Taipei Veterans General Hospital Practices Guidelines for Urothelial Carcinoma of Upper Urinary Tract

2021年 9月 28 日制訂

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Outlines

- **Epidemiology**
- **Risk factors**
- **Histologic types**
- **Classification: tumor grade, TNM**
- **Symptoms**
- **Diagnosis: imaging, urine cytology, ureteroscopy**
- **Treatment: localized, advanced disease**
- **Follow-up**

Epidemiology

- 5 – 10% of all urothelial carcinoma (UC)
- Recurrence in UB in 22 – 47%, in contralateral upper tract in 2 – 6%
- 60% invasive at diagnosis (UB Ca 15 – 25%)
- Peak incidence in 70s and 80s
- 3 times more prevalent in men than in women

Risk Factors

- **Cigarette smoking: OR 2.5 – 7**
- **Aromatic amines: OR 8.3, exposure duration 7Y, latency period 20Y**
- **Phenacetin: banned 1970s**
- **Balkan nephropathy: aristolochic acid (馬兜鈴酸)**
- **Taiwan: aristolochic acid, arsenic**
- **Chemotherapy: cyclophosphamide**
- **Pelvic radiation therapy**

Histologic Types

- **Urothelial carcinoma: 95%**
- **Squamous cell carcinoma: < 10%**
- **Adenocarcinoma: < 1%**
- **Small cell carcinoma**
- **Sarcoma**

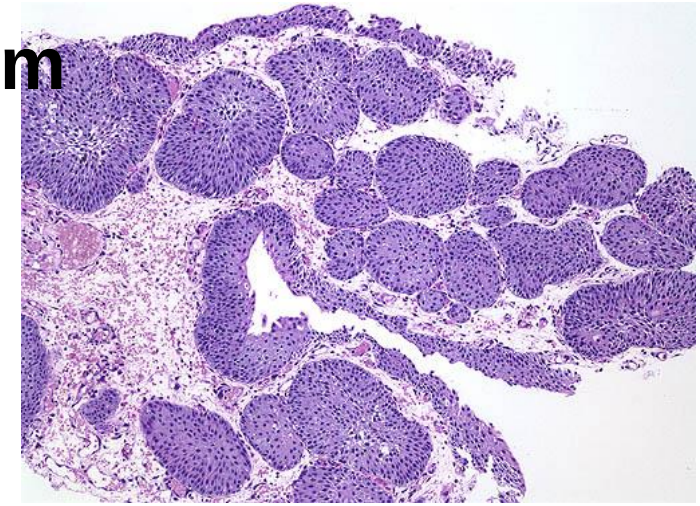
Classification – Histologic Grade

- **2016 WHO/ISUP grading system**

  Urothelial Histologies

  –Low-grade urothelial carcinoma

  –High-grade urothelia carcinoma



- **Squamous cell carcinoma and Adenocarcinoma**

  –Gx:grade cannot be assessed

  –G1: well differentiated

  –G2: moderate differentiated

  –G3: poorly differentiated

Classification – Histologic Type

- **Noninvasive carcinoma**
  - **--Low grade papillary urothelial carcinoma**
  - **--High grade papillary urothelial carcinoma**
  - **--Urothelial carcinoma in situ**
- **Invasive carcinoma**
  - **--Conventional urothelial(transitional cell)carcinoma**
  - **--Urothelial carcinoma variants**
    - **Urothelial carcinoma with divergent differentiation (squamous,glandular,and/or trophoblastic)**
    - **Neted urothelial carcinoma (including large nested carcinoma)**
    - **Microcystic urothelial carcinoma**

- Micropapillary urothelial carcinoma
- Lymphoepithelioma-like urothelial carcinoma
- Plasmacytoid urothelial carcinoma
- Giant cell urothelial carcinoma
- Lipid-rich urothelial carcinoma
- Clear cell(glycogen-rich) urothelial carcinoma
- Sarcomatoid urothelial carcinoma
- Poorly differentiated urothelial carcinoma (including those with osteoclast-like giant cells)

-- Squmous cell

--Adenocarcinomacarcinoma

--Small cell carcinoma

Classification – TNM (AJCC 2016)

T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive tumor
Tis	Carcinoma in situ: “flat tumor”
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades the muscularis
T3	(For renal pelvis only) Tumor invades beyond muscularis into peripelvic fat or the renal parenchyma
	(For ureter only) Tumor invades beyond muscularis into periureteric fat
T4	Tumor invades adjacent orgens, or through the kidney into the perinephric fat

Classification – TNM (AJCC 2016)

N	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node, ≦ 2 cm in greatest dimension
N2	Metastasis in a single lymph node, > 2 cm; or multiple lymph nodes

M	Distant metastases
M0	No distant metastasis
M1	Distant metastasis

Classification – TNM (AJCC 2016)

