NHS Lancashire and South Cumbria Integrated Care Board | Cancer Alliance

PROTOCOLS

FOR THE MANAGEMENT OF PATIENTS WITH

UROLOGICAL MALIGNANCY

2024

Guidelines developed by the Urology Clinical Reference Group **(CRG)** (Lancashire & South Cumbria)

Reviewed: **January 2024**
Review date: **January 2026 or earlier if new guidance dictates**
Amendment: **To include Upper Tract January 2024**

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Bladder Cancer

The network should agree:

- *Protocols for diagnosis and assessment of primary and recurrent disease, including indications, agreed with a network representative from primary care, for GP referral to the designated haematuria clinic (see Topic 2G Peer Review Measures).*
- *The parameters of disease stage and patient fitness which determine when each of the treatments and procedures classified as local and specialist care in the introduction are indicated, including those patients with T2 muscle invasive cancer who are potential candidates for curative surgery and for radiotherapy.*
- *That patients who need specialist care are referred to a named specialist team for treatment.*
- *The respective roles of the local and specialist teams in the management of high-risk superficial bladder cancer.*
- *For bladder reconstruction and urinary diversion, where they are not being provided by all specialist teams in the network, the specialist teams to which patients should be referred for these treatments.*
- *Protocols for frequency of cystoscopy during follow up.*

CLINICAL AND REFERRAL GUIDELINES FOR BLADDER CANCER

All patients with suspected bladder tumours should be referred to the local urologist with special interest in cancer management.

Patients usually present with a history of overt/microscopic haematuria.

Patients should be referred to a dedicated haematuria clinic to facilitate rapid access to investigative procedures.

The patient's pathway can be shortened:

- Referral via 2-week rule pathway

The initial cystoscopy should note the number, size, and position of all tumours together with the capacity of the bladder and findings on bi-manual examination. Random biopsies of the bladder are required only if there is suspicion of carcinoma in situ (CIS). When a resected tumour is pathologically staged as T1, a repeat cystoscopy and re-resection of the tumour site should be undertaken promptly (approx. 6/52 after the initial cystoscopy) to confirm complete resection and to confirm the staging is correct, ensuring that the tumour is not under staged and subsequently treated inappropriately.

Initial TURBT does not count as primary treatment and therefore the target time to treatment is not achieved by TURBT, but by definitive treatment.

Tumours will be graded according to the TNM classification system.

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, uterus, vagina, pelvic wall, abdominal wall
T4a Tumour invades prostate, uterus, or vagina
T4b Tumour invades pelvic wall or abdominal wall

N - Lymph nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single regional lymph node in the true pelvis
N2 multiple regional lymph node metastases in the true pelvis

N3lymph node metastasis to the common iliac lymph nodes

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

All patients should be discussed at the local MDT meeting at the time of initial diagnosis and again if there is planned significant change in the management.

The local team will manage all patients diagnosed with low-risk superficial bladder cancer. Ta –T1 are superficial tumours and treatment will be directed towards prevention of recurrence and progression. They should be considered for a single dose of intravesical Mitomycin C or Epirubicin.

G3pT1 has a tendency to progress, however, 50% of patients can conserve their bladder with bladder instillations of chemotherapeutic agents or BCG therapy (see below for CIS). Early cystectomy should be considered for patients in the very high-risk category.

CIS is a potentially highly malignant disease that can still be treated, in the majority of cases, with bladder instillations of BCG given as an induction course (six x weekly instillations followed by three x weekly installations commencing six weeks after the initial course) and ideally followed by 'maintenance' treatment of three x weekly instillations every six months over a three-year period (with close cystoscopic and cytological follow up). Complete remission is obtained in up to 70% of cases. If cytology and biopsies remain positive, another cycle may produce a further 15% complete remission. If remission is not achieved after the first or second cycle a cystectomy should be considered.

Tumours of T2 or higher category (MIBC) are infiltrating tumours and radical treatment with either Cystectomy and bladder reconstruction / ileal conduit or Radical Radiotherapy (gold standard is chemoradiation with radiosensitiser) will be necessary in the majority of cases. In these cases, neo-adjuvant chemotherapy has been shown to confer a 5% long-term overall survival benefit and should be offered to for fit patients with adequate renal function.

The following groups of patients will be notified to the Network MDT co-ordinator for inclusion on specialist MDT meeting:

- All patients diagnosed with high-risk superficial bladder cancer:
  - Grade 3 Transitional cell carcinoma with no sub mucosal invasion (G3 pTa)
  - Grade 3 Transitional cell carcinoma with sub mucosal invasion (G3 pT1)
  - Extensive Grade 2
  - Recurrent Grade 2 or multifocal Grade 2
  - Carcinoma in situ

- All patients diagnosed with muscle invasive bladder cancer (T2-T4 tumours

- All patients who present with metastatic bladder cancer prior to them being managed by the local team.

Following discussion at MDT:

- Patients who are suitable for radical cystectomy and ileal conduit /bladder reconstruction will be managed by the specialist team.
- Patients who are not suitable for radical cystectomy and require urinary diversion can be managed by the local team.
- Patients who are suitable for chemoradiation / radiotherapy +/- neoadjuvant or adjuvant chemotherapy will be referred to the oncologist from the local team.

The Network group supports use of unlicensed BCG in view of supply difficulties.

FOLLOW UP

Follow up will be in accordance with the guidelines outlined below.

Follow-up of patients with NMIBC

The findings at cystoscopy are strong prognostic factors for recurrence and for progression, risk calculators can be used for patient counselling.

Calculation of Recurrence and Progression Scores (EORTC scoring and risk tables).

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2 to 7	3	3
> 8	6	3
Tumour diameter		
< 3 cm	0	0
> 3 cm	3	3
Prior recurrence rate		
Primary	0	0
< 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concomitant CIS		
No	0	0
Yes	1	6
Grade (1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total Score	0 – 17	0 - 23

Probability of recurrence and progression according to total score

Recurrence score	**Prob. recurrence** 1 year	**Prob. recurrence** 5 years
0	15%	31%
1-4	24%	46%
5-9	38%	62%
10-17	61%	78%

Progression score	**Prob. progression** 1 year	**Prob. progression** 5 years
0 0.	2%	0.8%
2-6	1%	6%
7-13	5%	17%
14-23	17%	45%

NMIBC Risk Stratification and follow up

This risk stratification and follow up is based upon NICE, EAU and NCCN guidelines, much of which are without a strong evidence base and often rely on consensus statements, particularly with regard to follow up protocols. Patients in the very high-risk category should be considered for primary cystectomy if fit. The full NICE, EAU and AUA risk categories and follow up schedules are included at the end of the guidelines for information only

Risk Stratification

Low Risk	• PUNLMP • LG pTa - <3cm AND solitary AND no cis
Intermediate Risk	Urothelial cancer that is not low risk or high risk, including: • solitary LG pTa with a diameter of > 3 cm • multifocal LG pTa • pTa G2 (high grade) • pTa HG or LG pT1 – solitary and <3cm • any low-risk non-muscle-invasive bladder cancer recurring within 12 months of last tumour occurrence
High Risk	Urothelial cancer with any of: • pTaG3 multifocal or >3cm • pT1 LG multifocal or >3cm • pT1HG • pTis (Cis)
Very High Risk	• Variant Histology (e.g., micropapillary, nested variant, sarcomatoid) • pTa HG or pT1 G2 (high grade) +cis + multifocal +>3cm • pT1HG +cis AND >3cm or multifocal • pT1 HG + no cis AND >3cm AND multifocal • BCG unresponsive • LVI

Follow up Protocol

Cystoscopy Schedule

Follow up schedule whilst free from recurrence.
Modify to fit maintenance regimen, if receiving intravesical maintenance therapy
Modify in discussion with consultant if extremely comorbid

Year	1	2	3	4	5	5-10	>10 years
Low Risk	3 and 12 months	annual	annual	annual	annual	discharged	
Intermediate Risk	3, 6 and 12 months	18 and 24 months	annual	annual	annual	discharged	
High or Very High Risk *	3 monthly	3 monthly	6 monthly	6 monthly	6 monthly	annually	discharged

- **High risk patients to have cytology specimen collected prior to each cystoscopy, send for analysis if cystoscopy clear.**

Imaging

High and very high-risk cases need CTU at 12 months and then every 1-2 years. Annually if initially multifocal and or involvement of trigone, or frequent recurrences.
No routine upper tract imaging for low and intermediate risk unless frequent bladder recurrences.

Follow-up: After treatment with curative intent (cystectomy / radiotherapy)

Rationale for follow-up

Follow-up of patients with invasive bladder cancer after cystectomy and radiotherapy is recommended, to detect local recurrence and distant metastases as early as possible to permit additional treatment when indicated and if possible. Such therapy may include salvage cystectomy, urethrectomy, nephro-ureterectomy and/or systemic chemotherapy/immunotherapy with or without secondary surgery for residual tumour. Moreover, side effects of urinary diversion, neobladder and chemoradiation should be recognized early on and corrected if possible.

Principles

Prognostic factors and type of intervention (cystectomy, radiotherapy) are relevant in determining the most efficient follow-up regimen. The pT and pN-stage are the most important prognostic factors and in addition risk factors such as CIS will guide the follow-up procedures.

Cystectomy Follow Up Protocol

Clinic Visit (Consultant review 6 weeks, 2 years, and 10 years)

1) Blood tests pre –clinic (provide form for next test): - FBC, U+E, LFTs, Bone profile, B12 (PSA if concurrent CA prostate), VitD, Bicarbonate
2) BP
3) Examine stoma + abdomen – hernias, retraction, mass
4) Offer ED treatment

Urethral Surveillance

6 monthly for 2 years, then annually for 5 years, extend to 10 years if high risk and fit for intervention.

Imaging

Stratify re risk of urothelial recurrence (upper tract or urethra)

1) Standard risk with Invasive TCC or SCC + fit for additional treatment
   - CTTAP 6, 12, 24 and 36 months. Additional 3-month scan if N+
   - Annual US thereafter up to 10 years dependent on fitness.
2) **High risk** of urothelial recurrence
   - Multifocal TCC, particularly superficial TCC in absence of MIBC
   - History of upper tract disease
   - Involvement of trigone, bladder neck or prostatic urethra
   - Positive ureteric or urethral margin

Annual CTU to 10 years after 3 years whilst remain fit for intervention, consider loopogram if eGFR<30 or contrast allergy.

3) Unfit for chemotherapy / new agents or major surgery
   Stop CT scanning + consider discharge to GP if limited life expectancy, otherwise annual clinic review as above.

Interval	6/52 C*	3/12 if N+	6/12	12/12	18/12	24/12 C*	36/12	Annually 4 to 5 years	Annually years 5-10
Clinic	x	x	x	x	x	x	x	x	x
CTTAP		x	x	x	N+	x	x		
CTU (High risk)								**x**	**x**
US (not high risk)								x	x
Urethroscopy (men)		x (+ve margin)	x	x	x	x	x	x	**High risk**

C* - consultant review

Urological follow up post Radical Radiotherapy for Invasive Bladder Cancer

Cystoscopy schedule (Nice guidance)

	3/12	6/12 to 2 years	2-4 years	4-10 years
rigid	x			
flexi		3 monthly	6 monthly	annually

Modify if patient frail / unfit for salvage cystectomy

Imaging

Interval	3/12 if N+	6/12	12/12	24/12	36/12	Annually year 3 - 10
CTTAP	x	x	x	x	x	
CTU (High risk)						**x**

High risk definition as for cystectomy cases. Reduce / shorten schedule on an individual basis if unfit for intervention.

The teams referring patients for discussion by specialist MDT are:

- Lancashire Teaching Hospitals NHS Foundation Trust
- East Lancashire Hospitals (Blackburn, Burnley)
- Blackpool, Fylde, and Wyre Hospitals
- Morecambe Bay Hospitals

T2 Muscle Invasive Urothelial Bladder Cancer Choosing treatment options and counselling patients.

The network should agree:

- *A list of local teams in the network which may counsel patients in order for them to select their primary treatment option from curative surgery, curative radiotherapy or other options.*
- *A set of written arrangements governing which core team members, and on which occasions, will present the options and counsel patients*

Notes: Specialist teams should counsel all patients from their own local catchment population.

The list of teams need not include all local teams in the network.

The network may agree that for certain options, patients should be counselled by the specialist team.

Patients who might otherwise be counselled by the local team may be counselled by the specialist team if agreed and desired by the patient and relevant consultants.

CLINICAL AND REFERRAL GUIDELINES FOR T2 MUSCLE INVASIVE BLADDER CANCER

Choosing treatment options and counselling patients

Bladder cancer

All patients diagnosed with muscle invasive bladder cancer (T2 tumours) will be notified to the Network MDT co-ordinator for inclusion on specialist MDT meeting.

Patients with invasive urothelial bladder cancer should have cross sectional imaging with MRI of pelvis, and CT chest and abdomen prior to treatment. If the patient is unlikely to have radical treatment, CT of pelvis rather than MRI is acceptable.

Cross sectional imaging should ideally take place before TURBT to avoid artefact.

Following discussion at MDT:

Many UK centres have favoured cystectomy as the treatment of choice for muscle invasive bladder cancer, or radical radiotherapy with salvage cystectomy reserved for treatment failures. There are no randomised data comparing radical radiotherapy with radical cystectomy alone. The choice of primary treatment for muscle invasive bladder cancer should be taken after patient has been fully counselled on short- and long-term risks of both surgery and radiotherapy. Performance status, co-morbidity and tumour stage may all affect treatment choice.

Relative indications for radical cystectomy

- High risk superficial tumours & CIS
- Extensive papillary disease that cannot be controlled with conservative measures
- Salvage cystectomy for post radiotherapy relapse
- Patient preference
- Severe bladder symptoms

Relative indications for radical radiotherapy/radical chemoradiation

- Good bladder functions
- Low volume organ confined (T2/T3) disease
- Prior complete macroscopic resection where possible, however residual disease is usually an indication merely of higher stage tumour rather than contraindication for bladder preservation

Patients with good renal function and performance status should have a discussion regarding selective bladder preservation following neoadjuvant chemotherapy

Neoadjuvant chemotherapy

There is strong evidence to support the use of neoadjuvant chemotherapy prior to definitive radical treatment for T2-T4 TCC of the bladder. A survival advantage of 5% at 5 years was clearly demonstrated in the ABC meta-analysis, for all tumour stages, irrespective of the type of subsequent definitive local treatment.

Neoadjuvant chemotherapy should be offered to all suitable patients prior to definitive radical treatment, for patients with T2-T4 TCC of the bladder.

- Patients referred for neoadjuvant chemotherapy or radical radiotherapy should have undergone maximal TURBT where possible within 6 weeks of commencement of treatment.
- Patients who are suitable for radical cystectomy will be managed by the specialist team and continent urinary diversion should be considered. Bladder reconstruction should be discussed where appropriate.
- Patients undergoing cystectomy must have 28 days of prophylactic low molecular weight heparin as per NICE guidance 2010
- Patients who are suitable for radiotherapy +/- neoadjuvant or adjuvant chemotherapy will be referred to the oncologist from the local team.

- Patients who have undergone radiotherapy should have a check cystoscopy at 3 months of completion by the local team. If salvage cystectomy is required, this should be managed by the specialist team.

All local teams within the Network will counsel patients from their own catchment population in order for them to select their primary treatment option from curative surgery, curative radiotherapy. Following publication of BC2001 data, all patients should be considered for chemoradiation with addition of Mitomycin C/5FU as radiosensitiser. The Surgeon, Oncologist and Nurse Specialist will discuss the treatment options and counsel patients.

In addition: patients considering radical cystectomy will be seen and counselled by a surgeon from the specialist team.

Adjuvant chemotherapy

There is no evidence to support the routine use of adjuvant chemotherapy in patients with locally advanced disease. Patients with high-risk pathological features such as node positive disease, T3/T4 tumours, positive surgical margins should be considered for entry into appropriate trials of adjuvant chemotherapy.

Where no trials are available locally, some patients may wish to discuss the possibility of adjuvant treatment. Patients should be clearly informed of the lack of evidence to support its use in terms of overall survival.

Palliative radiotherapy

For patients with poor performance status, significant co-morbidities and muscle invasive disease, palliative radiotherapy can be considered, in particular for patients with significant local symptoms such as haematuria.

Metastatic disease

Patients should be considered for palliative radiotherapy for local symptom control or for palliative chemotherapy. Chemotherapy in this setting offers response rates of ~50% based on patient selection. Cisplatin / carboplatin & gemcitabine chemotherapy is recommended. Patients should be identified via the local MDT for early referral to oncology. Stenting or nephrostomy should be considered for patients with hydronephrosis in whom chemotherapy or radiotherapy is contemplated. Immunotherapy may also be considered in first line treatment of metastatic disease for patients with PDL-1 positivity.

