高 雄 榮 民 總 醫 院
膀胱癌診療原則

2021年02月23日第一版

泌尿道癌醫療團隊擬訂

注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如你是一個癌症病人，直接引用這個診療原則並不恰當，只有你的醫師才能決定給你最恰當的治療。

會議討論

上次會議：2020/02/18

本共識與上一版的差異

上一版	新版
	審視

膀胱癌(圖一)

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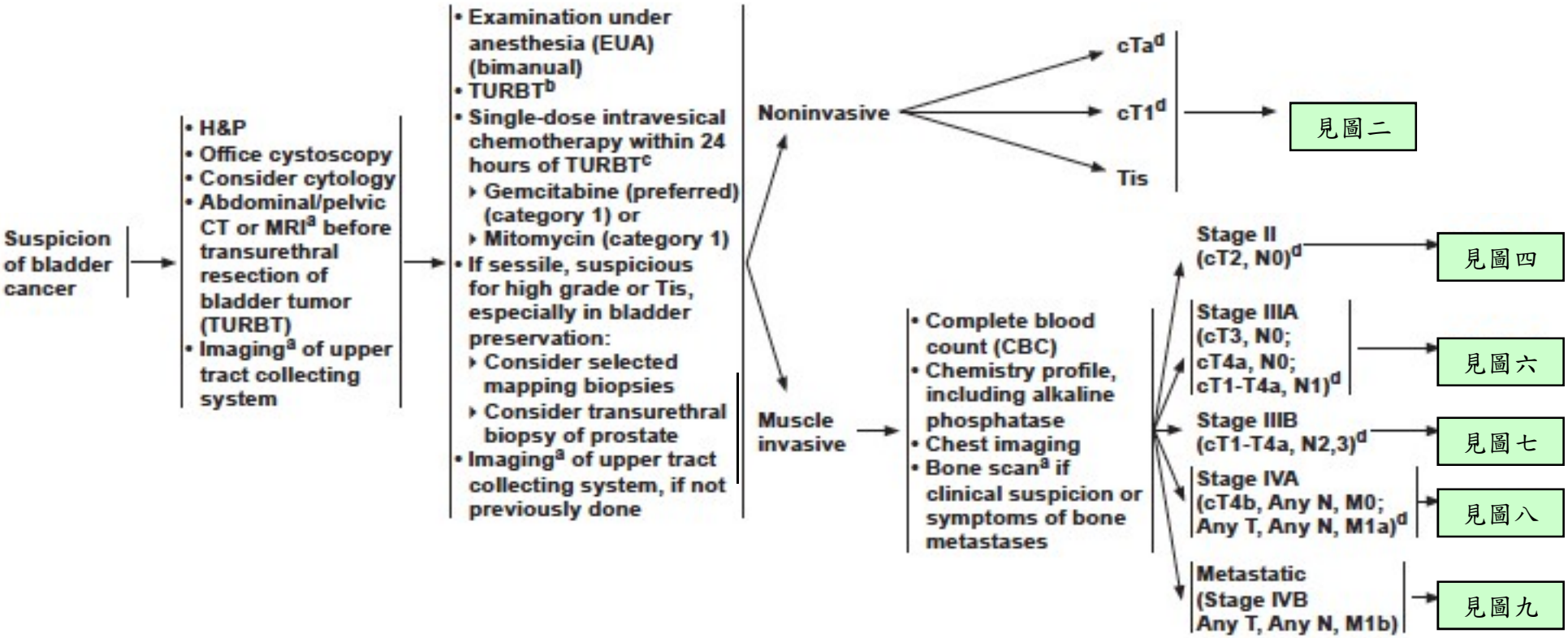
臨床診療指引　2021年第一版

臨床表徵	初期評估	主要評估/手術治療	推定臨床分期	針對不同分期附加性檢查



c Immediate intravesical chemotherapy reduces the recurrence rate by 35%.
d The modifier “c” refers to clinical staging based on bimanual examination under anesthesia, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier “p” refers to pathologic staging based on cystectomy and lymph node dissection.
必要項目：cystoscopy、CXR、image

膀胱癌(圖二)

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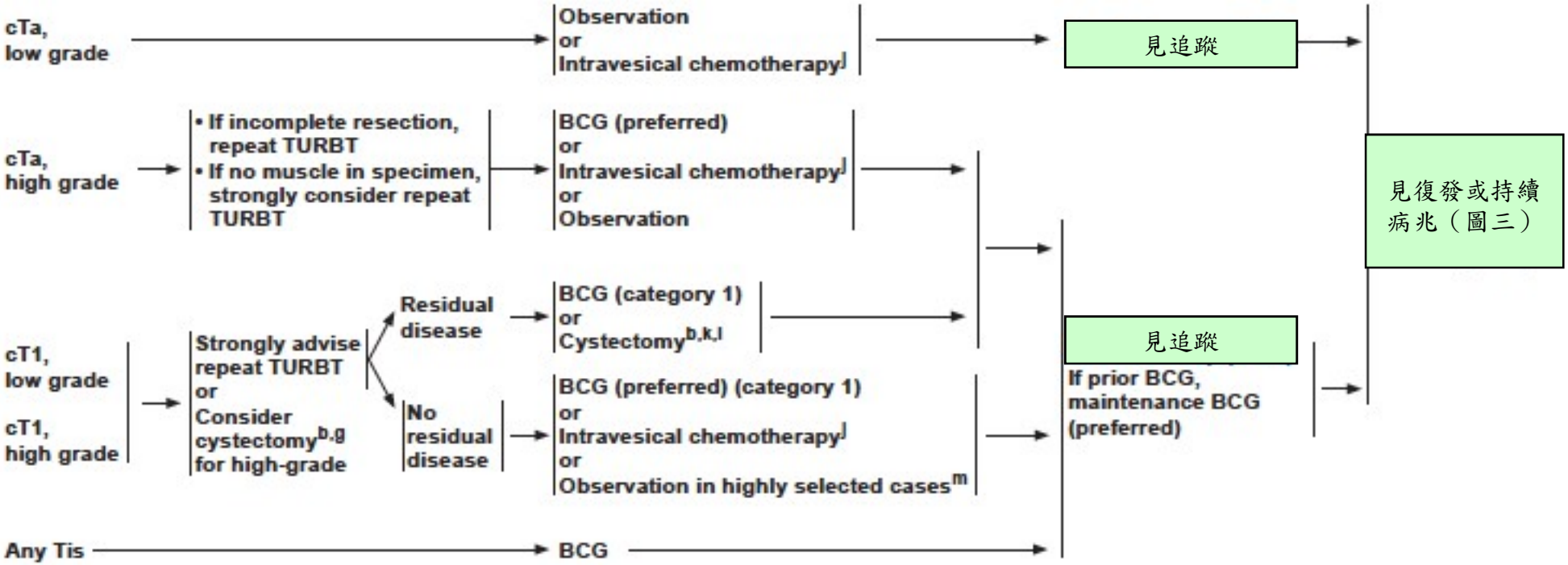
臨床分期	二度手術治療	輔助性膀胱內灌注治療	追蹤



h Indications for adjuvant induction therapy: Based on probability of recurrence and progression to muscle-invasive disease, such as size, number, and grade.
j The most commonly used options for intravesical chemotherapy are mitomycin and epirubicin.
k If not a cystectomy candidate, consider concurrent chemoradiotherapy (category 2B) or a clinical trial.
l Cystectomy is generally reserved for residual T1, high-grade, and muscle invasive disease at re-resection.
m Highly selected cases with small-volume tumors with limited lamina propria invasion and no CIS.