AJCC PROGNOSTIC STAGE GROUPS				
Stage	0a	Ta	N0	M0
Stage	0is	Tis	N0	M0
Stage	I	T1	N0	M0
Stage	II	T2	N0	M0
Stage	III	T3	N0	M0
Stage	IV	T4	N0	M0
		AnyT	N1	M0
		AnyT	N2	M0
		AnyT	AnyN	M1

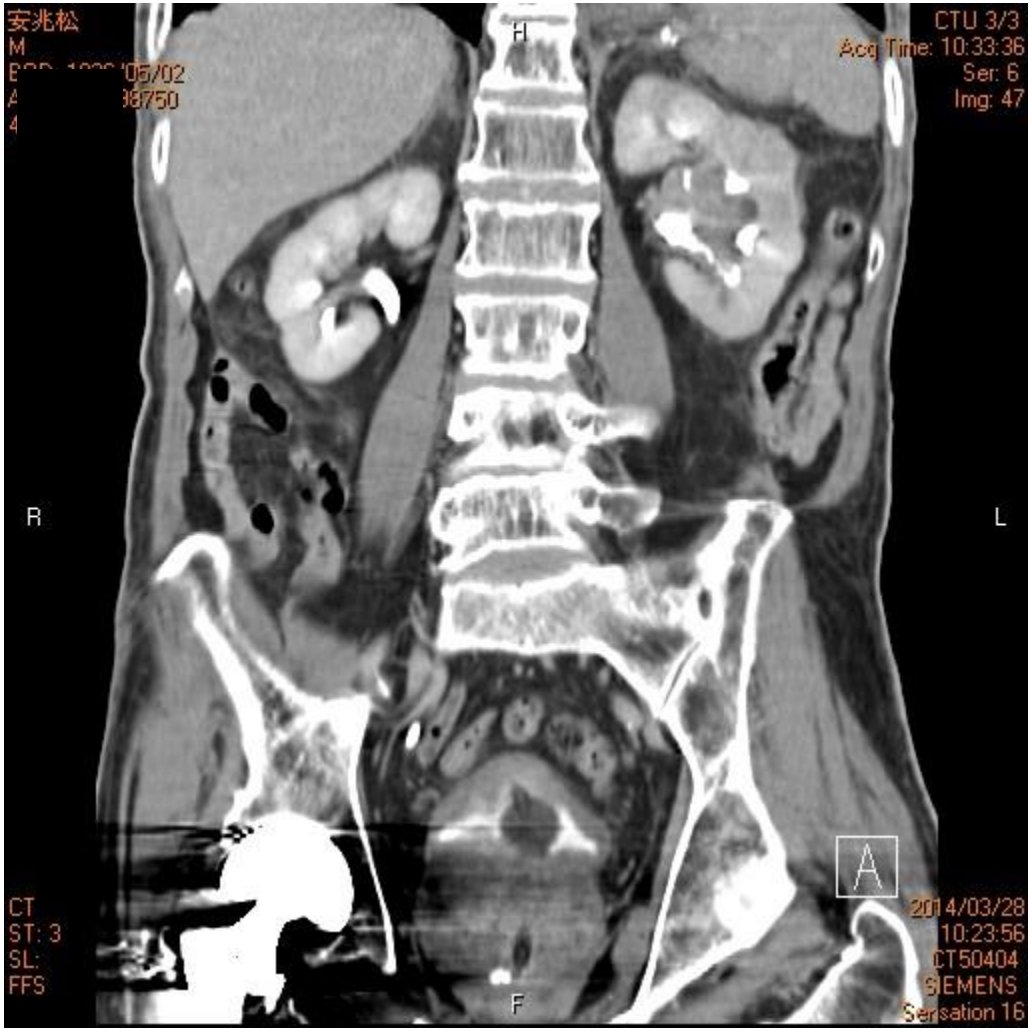
Symptoms

- **Gross or microscopic hematuria: 70 – 80%**
- **Flank pain: 20 – 40%**
- **Lumbar mass:10 – 20%**
- **Systemic symptoms**
  - Anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough

Diagnosis – Imaging

- **CT urography**
  - Having the highest diagnostic accuracy
  - Having replaced IVU and ultrasonography as the first-line imaging test
  - Sensitivity 0.67 – 1.0, specificity 0.93 – 0.99
- **MRI**
  - Indicated in patients who cannot undergo CT urography
  - Sensitivity 75%