Palliative care referral should be involved at any early point in patients with metastatic disease.

UPPER TRACT

The network recommends the use of the EAU guideline which can be found via the following link;

Upper Urinary Tract Urothelial Cell Carcinoma - INTRODUCTION - Uroweb

KIDNEY CANCER

Kidney Cancer

The network should agree:

- *Protocols for diagnosis and assessment of primary and recurrent disease, including specific indications for CT, MRI, and biopsy.*
- *The parameters of disease stage and patient fitness, which determine when each of the treatments and procedures classified as local, and specialist care, in the introduction, are indicated.*
- *Those patients who need specialist care are referred to a named specialist team for treatment, and patients who are potential candidates for nephron sparing surgery are discussed with the named specialist team.*
- *That certain patients (as defined below) are referred for resection of the primary and metastases by a named specialist team.*
- *The parameters which determine which patients are potential candidates for nephron sparing surgery and resection of primary and metastases.*

CLINICAL AND REFERRAL GUIDELINES FOR KIDNEY CANCER

All patients with suspected renal tumours should be referred to the local urologist with special interest in cancer management.

Patients used to present with a history of haematuria, mass and/or pain in abdomen. However, with widespread use of ultrasound and CT scan patients are more commonly diagnosed with asymptomatic, small tumours.

The patient's pathway can be shortened:

- Referral via 2-week rule pathway
- In the case of incidental finding the Radiologist should advise referring clinician to refer patient urgently to urologist.

Pre-treatment investigations

- Ultrasound scan: This is most likely to be the initial investigation and the report should include the site and size of the lesion together with a comment as to the presence or absence of involvement of the renal vein or inferior vena cava.
- CT scan / MRI scan: Radiologists should be encouraged to proceed with the CT scan rather than wait for this to be requested by the referring clinician. The scan should include cross sectional imaging of the abdomen and chest. The use of MRI instead or in addition to CT scan should be at the discretion of individual urologists.

- Bone scan: should be performed if there is clinical suspicion of bony metastases or the patient has an elevated serum alkaline phosphatase or calcium.
- Biochemical and haematological investigations: All patients must have a full blood count and assessment of their renal profile, liver, and bone profiles. Patients with impaired renal function (raised creatinine) have an eGFR and be considered for a DMSA/isotope renal scan.

Patients with kidney cancer who:

- Have tumours which have, or may have invaded major blood vessels
- Present with metastases
- Might benefit from resection of metastases
- Have bilateral disease or who will require dialysis
- Have T1 tumours for which nephron-sparing surgery may be possible
- Have von Hippel-Lindau disease or hereditary papillary tumours.

Will be notified to the Network MDT co-ordinator for inclusion on specialist MDT meeting prior to them being managed by the local team.

Following discussion at MDT:

• Patients with metastatic disease who are suitable for angiogenesis inhibitors / Immunotherapy will be referred to the oncologist from the local team.
Treatment will be given by the specialist team.

- Patients who are suitable for radical nephrectomy will be referred back to the local team for management, but should be offered laparoscopic surgery where clinically appropriate
- Patients who are suitable for partial nephrectomy should be referred back to the clinicians within the Network who have appropriate experience.
- Patients with metastatic disease who are suitable for angiogenesis inhibitors/ immunotherapy will be referred to the oncologist from the local team.
  Treatment will be given by the specialist team.

Treatment

- Radical nephrectomy: In the absence of universal agreement for the definition of 'radical nephrectomy' the surgeon who performs the nephrectomy must record whether or not the adrenal gland is removed. Adrenalectomy is not necessary if the adrenal is normal on preop imaging. Routine lymphadenectomy should be considered only if the patient has been entered into a clinical trial where staging is necessary.

  Radical nephrectomy would usually be undertaken in patients with a single tumour greater than 7cm or where involvement of the perinephric fat is suspected.

- Laparoscopic nephrectomy: should be offered to patients with T2 tumours and T1 tumours not suitable for partial nephrectomy

- Partial nephrectomy: should be considered for
  - Patients with a single tumour up to 7 cm diameter in patients with normal renal function.
  - Patients with impaired renal function
  - Patients with a solitary kidney
  - Patients with Von Hippel-Lindau syndrome

Solitary metastases: Patients with a renal tumour and a solitary metastasis should be considered for nephrectomy and excision of the metastasis. Patients who develop an apparent solitary metastasis after treatment for the primary tumour should also be considered for surgical excision/radiotherapy of the metastasis.

- Multiple metastases: Nephrectomy in patients with multiple distant metastases should be considered only for palliation of symptoms such as pain, haematuria, or profuse nocturnal sweats or if they are being considered for angiogenesis inhibitors / immunotherapy. The indication must be clearly stated in the case notes. If nephrectomy is not feasible, embolisation should be considered along with radiotherapy to painful metastases.
  Patients with multiple metastases whose performance status is good and co-morbidity minimal should be considered for angiogenesis inhibitors / immunotherapy, a biopsy being required in the absence of nephrectomy

Tumours will be classified using the TNM classification system.

T - Primary tumour
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Tumour < 7 cm in greatest dimension, limited to the kidney
T1a Tumour < 4 cm in greatest dimension, limited to the kidne

T1b Tumour > 4 cm but < 7 cm in greatest dimension, but not more than 7 cm
T2 Tumour > 7 cm in greatest dimension, limited to the kidney
T2a Tumour > 7cm but </= 10cm, limited to the kidney
T2b Tumour > 10cm, limited to the kidney
T3 Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a Tumour grossly extends into the renal vein or its segmental branches, or tumour invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b Tumour grossly extends into the vena cava below the diaphragm
T3c Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava

T4 Tumour directly invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

N - Regional lymph nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single regional lymph node
N2 Metastasis in more than 1 regional lymph node
pN0 lymphadenectomy specimen ordinarily includes 8 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0

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

TNM stage grouping
Stage I T1 N0 M0
Stage II T2 N0 M0
Stage III T3 N0 M0
T1, T2, T3 N1 M0
Stage IV T4 N0, N1 M0
Any T N2 M0
Any T Any N M1
1Includes renal sinus (prepelvic fat).
2Includes segmental (muscle-containing branches).

Follow up:

<u>Rational for follow up</u>
Follow up of patients with RCC after surgical treatment is recommended to

detect local recurrence and distant metastases as early as possible to permit additional treatment when indicated and if possible. Such therapy may include

resection of pulmonary metastasis or local recurrences; certain cases may also be candidates' angiogenesis inhibitors /immunotherapy. With this background in mind, a regular postoperative follow up of patients with RCC is proposed

Principles

Prognostic factors and the type of surgical intervention (radical vs partial or nephron sparing surgery) are relevant in determining the most efficient follow up regimen. The only established prognostic factor is tumour stage according to the TNM system. After nephron sparing tumour resection (elective or mandatory indication), the local recurrence rate may vary between 0 and 10%. In a small proportion of patients with a genetic predisposition, a different follow-up procedure may be required

Follow-up procedures

The first assessment is within 3 months and includes:

- Physical examination to exclude surgical complications
- Serum creatinine to assess the remaining kidney function
- Haemoglobin to assess recovery of perioperative blood loss (If these values are normal, repeat investigation is usually unnecessary).

If alkaline phosphatase is abnormal preoperatively, repeat measurement is recommended because recurrent or persistent alkaline phosphatase elevation after surgery suggests distant metastasis, or residual tumour. Alkaline phosphatase elevation together with bone pain is suspicious for bone metastasis. Elevation may also occur in case of liver metastasis or paraneoplastic manifestations.

A chest imaging is recommended to detect pulmonary metastases, which occur most commonly within 3 years after surgery.

Imaging of the contralateral kidney is advocated in case of enhanced risk of developing metachronous occurrence (as in familial papillary RCC or VHL (von Hippel-Lindau disease).

For selected high-risk patients consider referral for adjuvant trials.

Imaging of the retro peritoneum by abdominal CT is recommended on the basis of Mayo risk stratification in accordance with the EAU guidelines as below:

Feature	Score
Primary tumor / T-stage	
T1a	0
pT1b	2
pT2	3
pT3 - pT4	4
Tumor size	
<10cm	0
>10cm	1
Regional Lymph Node status	
pNx/pN0	0
pN1 - pN2	2
Nuclear grade	
Grade 1-2	0
Grade 3	1
Grade 4	3
Tumor necrosis	
No necrosis	0
Necrosis	1

Risk groups can be stratified by the scoring system, characterized into low-risk 0-2, intermediate risk 3-5 and high-risk >6 according to the Mayo Scoring System (13).

RCC follow up

Risk profile (*)	Oncological follow-up after date of surgery								
	3 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	> 3 yr (**) (***)	> 5 yr (**) (***)
Low risk of recurrence For ccRCC: Leibovich Score 0-2 For non-ccRCC: pT1a-T1b pNx-0 M0 and histological grade 1 or 2.	-	CT	-	CT	-	CT	-	CT once every two yrs	-
Intermediate risk of recurrence For ccRCC: Leibovich Score 3-5 For non-ccRCC: pT1b pNx-0 and/or histological grade 3 or 4.	-	CT	CT	-	CT	-	CT	CT once yr	CT once every two yrs
High risk of recurrence For ccRCC: Leibovich Score ≥ 6 For non-ccRCC: pT2-pT4 with any histological grade or pT any, pN1 cM0 with any histological grade	CT	CT	CT	CT	CT	-	CT	CT once yr	CT once every two yrs

ccRCC = clear cell renal cell carcinoma, CT = computed tomography, mo = months, non-ccRCC = non clear cell renal cell carcinoma; yr = years.

Prostate cancer

The network should agree:
- *Protocols for diagnosis and assessment of primary and recurrent disease, including specific indications for MRI and bone scans, and indications, agreed with a network representative from primary care, for GP referral to the designated prostate assessment clinic*
- *The parameters of disease stage and patient fitness which determine when each of the treatments and procedures classified as local and specialist care in the introduction are indicated, including those patients with organ confined prostate cancer who are potential candidates for curative surgery or curative radiotherapy.*
- *That patients who need specialist care, as in the introduction, are referred to a named specialist team for treatment.*
- *For brachytherapy for prostate cancer, the named team in which named network, to whom patients may be referred for this treatment.*

CLINICAL AND REFERRAL GUIDELINES FOR PROSTATE CANCER

All patients with suspected prostate cancer should be referred urgently to the local urologist with special interest in cancer management.

Patients usually present with an elevated age-related PSA (asymptomatic or with lower urinary symptoms), or an abnormal digital rectal examination of prostate.

The two-week referral pathway can be used for these patients
- An elevated age specific PSA in men with a ten-year life expectancy
- A high PSA (>20ng/ml) in men with clinically malignant prostate or bone pain.

Patients should follow the timed prostate cancer pathway (NHS England v1)
This consists of senior clinical decision makers assessing patients.
Pre biopsy MRI should be performed in suitable patients –
- High risk for cancer
- Age < 75
- Localised disease at presentation (PSA <30)
- No contraindications to MRI scan

Patients should have a prostate biopsy under prophylactic antibiotic cover by the local team or listed for a template/precision biopsy dependant on the MRI result.
A bone scan should be performed for all patients whose PSA >20ng/ml and should be considered in those whose Gleason score is over 7, or who have symptoms.

MRI should be considered in all patients undergoing radical treatment as per NICE guidance.

Tumours will be classified using the TNM and CPG classification system.

T - Primary tumour
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Clinically inapparent tumour not palpable or visible by imaging
T1a Tumour incidental histological finding in 5% or less of tissue resected
T1b Tumour incidental histological finding in more than 5% of tissue resected
T1c Tumour identified by needle biopsy (e.g., because of elevated prostate-specific antigen (PSA) level)
T2 Tumour confined within the prostate1
T2a Tumour involves one half of one lobe or less
T2b Tumour involves more than half of one lobe, but not both lobes
T2c Tumour involves both lobes
T3 Tumour extends through the prostatic capsule2
T3a Extracapsular extension (unilateral or bilateral)
T3b Tumour invades seminal vesicle(s)
T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall
N - Regional lymph nodes3
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
M - Distant metastasis
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a Non-regional lymph node(s)
M1b Bone(s)
M1c Other site(s)

Urological cancer MDTs should assign a risk category to all patients with newly diagnosed localised or locally advanced prostate cancer.

Risk stratification for patients with localised or locally advanced prostate cancer **Cambridge Prognostic Group:**

Criteria	
CPG1	Gleason score 6 (grade group 1) and prostate-specific antigen (PSA) less than 10 microgram/litre and Stages T1–T2
CPG2	Gleason score 3 + 4 = 7 (grade group 2) or PSA 10 microgram/litre to 20 microgram/litre and Stages T1–T2
CPG3	Gleason score 3 + 4 = 7 (grade group 2) and PSA 10 microgram/litre to 20 microgram/litre and Stages T1–T2 or Gleason 4 + 3 = 7 (grade group 3) and Stages T1–T2
CPG4	One of: Gleason score 8 (grade group 4), PSA more than 20 microgram/litre, Stage T3
CPG5	Two or more of: Gleason score 8 (grade group 4), PSA more than 20 microgram/litre, Stage T3 or Gleason score 9 to 10 (grade group 5) or Stage T4

Guidelines on primary treatment of cancer of the prostate:

CPG 1 localised prostate cancer:	offer active surveillance consider radical prostatectomy or radical radiotherapy if active surveillance is not suitable or acceptable to the person.
CPG 2 localised prostate cancer:	offer a choice between active surveillance, radical prostatectomy, or radical radiotherapy
CPG 3 localised prostate cancer:	offer radical prostatectomy or radical radiotherapy and consider active surveillance
Offer radical prostatectomy or radical radiotherapy to patients with CPG 4 and 5 localised and locally advanced prostate cancer when it is likely the patient's cancer can be controlled in the long term.	
Consider pelvic radiotherapy for patients with locally advanced prostate cancer who have a higher than 15% risk of pelvic lymph node involvement and who are to receive neoadjuvant hormonal therapy and radical radiotherapy. **Radiotherapy includes LDR or HDR brachytherapy with boost as indicated.** **Enrol pts into trials when available.**	
Consider bone health management for patients on ADT for more than a year	

M+	Watchful waiting	No standard option. May have worse survival/more complications than with immediate hormonal therapy
	Radical prostatectomy	Not an option
	Radiotherapy	to prostate for oligometastatic disease as defined by Stampede trial protocol
	Hormonal	Standard therapy. Symptomatic patients should not be denied treatment
	Combination Chemotherapy	Not an option May be considered on case basis for fit patients in addition to hormonal treatment
	Radium 223	To offer as needed
	Novel hormonal agents	To offer to patients with metastatic (or non metastatic castrate resistant) disease as per license and funding indications.

PROSTATE CANCER

Patients with localised prostatic carcinoma will be notified to the Network MDT co-ordinator for inclusion on specialist MDT meeting prior to them being managed:

Local team:
Patients with localised prostatic carcinoma, requiring active monitoring, will be managed by the local team.

Patients with localised prostatic carcinoma, requiring radiotherapy will be referred to the local oncologist or radiographer and managed by the local team.

Patients with locally advanced prostatic carcinoma will be managed with neo-adjuvant hormone therapy and radiotherapy. Patients who are not suitable for radiotherapy will be managed with hormone therapy alone.

Patients with metastatic disease requiring hormone manipulation will be managed by the local team. Palliative radiotherapy for symptom control will be referred to the local oncologist. Patients who may be suitable for chemotherapy should be referred to the specialist MDT for discussion.
A PSMA scan may be considered for patients where pathology and imaging are discordant or where equivocal results or oligometastatic disease on imaging would significantly affect the choice of treatment.

Specialist team:

Patients with localised prostatic carcinoma, requiring radical prostatectomy will be managed by the specialist team. All patients should receive 28 days of DVT prophylaxis by low molecular weight heparin as per NICE guidance 2010.

Do not offer high-intensity focused ultrasound and cryotherapy to people with localised prostate cancer, other than in the context of controlled clinical trials comparing their use with established interventions.

All patients requiring brachytherapy for prostate cancer will be referred to the Urology Oncology team at Christie Hospital for treatment.

Follow-up

Follow up will be in accordance with the EAU guidelines outlined below.

Guidelines for patients on active surveillance

These patients should be managed and followed up in secondary care.
Year 1 of active surveillance –

Every 3 to 4 months: measure prostate specific antigen (PSA)
Throughout active surveillance: monitor PSA kinetics

At 12 months: digital rectal examination (DRE)
At 12 to 18 months: multiparametric MRI

Year 2 and every year thereafter until active surveillance ends –
Every 6 months: measure PSA
Throughout active surveillance: monitor PSA kinetics
Every 12 months: DRE
(NICE 2019)

Active treatment may be considered for patients with

- PSA doubling time <3 years (in most cases, based on at least 8 determinations)
- Grade progression to Gleason score 7 (4 + 3) or higher

These are guidelines and should be modified according to patient age and co morbidity.