膀胱癌(圖三)

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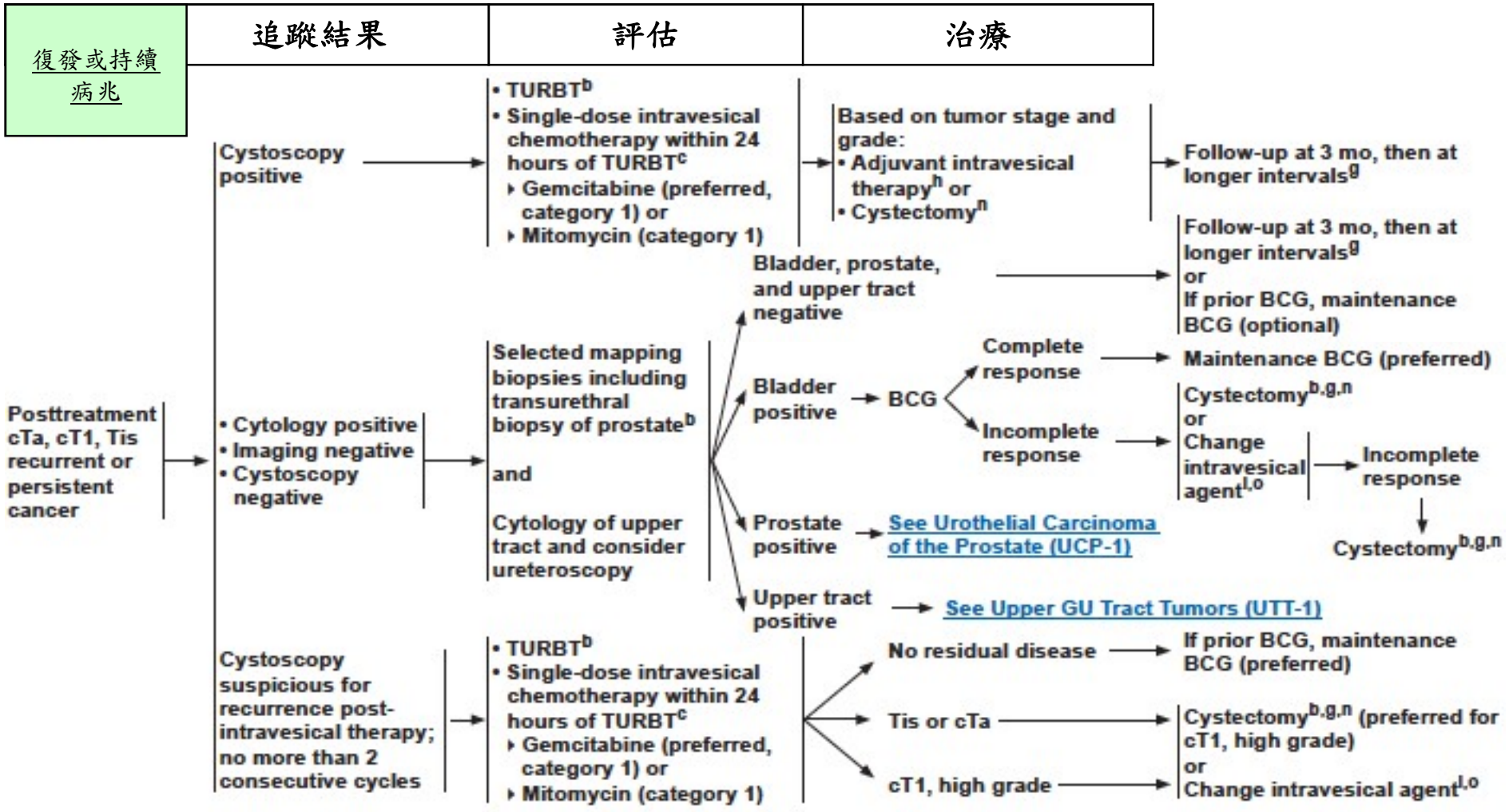

n If not a cystectomy candidate, and recurrence is cTa or cT1, consider concurrent chemoradiotherapy (category 2B for cTa, category 2A for cT1) or a clinical trial.

膀胱癌(圖四)

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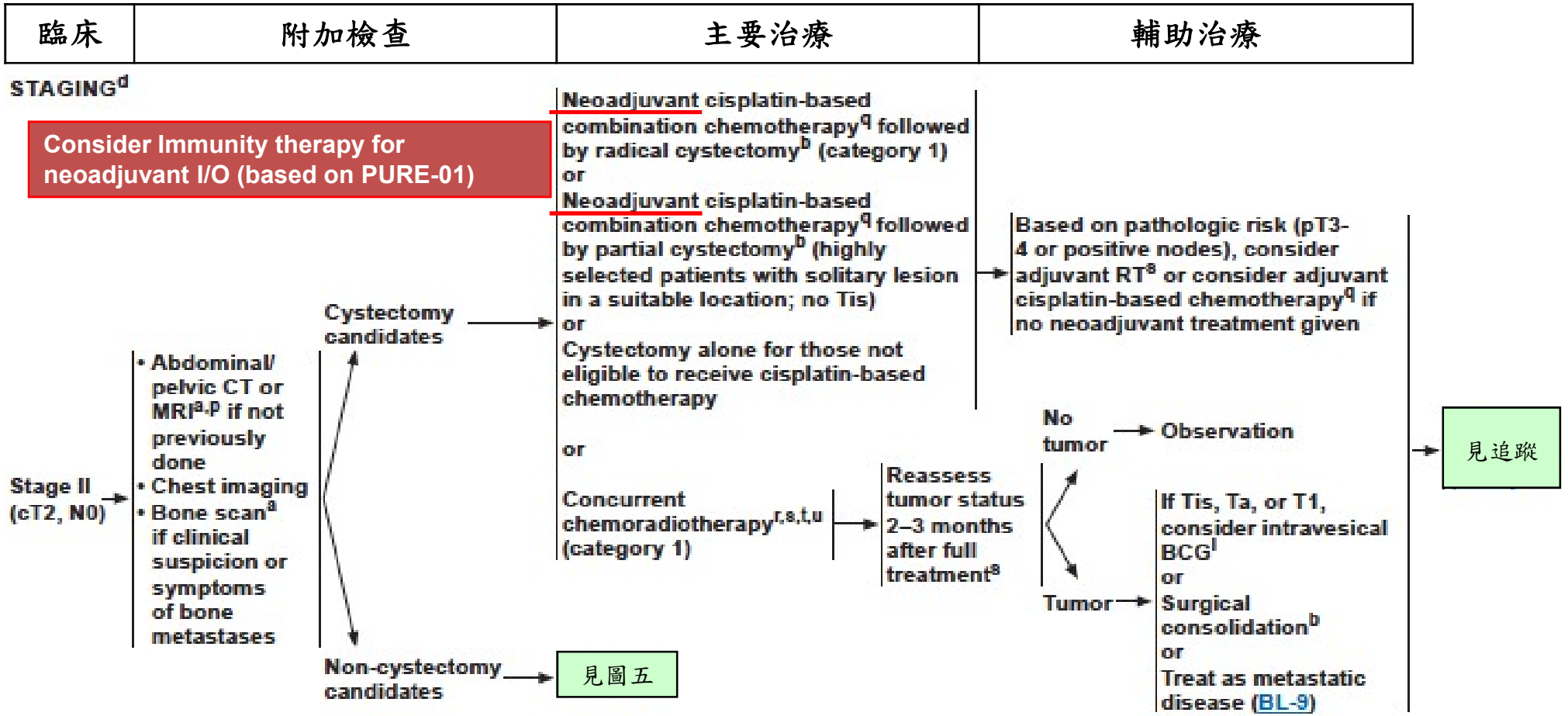

p Consider PET/CT scan (skull base to mid-thigh) (category 2B).
t There are data to support equivalent survival rates. Not all institutions have experience with these multidisciplinary treatment approaches, which require a dedicated team.
u Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without hydronephrosis, are without concurrent extensive or multifocal Tis, and are <6 cm. Ideally, tumors should allow a visually complete or maximally debulking TURBT.