CT Urography



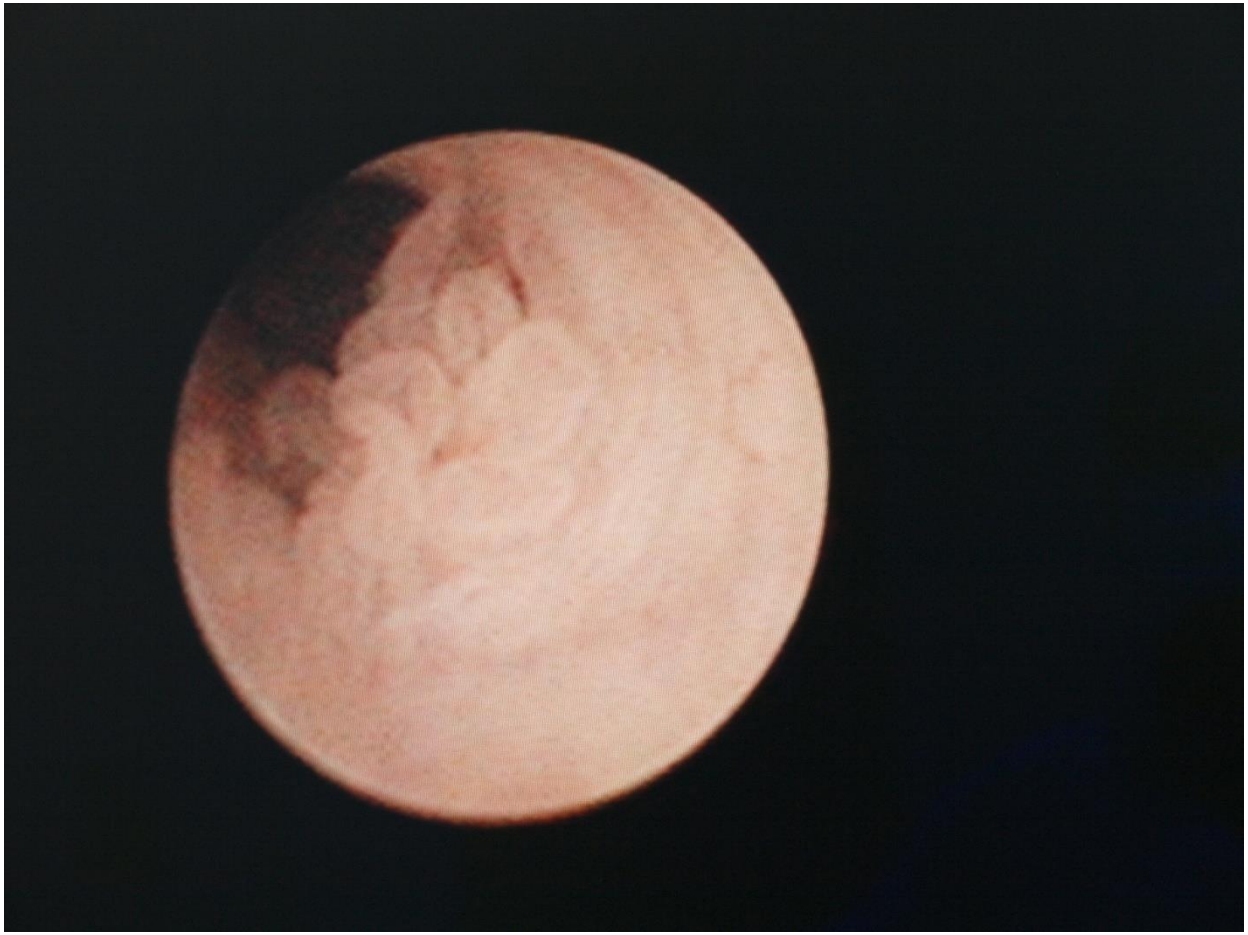
Diagnosis – Urine Cytology

- **Highly suggestive of UTUC when cystoscopy is normal and if CIS of the bladder or prostatic urethra has been largely excluded**
- **Less sensitive for UTUC than for bladder tumors, even for high-grade lesions**
- **RP, cytology preferably be performed prior to application of contrast agent**

Diagnosis – Ureteroscopy

- **Technical success approaching 95%**
- **Can determine tumor grade in 90% of cases with a low false-negative rate**
- **If available, ureteroscopy and biopsy should be performed in the preoperative assessment of any UTUC patient**