Guidelines for follow-up after treatment with curative intent

1. In asymptomatic patients, a disease-specific history and a serum PSA measurement are the recommended tests for routine follow-up. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually

2. After radical prostatectomy, a recordable, rising serum PSA can be associated with residual or recurrent disease. Patients with three rises and with absolute PSA of 0.1 or greater should be discussed at SMDT

3. After radiation therapy, a rising PSA level, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease. Biochemical failure defined as per Phoenix definition of nadir +2ng/ml

4. Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence

5. Detection of local recurrence by TRUS and biopsy is only recommended if it will affect the treatment plan. In most cases TRUS and biopsy are not necessary before second-line therapy

6. Routine bone scans and other imaging studies are not recommended in asymptomatic patients with slow doubling time. For patients with PSADt < 6-12 months imaging with CT/bone scan should be undertaken with

frequency of imaging 4 monthly if rapid rise in PSA to 10 or greater or PSADT of 6-12 months (post radiotherapy) PSMA scan may be considered in patients with rapid psa doubling times especially in patients post prostatectomy being considered for salvage radiotherapy. If a patient has bone pain, a bone scan should be considered irrespective of the serum PSA level (unless there is a PSMA scan already performed)

Guidelines for follow-up after hormonal treatment

1. Patients should be evaluated at 3 and 6 months after initiating treatment. Tests should include at least serum PSA measurement and careful evaluation of symptoms in order to assess the treatment response and the side-effects of treatments given.

2. Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given.

3. In patients with stage M0 disease with a good treatment response, follow-up is scheduled every 6 months, and should include at least a disease-specific history and serum PSA determination.

4. In patients with stage M1 disease with a good treatment response (PSA <4 at 3 months following treatment onset), follow-up is scheduled for every 3-6 months. A minimal follow-up should include a disease-specific history and serum PSA determination, supplemented with haemoglobin, serum creatinine and alkaline phosphatase, liver function and testosterone measurements.

5. When disease progression occurs or if the patient does not respond to the treatment given, the follow-up needs to be individualized with consideration of the use of bisphosphonates, chemotherapy, or further hormone therapy.

6. All patients commencing androgen deprivation for period of 12 months or greater should have a dexa scan.

7. All patients commencing hormonal therapy should have advice on diet, exercise and referral to local exercise program should be considered.

8. In cases of PSA failure, the testosterone levels should be checked.

Treatment of biochemical failure after treatment with curative intent

Guidelines for second-line therapy after curative treatment

Presumed local failure after radical prostatectomy	Patients with presumed local failure only may be candidates for salvage radiotherapy. Radiotherapy should be given preferably before PSA rises above 0.1.and based on 3 successive rises post op. Other patients are best offered a period of watchful waiting (active monitoring) with possible hormonal therapy later on.
Presumed local failure after radiotherapy	Most patients are best offered a period of watchful waiting (active monitoring) with possible hormonal therapy later on. Imaging frequency determined by PSADT .
Presumed distant +/- local failure	There is some evidence that early hormonal therapy may be of benefit in delaying progression and possibly achieve a survival benefit in comparison with delayed therapy. The results are not without controversy. Local therapy is not recommended except for palliative reasons.

The teams referring patients for discussion by specialist MDT are:

- Lancashire Teaching Hospitals NHS Foundation Trust
- East Lancashire Hospitals (Blackburn, Burnley)
- Blackpool, Fylde, and Wyre Hospitals
- Morecambe Bay Hospitals

Organ Confined Prostate Cancer – Choosing treatment options and counselling patients.
The network should agree:
• A list of local teams in the network which may counsel patients in order for them to select their primary treatment option from curative surgery, curative radiotherapy or other options.
• A set of written arrangements governing which core team members, and on which occasions, will present the options and counsel patients (see Topic 2G).
Notes:
Specialist teams should counsel all patients from their own local catchment population.
The list of teams need not include all local teams in the network.
The network may agree that for certain options, patients should be counselled by the specialist team.
Patients who might otherwise be counseled by the local team may be counseled by the specialist team if agreed and desired by the patient and relevant consultants.

CLINICAL AND REFERRAL GUIDELINES FOR ORGAN CONFINED PROSTATE CANCER

Choosing treatment options and counselling patients

Patients with localised prostatic carcinoma should be offered options of treatment including:

- Radical prostatectomy
- Radical radiotherapy
- Active monitoring

and will be notified to the Network MDT co-ordinator for inclusion on specialist MDT meeting prior to them being managed by the specialist team. High intensity focused ultrasound (HIFU - not routinely offered outside of onward referral for a trial) may be offered but the patient should be made aware that long-term data on effect is not available. Patients requiring active monitoring will be managed by the local team.

All local teams within the Network will counsel patients from their own catchment population in order for them to select their primary treatment option from curative surgery, curative radiotherapy or other options.

In addition: patients considering radical prostatectomy will be seen and counselled by a surgeon from the specialist team.

Personalised Stratified Follow Up (PSFU)

Personalised stratified follow up (PSFU)

The patient will be identified as suitable for PSFU when they attend their appointment with their health care professional: using the Stratification Criteria. All patients entering onto this pathway will have been diagnosed with prostate cancer and completed or started their initial treatment or management.

When a patient is selected for PSFU, the criteria consider individual needs alongside the staging and grading of the cancer. Patients must have a good understanding of PSFU and be willing to self-manage along with an agreement to attend PSFU patient education workshop. Patients, who are non-compliant, socially isolated and with complex needs will not be eligible for PSFU.

Effective delivery of PSFU will require all patients to have access to the elements of the LTP personalised care interventions i.e., Personalised care and support plan based on Holistic Needs Assessment (HNA), Treatment Summaries, Health and Wellbeing Information and Support, or similar, and a primary care Cancer Care Review.

Principles that underpin supported self-management:

- An agreed stratification criterion to identify those patients suitable for supported self-management considering both risk of recurrence and the individual needs of the patient.
- A reliable, safe, remote surveillance digital software system to track and monitor investigation requests and results.
- Access to timely education and support for the patient in the form of workshops (online or face to face), supported by written material which can be assessed online or in printed format.
- Follow up criteria will remain in line with national guidelines.
- A Cancer Support Worker will manage the database and be the first point of contact for patients.
- Rapid re-access into traditional follow up if required at any point in the journey.

TESTICULAR CANCER

The L&SC Urology CRG and MDTs are in agreement with the L&SC/GMCN Supranetwork Clinical Guidelines for Germ Cell Tumours of the Testis and other sites (Version 5 June 2015) and will work to these guidelines for the management of all testicular cancer patients in L&SC.

Professor Alison Birtle and Dr Catherine Mitchell are named core members of the Supranetwork Testicular MDT.

All newly diagnosed cases of testicular cancer should be referred to a member of the Supranetwork MDT within 24 hours of surgery.

All patients with raised tumour markers, and /or evidence of metastatic disease should be discussed with a member of the supranetwork MDT before orchidectomy.

Sperm banking +/prosthesis insertion should be considered and offered prior to orchidectomy.

All patients will be referred to the Supranetwork MDT meeting by a core member of the testis Supranetwork MDT, to whom all referrals from the local and network MDT should be addressed. (Prof Birtle/ Dr Mitchell)

Exceptions to the above include patients where there is uncertainty about diagnosis e.g., testicular mass on imaging and seeking further advice re orchidectomy or observation. Other exception would include cases where partial orchidectomy could be considered.

In such situations a Supranetwork MDT proforma may be completed by the referring urologist who should link into the testis Supranetwork MDT.
All other cases should be referred to Prof Birtle/ Dr Mitchell for Supranetwork MDT discussion.

Stage 1 seminoma/NSGCT may be managed by Dr Parikh in East Lancashire after discussion with the supranetwork MDT.

Blackpool patients are referred to Prof Birtle at LTHTR.

Guidelines are currently under review, but can be found at Appendix 2 pages 36 - 80

PENILE CANCER

The L&SC Urology CRG and MDTs are in agreement with the L&SC/GMCN Supranetwork Clinical Guidelines for Penile Cancer and will work to these guidelines for the management of all penile cancer patients in L&SC.

Guidelines can be found at Appendix 3 pages 81 - 106

Appendix 1

Local MDTs/Teams

Name of Hospital /Local Urology MDT	Name of Trust	Referring CCGs	Pop Referred
Royal Lancaster Infirmary/Furness General Hospital via VC MDT Referring pop: 310,000	University Hospital of Morecambe Bay NHS Trust	Cumbria (Furness and South Lakeland) North Lancashire (Lancaster)	176,981 160,537
Blackpool Victoria Hospital Referring pop: 328,000	Blackpool, Fylde & Wyre Hospitals NHS Trust	Blackpool Fylde & Wyre	172,375 151,372
Royal Preston Hospital Referring pop: 449,000	Lancashire Teaching Hospitals NHS Foundation Trust	Greater Preston Chorley & South Ribble	212,462 173,686
Blackburn Royal Hospital Referring pop: 522,000	East Lancashire Hospitals NHS Trust	Blackburn with Darwen East Lancashire	169,187 371,435
		Total Population	1,609,000

Specialist MDT/Team

SPECIALIST MDT HOSPITAL SITE & TRUST	REFERRING PCTs	REFERRING POP OF PCT
Video-Conference Network SMDT Complex pelvic surgery to be undertaken across two sites: ❑ Royal Preston Hospital part of Lancashire Teaching Hospitals NHS Trust (patients from Central Lancs, Blackpool, North Lancs (Fylde & Wyre) PCTs) ❑ Royal Blackburn Hospital part of East Lancashire Hospitals NHS Trust (patients from Cumbria (South Lakes), North Lancs (Lancaster), East Lancs and Blackburn with Darwen PCTs)	Blackpool North Lancashire (Fylde & Wyre)	143,000 185,000
	Central Lancashire	449,000
	Blackburn with Darwen East Lancashire	140,000 382,000
	Cumbria (South Lakeland) North Lancashire (Lancaster)	173,000 137,000
	Total	1,609,000

Supranetwork MDT for penile cancer

Referring Networks/Urology MDTs	Catchment Population	Penile Cancer Supranetwork MDT	Total Catchment Population
Greater Manchester & Cheshire Cancer Network Local urology MDTs	3.125m	Hosted by Christie Hospitals NHS Trust	7,725,000
Merseyside & Cheshire Cancer Network	2.3m		
Lancashire & South Cumbria Cancer Network - Local MDTs BFWHT – Blackpool Victoria Hospital ELHT – Royal Blackburn Hospital LTHT – Royal Preston Hospital UHMBT - Royal Lancaster Infirmary	1.7m		
North Wales Local Urology MDTs	0.6m		

Supranetwork MDT for testicular cancer

Referring Networks/Urology MDTs	Catchment Population	Testicular Cancer Supranetwork MDT	Total Catchment Population
Greater Manchester & Cheshire Cancer Network Local urology MDTs	3.125m	Hosted by Christie Hospitals NHS Trust	5,425,000
Lancashire & South Cumbria Cancer Network - Local MDTs BFWHT – Blackpool Victoria Hospital ELHT – Royal Blackburn Hospital LTHT – Royal Preston Hospital UHMBT - Royal Lancaster Infirmary	1.7m		
North Wales Local Urology MDTs	0.6m		

Appendix 2

Greater Manchester & Cheshire and Lancashire & South Cumbria Supra Network Clinical Guidelines For Germ Cell Tumours of the Testis and other sites

Version 5
June 2015

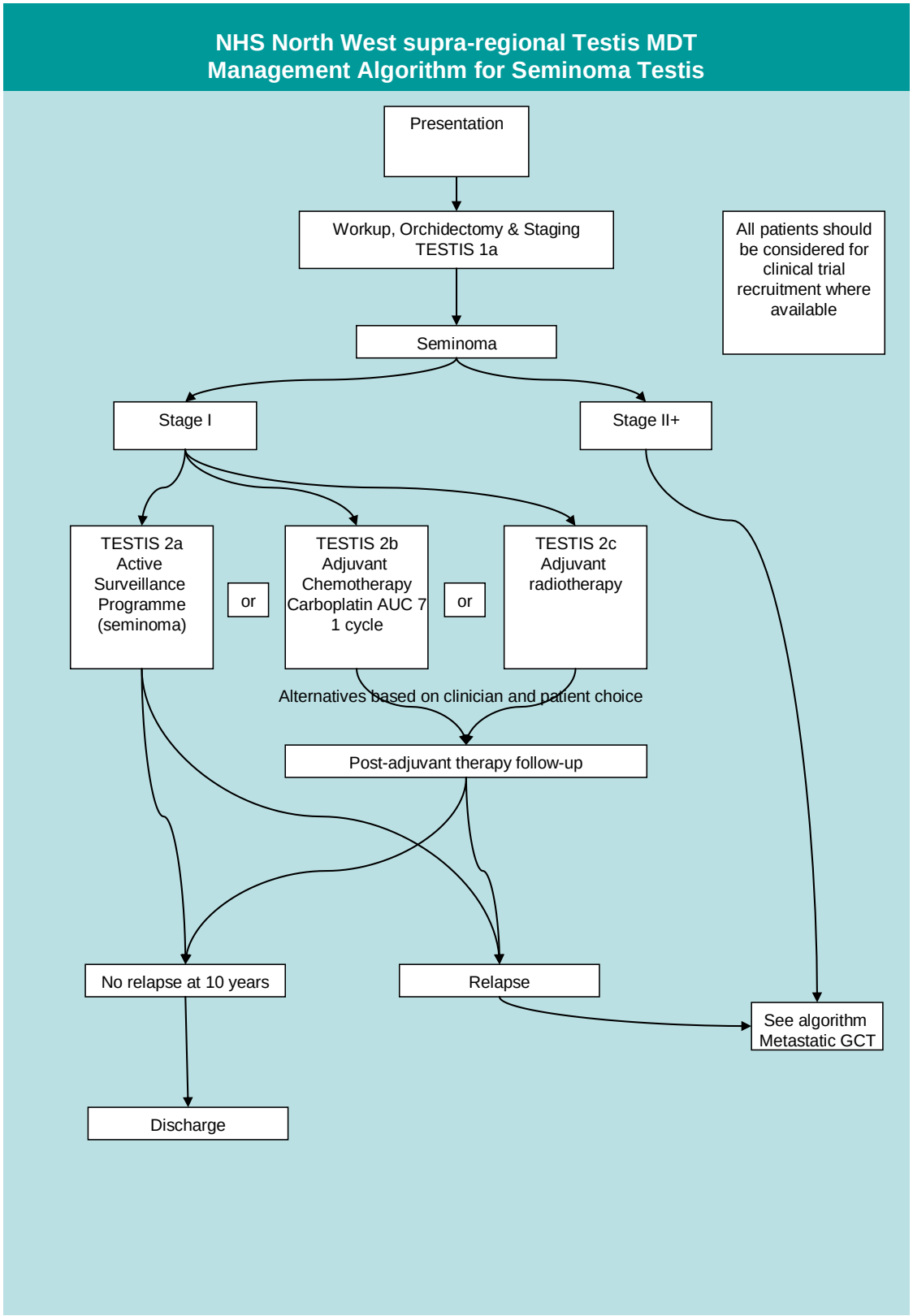
These Network Clinical Guidelines have been agreed by the Core Members of the Testis snMDT:		
Dr Michael Leahy	snMDT Lead Clinician.	Date signed:

(CURRENTLY UNDER REVIEW)	
Date	Review
1st July 2016	No substantial changes

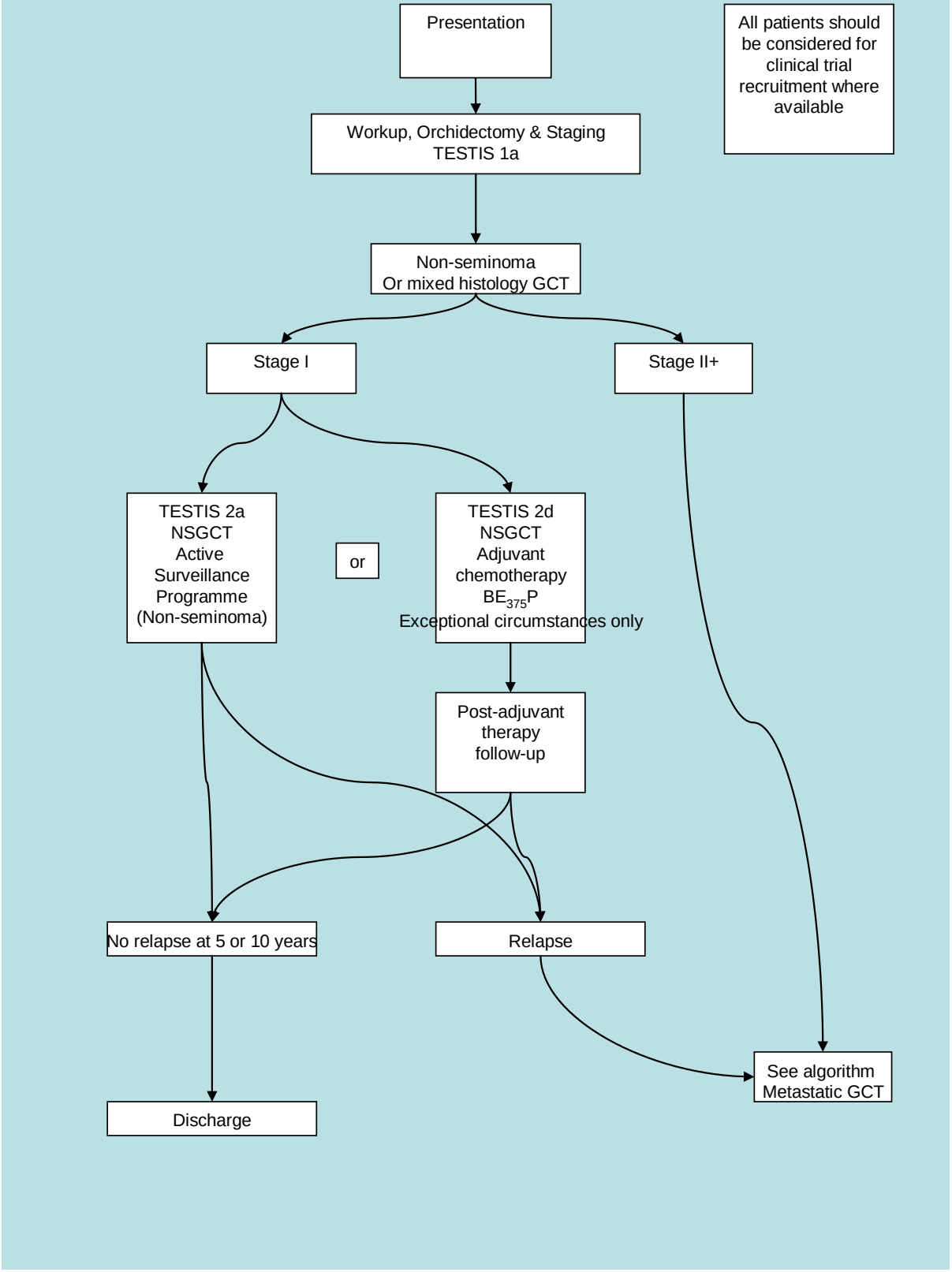
CONTENTS

Overview

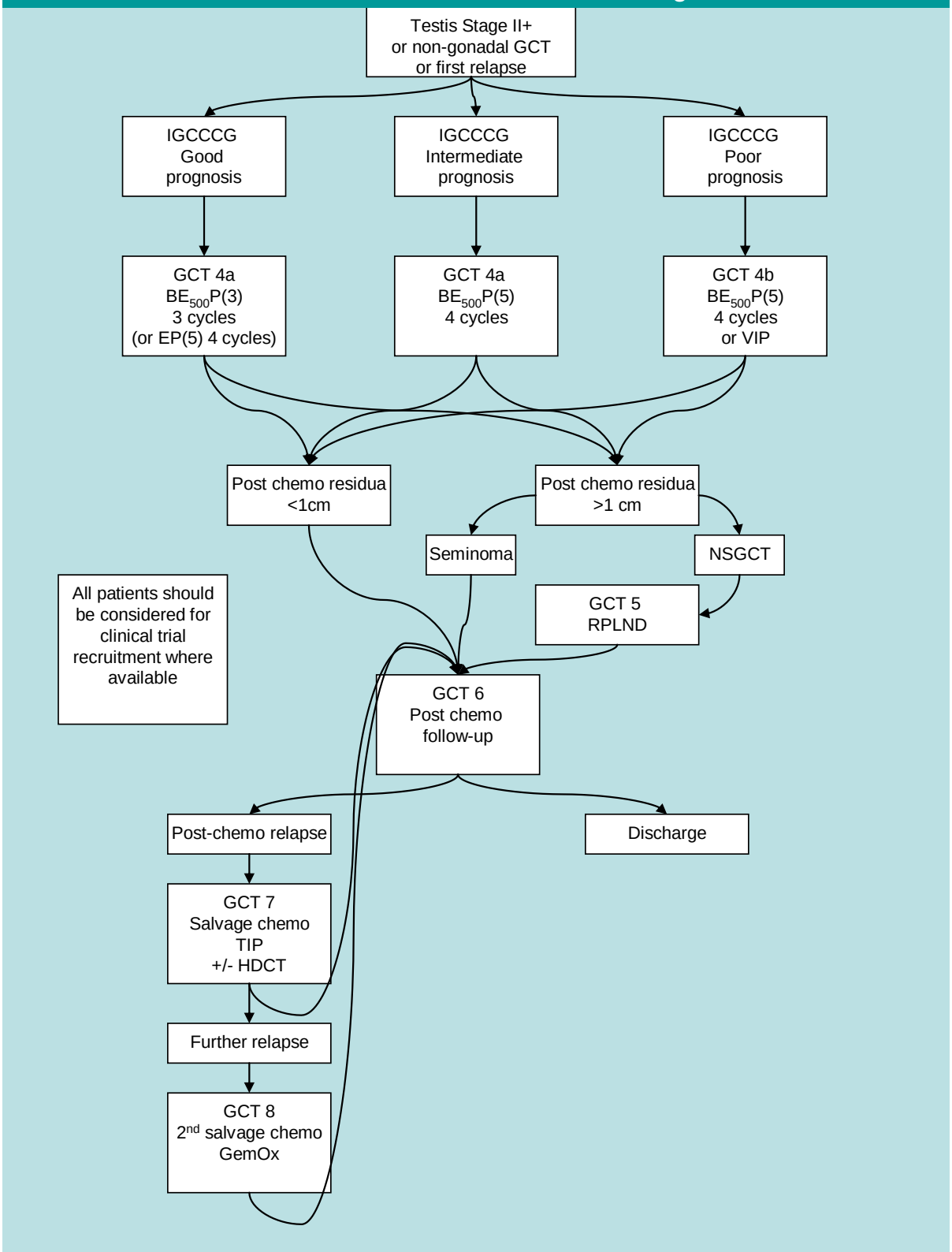
These flow diagrams indicate the main clinical pathways for patients with germ cell cancer of the testis and other sites:



NHS North West supra-regional Testis MDT
Management Algorithm for NSGCT Testis



NHS North West supra-regional Testis MDT
Management Algorithm for
Metastatic Germ Cell Cancer of Testis and non-gonadal sites



TESTIS 1a: Workup staging and diagnosis for newly diagnosed GCT testis

Background

This care plan is based on the results from the North West Urology Audit of Initial Assessment / Diagnosis and Primary Orchidectomy, Ramani *et al* December 2006

Patient group

Patients presenting with a new diagnosis of primary and or metastatic testis cancer

Inclusion criteria

- Male patient, palpable testicular mass, > 16 years of age
- Other suspicion of testicular cancer e.g., gynaecomastia with high serum B-HCG

Exclusion Criteria

- Female: see primary ovarian germ cell tumour guideline
- < 16 years of age: patient should be referred to paediatric services
- Primary non-germ cell cancer of testis

Initial investigations and work up prior to start of treatment

- All patients presenting with suspected testicular cancer should be referred urgently to the local urologist with a nominated role in cancer management
- Two-week referral pathway should be used for patients with swelling in the body of the testis

Initial assessment

- H&P
- Tumour serum markers: Alpha-fetoprotein (AFP); beta-hCG; LDH (pre-operatively)
- Biochemistry profile
- Chest x-ray
- Urgent **bilateral** USS testes

Expedite referral to the snMDT prior to orchidectomy

- Obvious metastatic disease
- Very high tumour markers
- Non-gonadal germ cell tumour of (mediastinum, retroperitoneum, brain)
- Severe constitutional symptoms

Orchidectomy

- Discuss sperm banking prior to surgery and arrange if required (NB. HepB, HepC and HIV serology results are required prior to arranging sperm banking)
- Patients should be offered/counselled about testicular prosthesis insertion, and this should be recorded in the case notes.
- Patients undergoing testicular prosthesis insertion should receive a stat dose of antibiotic at surgery / induction
- Notify Testis snMDT prior to surgery, if possible, within 24 hours
- Notify Teenage & Young Adult (TYA) MDT at primary treatment centre (Christie YOU) if < 25 years

- Surgery should be performed within 31 days of referral (including non HSC205 referrals)
- DVT prophylaxis – either flowtron boots, TEDS and low molecular weight heparin should be administered and documented
- Where there is a clinical suspicion of Ca testis then the preferred approach is a groin incision (not scrotal).
- Consider open inguinal biopsy of contra lateral testis if any of the following factors are present
    - Suspicious ultrasound for intra-testicular abnormalities including micro-calcification
    - Cryptorchid testis
    - History of testicular maldescent
    - Marked testicular atrophy or hypoplastic testis
    - Age > 30 years
- The orchidectomy specimen should be placed in an adequate volume (at least 5:1) of formaldehyde fixative.
- The specimen should be bivalved through the rete testis and epididymis either in theatre or as soon as it arrives in the pathology department in order to allow proper fixation.

Organ sparing surgery

- Although organ-sparing surgery is not generally indicated, it can be attempted in the following special situations with all the necessary precautions
    - in suspicion of a benign lesion
    - in synchronous, bilateral testicular tumours
    - in metachronous, contra lateral tumours, with normal preoperative testosterone levels
    - in a tumour in a solitary testis, with normal preoperative testosterone levels
- Counselling should be given about future radiotherapy / residual orchidectomy / GCNIS risk.
- The surgeon must biopsy seminiferous tissue around the lesion to establish the presence or absence of GCNIS Refs in EGCCCG Ann Oncol Paper (See Heidenreich et al)

Histopathologic diagnosis

- At least 1 block of tumour should be taken for each cm of maximum tumour dimension and blocks should be taken from the surrounding testis, the rete testis and adjacent epididymis, mid portion of cord and the resection margin of cord.
- Specimens should be reported according to the national guidelines produced by the Royal College of Pathologists (updated May 2014).
- Sample form included as appendix
- Histology should be classified and reported using the WHO 2016 terminology and snomed codes.
- Expert pathological review will be obtained on referral of the patient to the snMDT but will concentrate on confirmation of the diagnosis and does not replace the need for the local report.

Staging

- Patients may be referred to the snMDT without further staging
- If cross sectional imaging is requested by the local team, then it should include imaging of thorax abdomen and pelvis (CT preferable)

- Both the UICC TNM 7th ed and the RMH staging system will be used (tables 1 and 2)
- Patients with metastatic disease will also be assessed according to the IGCCCG prognostic group (table 3)
- Patients with Stage I disease will be further classified for risk of relapse as per Warde et al. 2002 {Warde, 2002 #14} and Hoskin et al. 1986 {Hoskin, 1986 #16}
    - Seminoma high risk features: size > 4cm; rete testis involvement
    - Non-seminoma high risk features: Lymphovascular invasion

Post-orchidectomy Labs and Rads on all patients

- FBC & differential
- U & E
- LFT's (+gammaGT)
- Baseline Testosterone
- Tumour Markers- HCG, AFP, LDH
- CT scan of chest, abdomen, and pelvis
- The CT scan should be performed according to a defined protocol and should be reviewed by a Radiologist experienced in the interpretation of germ cell tumour patients' investigations. Any previous radiology should also be reviewed by this Radiologist
- Ultrasound testes if not performed pre-operatively

Additional Staging

- CNS staging (Gadolinium-enhanced MRI) is indicated in patients with > 20 lung metastases or HCG>20,000
- Bone Scan – may be considered in patients with metastatic seminoma or with symptoms consistent with skeletal disease

Referral to snMDT

- All patients undergoing orchidectomy for suspected malignancy should be referred to the snMDT hosted at the Christie Hospital within 24 hours of surgery
- Patients should be referred to a named member of the snMDT

snMDT meeting

- All new cases will be reviewed at least once at the snMDT meeting (Christie Hospital, Wednesday 1pm).
- Uncomplicated cases will normally be reviewed post-orchidectomy once staging and pathological review is complete to formulate the post-orchidectomy treatment plan
- The responsible clinician should complete the snMDT request form and submit this to the MDT co-ordinator
- The responsible clinician (or a deputy who has physically assessed the patient) should attend the snMDT meeting to discuss the patient.
- Attendance through video link is acceptable e.g., for patients from LSCCN, Bolton and North Wales

Patient information

Patients will receive written information setting out the nature of their condition, and the treatment options available. Patients will also have access to and discussion with a specialist Urological cancer nurse as early as possible

during the course of their treatment. The patient's receipt of this information should be recorded in the patient's case notes.

Place of on-going further management

The following patients should be managed in the supraregional centre:

- Patients requiring post chemotherapy surgery (GCT 5)
- TYA patients 16 – 18 years 11 months should be managed at Primary Treatment Centre for TYA patients (Christie YOU)
- TYA patients 19 – 24 years 11 months should be offered unhindered access to PTC for TYAs

Table 1: UICC 7th Edition TNM staging for testicular tumours

pT	
pTx	Cannot be assessed (no orchidectomy)
pT0	No evidence tumour (Azopardi nodule)
pTis	"Carcinoma in situ" Note that the terminology has since been changed by WHO in 2016 to Germ cell neoplasia in situ GCNIS. This was also previously called intratubular germ cell neoplasia, unclassified type (IGCNU) and testicular intraepithelial neoplasia (TIN)
pT1	Limited to testis and epidydimis, No vascular or lymphatic invasion. May invade into tunica albuginea but not tunica vaginalis
pT2	Limited to testis and epidydimis with vascular or lymphatic invasion or extending through tunica albuginea into tunica vaginalis
pT3	Tumour invades spermatic cord with or without lymphatic / vascular invasion
pT4	Tumour invades scrotum with or without lymphatic / vascular invasion
N	
Nx	Cannot be assessed
N0	No regional lymph node metastasis
N1	LN mass < 2 cm or multiple small LN
N2	LN mass 2 – 5 cm or multiple LN none more than 5 cm
N3	LN mass > 5cm
M	
Mx	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases present
M1a	Non-regional nodal or lung metastases
M1b	Distant metastases other than non-regional nodal or pulmonary metastases
S	**Tumour markers**
SX	Marker studies not available or not performed
S0	Marker studies within normal limits
S1	LDH < 1.5 x ULN and hCG < 5000 and AFP < 1000
S2	LDH 1.5 – 10 x ULN or hCG 5000 – 50,000 or AFP 1000 – 10,000
S3	LDH > 10 x ULN or hCG > 50,000 or AFP > 10,000

Table 2: RMH Staging System for testicular cancer

I	No evidence of disease outside the testis
IM	As above but with **persistently** raised tumour markers (i.e., post op)
II	Infradiaphragmatic nodal involvement
IIA	Maximum diameter < 2 cm
IIB	Maximum diameter 2-5 cm
IIC	Maximum diameter > 5-10 cm
IID	Maximum diameter > 10 cm
III	Supra and infradiaphragmatic node involvement
	Abdominal nodes A, B, C, as above
	Mediastinal nodes M +
	Neck nodes N +
IV	Extralymphatic metastases
	Abdominal nodes A, B, C, as above
	Mediastinal or neck nodes as for stage 3
Lungs:	
L1	< 3 metastases
L2	Multiple metastases < 2 cm maximum diameter
L3	Multiple metastases > 2 cm in diameter
H+	Liver involvement
	Other sites specified

Table 3: IGCCC prognostic group

Teratoma (NSGCT)	Seminoma
Good prognosis	
Testis/retroperitoneal primary; no non-pulmonary visceral metastases;	Any primary site; no non-pulmonary visceral metastases;
AFP < 1000 ng/ml;, HCG < 5000 IU/l; and LDH < 1.5 x upper limit of normal.	Normal AFP; any HCG; any LDH
56% of teratomas: 5-year survival 92%	90% of seminomas: 5-year survival 86%
Intermediate prognosis	
Testis/retroperitoneal primary; no non-pulmonary visceral metastases	Any primary site; non-pulmonary visceral metastases
AFP > 1000 and < 10,000 ng/ml; HCG > 5000 and < 50000 IU/l; LDH > 1.5 x normal < 10 normal.	Normal AFP; any HCG; any LDH
28% of teratomas: 5-year survival 80%	10% of seminomas: 5-year survival 73%.
Poor prognosis	
Mediastinal primary or non-pulmonary visceral metastases AFP > 10,000 ng/L and/or HCG > 50,000 IU/l and/or LDH > 10 normal	No patients in this group
16% of teratomas: 5-year survival 48%	-

Appendix C Reporting proforma for testicular cancer (orchidectomy)

Surname..... Forenames..... Date of birth..... Sex.....