膀胱癌(圖五)

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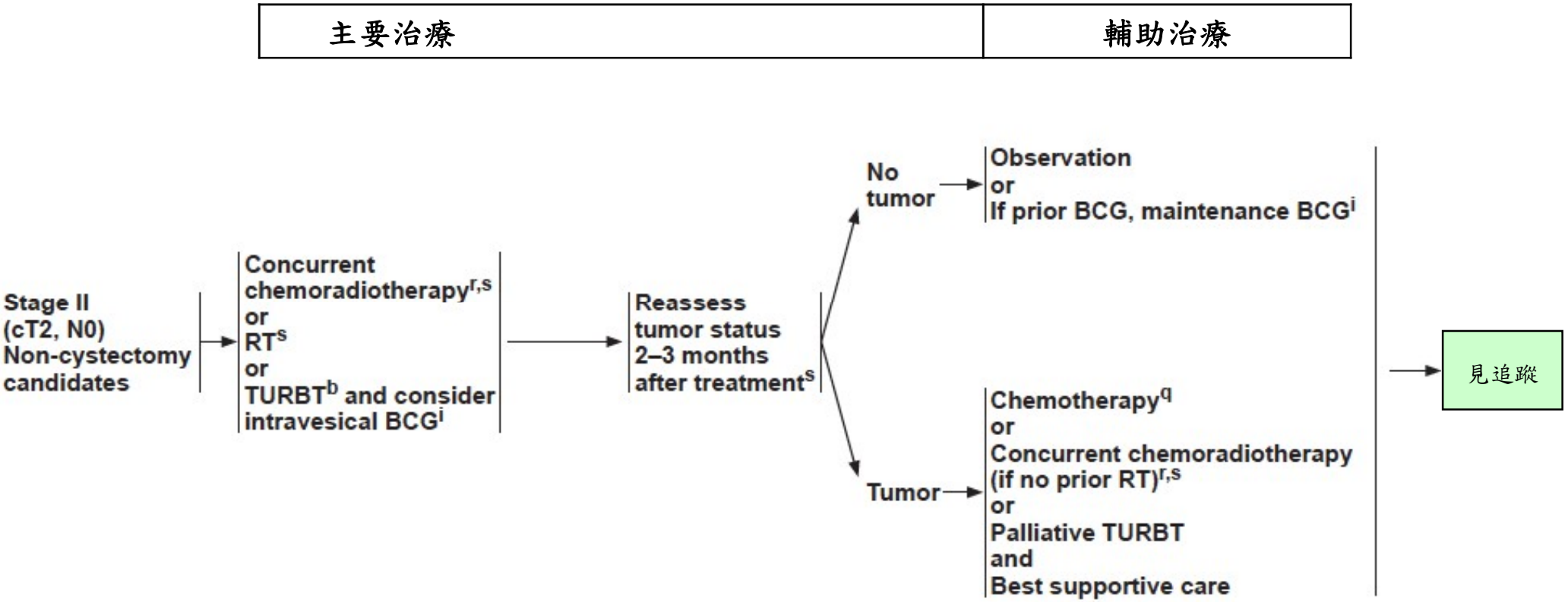

膀胱癌(圖六)

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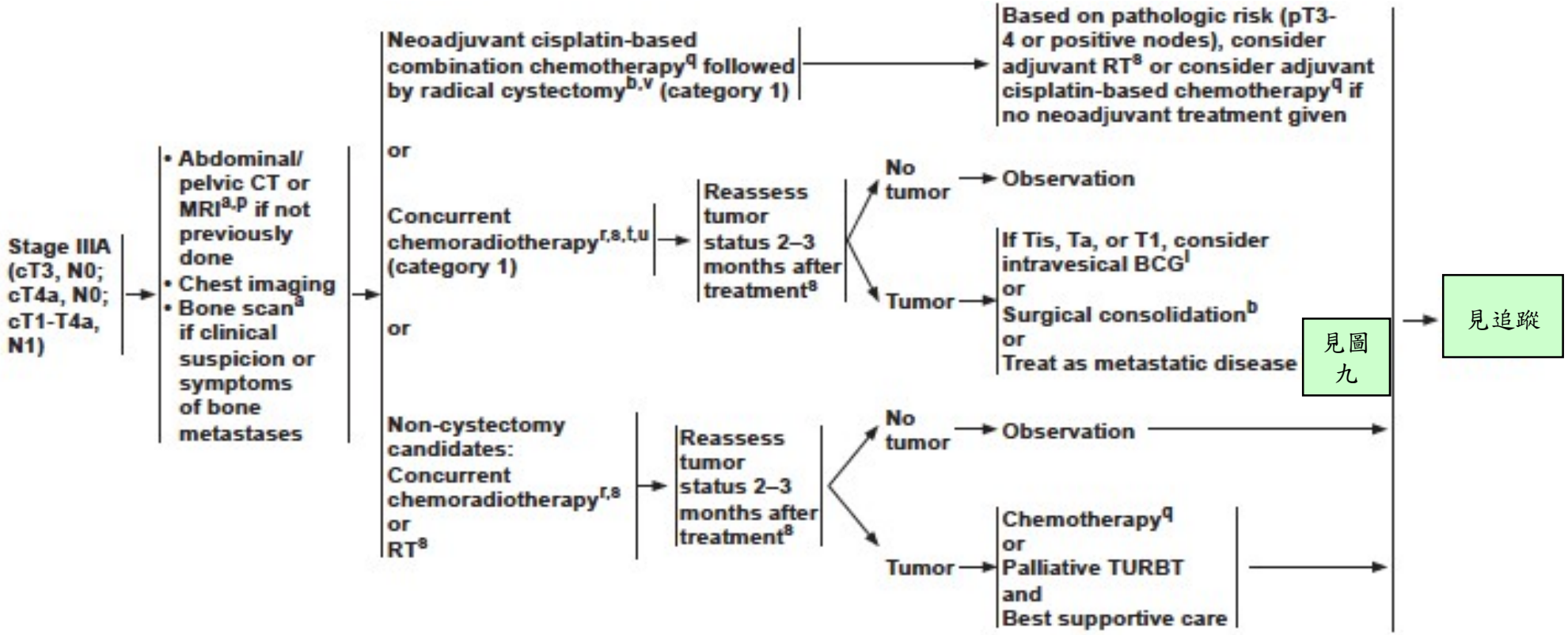
臨床分期	附加檢查	主要治療	輔助治療



v Cystectomy alone is appropriate for those not eligible to receive cisplatin-based chemotherapy. Patients with N1 disease do better if there is a response to neoadjuvant chemotherapy than if there is a response to surgery alone.

膀胱癌(圖七)

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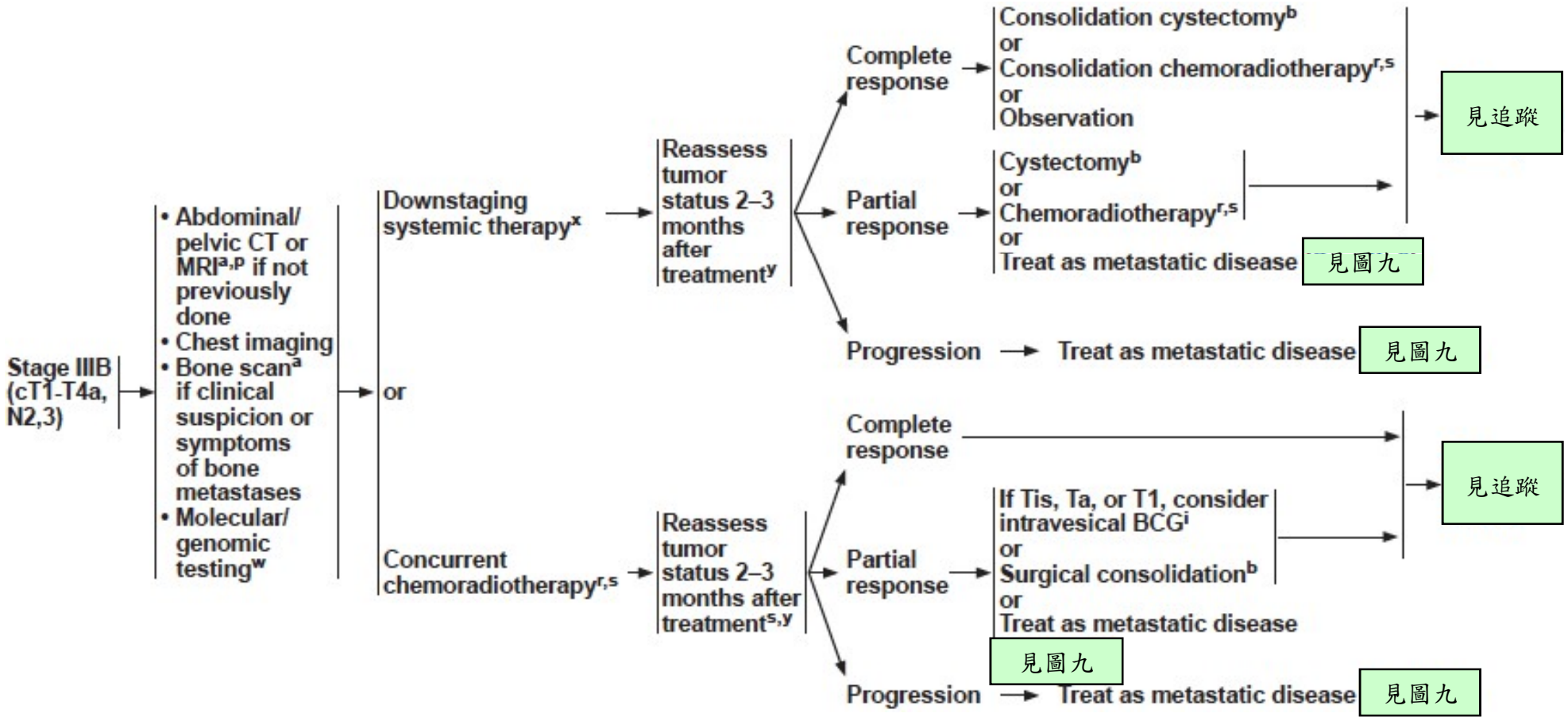
臨床分期	附加檢查	主要治療	後續治療