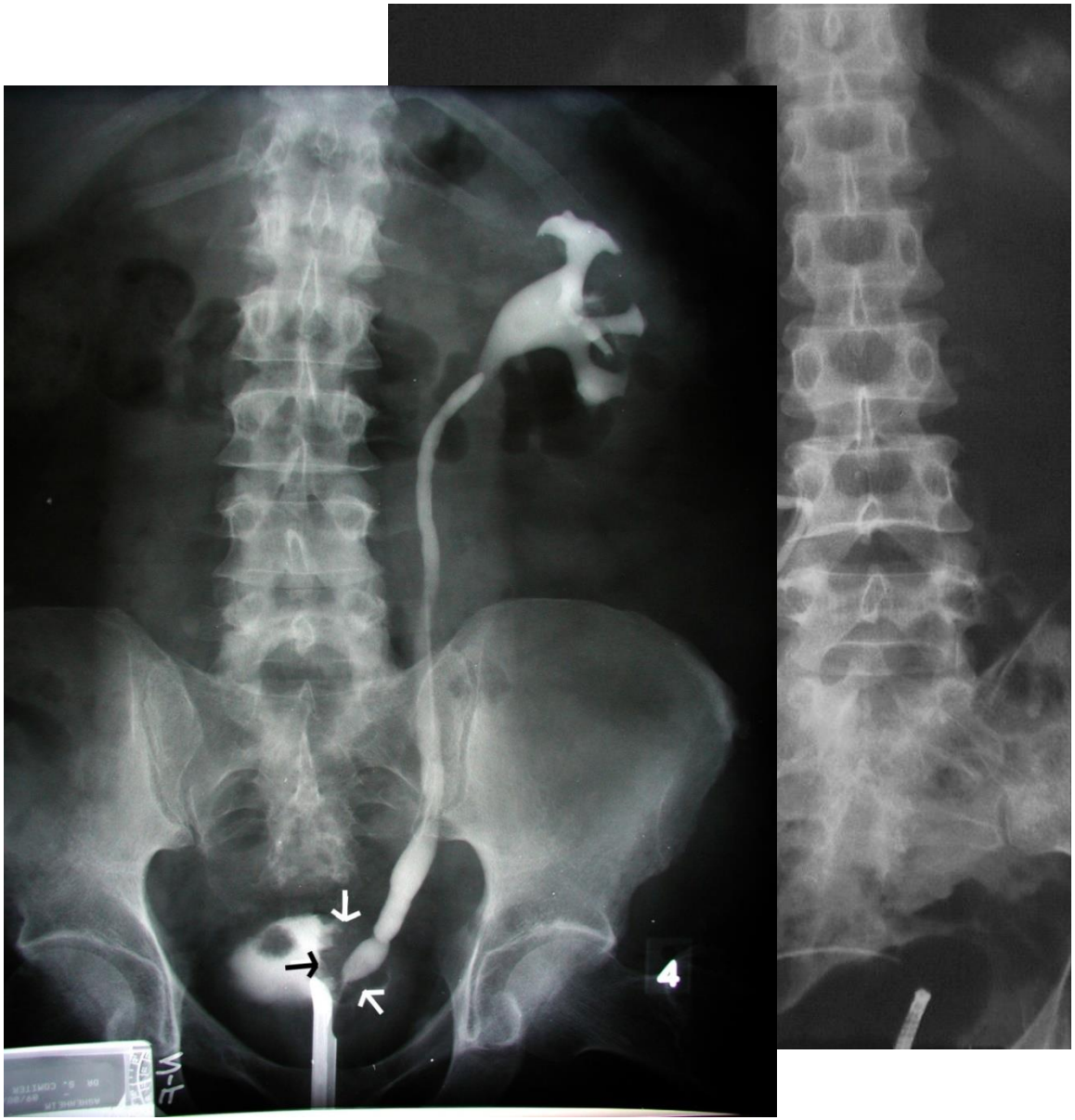
Ureteroscopy



Diagnosis – Recommendations

- Urine cytology
- Cystoscopy to rule out a concomitant bladder tumor
- CT urography
- Diagnostic ureteroscopy and biopsy
- Retrograde ureteropyelography

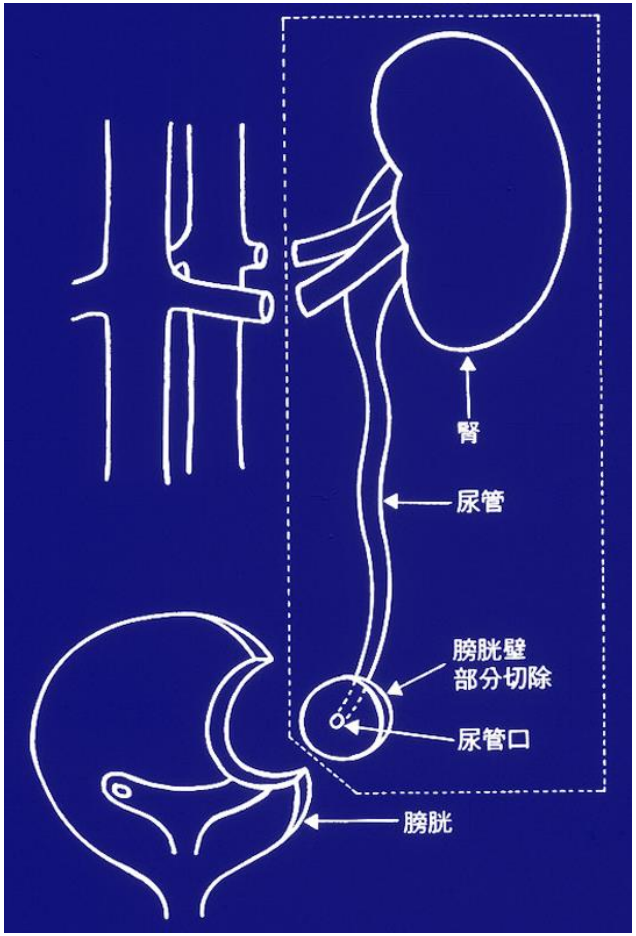
Retrograde Pyelography (RP)

