapy
2. In poor performance status patients or those who are not candidates for further chemotherapy symptomatic Follow-up is advised

SACT Regimen*	Treatment Intent
Avelumab	Non-curable
Carboplatin + etoposide	Non-curable
Gemcitabine + Cisplatin	Curable or Non-curable
Gemcitabine + Carboplatin	Curable or Non-curable
Gemcitabine + Cisplatin	Non-curable
Gemcitabine - weekly (with radiotherapy)	Radical
Paclitaxel (weekly)	Non-curable
Paclitaxel + Carboplatin	Non-curable
Mitomycin + 5FU (with radiotherapy)	Radical
Pembrolizumab	Non-curable

*Until Regional SACT Protocols are developed, full details of each agreed SACT Regimen may be found on the Bladder Cancer SACT Regimen Spreadsheet, hosted on the NCA website

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TNM Staging for Urinary Bladder (C66)

Union for International Cancer Control (8th Edition; 2017)

Primary Tumour (T)		
Tx	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
Regional Lymph Nodes (N)		
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 a common iliac lymph node(s)	
Distant Metastasis (M)		
M0	No distant metastasis	
M1a	Non regional lymph nodes	
M1b	Other distant metastasis	

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Definitions

ASA	American Society of Anaesthesiologists (classification)
BCG	Bacillus Calmette Guerin
CIS	Carcinoma In Situ
CMG	Clinical Management Guideline
CTU	Computed Tomography Urography
EUA	Examination Under Anaesthetic
FBC	Full Blood count
GA	General Anaesthetic
IV	Intravenous
LA	Local Anaesthetic
LUTS	Lower urinary tract symptoms
MIBC	Muscle Invasive Bladder Cancer
MDT	Multi-Disciplinary Team
MRU	Magnetic Resonance Urography
NACT	Neo-adjuvant Anti Cancer Therapy
NBI	Narrow Band Imaging
NMIBC	Non Muscle Invasive Bladder Cancer
OAB	Overactive Bladder
PUNLMP	Papillary urothelial neoplasm of low malignant potential
PDD	Photodynamic Diagnosis
SACT	Systemic Anti-Cancer Therapy
TURBT	Transurethral resection of a bladder tumour
UC	Urothelial Carcinoma
USS	Ultra Sound Scan
UTI	Urinary Tract Infection
USS	Ultra Sound Scan
UTUC	Upper Tract Urothelial Carcinoma

References

NICE guidelines on mitomycin C after TURBT
https://www.nice.org.uk/sharedlearning/immediate-instillation-of-intravesical-chemotherapy-mitomycin-c-following-transurethral-resection-for-bladder-tumour

European Association of Urology Guidelines on Non Muscle Invasive Bladder Cancer
https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/

European Association of Urology Guidelines on Muscle Invasive & Metastatic Bladder Cancer
https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/