w Including FGFR RGQ RT-PCR for FGFR3 or FGFR2 genetic alterations.
y Imaging with CT of chest/abdomen/pelvis with contrast. If there is no evidence of distant disease on imaging reassessment, further cystoscopic assessment of tumor response in the bladder is recommended.

膀胱癌(圖八)

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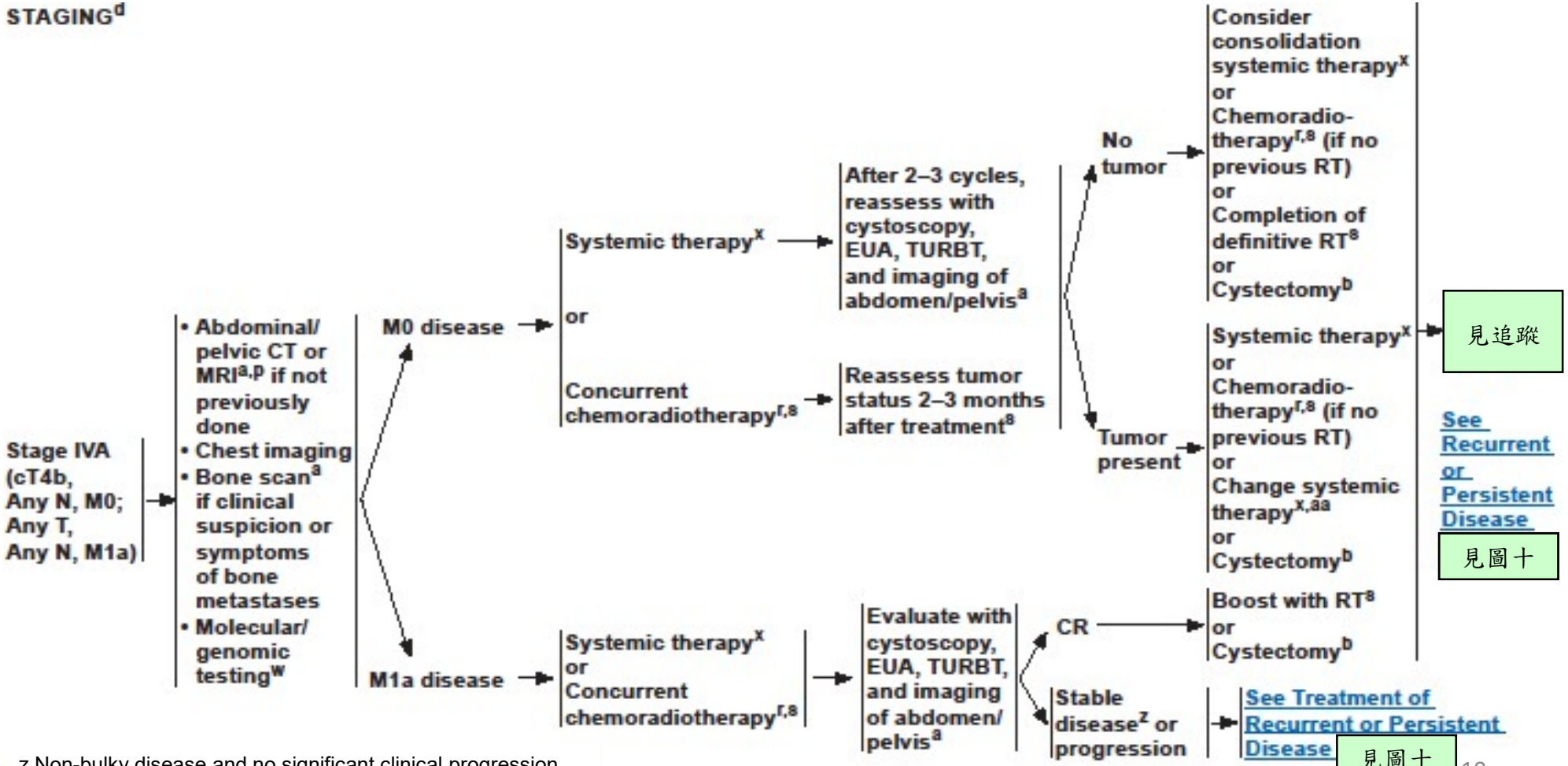
臨床分期	附加檢查	主要治療	後續治療



z Non-bulky disease and no significant clinical progression.

膀胱癌(圖九)

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臨床分期	附加檢查	主要治療
Metastatic[bb] (Stage IVB Any T, Any N, M1b)	• Bone scan[a] if clinical suspicion or symptoms of bone metastases • Chest CT • Consider CNS imaging[a] • Estimate GFR to assess eligibility for cisplatin • Consider biopsy if technically feasible	→ Systemic therapy[x,aa]

bb Consider molecular/genomic testing in a CLIA-approved laboratory, including FGFR RGQ RT-PCR for FGFR3 or FGFR2 genetic alterations.

膀胱癌(圖十)