Hospital..... Hospital no..... NHS/CHI no.....

Date of receipt..... Report no..... Surgeon.....

Nature of specimen/procedure and core macroscopic items

Biopsy ☐ Right ☐ Radical orchidectomy ☐ Right ☐

Left ☐ Partial orchidectomy ☐ Left ☐

Tumour location .....

Tumour description .....

Macroscopic tunica vaginalis invasion: Yes ☐ No ☐ Not assessable ☐

Cord invasion: Yes ☐ No ☐ Not assessable ☐

Multifocality: Yes ☐ No ☐ Not assessable ☐

Maximum tumour size if assessable: ..... (mm)

Core microscopic items

1. Tumour typing – state percentage of each tumour element present

Tumour type/s (one or more)	**Germ cell tumour**	**%**	**Non-germ cell tumour**	
	Classical seminoma		Please specify	
	Embryonal carcinoma			
	Yolk sac tumour			
	Choriocarcinoma			
	Teratoma			
	Scar			
	Other			
	Please specify:.....			

TESTIS 1b: Germ cell neoplasia in situ (GCNIS)

Patient group

Patients diagnosed with GCNIS on biopsy of contralateral testis at time of orchidectomy

Inclusion criteria

- Histologically proven GCNIS

Exclusion Criteria

- None

Guidance.

Note that terminology has been changed by WHO in 2016 from "Intratubular germ cell neoplasia, unclassified type (IGCNU)" and also previously "Testicular intraepithelial neoplasia (TIN)" and "carcinoma in situ (CIS)".
Patients with biopsy-proven GCNIS of the contralateral testis should be counselled regarding the high lifetime risk of developing an invasive tumour if no further therapy is undertaken and the following options should be offered

Option 1: Testicular irradiation

Irradiation of the testis (dose: 18 Gy in 9 fractions or 20 Gray in 10 fractions at treating physician's discretion, over 2 weeks).

Option 2: Orchidectomy

Radical inguinal orchidectomy

- Patients should be counselled that options 1 and 2 will destroy potential residual fertility. If they have not already done so, sperm banking should be offered.

Option 3: Active surveillance

For patients wishing to attempt to father children, active surveillance can be undertaken with interval testicular ultrasound. Once family plans are complete then the patient can receive irradiation or orchidectomy

Other investigations

- None

Follow-up

As per primary tumour

TESTIS 2a: Active surveillance programme for stage I GCT testis

Introduction/Background

Approximately 80% of patients with testicular cancer present with clinical stage I disease and if no further therapy is given approximately 20% of these will relapse over the next 5 years due to micro-metastatic disease that is clinically undetectable at the time of presentation. If high risk features are present in the pathologic assessment, then the risk of relapse may be as high as 50%.

Management options include adjuvant therapy or follow-up without therapy with a view to chemotherapy for patients who relapse. Managed properly, long term disease specific survival is probably equivalent for either approach. Active Surveillance is the term used to indicate a careful programme of intensive follow-up designed to detect relapse early and to ensure compliance with the follow-up requirements.

Advantages of active surveillance include reducing exposure to toxic therapy to only those who need it (i.e., those who relapse) and thereby avoiding late effects of therapy in many patients.

Disadvantages include burden of clinic visits on the patient and the hospital, and increased exposure to diagnostic radiation.

Active surveillance in non-seminoma is much assisted by the likelihood that relapse will be detected first through monitoring of tumour serum markers. In seminoma, tumour serum markers are often not present and therefore there is more reliance on diagnostic imaging. In seminoma, relapse after 2 years is not infrequently seen, and this means that diagnostic imaging must be continued longer than is usually thought necessary in non-seminoma

Patient Group

Active Surveillance is currently considered the optimal management option for patients with the following characteristics:

- Germ cell tumour of testis
- Non-seminoma histology or mixed seminoma + non-seminoma confirmed on expert review or pure classical seminoma
- Stage 1 confirmed by radiology review at Christie
- Willing and able to comply with visit schedule

Initial investigations

- Full clerking
- Staging and work-up complete (see TESTIS 1a)

Non-seminoma and mixed histology germ cell tumour

Visit Schedule

- Monthly for year 1 (more frequently initially if has residual markers which are declining)
- Every 2 months in year 2
- Every 3 months in year 3
- Every 6 months to year 5 then discharge or
- Annually to year 10 then discharge

Screening at each clinic

- Directed H&P (including LN, abdomen, and testis)
- Blood draw for serum tumour markers AFT, b-HCG and LDH
- Plain X-ray of chest

Routine CT scans

- Chest abdomen and pelvis
- 3 Months post orchidectomy
- 12 months post orchidectomy

Seminoma

Visit schedule

- Every 3 - 4 months years 1 – 3
- Every 6 months years 4 – 7
- Annually years 8 – 10 then discharge

Screening at each clinic

- Directed H&P (including LN, abdomen, and testis)
- Blood draw for serum tumour markers AFT, b-HCG and LDH

Routine CT scans

- CT abdomen and pelvis
- Every 4 – 6 months in years 1 – 2 post-orchidectomy then every 6 months to year 7 then annually to year 10.
- CXR at alternate visits to year 8 then annually with CT

TESTIS 2b: Adjuvant carboplatin for stage I seminoma testis

Patient group

This regimen is available for the treatment of patients with non-metastatic primary germ cell testicular cancer seminoma sub-type.

Inclusion criteria

- Histologically proven seminoma testis
- Stage I on CT scan

Exclusion Criteria

- Severe pre-existing renal impairment (GFR < 40 ml/min)

Initial investigations and work up prior to start of chemotherapy

Diagnostic review

- All histology must be reviewed by nominated network histopathologists

Staging

- As per Testis 1a

Work-up

- Routine biochemistry, haematology, CXR, ECG
- GFR by isotope estimation, 24 hr urine collection for creatinine clearance or calculated GFR using Cockcroft-Gault formula
- Offer semen storage (requires HepB, HepC and HIV status)
- ECHO or MUGA only if clinically indicated
- Patient information sheet
- Indoctrinate patient regarding risks of chemotherapy and 24-hour telephone advice service.
- Informed Consent Form

Drugs and Doses

Starting doses

- Starting doses will be calculated according to renal function using the Calvert formula rounded to the nearest relevant unit of volume within 10% of calculated dose.
- Carboplatin AUC 7 single dose
- Capping: Dose will **not** be capped for tall / large, framed patients.

Cycle length

- N/A – single cycle only

Number of cycles

1

Additional medication

Combination anti-emetics with 5-HT3 antagonist and steroids will be given as per hospital anti-emetic protocol. Laxatives may be advisable to offset effect of 5-HT3 antagonist

G-CSF

G-CSF support is not routinely required for this regimen

Other

- Nil

Assessments

- Standard assessment on day 1 of chemo as for any patient receiving chemotherapy

Dose modifications

- N/A

End of treatment assessments

Tumour response assessment

- No routine response assessment by CT scan – only if concern regarding tumour progression (new symptoms or marker rise)

Routine clinic visit schedule

- 3 – 4 monthly year 1 - 2
- 6 monthly year 3 - 5
- then annually to year 10

Relapse monitoring

- Examine remaining testis, lymph nodes, chest, abdomen
- CXR and markers each visit
- CT scan chest abdomen and pelvis at 1, 2, 3, and 5 years post treatment

Late effects monitoring

- Repeat GFR within one year of completing chemotherapy.
- Fertility and gonadal function. Screen for gonadal failure if complaining of symptoms (excessive tiredness, loss of libido, impotence) FSH, LH, Testosterone, SHBG. Refer to endocrinology if hormone replacement indicated.

TESTIS 2c: Adjuvant RT for stage I seminoma testis

Background

Patients with Stage 1 Seminoma have between a 12 and 20% chance of harbouring metastatic disease in the para-aortic lymph nodes or elsewhere. Radiotherapy when given as adjuvant to orchidectomy for stage 1 seminoma of the testis decreases the relapse rate to 3 to 4%. MRC trial TE18 (together with the results of some patients entered into MRC study TE19 who were also randomised into TE18) has shown that 20 Gy in 10 daily fractions is effective in controlling the disease but with lesser morbidity than the previous 'standard' regime of 30 Gy in 15 fractions. Data from the Christie on an equally large cohort of patients, using 20 Gy in 8 fractions, confirms a relapse rate of 3.8%. An extension of the radiation field as a 'dog leg' in patients with ipsilateral iliac, inguinal, or scrotal violations can be considered but there is a lack of evidence for a different treatment outcome

Patient group

Patients with stage I seminoma, following orchidectomy

Inclusion criteria

- Histologically proven pure seminoma (mixed histology germ cell tumours of the testis will be managed on the non-seminoma pathways)
- Expert review of histology at Christie (or other) confirmed

Exclusion Criteria

- Scrotal surgery (e.g., scrotal orchidectomy)
- Prior abdominal radiotherapy
- Horseshoe kidney

Initial investigations and work up prior to start of treatment

- Check staging investigations complete
- No special work-up required

Patient information

- Patients will be given standard information in respect of radiotherapy. Acute and delayed effects will be discussed to include information about increased risk of second malignancy and mild effect on fertility. Sperm banking will be offered to all men who wish to retain fertility.

Treatment planning, delivery, validation etc

Standard institutional practice will be followed

Dose: 20 Gy in 10 fractions over two weeks.

Follow-up (TESTIS 2e)

Patients will be reviewed 6 -8 weeks following the end of treatment to ensure all side effects have resolved. Thereafter the follow up will be:

Year 1 3 monthly (Clinical review, CXR and markers)

Year 2 : 4 monthly (Clinical review, markers, annual CXR)

Year 3, 4 6 monthly (Clinical review, markers, annual CXR)

Year 5 - 10 12 monthly (Clinical review, markers, annual CXR)

Discharge thereafter.

TESTIS 2d: Adjuvant BEP for stage I non-seminoma testis

References

Cullen MH, Stenning SP, Parkinson MC, et al. Short course adjuvant chemotherapy in high-risk stage 1 non-seminomatous germ cell tumours of the testis: a Medical Research Council report. J Clin Oncol 1996, vol. 14; 4: 1106-1113

Rationale / Background / Introduction / Objectives

Approximately 60% of patients with non-seminoma germ cell cancer of testis present with stage 1 disease. The current approved supra-regional guideline on initial treatment for NSGCTT is radical surgery (orchidectomy) followed by an active surveillance programme (TESTIS 2a).
High-risk stage 1 NSGCTTs can be defined by the presence of microscopic evidence of invasion of testicular blood vessels and/or lymphatics by tumour cells within the orchidectomy specimen.
These patients have a risk of relapse of 40 – 50% and most will then be cured by 3 cycles of BEP (bleomycin, etoposide, cisplatin with 500mg/m2 of etoposide per cycle)
An alternative approach using adjuvant BEP (2 cycles with reduced dose of etoposide 360mg/m2) achieves the same outcome for those patients destined to relapse and avoids intensive surveillance but delivers 33% more chemotherapy cycles on a population basis.
It is the recommended treatment in the SIGN guidelines 1998 (Scotland), the COIN guidelines 2000 (England), the ESMO guidelines 2008 and the European Consensus Conference on Diagnosis and Treatment of Germ Cell Cancer 2008 (Europe), and the NCCN guidelines 2008 (USA).

LSCCN and GMCCN position on use of adjuvant chemotherapy for non-seminoma

On the basis of the current data and in the absence of further evidence in support of adjuvant chemotherapy for non-seminoma, the snMDT recommends that this treatment is NOT offered to patients except under exceptional circumstances which must be agreed in the snMDT meeting on a patient-by-patient basis.

GCT 4: First line chemotherapy with BEP for metastatic GCT

Patient group

This regimen is usually used for patients with metastatic primary germ cell testicular cancer and primary extra-gonadal germ cell tumours (mediastinal or retroperitoneal) and for patients with primary ovarian germ cell cancer.

Inclusion criteria

- Histologically proven germ cell tumours of testis (seminoma or non-seminoma) N+ or M+, good, intermediate, or poor prognosis
- **OR** Histologically proven extra-gonadal germ cell tumour (mediastinal or retroperitoneal)
- **OR** Any widespread malignancy with high B-HCG with or without histology particularly in a younger male patient
- **OR** selected patients with metastatic malignancy of unknown origin, undifferentiated with elevated AFP and no other cause for this found (e.g., Hepatocellular carcinoma) after discussion in the snMDT meeting

Exclusion Criteria

- Severe pre-existing renal impairment (GFR < 40 ml/min)

Initial investigations and work up prior to start of chemotherapy

Diagnostic review

- All histology must be reviewed by nominated network histopathologists for germ cell cancer

Staging

- As per TESTIS 1a

Work-up

- Routine biochemistry, haematology (inc coagulation), CXR, ECG
- PFT (if to have bleomycin)
- GFR by isotope estimation, 24 hr urine collection for creatinine clearance or calculated GFR using Cockcroft-Gault formula
- Audiometry
- Offer semen storage (requires HepB, HepC and HIV status)
- ECHO or MUGA only if clinically indicated
- Patient information sheet
- Indoctrinate patient regarding risks of chemotherapy and 24-hour telephone advice service.
- Informed Consent Form

Where hydronephrosis is present and / or renal function is low at presentation this should be aggressively including insertion of nephrostomy and/ or ureteric stent and consideration should be given to treatment with an initial cycle of lower intensity chemotherapy such as single agent carboplatin or carboplatin AUC3 + etoposide 100mg/m2 for 2 – 3 days to initiate response, after which, if renal function improves, full treatment with BEP should then be given. These regimens may also be considered

for patients presenting in extremis with large volume disease irrespective of renal function

Drugs and Doses

Starting doses

- Starting doses will be calculated according to body surface area and rounded to the nearest relevant unit of volume within 10% of calculated dose.
    - Bleomycin 30 iu (flat dose) ivb over 30 mins weekly to a maximum total dose of 270 iu (i.e maximum 9 doses). The dates of interval doses may be adjusted to conveniently fit appropriate OP clinics. Consideration of ***omitting*** bleomycin will be given in the following circumstances:
    - Patient over the age of 40 years
    - Heavy smoking history
    - Co-morbid pulmonary conditions
    - Extensive lung metastases
    - Pure seminoma (optional, at physician's discretion)
- Etoposide total dose 500 mg / m^2 per cycle
- Cisplatin total dose 100 mg/m^2 per cycle

Cycle length

- 21 days

Number of cycles

BEP

Good prognosis group: 3 cycles
Intermediate and poor prognosis: 4 cycles

EP

4 cycles will be given if bleomycin is omitted

Additional medication

Trust policy for control of chemotherapy induced nausea and vomiting will be followed Combination anti-emetics with 5-HT3 antagonist and steroids will be used from the outset.

G-CSF

G-CSF support should be used in this regimen in the following circumstances:

- Secondary prophylaxis. Where patients have had a neutropenic event requiring admission, doses should be maintained, and G-CSF support given with all subsequent cycles.
- Dose maintenance. Where patients fail to recover counts within 21 days had have a cycle affected by dose delay or dose reduction, subsequent cycles will be given with G-CSF support to allow full dose to be delivered on time.
- In the treatment of complicated febrile neutropenia. Any patient admitted with FN complicated by hypotension, renal dysfunction or any other features of shock should be immediately started on G-CSF (as well as full rescuscitation according to Hospital Febrile Neutropenia policy)

- G-CSF should be started not sooner than 24 hours after end of chemo and should not be continued within 48 hours of restarting myelosuppressive drugs (cisplatin and etoposide)
- Primary prophylaxis (i.e., treatment with first and all subsequent cycles) will only be used in exceptional circumstances
  - High biomedical risk: e.g., multiple co-morbidities; high burden of disease at presentation
  - High psycho-social risk: e.g., considered risk of non-compliance with hospital contact for febrile episodes

On treatment assessments

Tumour response assessment

- No routine in-treatment response assessment by CT scan – only if concern regarding tumour progression (new symptoms or marker rise)

Dose modifications

Haematologic toxicity

- Day 1 WBC < 1.5 OR platelets < 50: DELAY 4 days. (Nadir counts are non-contributory)
- Treatment may proceed on time if WBC > 1.5 and platelets > 50 on day 1 if neutropenia / thrombocytopenia is purely due to delayed marrow recovery. The following dose modifications will apply for one cycle ONLY.