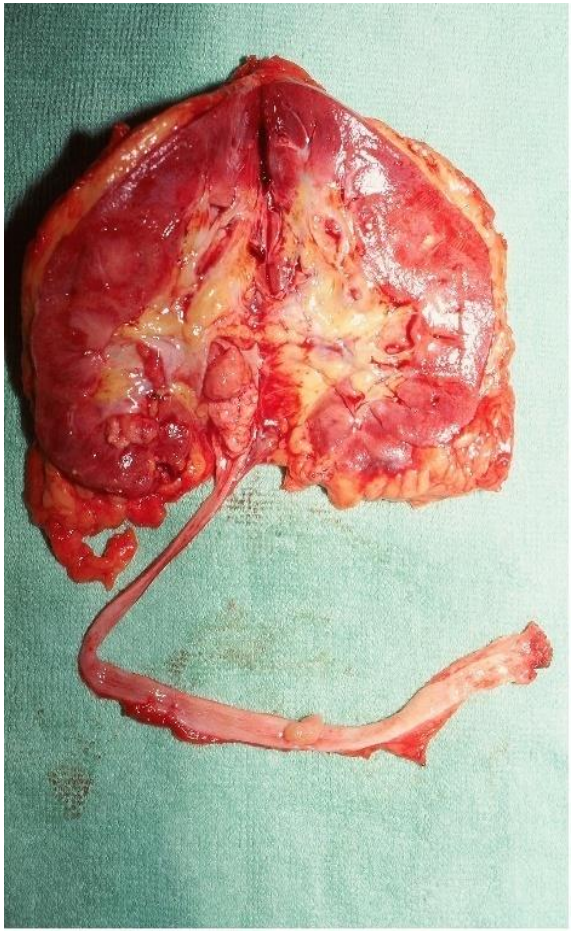


Treatment – Localized Disease

- **Gold standard: radical nephroureterectomy with excision of the bladder cuff (RNU)**
- **Lymph node dissection**
  - Therapeutic interest, optimal staging
  - Anatomical sites of LND not clearly defined
  - Unnecessary in cases of TaT1 UTUCs
- **Equivalent oncological outcomes after either laparoscopic or open RNU**

Nephroureterectomy with Bladder Cuff Excision





Indications for RNU

- **Suspicion of infiltrating UTUC on imaging**
- **High-grade tumor (urinary cytology)**
- **Multifocality (with two functional kidneys)**
- **Non-invasive but large (i.e. > 2 cm) UTUC**

Techniques for RNU

- **Open and laparoscopic access are equivalent in terms of efficacy**
- **Bladder cuff removal is imperative**
- **Several techniques for bladder cuff excision are acceptable, except stripping**
- **Lymphadenectomy is recommended in case of invasive UTUC**

Indications for Conservative Management

- **Unifocal tumor**
- **Tumor size less than 1 cm**
- **Low-grade tumor (cytology or biopsies)**
- **No evidence of an infiltrative lesion on CT urography**
- **Understanding of close follow-up**

Techniques Used in Conservative Management

- Laser should be used in case of endoscopic treatment
- Flexible ureteroscopy is preferable over rigid ureteroscopy
- A percutaneous approach remains an option in small low-grade caliceal tumors unsuitable for ureteroscopic treatment

Techniques Used in Conservative Management

- **Ureteroureterostomy is indicated for non-invasive low-grade tumors of the proximal ureter or midureter that cannot be removed completely by endoscopic means, and for high-grade or invasive tumors when RSS for preservation of renal function is a goal**

Techniques Used in Conservative Management

- **Complete distal ureterectomy and neocystostomy is indicated for non-invasive, low-grade tumors in the distal ureter that cannot be removed completely by endoscopic means and for high-grade, locally invasive tumors**

Treatment – Advanced Disease

- **RNU**
  - No benefits in metastatic disease, can be considered a palliative option
- **Chemotherapy**
  - Platinum-based chemotherapy is expected to produce similar results to those seen in bladder cancer
- **Radiotherapy**
  - May improve local control of the disease