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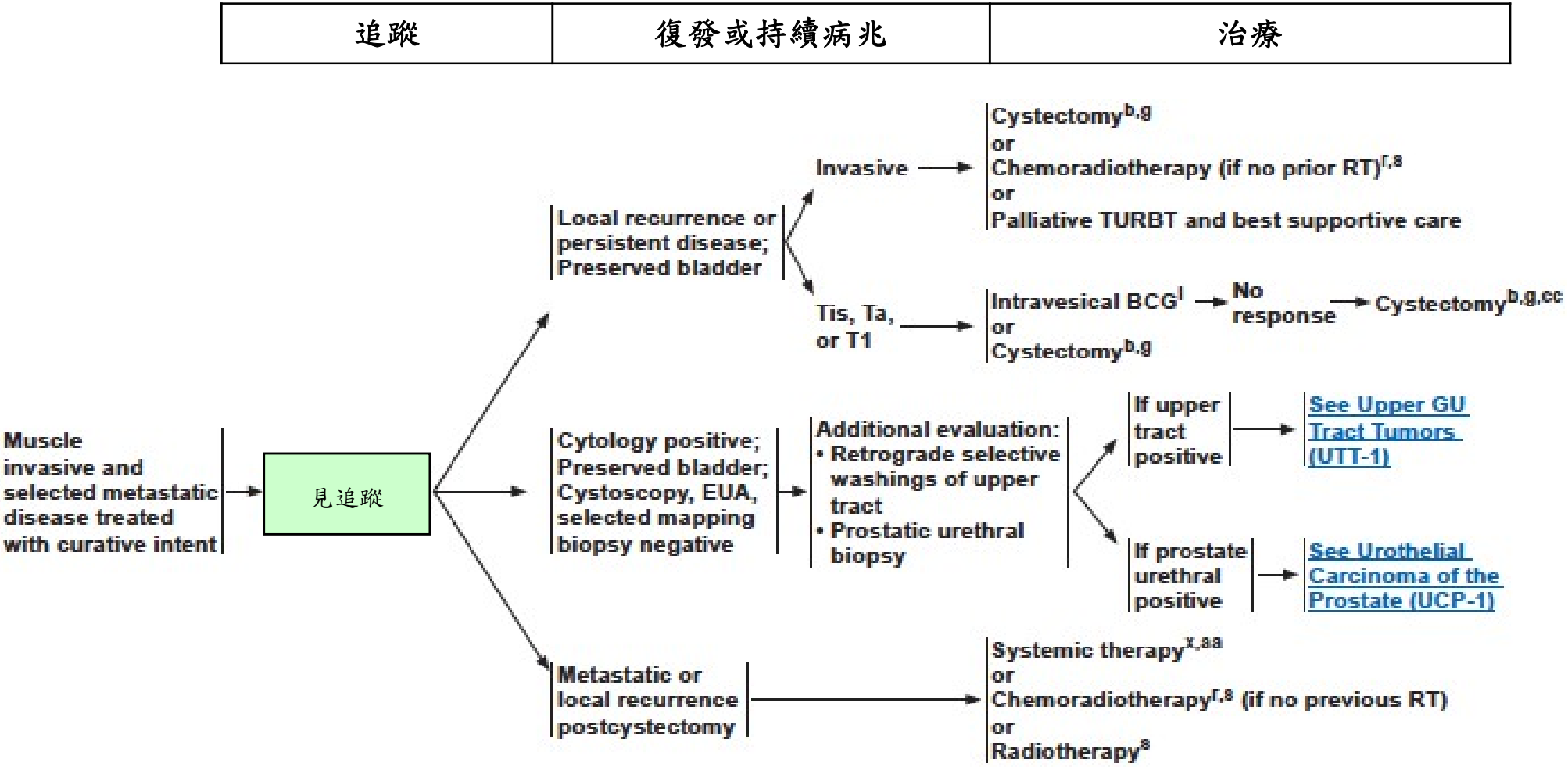

cc If not a cystectomy candidate, consider concurrent chemoradiotherapy (See BL-G 4 of 5) (if no prior RT), change in intravesical agent, or a clinical trial.

膀胱癌(追蹤)

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Table 1: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*

Low Risk	Intermediate Risk	High Risk
• Low grade (LG) solitary Ta ≤3 cm • Papillary urothelial neoplasm of low malignant potential	• Recurrence within 1 year, LG Ta • Solitary LG Ta >3 cm • LG Ta, multifocal • High grade (HG) Ta, ≤3 cm • LG T1	• HG T1 • Any recurrent, HG Ta • HG Ta, >3 cm (or multifocal) • Any carcinoma in situ (CIS) • Any BCG failure in HG patient • Any variant histology • Any lymphovascular invasion • Any HG prostatic urethral involvement

*Reproduced with permission from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021.

Table 2: Low-Risk,[1] Non-Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	3, 12	Annually				As clinically indicated	
Upper tract[2] and abdominal/ pelvic[3] imaging[4]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	N/A						

1 See Table 1: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer definitions.
2 Upper tract imaging includes CTU, MRU, intravenous pyelogram (IVP), retrograde pyelography, or ureteroscopy, Abdominal sono.
3 Abdominal/pelvic imaging includes CT or MRI.
4 See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
5 Urine cytology should be done at time of cystoscopy if bladder in situ.

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Table 3: Intermediate Risk,[1] Non-Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	3, 6, 12	Every 6 mo	Annually			As clinically indicated	
Upper tract[2] and abdominal/ pelvic[3] imaging[4]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	Urine cytology[5] 3, 6, 12	Urine cytology every 6 mo	Annually			As clinically indicated	

Table 4: High-Risk,[1] Non-Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	Every 3 mo		Every 6 mo			Annually	As clinically indicated
Upper tract[2] imaging[4]	Baseline imaging, and at 12 mo	Every 1–2 y					As clinically indicated
Abdominal/ pelvic[3] imaging[4]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	• Urine cytology[5] every 3 mo • Consider urinary urothelial tumor markers (category 2B)		Urine cytology every 6 mo			Annually	As clinically indicated

1 See Table 1: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer definitions.
2 Upper tract imaging includes CTU, MRU, intravenous pyelogram (IVP), retrograde pyelography, or ureteroscopy.
3 Abdominal/pelvic imaging includes CT or MRI.
4 See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
5 Urine cytology should be done at time of cystoscopy if bladder in situ.

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Table 5: Post-Cystectomy Non-Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	N/A						
Imaging[4]	CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) at 3 and 12 mo	CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) annually				Renal US annually[6]	As clinically indicated
Blood tests	• Renal function testing (electrolytes and creatinine) every 3–6 mo • LFT[7] every 3–6 mo • CBC, CMP every 3–6 mo if received chemotherapy	• Renal function testing (electrolytes and creatinine) annually • LFT[7] annually • B12 annually				B12 annually	
Urine tests	• Urine cytology[5] every 6–12 mo • Consider urethral wash cytology every 6–12 mo[8]	Urine cytology as clinically indicated Urethral wash cytology as clinically indicated					

5 Urine cytology should be done at time of cystoscopy if bladder in situ.
6 Renal US to look for hydronephrosis.
7 Liver function testing includes AST, ALT, bilirubin, and alkaline phosphatase.
8 Urethral wash cytology is reserved for patients with high-risk disease. High-risk disease includes: positive urethral margin, multifocal CIS, and prostatic urethralinvasion.

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Table 6: Post-Cystectomy Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	N/A						
Imaging[4]	• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo • Chest x-ray or CT chest every 3–6 mo or • PET/CT (category 2B) only if metastatic disease suspected		• Abdominal/pelvic CT or MRI annually • Chest x-ray or CT chest annually or • PET/CT (category 2B) only if metastatic disease suspected			Renal US annually[6]	As clinically indicated
Blood tests	• Renal function testing (electrolytes and creatinine) every 3–6 mo • LFT[7] every 3–6 mo • CBC, CMP every 3–6 mo if received chemotherapy	• Renal function testing (electrolytes and creatinine) annually • LFT[7] annually • B12 annually				B12 annually	
Urine tests	• Urine cytology[5] every 6–12 mo • Consider urethral wash cytology every 6–12 mo[8]	Urine cytology as clinically indicated Urethral wash cytology as clinically indicated					

5 Urine cytology should be done at time of cystoscopy if bladder in situ.
6 Renal US to look for hydronephrosis.
7 Liver function testing includes AST, ALT, bilirubin, and alkaline phosphatase.
8 Urethral wash cytology is reserved for patients with high-risk disease. High-risk disease includes: positive urethral margin, multifocal CIS, and prostatic urethralinvasion.