BEP dose modifications on day 1 according to % starting dose

	Platelets > 100		Platelets 75 – 100		Platelets 50 – 74		Platelets < 50	
	Etop	Cisp	Etop	Cisp	Etop	Cisp	Etop	Cisp
WBC > 2	100%	100%	75%	100%	50%	100%	Delay ~4 days	
WBC 1.5 – 2	75%	100%	75%	100%	50%	100%		
WBC < 1.5	Delay ~4 days							

Non-haematologic toxicity

Renal function

GFR should be calculated according to Cockcroft method on day 1 of each cycle

- GFR > 40 ml/min: cisplatin full dose
- GFR< 40 ml/min: omit cisplatin and bleomycin this cycle. If GFR recovers to > 40 ml/min then continue cisplatin at 75% dose

Mucositis / Diarrhoea

Delay start of new cycle until <= grade 1

Bleomycin Toxicity

Mild acute allergic type reactions such as flushing, fever and chill, transient erythematous rash are not an indication to omit bleomycin. Future doses should be given more slowly with pre-medication with histamine antagonists (piriton 4mg ivb)
Skin pigmentation and nodules, and signs of pulmonary fibrosis are more serious and will probably mean that further bleomycin is omitted.

Neurotoxicity

Tinnitus and mild peripheral neuropathy are not indications to reduce cisplatin dose. Grade 3 or 4 neurotoxicity: discontinue cisplatin and further treatment will be decided by consultant.

Interval assessment (weekly bleomycin)

Patients may proceed with bleomycin if:

- Patient feels well in themselves
- Afebrile
- No allergic type reactions with previous dose of bleomycin
- No cough, sputum, wheeze, dyspnoea, haemoptysis, chest pain (pleuritic or otherwise)

Note: there are no critical laboratory indices that must be met to permit treatment with bleomycin. Patients may frequently be neutropenic at this point in the cycle. Bleomycin is not a myelotoxic drug and may be given despite neutropenia if the above criteria are met.

End of treatment assessments

Tumour Assessment

CT scans of chest, abdomen, and pelvis with iv and oral contrast will be performed between 6 - 8 weeks after day 1 of the last cycle of chemotherapy
Early scanning can lead to ambiguous results with regard to final response and is therefore advised against.

Follow-up

Routine clinic visit schedule

- q3/12 for 1st year
- q4/12 in year 2
- q6/12 in yrs 3-5
- then either discharge to GP or annually to year 10

Relapse monitoring

- Examine remaining testis, lymph nodes, chest, abdomen
- CXR and markers each visit

CT abnormalities

- Seminoma: most will resolve spontaneously, re-scan after interval. Cases where post chemotherapy residual masses > 3 cm should be reviewed at snMDT meeting
- NSGCT: All cases with post-chemotherapy residual masses will be discussed at the snMDT meeting for consideration of RPLND or thoracotomy for resection of lung metastases etc Post-chemo masses =< 1 cm will not usually be considered for resection but those >1 cm will. Each case will be assessed individually taking into account the characteristics, location and multiplicity of their disease.
- PET scan should be considered for all post chemotherapy residual masses > 3cm with a view to recommending RPLND for PET +ve masses including seminoma

Late effects monitoring

- Repeat PFT; audiometry and GFR within one year of completing chemotherapy.
- Fertility and gonadal function. Screen for gonadal failure if complaining of symptoms (excessive tiredness, loss of libido, impotence) FSH, LH, Testosterone, SHBG. Refer to endocrinology if hormone replacement indicated. Refer for semen analysis and IVF if required

GCT 5: RPLND for post-chemotherapy residual disease in metastatic GCT

Background

RPLND for metastatic teratoma in the North West UK will generally be performed at the supraregional centre – The Christie Hospital. Where supplementary surgery is required (e.g., vascular replacement, hepatic / pancreatic / duodenal resection, intra-cranial residual tumours etc) surgery may be performed at The Christie with support from relevant surgical teams (e.g. from the Thoracic surgical centre at UHSM) or at relevant surgical centre with support from the Christie team as deemed most appropriate.

The standard protocol in the UK is to carry out Retroperitoneal Lymph Node Dissection (RPLND) for residual post chemotherapy masses. If a major remission has occurred after chemotherapy and it is considered that a reasonable prospect for complete remission to occur with further resolution a further period of observation may be justified. If the testicular primary tumour has not been removed, this should be done at the time of the resection of residual masses.

Seminoma

More than 90% of seminoma patients will have fibrotic residual tissue after post-chemotherapy partial remission (PR) with normal markers (M-). Even if the residual tumour is > 3 cm in greatest transverse diameter, the probability of viable malignant tissue is < 20%. Hence, CT surveillance is treatment of choice in most patients with residual masses in seminoma.

Because of the fibrotic reaction, the complete resection of residual masses of seminomatous tumours is more demanding compared to non-seminoma and, thus, the morbidity of this procedure is higher.

In pure seminoma, retroperitoneal tumour resection (post-chemotherapy retroperitoneal lymph node dissection, PC-RPLND) is only indicated in patients with residual tumour progression after chemotherapy with marker normalisation where there is a suspicion of residual non-seminoma elements.

Non-Seminoma

In patients with NSGCT in the primary tumour and a residual mass post chemotherapy (greater than 1 cm) and marker normalisation, surgical resection (RPLND) is indicated except in specific circumstances (see above).

Overall, following BEP induction chemotherapy approx 10% of the residual masses contain viable cancer, 50% contain mature teratoma and 40% contain necrotic – fibrotic tissue. In this group of patients with residual masses - the “growing teratoma syndrome” is a significant future risk.

In general, all non-seminoma elements have the potential to de-differentiate to active teratoma, sarcoma or other aggressive malignancies and, thus, PC-RPLND in non-seminoma patients is mostly indicated. The de-differentiation to teratoma or sarcoma is chemoresistant and this type of disease may be surgically curable. Only patients with a complete remission after CT restaging may be treated with surveillance only.

Persistently elevated markers after salvage chemotherapy (two different cisplatin containing regimens) is not a contraindication for surgery. The prognosis in these patients can be poor. However, complete surgical resection of residual disease provides long-term

cure in up to 47% of patients. Poor prognostic parameters in these patients are multiple sites of residual disease and/or incomplete resections.

In patients with lower disease burden, nerve sparing techniques should be adopted by use of surgical templates. The German testis cancer group found 8% of patients with vital cancer or teratoma outside the residual mass within the surgical template and this compared favourably with US groups undertaking full bilateral RPLND. The side effects following template approaches are significantly lower. Hence, the standard treatment at The Christie is to carry out a right or left sided template dissection when the disease burden is confined to the nodal landing sites of the ipsi-lateral testis. Even in PC-RPLND, preservation of sympathetic nerves for antegrade ejaculation is possible. However, in nearly all published series patients have been selected to undergo a nerve-sparing PC-RPLND (e.g., unilateral disease only, low volume residual tumour) and therefore it follows that when there is more extensive disease the patients should undergo a full bilateral non nerve sparing procedure. Prior to surgery patients must be counselled fully about surgical risk and in particular, the risk of loss of ejaculatory function. In full bilateral PC-RPLND this will approach 100%. (refs EGCCCG Paper see Heidenreich / Albers (Europe) and Seinfield (US)

If residual tumour is present in the retroperitoneum as well as in the lungs, primary resection of the retroperitoneal disease is recommended as long as the volume of the pulmonary disease does not exceed the volume of the retroperitoneal disease. If the retroperitoneal disease shows necrotic tissue only, the same histology can only be expected in 70%. Thus, patients with fibrosis in the post RPLND specimen who have residual thoracic disease should be considered for resection of the thoracic lesions. However, if there are bilateral thoracic masses and after the first resection, the histology shows fibrosis, the second thoracic resection is not necessary as there is virtually 100% concordance with the presence of fibrosis on the opposite side.

After a complete resection of teratomatous tissue, no adjuvant treatment is necessary. Even with a complete resection of vital undifferentiated tumour there is no evidence that adjuvant conventional chemotherapy is beneficial.

Patients with a late relapse of testis cancer (> 2 years after complete remission) represent a subgroup of patients with a very poor prognosis. In 80% of these tumours, chemoresistant carcinoma is to be found. Hence, with chemotherapy only most patients will not survive, and the long-term survivors of late relapse are patients in whom it is possible to carry out a complete resection of all visible disease.

Surgical aspects of PC-RPLND

Most residual tumours are infrarenal and the best approach is the midline incision. In retrocrural tumours or tumours with a significant component above the renal vein, a thoracoabdominal incision with extension to the midline is recommended. Having gross disease on both sides of the great vessels below the level of the renal hilum, a “Chevron” incision is advisable.

The main principle of the PC-RPLND is not to go for the tumour first but to isolate the big vessels and the ureters. Split-and-roll preparation along the great vessels (by ligating the lumbar arteries and veins) is advisable to get clearance. The ureters are isolated and secured with vessel loops. Even if it seems that the ureter runs into the tumour it mostly

runs laterally and can be isolated. If the residual tumour is unilateral, the preservation of the sympathetic nerve fibres may be possible. They run from the spinal canals above the lumbar vessels on both sides of the aorta to the inferior hypogastric plexus.

In large volume disease, the division of the inferior mesenteric vein is recommended to better expose the left paraaortic region. The inferior mesenteric artery can be spared in many of the cases. Nephrectomy may be necessary to achieve a complete resection. This decision is mostly an intraoperative one. If the renal vein is completely compressed (and the kidney drains through collaterals) and if the renal artery is running straight through the tumour, it might be better to do a nephrectomy en bloc with main mass.

In some cases, multi-visceral resection is required. This may include major vessels, bowel, liver, and pancreas. Where vascular resection is needed it might be necessary to substitute the aorta, the iliac artery, or the vena cava. This is only necessary if vital cancer or teratoma cannot be completely resected off these vessels. If the vena cava is obstructed, it is usually bypassed by collaterals and a cava resection may be possible without caval replacement.

Patient group

- Patients with confirmed histological diagnosis of germ cell cancer metastatic to retroperitoneal LN, with post chemotherapy residual masses

Inclusion criteria

- Histologically germ cell tumours of the testis
- Expert review of histology by nominated germ cell histopathologst
- Post chemo residual masses > 1cm

Exclusion Criteria

- Elevated aFP or BHCG (such cases may be offered surgery on a case-by-case basis after discussion in snMDT meeting
- Prior abdominal radiotherapy (relative contra-indication)
- Severe co-morbidity which would lead to unacceptable operative risk
- Unresectable metastatic disease at other sites (relative contra-indication)

Initial investigations and work up prior to start of treatment

- Complete re-staging within 2 months of surgery date
  - CT scan chest abdo pelvis
  - Tumour serum markers (aFP, bHCG, LDH)
- Standard pre-operative work up
- MAG3 Radioisotope renogram

Patient information

Patient will be counselled on risk of:

- operative mortality
- post-operative complications
  - Wound infection
  - Sepsis
  - Dry ejaculation

Treatment planning, delivery, validation etc

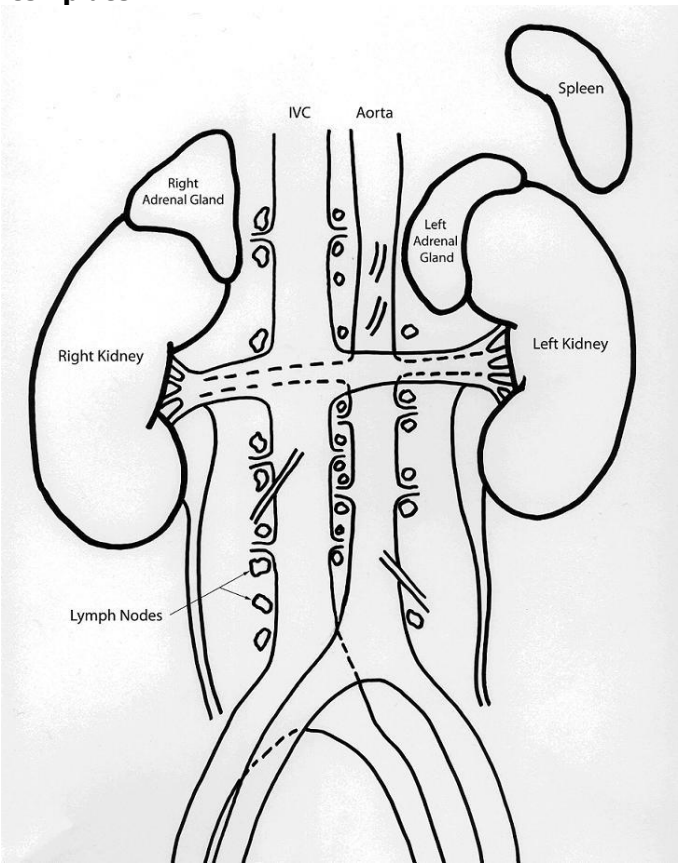
Timelines

- Final response assessment by CT should be no sooner than 6 weeks after last dose of chemotherapy
- RPLND should be performed within 6 weeks of the decision to operate
- Thoracic surgery (if required) should be performed within 3 months of end of chemotherapy

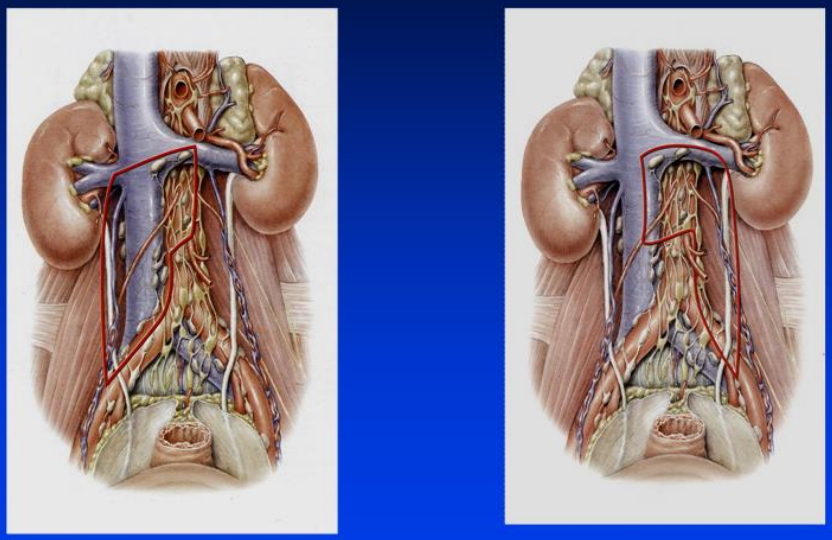
Surgery

Where small volume disease is present and template dissection will be performed as below:

Figure 1: RPLND template



Template Dissection



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Histopathological specimen handling and reporting of post chemotherapy specimens

Fixation and Macroscopy: The specimen should be immersed in an adequate volume of fixative (at least 5 times the specimen volume). Assuming the specimen is in one piece, inking the outer surface of mass lesion(s) is required prior to further dissection to assist with excision margin assessment. The specimen is described (tissues present, dimensions of the whole specimen(s), number of lymph nodes identifiable and the maximum dimension of the largest, dimensions and appearance of any lesion(s), including description of whether cystic and/or solid and mention of any obvious necrosis).

It is helpful to draw a diagram indicating where blocks are taken. Photographs (including cut surface) of lesions present may also be useful. At least 1 block per 10mm maximum dimension of any lesions should be taken, preferentially sampling any solid areas. A block key is essential, including (for any smaller lymph nodes) an indication of number of lymph nodes per cassette.

Microscopy: Patients with testicular non-seminomatous germ cell tumours may show metastases that either resemble the primary tumour or have different components from the primary tumour. The histological features of metastatic tumour in post-chemotherapy retroperitoneal lymph node dissection (RPLND) specimens are usually also modified by the effects of chemotherapy. The British classification of testicular germ cell tumours, as applied to primary testicular teratomas is applicable to the testicular primary tumour but is not used for metastatic teratomas. Instead, a description of the various elements present is given with some indication of their relative amounts. If there is viable metastatic non-seminomatous germ cell tumour (whether composed of differentiated or undifferentiated elements or a combination [either of which may also include elements listed in points 3-7 below]) in the retroperitoneum of a patient with a testicular primary, the case is reported as metastatic teratoma and the elements present are described. Terms such "mature cystic teratoma" or "benign cystic teratoma" should be avoided since this potentially leads to confusion with the common benign ovarian tumour of this name. The presence or absence of undifferentiated teratoma ('embryonal carcinoma') and/or yolk sac tumour should always be mentioned since the presence of these is an indication for further chemotherapy. Sometimes there is no viable tumour, only tissue showing coagulative necrosis and/or fibrosis/histiocytic reaction. In this situation the presence of coagulative necrosis should be mentioned with a comment that this may represent necrotic tumour, although this cannot be confirmed in the absence of any viable tumour.