Chemotherapy Regimen for Neoadjuvant Therapy

	Chemotherapy regimen	Schedules
MVAC/ddMVAC	vinblastine 3mg per BSA in D5W 100ml IV for 15mins ST D1 methotrexate 30mg per BSA in D5W 100ml IV for 30mins ST D1 doxorubicin 30mg per BSA in D5W 100ml IV for 45mins QD D1 Cisplatin 70mg per BSA (adjusted by CCr) in NS 500ml IV for 3.5hrs ST D1 Leucovorin (15 mg) 1tab PO QID D2-3	Q4W for 3-6 cycles (ddMVAC: Q2W with GCSF support)
GC-G(GC)	Gemcitabine 1000mg per BSA in NS 100 ml IV for 30mins ST D1 cisplatin 70mg per BSA (adjusted by Ccr) in NS 500ml IV for 4hrs ST D1	Q3W or Q4W for 4 cycles
GCarbo*-G	gemcitabine 1000mg per BSA in NS 250ml IV for 30mins ST D1 carboplatin 4mg AUC in D5W 250ml IV for 1hrs ST D1 *Carboplatin should be given only if cisplatin infeasible	Q3W or Q4W for 4 cycles
CMV	methotrexate 40mg per BSA in D5W 100ml IV for 30mins ST D1 vinblastine 4mg per BSA in D5W 100ml IV for 20mins ST D1 cisplatin 70 mg per BSA (adjusted by CCr) in NS 500ml IV for 3.5hrs ST D1 Leucovorin 1tab PO QID D2-3	Q3W for 3 cycles

Chemotherapy Regimen for Adjuvant Therapy

	Chemotherapy regimen	schedules
MVAC/ddMVAC	vinblastine 3mg per BSA in D5W 100ml IV for 15mins ST D1 methotrexate 30mg per BSA in D5W 100ml IV for 30mins ST D1 doxorubicin 30mg per BSA in D5W 100ml IV for 45mins QD D1 Cisplatin 70mg per BSA (adjusted by CCr) in NS 500ml IV for 3.5hrs ST D1 Leucovorin (15 mg) 1tab PO QID D2-3	Q4W for 3-6 cycles (ddMVAC: Q2W with GCSF support)
GC-G(GC)	Gemcitabine 1000mg per BSA in NS 100 ml IV for 30mins ST D1 cisplatin 70mg per BSA (adjusted by Ccr) in NS 500ml IV for 4hrs ST D1	Q3W or Q4W for 4-6 cycles
GCarbo*-G	Gemcitabine 1000mg per BSA in NS 100ml IV for 30mins ST D1 carboplatin 4mg AUC in D5W 250ml IV for 1hrs ST D1 *Carboplatin should be given only if cisplatin infeasible	Q3W or Q4W for 4-6 cycles
CMV	methotrexate 40mg per BSA in D5W 100ml IV for 30mins ST D1 vinblastine 4mg per BSA in D5W 100ml IV for 20mins ST D1 cisplatin 70 mg per BSA (adjusted by CCr) in NS 500ml IV for 3.5hrs ST D1 Leucovorin 1tab PO QID D2-3	Q3W for 4-6 cycles

Chemotherapy Regimen for CCRT

	Chemotherapy regimen
GC-G(GC)	Gemcitabine 1000mg per BSA in NS 100 ml IV for 30mins ST D1 cisplatin 70mg per BSA (adjusted by Ccr) in NS 500ml IV for 4hrs ST D1
GCarbo*-G	gemcitabine 1000mg per BSA in NS 250ml IV for 30mins ST D1 Carboplatin 4mg AUC in D5W 250ml IV for 1hrs ST D1 *Carboplatin should be given only if cisplatin infeasible
CMV	methotrexate 40mg per BSA in D5W 100ml IV for 30mins ST D1 vinblastine 4mg per BSA in D5W 100ml IV for 20mins ST D1 cisplatin 70 mg per BSA (adjusted by CCr) in NS 500ml IV for 3.5hrs ST D1 Leucovorin 1tab PO QID D2-3
Weekly cisplatin	weekly cisplatin 30 mg per BSA× 6 doses

*concurrent 5-FU and mitomycin C or gemcitabine could also be considered for CCRT regimen in patients with impaired renal function or unfit for platinum

Chemotherapy Regimen for Metastatic

	Chemotherapy regimen	schedules
MVAC	vinblastine 3mg per BSA in D5W 100ml IV for 15mins ST D1 methotrexate 30mg per BSA in D5W 100ml IV for 30mins ST D1 doxorubicin 30mg per BSA in D5W 100ml IV for 45mins QD D1 Cisplatin 70mg per BSA (adjusted by CCr) in NS 500ml IV for 3.5hrs ST D1 Leucovorin (15 mg) 1tab PO QID D2-3	Q4W for Till PD or maximal 8 cycles
GC-G(GC)	Gemcitabine 1000mg per BSA in NS 100 ml IV for 30mins ST D1 cisplatin 70mg per BSA (adjusted by Ccr) in NS 500ml IV for 4hrs ST D1	Q3W or Q4W till PD or maximal 8 cycles
Gemzar + Paclitaxel*	gemcitabine 1000mg per BSA in NS 100ml IV for 30mins ST D1, D8; paclitaxel 175mg per BSA in D5W 500ml IV for 3hrs ST D1;	Q3W for Till PD or maximal 8 cycles
GCarbo-G	gemcitabine 1000mg per BSA in NS 250ml IV for 30mins ST D1 carboplatin 4mg AUC in D5W 250ml IV for 1hrs ST D1	Q3W or Q4W till PD or maximal 8 cycles
CMV	methotrexate 40mg per BSA in D5W 100ml IV for 30mins ST D1 vinblastine 4mg per BSA in D5W 100ml IV for 20mins ST D1 cisplatin 70 mg per BSA (adjusted by CCr) in NS 500ml IV for 3.5hrs ST D1 Leucovorin 1tab PO QID D2-3	Q3W for till PD or maximal 8 cycles
Nivolumab†	3mg/kg IVA 30mins ST D1	Q2W till PD
Pembrolizumab†	2-3mg/kg (maximal 200mg/time) IVA 30mins ST D1	Q3W till PD
Atezolizumab	1200mg fixed dose IVA 30 mins ST D1	Q3W till PD
Avelumab	10 mg per kilogram of body weight, administered intravenously every 2 weeks	Q2W till PD