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Table 7: Post-Bladder Sparing (ie, Partial Cystectomy or Chemoradiation)

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	Every 3 mo		Every 6 mo		Annually		As clinically indicated
Imaging[4]	• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo for MIBC • Chest x-ray or CT chest every 3–6 mo for MIBC or • PET/CT (category 2B) only if metastatic disease suspected		• Abdominal/pelvic CT or MRI annually • Chest x-ray or CT chest annually or • PET/CT (category 2B) only if metastatic disease suspected[9]			As clinically indicated	
Blood tests	• Renal function testing (electrolytes and creatinine) every 3–6 mo • LFT[6] every 3–6 mo • CBC, CMP every 3–6 mo if received chemotherapy	• Renal function testing (electrolytes and creatinine) as clinically indicated • LFT[6] as clinically indicated					
Urine tests	Urine cytology[4] every 6–12 mo		Urine cytology as clinically indicated				

6 Renal US to look for hydronephrosis.
9 PET/CT not recommended for NMIBC.

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Principles of Surgical Management

Transurethral Resection of the Bladder Tumor (TURBT) for Staging

- Adequate resection with muscle in specimen

➢Muscle may be omitted in cases of documented low-grade Ta disease

➢In cases of suspected or known carcinoma in situ:

◊ Biopsy adjacent to papillary tumor

◊ Consider prostate urethral biopsy

➢Papillary appearing tumor (likely non-muscle invasive)

◊ Early repeat TURBT (**within 6 weeks**) if:

– Incomplete initial resection

– **No** muscle in original specimen for **high**-grade disease

– **Large (≥3 cm)** or **multi-focal** lesions

– Any **T1** lesion

➢Transurethral resection for sessile or invasive appearing tumor (likely muscle invasive)

◊ **Repeat TURBT** if:

– Prior resection did not include muscle in the setting of high-grade disease

– Any T1 lesion

– First resection does not allow adequate staging/attribution of risk for treatment selection

– Incomplete resection and considering tri-modality bladder preservation therapy

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Principles of Surgical Management

- Enhanced (blue light and narrow-band imaging) cystoscopy may be helpful in identifying lesions not visible using white light cystoscopy.
- Immediate postoperative intravesical chemotherapy within 24 hours is recommended if NMIBC and if no concern for bladder perforation.
- ✓ Gemcitabine (preferred) (category 1) and mitomycin (category 1) are the most commonly used options for intravesical chemotherapy.

TURBT/Maximal TURBT for Treatment

- Bladder preservation with maximally complete and safe TURBT and concurrent chemoradiotherapy is most suitable for patients with solitary tumors, negative nodes, no extensive or multifocal carcinoma in situ, no tumor-related hydronephrosis, and good pre-treatment bladder function.
- TURBT alone can be considered for non-cystectomy candidates.
- A visually complete TURBT is associated with improved patient outcomes in non-metastatic settings.

Transurethral Resection of the Prostate (TURP)

- Primary treatment option for urothelial carcinoma of the prostate with ductal/acini or prostatic urethral pathology.
- Postsurgical intravesical BCG is recommended

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Principles of Surgical Management

Transurethral Resection (TUR) of the Urethral Tumor

• Primary treatment of Tis, Ta, T1 primary carcinoma of the urethra.
• Patients with a prior radical cystectomy and a cutaneous diversion should consider a total urethrectomy.
• Postsurgical intraurethral therapy is recommended [see Principles of Intravesical Treatment (BL-F)].

Partial Cystectomy

• May be used for cT2 muscle-invasive disease with **solitary lesion** in location amenable to segmental resection with **adequate margins**. May also be appropriate in other select situations including cancer in a bladder **diverticulum**.
• No carcinoma in situ as determined by random biopsies.
• Should be given with **neoadjuvant** cisplatin-based combination chemotherapy.
• **Bilateral pelvic lymphadenectomy** should be performed and include at a minimum common, internal iliac, external iliac, and obturator nodes.

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Principles of Surgical Management

Radical Cystectomy/Cystoprostatectomy

• In non-muscle-invasive disease, radical cystectomy is generally reserved for residual high-grade cT1.
• Cystectomy should be done within 3 months of diagnosis if no therapy is given.
• Primary treatment option for cT2, cT3, and cT4a disease. Highly select patients with cT4b disease that responds to primary treatment may be eligible for cystectomy.
• Should be given with neoadjuvant cisplatin-based combination chemotherapy for patients with cT2-cT4a disease. For patients who cannot receive neoadjuvant chemotherapy, radical cystectomy alone is an option.
• Bilateral pelvic lymphadenectomy should be performed and include at a minimum common, internal iliac, external iliac, and obturator nodes.

Radical Nephroureterectomy with Cuff of Bladder

• Primary treatment option for non-metastatic high-grade upper GU tract tumors.
• For UTUC, strongly consider single-dose immediate postoperative intravesical chemotherapy, as randomized trials have shown a decrease in intravesical recurrence. The most commonly used option for intravesical chemotherapy is mitomycin.
• Neoadjuvant chemotherapy should be considered in select patients with high-grade disease.

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Principles of Surgical Management

Urethrectomy

- Neoadjuvant chemotherapy (category 2B) or chemoradiation should be considered.
- Distal urethrectomy may include inguinal lymph node dissection in selected cases.
- Total urethrectomy may include inguinal lymphadenectomy in selected cases.
- Male patients with T2 primary carcinoma of the urethra in the bulbar urethra may be treated with a urethrectomy with or without a cystoprostatectomy.
- Male patients with T2 primary carcinoma of the urethra in the pendulous urethra may receive a distal urethrectomy. Alternatively, a partial penectomy can be considered. A total penectomy may be necessary in cases of recurrence.
- Female patients with T2 primary carcinoma of the urethra may be treated with urethrectomy and cystectomy.

Pelvic Exenteration (category 2B)

- Therapy for recurrence in female patients with ≥T2 primary carcinoma of the urethra.
- Ilioinguinal lymphadenectomy and/or chemoradiotherapy can be considered in patients with ≥T3 disease.

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Non-Urothelial AND urothelial with Variant History

Mixed Histology:

• Urothelial carcinoma plus squamous, adenocarcinoma, micropapillary, nested, plasmacytoid, and sarcomatoid should be identified because of the potential to have a more aggressive natural history.
• These are usually treated in a similar manner to pure urothelial carcinoma of the bladder.
• Micropapillary, plasmacytoid, and sarcomatoid histologies are generally at higher risk for progression to muscle-invasive disease and a more aggressive approach should be considered.

Pure Squamous:

• No proven role for neoadjuvant/adjuvant chemotherapy for pure squamous cell carcinoma of the bladder.
• Local control with Surgery or RT and best supportive care recommended.
• For advanced disease, clinical trial preferred. For selected patients, combination chemotherapy with paclitaxel, ifosfamide, and cisplatin may be considered.
• Consider postoperative RT in selected cases (positive margins).

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Non-Urothelial AND urothelial with Variant History

Pure Adenocarcinoma Including Urachus:

• No proven role for neoadjuvant/adjuvant chemotherapy for pure adenocarcinomas of the bladder including urachal carcinoma.
• Local control with Surgery or RT and best supportive care recommended.
• For urachal carcinoma with localized disease, a partial or complete cystectomy with en bloc resection of the urachal ligament with umbilicus and lymph node dissection is recommended.
• For node-positive disease, consider chemotherapy with colorectal regimen (FOLFOX [oxaliplatin, leucovorin, and 5-FU] or GemFLP [5-FU, leucovorin, gemcitabine, and cisplatin]). Consider post-chemotherapy surgical consolidation in responding disease.
• For advanced disease, clinical trial preferred. For selected patients, combination chemotherapy with a 5-FU–based regimen (FOLFOX or GemFLP) or ITP (paclitaxel, ifosfamide, and cisplatin). Alternatively, combination paclitaxel and platinum may be considered.
• For non-urachal pure adenocarcinoma, consider additional metastatic workup.

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Non-Urothelial AND urothelial with Variant History

Any Small-Cell Component (or neuroendocrine features):

• Neoadjuvant chemotherapy followed by local treatment (cystectomy or radiotherapy) is recommended for any patient with small-cell component histology with localized disease regardless of stage.

• Neoadjuvant chemotherapy

➢Standard cisplatin eligible

◊ Etoposide + cisplatin

◊ Alternating ifosfamide + doxorubicin with etoposide + cisplatin

➢Standard cisplatin ineligible

◊ Etoposide + carboplatin

• Metastatic chemotherapy

➢Standard cisplatin eligible

◊ Etoposide + cisplatin

➢Standard cisplatin ineligible

◊ Etoposide + carboplatin

➢Alternate regimen for select patients

◊ Alternating ifosfamide + doxorubicin with etoposide + cisplatin

Primary Bladder Sarcoma:

• Treatment as per NCCN Guidelines for Soft Tissue Sarcoma.