Germ cell elements which may be present in RPLND specimens:

1. Metastatic differentiated ('mature') teratomatous elements (commonly cysts lined by differentiated glandular or squamous epithelium). This is by far the commonest finding in these specimens and may be accompanied by necrosis or (much less commonly) by undifferentiated teratoma ('embryonal carcinoma'). Various differentiated stromal tissues, including cartilage, may be present. Sometimes the cystic lining can show cytological atypia thought to be induced by chemotherapy. This atypia may be mentioned in the report but does not constitute undifferentiated teratoma. Although a RPLND may consist of only differentiated teratomatous elements, it is still regarded as a metastatic tumour (albeit one which usually has a prolonged natural clinical course and a good prognosis, amenable to surgical resection). They may impinge on vital structures (e.g., in the

mediastinum ('growing teratoma syndrome'). Karyotypic and ploidy studies have demonstrated that the differentiated epithelium present differs from entirely benign epithelium in other settings and there is always potential for more aggressive clones to develop with consequent progression.

2. Metastatic undifferentiated teratoma ('embryonal carcinoma'). The presence or absence of this should be stated in all reports. Its presence is an indication for further chemotherapy.

3. Metastatic yolk sac tumour. This almost invariably occurs in conjunction with other teratomatous elements, in particular, if present, is usually admixed with undifferentiated teratoma. It can be difficult sometimes to separate from undifferentiated teratoma morphologically. Immunohistochemistry is helpful if there is doubt (yolk sac tumour is negative for OCT3/4, whilst undifferentiated teratoma (and seminoma) is positive). There is evidence that the presence of yolk sac elements in metastatic lesions is an adverse prognostic feature (compared with undifferentiated teratatomatous elements alone), especially if incompletely excised. This is because yolk sac elements are said to be more resistant to chemotherapy.

4. Immature teratomatous elements. This is uncommonly present and is usually in the form of primitive stromal tissue, resembling that found in the developing foetus. Such immature stroma, in the context of a testicular tumour, usually shows a low proliferative index (unlike the undifferentiated highly malignant appearance of undifferentiated teratoma or yolk sac tumour). It is regarded as a low-grade tumour element which probably does not adversely affect prognosis if mixed with otherwise differentiated elements. A possible exception to this is the vanishingly rare occurrence of immature neuroepithelial elements and/or blastema (the latter resembling Wilms' tumour). These can be regarded as a high-grade immature element, though their significance as regards therapy and prognosis is undetermined from literature experience (due to the extreme rarity of this finding in RPNLD specimens from testicular tumour patients).

5. Metastatic choriocarcinomatous elements. This is rare. It may be mixed with other teratomatous elements. Choriocarcinoma may lack syncytiotrophoblastic cells in this setting and may be composed only of cytotrophoblast. Conversely, presence of isolated syncytiotrophoblastic giant cells (which occur, for example in classical seminoma) do not have adverse clinical significance. Metastatic choriocarcinoma would be an indication for salvage chemotherapy and its presence should always be mentioned.

6. The transformation of differentiated elements into somatic malignancies (carcinoma, sarcoma, lymphoma/leukaemia) although rare, must be identified, when present, as they will generally not respond to germ cell tumour therapy. Surgical resection with complete margins is indicated, where feasible.

7. Metastatic seminoma, either pure or mixed with non-seminomatous elements

In practice, undifferentiated teratomatous elements and/or seminoma tend to be very uncommon in these specimens because they tend to respond well to chemotherapy, unlike the more resistant elements (e.g., differentiated components).

Germ cell tumour may occasionally arise in the retroperitoneum as a primary and this possibility should be considered if there is no testicular lesion. Also bear in mind that sometimes a testicular primary may undergo regression, either spontaneously or chemotherapy-induced, although an area of necrosis or fibrous scarring is usually seen in the testis in such instances.

References:

Ulbright TM Neoplasms of the testis. In Bostwick DG and Eble JN Urologic Surgical Pathology. Mosby 1997 pp612-616.

Michael H, Lucia J, Foster RS, Ulbright TM. The pathology of late recurrence of testicular germ cell tumours. Am J Surg Pathol 2000; 24:257-273.

Parkinson MC, Harland SJ, Harnden P, Sandison A. The role of the histopathologist in the management of testicular germ cell tumour in adults. Histopathology 2001; 38:183-194.

Further explanatory notes:

In the context of testicular tumours, the term "teratoma" in American publications on testicular tumours (and their metastases) equates to differentiated teratomatous elements [if these are the only elements present in a testicular primary equates to teratoma differentiated (TD) in the British testicular tumour classification]. TD as a testicular primary is regarded as a malignant tumour with definite metastatic potential (except when arising in pre-pubertal boys when it has benign behaviour). TD in adults may metastasise as undifferentiated teratoma or may have a differentiated appearance in metastases.

"Embryonal carcinoma" equates to undifferentiated teratoma [if the only element present in a testicular primary equates to malignant teratoma undifferentiated (MTU) in the British testicular tumour classification]

Malignant teratoma intermediate (MTI) in the British testicular tumour classification refers to a *primary* testicular tumour with undifferentiated and differentiated elements, whatever what the relative proportions of each.

Malignant teratoma trophoblastic (MTT) in the British testicular tumour classification refers to a *primary* testicular tumour with biphasic syncytiotrophoblastic and cytotrophoblastic elements. American classifications refer to choriocarcinoma of testis.

Further management

Orchidectomy

- If orchidectomy has not already been performed this can be done prior to the RPLND when clinically indicated.
- The orchidectomy may be performed by either the patients local Urologist or the Christie Urology team as appropriate and after discussion with the patient.

snMDT review

- Cases will be reviewed pre-operatively at the snMDT meeting
- Cases will also be discussed at the snMDT meeting post-operatively once they have recovered from their surgery and pathology reports are available.

Where no immature elements are seen

The patient has a high chance of long-term relapse free survival and requires no further therapy (chemotherapy or radiotherapy) and should be offered clinical follow-up (see below)

Where immature elements are seen

The chance of long-term relapse free survival is low and further treatment needs to be considered. Options include:

1. Expectant management with salvage chemotherapy delayed until clinical relapse (marker or CT scan confirmed)
2. Immediate salvage chemotherapy

Follow-up

General

Clinical assessment should include BP monitoring

Surgical follow-up

Patients will be seen at 6 weeks post-op to check on wound healing and ensure there are no immediate post-operative problems.
Following this they may be discharged to the treating oncology team for ongoing follow-up

Oncology follow-up

Follow up will be directed at screening for relapse and managing any on-going medical issues from oncological therapies given.

GCT 7: Salvage therapy for relapsed metastatic GCT after first line chemo: TIP Regimen

References

Motzer, Sheinfeld et al. 2000; Kondagunta, Bacik et al. 2005; Mead, Cullen et al. 2005

Kondagunta, G. V., J. Bacik, et al. (2005). "Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors." J Clin Oncol 23(27): 6549-55.

Mead, G. M., M. H. Cullen, et al. (2005). "A phase II trial of TIP (paclitaxel, ifosfamide and cisplatin) given as second-line (post-BEP) salvage chemotherapy for patients with metastatic germ cell cancer: a medical research council trial." Br J Cancer 93(2): 178-84.

Motzer, R. J., J. Sheinfeld, et al. (2000). "Paclitaxel, ifosfamide, and cisplatin second-line therapy for patients with relapsed testicular germ cell cancer." J Clin Oncol 18(12): 2413-8.

Patient group

This regimen is for patients with metastatic primary germ cell testicular cancer and primary extra-gonadal germ cell tumours (mediastinal or retroperitoneal) and for patients with primary ovarian germ cell cancer who have relapsed after initial chemotherapy with BEP.

Use in second line

TIP is an internationally recognised option for use in second line i.e., for relapse following BEP chemotherapy. This is its main indication

Use in first line

TIP may be considered as the preferred chemotherapy regimen in first line for patients where there are concerns regarding the use of Bleomycin. In this case, the options are either to use EP (5) or consideration may be given to using TIP. Situations where Bleomycin may be contra-indicated include significant pre-existing pulmonary co-morbidity; widespread pulmonary metastases; intercurrent pulmonary infection or haemorrhage

Inclusion criteria

- Histologically proven germ cell tumours of testis (seminoma or non-seminoma) N+ or M+, good, intermediate, or poor prognosis
- **OR** histologically proven extra-gonadal germ cell tumour (mediastinal or retroperitoneal)
- **OR** Any widespread malignancy with high B-HCG with or without histology particularly in a younger male patient
- **OR** selected patients with metastatic malignancy of unknown origin, undifferentiated, with elevated AFP and no other cause for this found (e.g., Hepatocellular carcinoma) after discussion in the snMDT meeting

Exclusion Criteria

- Severe pre-existing renal impairment (GFR < 50 ml/min)

Anticipated benefit

Good risk patients defined as (MSKCC)

- Testicular primary
- AND
- CR at end of primary therapy (including with surgery)

Poor risk patients

- Non testicular primary
- OR
- IR (incomplete) at end of primary therapy
- OR
- Late relapse (> 2years after end of treatment)

	N	Dose mg/m2	CR	PR	PD	ORR	mTTP	OS
Motzer / Kondagupta (All good risk)	46	T 250 I 6000 P 100	63%	37%	0%	100%	2 yr PFS 65%	2 yr OS 78%
Mead	43	T 175 I 5000 P 100	19%	73%	9%	92%	1 yr FFS 38%	1 yr OS 70%
Mead Good Risk	26		27%	66%	8%	93%	1 yr FFS 43%	1 yr OS 81%
Mead Poor Risk	17		6%	82%	12%	90%	1 yr FFS 29%	1 yr OS 53%

Expected toxicity

Toxicity	CTC G3 – 4
Alopecia	100%
Neutropenia	70%
Thrombocytopenia	35%
Febrile neutropenia	30%
CINV	
Fatigue	
Neurotoxicity	7%
Renal toxicity	7%
Haematuria	
Encephalopathy	
Toxic death	2%

Initial investigations and work up prior to start of chemotherapy

Indications for biopsy

Tissue diagnosis will usually be available from orchidectomy. Situations where orchidectomy has not been done would include extra-gonadal primary tumour (retroperitoneum or mediastinum) and patients presenting with over-whelming disease unfit for surgery. In these situations, a percutaneous needle biopsy (18G at least) should be performed unless: the clinical diagnosis is not in doubt (on the basis of age, clinical

pattern of disease and markedly elevated AFP/ HCG) AND delay in treatment from obtaining a biopsy may put the patient at risk of further deterioration.

Diagnostic review

- All histology must be reviewed by nominated network histopathologists for GCT

Staging

- As per Testis 1a

Work-up

- Routine biochemistry, haematology (inc coagulation), CXR, ECG
- GFR by isotope estimation, 24 hr urine collection for creatinine clearance or calculated GFR using Cockcroft-Gault formula
- Audiometry (optional)
- Offer semen storage (requires HepB, HepC and HIV status)
- ECHO or MUGA only if clinically indicated
- Patient information sheet
- Indoctrinate patient regarding risks of chemotherapy and 24-hour telephone advice service.
- Informed Consent Form

Drugs and Doses

Starting doses

- Starting doses will be calculated according to body surface area and rounded to the nearest relevant unit of volume within 10% of calculated dose.
- Paclitaxel 175 – 250 mg / m^2 Day 1
- Ifosfamide 1200 mg / m^2 Days 1 – 5
- Cisplatin 20mg / m^2 IVI Days 1 – 5

Cycle length

- 21 days

Number of cycles

- Generally, aim for 4 cycles.
- Cycles beyond #4 can be considered if:
  - Paclitaxel dose was reduced to 175mg/m2 and or
  - Continuing to respond by markers or imaging at #4 and able to tolerate more
  - Poor prognosis relapse and able to tolerate more

Additional medication

Anti-emetics

Combination anti-emetics with 5-HT3 antagonist and steroids will be used from the outset.
Trust anti-emetic policy will be followed

G-CSF

G-CSF support should be used in this regimen in the following circumstances:

- Primary prophylaxis. All patients should receive G-CSF from the first cycle and with each subsequent cycle
- In the treatment of complicated febrile neutropenia. Any patient admitted with FN complicated by hypotension, renal dysfunction or any other features of shock should be immediately started on G-CSF (as well as full rescuscitation according to Hospital Febrile Neutropenia policy)
- G-CSF should be started not sooner than 24 hours after end of chemo and should not be continued within 48 hours of restarting myelosuppressive drugs (paclitaxel, cisplatin and ifosfamide)

On treatment assessments

Tumour response assessment

- No routine in-treatment response assessment by CT scan – only if concern regarding tumour progression (new symptoms or marker rise)

Dose modifications

Haematologic toxicity

- Day 1 WBC < 1.5 OR platelets < 50: DELAY ~4 days. (Nadir counts are non-contributory)
- Treatment may proceed on time if WBC > 1.5 and platelets > 50 on day 1 if neutropenia / thrombocytopenia is purely due to delayed marrow recovery. The following dose modifications will apply for one cycle ONLY.

Non-haematologic toxicity

Renal function

GFR should be calculated according to Cockcroft method on day 1 of each cycle

- GFR > 40 ml/min: cisplatin full dose
- GFR< 40 ml/min: omit cisplatin. If GFR recovers to > 40 ml/min then continue cisplatin at 75% dose

Mucositis / Diarrhoea

Delay start of new cycle until <= grade 1

Neurotoxicity

Tinnitus and mild peripheral neuropathy are not indications to reduce cisplatin dose. Grade 3 or 4 neurotoxicity: discontinue cisplatin and further treatment will be decided by consultant.

Consultant review on treatment

- All patients will be reviewed by consultant on each admission

End of treatment assessments

Tumour Assessment

CT scans of chest, abdomen, and pelvis with iv and oral contrast will be performed between 6 - 8 weeks after day 1 of the last cycle of chemotherapy

High dose chemotherapy

Consideration should be given to consolidating good response in salvage chemotherapy with high dose chemotherapy usually using the CarboPEC regimen. This would be most suitable for patients who have a good response to salvage chemo and are marker negative.

Follow-up

Routine clinic visit schedule

- q3/12 for 1st year
- q4/12 in year 2
- q6/12 in yrs 3-5
- then either discharge to GP or annually to year 10

Relapse monitoring

- Examine remaining testis, lymph nodes, chest, abdomen
- CXR and markers each visit

CT abnormalities

- All cases with significant (> 1 cm) post-chemotherapy residual masses will be presented at the snMDT meeting for consideration of surgical resection.

Late effects monitoring

- Repeat PFT ; audiometry and GFR within one year of completing chemotherapy.
- Fertility and gonadal function. Screen for gonadal failure if complaining of symptoms (excessive tiredness, loss of libido, impotence) FSH, LH, Testosterone, SHBG. Refer to endocrinology if hormone replacement indicated. Refer for semen analysis and IVF if required

GCT 8: Palliative chemotherapy for relapsed metastatic GCT after salvage chemo

References

Gemcitabine and Oxaliplatin (GEMOX) in patients with cisplatin-refractory germ cell tumors: a phase II study Pectasides et al Annals of Oncology 15: 493 – 497 2004

Patient group

This regimen is for patients with metastatic primary germ cell testicular cancer and primary extra-gonadal germ cell tumours (mediastinal or retroperitoneal) and for patients with primary ovarian germ cell cancer who have relapsed after two platinum containing regimens (usually BEP and TIP) and are considered refractory to curative therapy.

Inclusion criteria

- Histologically proven germ cell tumours of testis (seminoma or non-seminoma) N+ or M+, good, intermediate, or poor prognosis
- **OR** Histologically proven extra-gonadal germ cell tumour (mediastinal or retroperitoneal)
- **OR** Any widespread malignancy with high B-HCG with or without histology particularly in a younger male patient
- Previous chemotherapy two previous lines of platinium containing chemotherapy

Exclusion Criteria

- Severe pre-existing renal impairment (GFR < 50 ml/min)

Anticipated benefit

This is non-curative therapy will approx 35 % chance of patient benefit with temporary partial response which may be associated with improved quality of life and modest improvement in survival

Expected toxicity

- Neurotoxicity: peripheral neuropathy
- Myelosuppression
- Fatigue
- Flu-like symptoms

Initial investigations and work up prior to start of chemotherapy

Diagnostic review

- All histology must be reviewed by nominated network histopathologists for GCT

Staging

- As per Testis 1a

Work-up

- Routine biochemistry, haematology (inc coagulation), CXR, ECG
- GFR by isotope estimation, 24 hr urine collection for creatinine clearance or calculated GFR using Cockcroft-Gault formula

- ECHO or MUGA only if clinically indicated
- Patient information sheet
- Indoctrinate patient regarding risks of chemotherapy and 24-hour telephone advice service.
- Informed Consent Form

Drugs and Doses

Starting doses

Gemcitabine 1000mg /m2 ivi over 30 mins Day 1 and 8
Oxaliplatin 130mg/m2 ivi over 120 mins Day 1

Cycle length

- 21 days

Number of cycles

- 6 – 8 cycles or until tumour progression

Additional medication

Anti-emetics

Combination anti-emetics with 5-HT3 antagonist and steroids will be used from the outset.
Trust anti-emetic policy will be followed

G-CSF

G-CSF support is not routinely advised in this regimen and will be at the treating clinician's discretion.