Chemotherapy guidelines by treatment line

Cisplatin eligible	Gemcitabine + Cisplatin (category 1)
	MVAC (or ddMVAC with G-CSF support, (category 1))
	May be considered: Atezolizumab + Gemcitabine/Cisplatin *
Cisplatin ineligible	Gemcitabine + Carboplatin
	Atezolizumab (PD-L1 positive required) #
	Pembrolizumab (PD-L1 positive required) ##
	Gemcitabine with or without paclitaxel

* As of 2021/10/25, FDA and TFDA approval are still pending, **therefore use of this regimen is off-label use**

PD-L1 ≥ 5% (IC2/3) by Ventana SP142 IHC staining

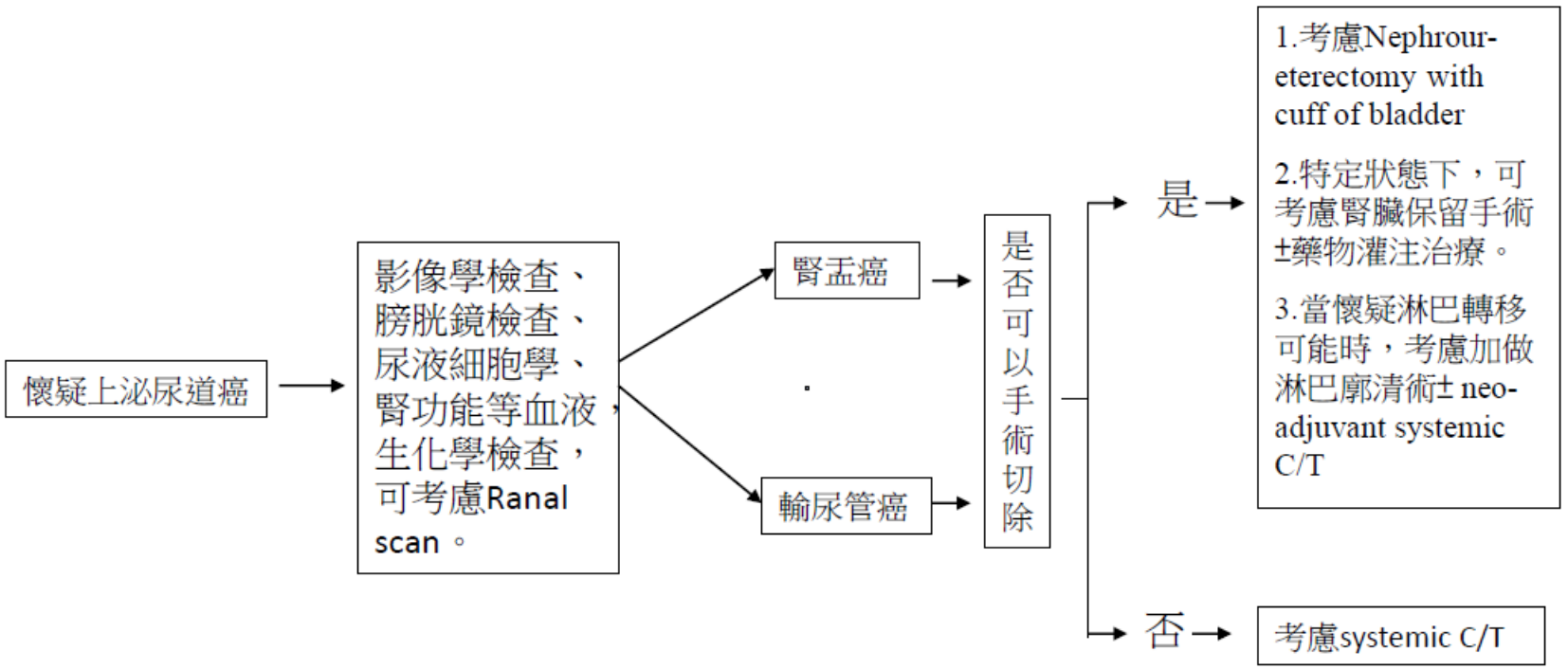
##PD-L1 CPS score ≥ 10% by Dako 22C3 staining