Principles of Intravesical Treatment

Indications: Based on probability of recurrence and progression to muscle-invasive disease, such as size, number, and grade.

Intravesical Therapy for Bladder Cancer

Immediate Postoperative Intravesical Chemotherapy

• A single instillation of chemotherapy is administered within 24 hours of surgery (ideally within 6 hours).
• Mitomycin (category 1) and epirubicin are the most commonly used agents in the KSVGH for intravesical chemotherapy.
• Immediate postoperative intravesical chemotherapy reduces the 5-year recurrence rate by approximately 35% and has a number needed to treat to prevent a recurrence of 7. However, it does not reduce the risk of progression or the risk of cancer mortality.
• It is not effective in patients with an elevated EORTC recurrence risk score (≥5). This includes patients with ≥8 tumors and those with ≥1 recurrence per year.
• Contraindications include: bladder perforation, known drug allergy

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Principles of Intravesical Treatment

Induction (Adjuvant) Intravesical Chemotherapy or BCG

• The most commonly used agents are BCG, mitomycin, and epirubicin.
• In the event of a BCG shortage, BCG should be prioritized for induction of high-risk patients (eg, CIS and high-grade T1). Preferable alternatives to BCG include mitomycin or epirubicin. If feasible, the dose of BCG may be split (1/3 or 1/2 dose) so that multiple patients may be treated with a single vial in the event of a shortage.

• Initiated 3–4 weeks after TURBT with or without maintenance.
• Weekly instillations during induction are given for approximately 6-8 weeks.
• Maximum of 2 consecutive cycle inductions without complete response.
• Withhold if traumatic catheterization, bacteriuria, persistent gross hematuria, persistent severe local symptoms, or systemic symptoms.

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Principles of Intravesical Treatment

Maintenance Intravesical BCG

• In the event of a BCG shortage, BCG should be prioritized for high-risk patients (eg, high-grade T1 and CIS), especially in the early maintenance period (ie, 3 and 6 months post-induction).

If feasible, the dose of BCG may be split (1/3 or 1/2 dose) so that multiple patients may be treated with a single vial in the event of a shortage.

• Ideally maintenance should be given for 1 yr for intermediate-risk & 3 yrs for high-risk NMIBC.

• Dose reduction is encouraged if there are substantial local symptoms during maintenance therapy.

• Data suggest the benefit of maintenance BCG therapy through a decreased rate of recurrence for NMIBC.

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Principles of Intravesical Treatment

Postsurgical Intraprostatic BCG for Urothelial Carcinoma of the Prostate

- Treatment for patients with ductal + acini, or prostatic urethra involvement.
- Induction (adjuvant) therapy should be initiated 3–4 weeks after TURP
- Induction BCG should be followed with maintenance BCG
- Data indicate a reduction in recurrence in the prostate in patients with superficial disease

Postsurgical Intraurethral Therapy for Primary Carcinoma of the Urethra

- Consider as primary treatment for select patients with Tis, Ta, or T1 disease.
- Induction (adjuvant) therapy should be initiated 3–4 weeks after TUR.
- The most commonly used agents are BCG, mitomycin C, and epirubicin.
- Role of maintenance in this context is uncertain.
- Efficacy of this treatment in primary carcinoma of the urethra has not been established.

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Principles of Systemic Therapy

Perioperative chemotherapy (neoadjuvant or adjuvant)
Preferred regimens • DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3 or 4 cycles[1,2] • Gemcitabine and cisplatin for 4 cycles[3,4]
Other recommended regimens • CMV (cisplatin, methotrexate, and vinblastine) for 3 cycles[5]

• For patients who are not candidates for cisplatin, there are no data to support a recommendation for perioperative chemotherapy.
• Randomized trials and meta-analyses show a survival benefit for **cisplatin**-based neoadjuvant chemotherapy (3 or 4 cycles) in patients with muscle-invasive bladder cancer.
• Meta-analysis suggests a survival benefit to adjuvant therapy for pathologic T3, T4 or N+ disease at cystectomy.
• Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.

Principles of Systemic Therapy

• **DDMVAC** is preferred over standard MVAC based on category 1 evidence for metastatic disease showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease. Based on these data, the traditional dose and schedule for MVAC is no longer recommended.
• Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category 1 evidence for metastatic disease showing equivalence to conventional MVAC in the setting of advanced disease.
• For gemcitabine/cisplatin, both 21- and 28-day regimens are acceptable. Better dose compliance may be achieved with fewer delays in dosing using the 21-day schedule.
• Carboplatin should not be substituted for cisplatin in the perioperative setting.

For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (such as 35 mg/m2 on days 1 and 2 or days 1 and 8) (category 2B). While safer, the relative efficacy of the cisplatin-containing combination administered with such modifications remains undefined.
• For patients with borderline renal function, estimate GFR to assess eligibility for cisplatin.

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Principles of Systemic Therapy

First-line systemic therapy for locally advanced or metastatic disease (Stage IV)	
Cisplatin eligible	Preferred regimens • Gemcitabine and cisplatin[4] (category 1) • DDMVAC with growth factor support (category 1)[2,8]
Cisplatin ineligible	Preferred regimens • Gemcitabine and carboplatin[11] • Atezolizumab[12] (only for patients whose tumors express PD-L1[a] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab[13] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) Other recommended regimens • Gemcitabine[14] • Gemcitabine and paclitaxel[15] Useful under certain circumstances • Ifosfamide, doxorubicin, and gemcitabine[16] (for patients with good kidney function and good PS)

• The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Pts without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.

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Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)[c] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1)[18]	Other recommended regimens • Albumin-bound paclitaxel[27] • Paclitaxel or docetaxel[25] • Gemcitabine[14] • Pemetrexed[26]
Alternative preferred regimens • Atezolizumab[19] • Nivolumab[20] • Durvalumab[21] • Avelumab[22,23] • Erdafitinib[d,24]	Useful in certain circumstances based on prior medical therapy • Ifosfamide[28] • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimen for cisplatin ineligible, chemotherapy naïve • Gemcitabine/carboplatin	Other recommended regimens • Albumin-bound paclitaxel[27] • Paclitaxel or docetaxel[25] • Gemcitabine[14] • Pemetrexed[26]
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]	Useful in certain circumstances based on prior medical therapy • Ifosfamide[28] • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15]

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Principles of Systemic Therapy

Radiosensitizing chemotherapy regimens for organ-preserving chemoradiation

Preferred regimens (doublet chemotherapy is preferred when feasible)

- Cisplatin and 5-FU
- Cisplatin and paclitaxel
- 5-FU and mitomycin
- Cisplatin alone

Other recommended regimen

- Low-dose gemcitabine33,34 (category 2B)

Radiosensitizing chemotherapy given concurrently with conventionally fractionated radiation for palliation of metastases or recurrence

Preferred regimen

- Cisplatin

Other recommended regimens

- Taxane (docetaxel or paclitaxel) (category 2B)
- 5-FU (category 2B)
- 5-FU and mitomycin (category 2B)
- Low-dose gemcitabine (category 2B)
- Capecitabine (category 3)

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Principles of Radiation Management of Invasive Disease

Carcinoma of the Bladder: Unless otherwise stated, doses are 1.8–2.0 Gy daily fractionation.

- Precede radiation therapy (RT) alone or concurrent chemoradiotherapy by maximal TUR of the tumor when safely possible.
- Simulating and treating patients when they have an empty bladder is preferred for daily reproducibility (bladder full for tumor boosts is acceptable with image guidance).
- For invasive tumors, consider low-dose preoperative RT prior to segmental cystectomy (category 2B).
- Concurrent chemoradiotherapy or RT alone is most successful for patients without hydronephrosis and without extensive carcinoma in situ associated with their muscle-invading tumor.
- For patients with stage Ta, T1, or Tis, external beam RT (EBRT) alone is rarely appropriate. For patients with recurrent Ta-T1 disease usually following BCG therapy but without extensive Tis who are not candidates for cystectomy, concurrent chemoradiotherapy may be considered as a potentially curative alternative to radical cystectomy, which is the standard treatment by NCCN Guidelines.