Chemotherapy guidelines by treatment line

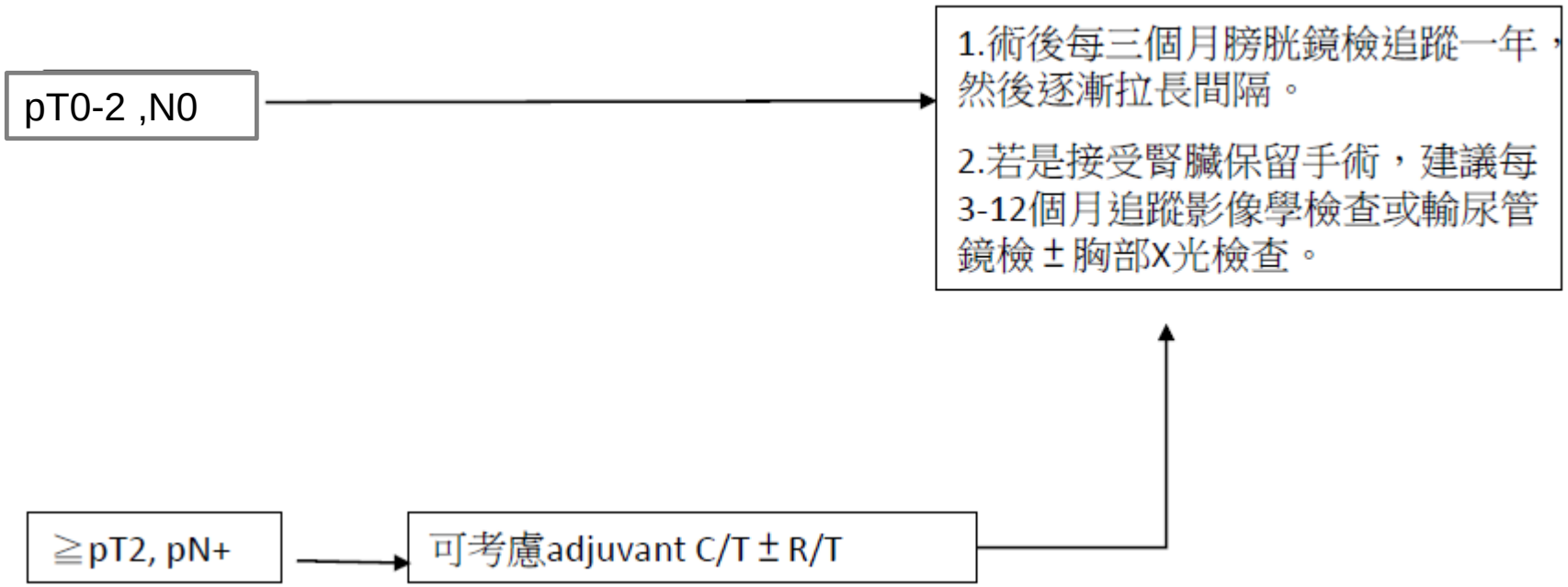
Second line

Post platinum	**Note: if progression free survival is ≥ 12 months after cisplatin/carboplatin, retreatment with platinum can be considered if patient is still platinum eligible.**
Pembrolizumab (category 1)	
Atezolizumab	
Nivolumab	
Durvalumab	
Docetaxel (or paclitaxel)	
Gemcitabine	
Post checkpoint inhibitor	
Gemcitabine/Cisplatin (or carboplatin if cis-ineligible)	
ddMVAC with growth factor support	
Switch maintenence	Avelumab *no disease progression (i.e., an ongoing complete response, partial response, or stable disease) after the receipt of 4-6 cycles of chemotherapy with gemcitabine plus cisplatin or carboplatin; and a treatment-free interval of 4 -10 weeks since the last

Flowchart for Treatment



Follow-up


pT0-2 ,N0
1.術後每三個月膀胱鏡檢追蹤一年，然後逐漸拉長間隔。
2.若是接受腎臟保留手術，建議每3-12個月追蹤影像學檢查或輸尿管鏡檢±胸部X光檢查。
≧pT2, pN+
可考慮adjuvant C/T±R/T

Conclusions

- **When determining the optimal treatment regimen for our patients, we must take into account each individual patient's specific clinical characteristics with regard to renal function including medical comorbidity and tumour location, grade, and stage**

參考資料

1.National Comprehensive Cancer Network Guidelines
2.European Association of Urology Guidelines
3.American Urological Association Guidelines
4.台灣泌尿科醫學會上尿路尿路上皮癌診治共識