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Principles of Radiation Management of Invasive Disease

• Treat the whole bladder with or without pelvic nodal radiotherapy **39.6–50.4 Gy** using conventional or accelerated hyperfractionation. Elective treatment to the lymph nodes is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. Then boost either the whole or partial bladder between **60–66 Gy**. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate DVH parameters based on the clinical scenario. Reasonable alternatives to conventional fractionation include taking the whole bladder to **55 Gy in 20 fractions**, or using simultaneous integrated boosts to sites of gross disease.
• When irradiating the bladder only or bladder tumor boost, consider daily image guidance.
• Concurrent chemoradiotherapy is recommended for added tumor cytotoxicity, and can be given without significant increased toxicity over RT alone.
Concurrent 5-FU and mitomycin C or low-dose gemcitabine can be used instead of cisplatin-containing regimens in patients with low or moderate renal function. Such therapy is optimally given by dedicated multidisciplinary teams.
• Concurrent chemoradiotherapy or RT alone should be considered as potentially curative therapy for medically inoperable patients or for local palliation in patients with metastatic disease.

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Principles of Radiation Management of Invasive Disease

• When giving palliative radiation for metastatic bladder cancer or for recurrent pelvic tumor, combining radiation with radiosensitizing chemotherapy should be considered. Chemotherapy should not be used concurrently with high-dose (>3 Gy per fraction) palliative radiation.
• Treatment field should include whole bladder and all sites of gross disease plus or minus uninvolved regional lymph nodes. Regional lymph nodes include the hypogastric, obturator, internal and external iliac, perivesical, sacral, and presacral nodes. For involved nodal disease, the common iliac nodes are a site of secondary involvement.
• For patients with pT3/pT4 pN0-2 urothelial (pure urothelial or primary urothelial mixed with other subtypes) bladder cancer following radical cystectomy with ileal conduit, consider postoperative adjuvant pelvic RT. Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include cystectomy bed and pelvic lymph nodes with doses in the range of 45 to 50.4 Gy. Involved resection margins and areas of extranodal extension could be boosted to 54–60 Gy if feasible based on normal tissue constraints.
• Tumor status assessment after completion of full-dose primary chemoradiotherapy: After 2–3 months, imaging with CT of chest/abdomen/pelvis with contrast ± bone scan. Cystoscopic surveillance and biopsy are also recommended as follow-up after completion of full-dose chemoradiotherapy.
• In highly selected T4b tumor cases, may consider intraoperative RT.

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Principles of Radiation Management of Invasive Disease

Carcinoma of the Urethra: Unless otherwise stated, doses are 1.8–2.0 Gy daily fractionation.
• Data support the use of RT for urothelial carcinoma and squamous cell carcinoma of the urethra (case series and experience treating these carcinomas arising from other disease sites); radiation can also be considered for adenocarcinomas of the urethra.
• Definitive Radiation Therapy (organ preservation)
➢cT2 cN0
◊ 66–70 Gy EBRT delivered to gross disease with a margin to encompass areas of potential microscopic spread. Concurrent chemotherapy with regimens used for bladder cancer is encouraged for added tumor cytotoxicity.
◊ Strongly consider prophylactic radiation treatment of regional-nodal basins (inguinal and low pelvic nodes for female and distal male tumors; pelvic lymph nodes for proximal male tumors).

➢cT3-T4, or lymph node positive
◊ 45–50.4 Gy EBRT delivered to gross disease with a margin to encompass areas of microscopic spread and to regional-nodal basins (inguinal and low pelvic nodes for female and distal male tumors; pelvic lymph nodes for proximal male tumors). Boost gross primary disease to 66–70 Gy and gross nodal disease to 54–66 Gy, if feasible. Dose delivered to gross nodal disease may be limited secondary to normal tissue dose constraints. Concurrent chemotherapy should be administered for added tumor cytotoxicity.

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Principles of Radiation Management of Invasive Disease

- Postoperative adjuvant radiation therapy

◊ Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include resection bed, inguinal lymph nodes, and pelvic lymph nodes. Areas at risk for harboring residual microscopic disease should receive 45–50.4 Gy EBRT. Involved resection margins and areas of extranodal extension should be boosted to 54–60 Gy if feasible based on normal tissue constraints. Areas of gross residual disease should be boosted to 66–70 Gy, if feasible based on normal tissue constraints. Concurrent chemotherapy with regimens used for bladder cancer should be considered for added tumor cytotoxicity.

- Recurrent disease

◊ Clinical target volume (CTV) should include gross disease in any suspected areas of spread at 66–74 Gy (higher dose up to 74 Gy for larger tumor and non-urothelial histology) and consideration can be given to elective regional-nodal basins (45–50.4 Gy) as discussed above, if feasible based on normal tissue constraints.

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＊Perioperative chemotherapy（Neoadjuvant 3-4 Course or Adiuvant 4-6 Course）
Regimens ：

Regimen	Dosage	
Dose-Dense MVEC	Methotrexate	30MG/M2 on D1 or D2 of a 14 day cycle
	vinblastine	3MG/M2 on D1 or D2
	Epirubicin	45MG/M2 on D1 or D2
	Cisplatin	70MG/M2 on D1　References:NO2
MVEC	Methotrexate	30MG/M2 on D1,15,22
	vinblastine	3MG/M2 on D2,15.22
	Epirubicin	45MG/M2 on D2　References:NO3
	Cisplatin/Carbopatin	70MG/M2 on D2/AUCx4~6MG
Gemcitabine/Cisplatin	Gemcitabine	1000MG/M2 on D1,8,15 of a 28 day cycle
	Cisplatin/Carbopatin	70MG/M2 on D2/AUCx4~6MG　References:NO4

註：1.CCr ＜60使用Carbopatin　2.This dose should not combined with radiation

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＊Perioperative chemotherapy （Neoadjuvant or Adiuvant）
Regimens ：

Regimen	Dosage	
CMV	Methotrexate	30MG/M2 IVA on D1 or D8 of a 21 day cycle
	Vinblastine	4MG/M2 IVA on D1 or D8
	Cisplatin	100mg/m^2 IVA on D2　　References:NO2

註：1.CCr ＜60使用Carbopatin　2.This dose should not combined with radiation

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＊Chemotherapy for metastatic disease
Regimens ：

Regimen	Dosage	
Dose-Dense MVEC	Methotrexate	30MG/M2 on D1 or D2 of a 14 day cycle
	vinblastine	3MG/M2 on D1 or D2
	Epirubicin	45MG/M2 on D1 or D2
	Cisplatin	70MG/M2 on D1　References:NO2
MVEC	Methotrexate	30MG/M2 on D1,15,22
	vinblastine	3MG/M2 on D2,15.22
	Epirubicin	45MG/M2 on D2　References:NO3
	Cisplatin/Carbopatin	70MG/M2 on D2/AUCx4~6MG
Gemcitabine/Cisplatin First-line	Gemcitabine	1000MG/M2 on D1,8,15 of a 28 day cycle
	Cisplatin/Carbopatin	70MG/M2 on D2/AUCx4~6MG　References:NO4

註：1.CCr ＜60使用Carbopatin　2.This dose should not combined with radiation

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＊Perioperative immunity therapy（Neoadjuvant 3-4 Course or metastativc disease ）
Regimens ：

Regimen	Dosage	
Aterolizumab	1200MG	in N/S 250ml IVD 60 min (3週一次) References:NO7
Nivolumab	3MG/KG	in N/S 100ml drip 60 min (2週一次)References:NO9
Pembrolizumab	200MG	in N/S 100ml drip 30 min (3週一次)References:NO8
Durvalumab	10mg/KG	in N/S 100ml drip 60 min (2週一次)References:NO10

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Principles of chemotherapy in KSVGH

- Dose-Dense MVEC regimen with growth factor support for 3 or 4 cycles
- MVEC regimen regimen for 6 cycles (not recommended)
- Gemcitabine/Cisplatin regimen for 6 cycles
- CMV regimen for cycles

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＊CCRT　Regimens：

Regimen	Dosage	
Cisplatin alone	Cisplatin	35MG/M2 weekly　　References:NO3

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