On treatment assessments

Tumour response assessment

- Response assessment is advised every 9 weeks

End of treatment assessments

Tumour Assessment

CT scans of chest, abdomen, and pelvis with iv and oral contrast will be performed between 6 - 8 weeks after day 1 of the last cycle of chemotherapy

Follow-up

Patients will be followed up indefinitely in the expectation of tumour progression and palliative care

GCT 9: High dose chemotherapy for GCT

References

Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database. Lorch A, Bascoul-Mollevi C, Kramar A, Einhorn L, Necchi A, Massard C, De Giorgi U, Fléchon A, Margolin K, Lotz JP, Germà-Lluch JR, Powles T, Kollmannsberger C, Beyer J.
J Clin Oncol. 2011 Jun 1;29(16):2178-84. doi: 10.1200/JCO.2010.32.6678. Epub 2011 Mar 28.

Patient group

The use of high dose (bone marrow ablative) chemotherapy for patients with germ cell cancer is controversial. A recently published analysis reviewed 1,984 patients with GCTs who experienced progression after at least three cisplatin-based cycles and were treated with either cisplatin-based CDCT or carboplatin-based HDCT chemotherapy at 38 centers or groups worldwide. Of 1,984 patients, 1,594 (80%) were eligible, and among the eligible patients, 1,435 (90%) could reliably be classified into one of the following five prognostic categories based on prior prognostic classification: very low (n = 76), low (n = 257), intermediate (n = 646), high (n = 351), and very high risk (n = 105). Within each of the five categories, the progression-free survival (PFS) and overall survival (OS) after CDCT and HDCT were compared using the Cox model adjusted for significant distributional differences between important variables. The results showed that overall, 773 patients received CDCT, and 821 patients received HDCT. Both treatment modalities were used with similar frequencies within each prognostic category. The hazard ratio for PFS was 0.44 (95% CI, 0.39 to 0.51) stratified on prognostic category, and the hazard ratio for OS was 0.65 (95% CI, 0.56 to 0.75), favoring HDCT. These results were consistent within each prognostic category except among low-risk patients, for whom similar OS was observed between the two treatment groups. In conclusion, this retrospective analysis suggests a benefit from HDCT given as intensification of first salvage treatment in male patients with GCTs.

Inclusion criteria

- Histologically proven germ cell cancer any site
- **AND**
- Confirmed relapse on markers or imaging after first line chemotherapy
- **AND**
- Demonstrated evidence of chemosensitive disease as shown by complete or good partial response on markers and imaging to a standard second line regimen
- **AND**
- Renal and liver function within acceptable parameters

Exclusion Criteria

- Evidence of progressive tumour growth despite re-induction chemotherapy
  - Rising markers
  - New or growing metastases on imaging

Anticipated benefit

Expected toxicity

Initial investigations and work up prior to start of chemotherapy

Diagnostic review

- All histology must be reviewed by nominated network histopathologists for GCT

Staging

- As per Testis 1a

Work-up

- Routine biochemistry, haematology (inc coagulation), CXR, ECG
- GFR by isotope estimation, 24 hr urine collection for creatinine clearance or calculated GFR using Cockcroft-Gault formula
- ECHO or MUGA only if clinically indicated
- Patient information sheet
- Indoctrinate patient regarding risks of chemotherapy and 24-hour telephone advice service.
- Informed Consent Form

Drugs and Doses

CarboPEC regimen

Starting doses

Carboplatin (dose adjusted to GFR)
Etoposide 1.8g/m2
Cyclophosphamide 6.4 g / m2

Cycle length

- 21 days

Number of cycles

- Single or tandem transplant

Additional medication

-

On treatment assessments

Tumour response assessment

-

End of treatment assessments

-

Tumour Assessment

Follow-up

Patients will be followed up indefinitely in the expectation of tumour progression and palliative care

Appendix 3

Penile Cancer Guidelines

North West & North Wales Cancer Networks' Clinical and Referral Guidelines for Penile Cancer

(Diagnosis, Assessment and MDT Discussion)

2019-2020

Supranetwork Penile Cancer Guidelines

SERVICE OBJECTIVES

The objectives of concentrating this care into the hands of the Specialist Penile Team are:

- To ensure that designated specialists work effectively together in the team such that decisions regarding all aspects of diagnosis, treatment and care of individual patients and decisions regarding the team's operational policies are multidisciplinary decisions.

- To ensure that care is given according to recognised guidelines (including guidelines for onward referrals) with appropriate information being collected to inform clinical decision-making and to support clinical governance/audit.

- To ensure that mechanisms are in place to support entry of eligible patients into clinical trials, subject to patients giving fully informed consent.

1 ORGANISATION

1.1 The Supranetwork multidisciplinary team for penile cancer is based upon the specialist urological team at Christie Hospital NHS Foundation Trust.

1.2 The team delivers Supranetwork care to Lancashire & South Cumbria, Greater Manchester & Cheshire, Merseyside & Cheshire, and North Wales - a population of 7.8m.

1.3 The team members will deliver all of the care, including local and specialist care, to at least part of their own cancer networks for the local catchment of their host locality.

1.4 For the team to add their full potential value to patient care, the supranetwork surgical procedures and their immediate post-op care are required to be restricted to certain named hospitals.

- **Christie Hospital**

1.5 The host hospital for the Supranetwork MDT is Christie Hospital NHS Foundation Trust.

2 PENILE CANCER SUPRANETWORK & SPECIALIST CARE REFERRAL/CLINICAL GUIDELINES

(Clinical and referral guidelines for penile cancer - diagnosis, assessment & MDT discussion)

2.1 **Local care** is classed as:

The diagnostic process only.

Local care will be carried out by local teams for their catchment. It will also be carried out by specialist teams and the supranetwork team for the local catchment of their host locality.

2.2 **Local and specialist care MDTs**

Local care

Is any diagnostic procedure only. (See section 2.4.4)

Specialist care penile lead:

Lead for an individual network
Manage patients unwilling to travel/infirm
No penile preserving surgery/lymph node surgery
May wish to work within the supra-network centre

2.3 **Specialist Supra-Network care (SnMDT)** is classed as:

2.3.1 **All Resections**. All resections should be carried out by the named supra-network hospital specialist team at The Christie NHS FT. (See Appendix C).

2.3.2 **Radiotherapy and chemotherapy**.
Radiotherapy will be carried out at The Christie NHS FT, Clatterbridge Centre for Oncology NHS FT and Lancashire Teaching Hospitals NHS Trust.
Chemotherapy will be carried out in appropriate facilities, approved by the SMDT, throughout the Networks.

2.3.3 Specialist care will be carried out by the Supranetwork team members for the local catchment of their host locality.

2.3.4 Specialist care will only be carried out by teams designated as specialist teams within each Network.

2.3.5 It will not be delivered by local urology teams in any of the Networks across the North West and Wales.

2.3.5 All penile cancer cases should be discussed with the Supranetwork team prior to proposed treatment if not referred directly to that team.

2.3.6 The Specialist MDTs will agree a policy whereby patients with early (stage 1) penile cancer should be offered the option of a joint meeting with the surgeon, oncologist, and specialist nurse to discuss treatment options prior to deciding which modality of treatment to use. It is understood that the preferred recommended treat for the Primary lesion is now surgical.

2.4 Supranetwork Care - Referral to Supra-Network MDT (SnMDT)

Supranetwork care is classed as:

2.4.1 All Resections, including cases needing penile reconstruction or lymph node resection. All resections will be carried out at The Christie. All such operations will be delivered by the ***Supranetwork team*** *listed in section 6 below.*

2.4.2 The treatment planning decisions on patients with penile cancer will be made by the Supranetwork penile cancer team during the regular weekly meetings at Christie Hospital, as and when those patients are referred.

2.4.3 The Supranetwork MDT at their regular meetings will agree and record patients' diagnosis and subsequent treatment plans. The record should include:

- The identity of patients discussed.
- The diagnosis.
- The multidisciplinary treatment planning decision i.e., to which modalities of Supranetwork or specialist care (surgery, radiotherapy, chemotherapy), they are to be referred for consideration.

2.4.4 **Referral to Supranetwork Team**

Any suspected penile cancer seen by a consultant urologist can be referred without histological diagnosis or staging investigations directly to the department.

Any suspected penile cancer or pre-malignant lesion referred to a consultant urologist via a dermatologist or genito-urinary medicine physician with histological diagnosis can be referred directly to the department without further investigation.

Any suspected penile cancer that becomes apparent at the time of a circumcision could be referred directly without histology results.

Any patient with a suspicious but not diagnostic lesion should have a generous deep biopsy for confirmation. Scrapings and/or punch biopsies are not usually adequate in these cases. Patients can be referred directly to the SnMDT for this if it is felt it will help the patient pathway.

Patients who are deemed unfit to travel or are unwilling to travel for whatever reason could be discussed directly with the consultant in charge and the supra regional MDT and advice given accordingly.

It is not mandatory to arrange further staging investigations; however, if imaging has been performed and/ or arranged this information should be sent with the referral.

The referral should be done by Fax and post. It should include patient details, clinical findings, and appropriate histology report if available. The referral should be made directly to one of the Lead Clinicians for Penile Cancer within the Cancer Network.

Fax Numbers:
Christie Hospital NHS Foundation Trust
0161 446 3352 or 3365

Wirral University Teaching Hospitals NHS Trust
0151 604 7481

2.4.5 Upon referral the patient should be seen in an outpatient clinic designated for Penile Cancer. A history and examination will be undertaken followed by an appropriate discussion regarding treatment. The treatment plan will subsequently be discussed between surgeon, oncologist and nurse specialist and further appointments arranged, as necessary. The appropriate Patient information booklets will be offered to each patient.

2.4.6 The patient will be discussed at the SnMDT. The Lead Clinician or designated cover, with the Nurse specialist will co-ordinate the discussion on each case.

2.4.7 The pathology should be reviewed at the SnMDT. Provision to obtain slides will be initiated at the time of receiving a referral. At this point the receiving clinician should inform the SnMDT Pathologist of this need, by fax / letter.

2.4.8 A decision should be made at that SnMDT as to whether the treatment plan is appropriate. The decision of the MDT will be relayed to the patient. If the plan is altered the patient will be informed accordingly.

2.5 Follow up care site

The primary treatment of penile cancer can cause significant psychological distress. In addition, follow-up treatments may be needed. Patients should be followed in a dedicated penile cancer clinic within the networks host hospital (in respect of MCN, patient may be followed up at Arrowe Park, within a designated facility).

3. Diagnosis & Assessment

3.1 Primary lesion

Patients should undergo history and physical examination. This should include medical/surgical history and risk factors. The examination should record:

i. Size
ii. Location
iii. Number of lesions
iv. Morphology
v. Relation to adjacent structures (corpora/urethra)

Cross-sectional imaging (MR with PGE1 or CT)) may be used to assess the lesion and its stage. The purpose is to obtain as much information as possible regarding the grade and stage of the cancer in order to select the most appropriate treatment. Clinical photographs may be taken with patient consent in order to maintain a record of pre- and post-operative appearances and to facilitate audit.

3.2 Regional nodes

Inguinal nodes should be examined carefully. Note:

i. **Non palpable nodes**. In Intermediate and high-risk disease, it is appropriate to undertake Ultrasound scan (with or without Fine Needle Aspiration Cytology) and offer Dynamic Sentinel node biopsy. Prophylactic groin node dissection is recommended only in mitigating circumstances.

ii. **Palpable nodes**. On examination note size, position, number, fixation, relationship, and oedema. In this scenario histological examination using FNA or core biopsy can be undertaken. In cases where this is negative, excision biopsy can be undertaken. In appropriate cases where there are palpable nodes with negative histology/cytology, these can be re-assessed 4-6 weeks after surgery.

3.3 Distant metastasis

Patients with palpable nodes should undergo MR/CT scan of the chest, abdomen, and pelvis. In patients with bone pain a bone scan is indicated.

3.4 Staging

TNM Staging 8th Edition (2017)

Primary tumour (T)

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ (PeIN)
Ta* Non-invasive localised squamous cell carcinoma*
T1a Tumour invades subepithelial connective tissue** without lymphovascular invasion or perineural invasion and is not poorly differentiated (i.e., grade 3 or sarcomatoid)
T1b Tumour invades subepithelial connective tissue** with lymphovascular invasion or perineural invasion or is poorly differentiated
T2 Tumour invades corpus spongiosum with or without invasion of the urethra
T3 Tumour invades corpus cavernosum
T4 Tumour invades other adjacent structures

*Including verrucous carcinoma. The author's view is that the category Ta is to be used with care as these tumours are exceptionally rare and are not evidence based

**Glans: Tumour invades lamina propria.
Foreskin: Tumour invades dermis, lamina propria or dartos fascia.
Shaft: Tumour invades connective tissue between epidermis and corpora and regardless of
location.

Regional lymph nodes (N)

Clinical stage definition

cNX Regional lymph nodes cannot be assessed
cN0 No palpable or visibly enlarged inguinal lymph nodes
cN1 Palpable mobile unilateral inguinal lymph node
cN2 Palpable mobile multiple or bilateral inguinal lymph nodes
cN3 Palpable fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral

Pathologic stage definition

pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in up to two regional lymph nodes
pN2 Metastases in three or more unilateral lymph nodes or bilateral inguinal lymph nodes
pN3 Extranodal extension of lymph node metastasis or pelvic lymph node(s), unilateral or bilateral

Distant metastasis (M)

M0 No distant metastasis (clinical category only)
M1 Distant metastasis – includes lymph node metastasis outside of the true pelvis in addition to visceral or bone sites

P16 immunohistochemical status should be recorded

4 Treatment

4.1 Primary lesion (see Appendix A)

4.1.1 PeIN

In penile intraepithelial neoplasia an organ preservation technique is advised and includes

- Circumcision – should be considered in most cases as adjunct to topical therapies
- Topical Imiquimod (5%)
- 5-Fluorouracil (5-FU) cream
- CO2 laser ablation
- Glans resurfacing

Other therapies should be done in a trial setting only. Pathological margins should be studied in surgical cases.

4.1.2 Surgery

Organ sparing surgery has been shown to significantly improve quality of life following treatment for penile cancer compared to amputation. There is however an increased risk of local recurrence. Despite this increase in local recurrence compared to amputation there was no significant disease specific survival between the 2. Therefore, penile preserving surgery should be considered in cases where this is feasible. Individual patient circumstances may however favour amputation even if penile preservation would be technically possible.

Appropriate penile reconstruction should be considered.

Penile preserving surgery may include:

Wide local excision
Total glansectomy
Partial glansectomy
Distal Urethrectomy

If penile preserving surgery not technically feasible or not considered appropriate, then partial or total amputation of the penis is appropriate.

In total amputation will need to consider urinary diversion technique; perineal urethrostomy, long term suprapubic catheterisation.

4.1.2 Radiotherapy

Radiotherapy can be considered in lesions <4 cm and not invading the corpora cavernosa (<T3)

4.2 Regional nodes (see appendix B)

Regardless of the treatment modality of the primary lesion all patients should undergo lymph node management.

4.2.1 Non palpable nodes

The three risk groups for nodal disease are

i. Low (Tis, TaG1-2 and T1aG1-2) risk less than 2%. In these cases, surveillance should be undertaken.

ii. Intermediate (T1bG3) risk up to 12%. The risk is greater in cases of lymphatic and vascular invasion and also in those with infiltrative growth patterns. USS +/- FNA and Dynamic sentinel node biopsy should be undertaken, with completion standard or video-endoscopic inguinal lymph

node dissection in positive cases. In negative cases following DSNB surveillance should be initiated.

iii. High (≥T1G3) risk up to 23%. In these cases, USS +/- FNA and Dynamic sentinel node biopsy should be undertaken with completion standard or video-endoscopic inguinal lymph node dissection in positive cases. In negative cases following DSNB surveillance should be initiated.

iv. In patients with high surgical risk surveillance may be considered instead.

v. In patients with suspicious ultrasound appearances but negative cytology, consider intraoperative ultrasound guided excision node biopsy in conjunction with standard DSNB.

4.2.2 Palpable nodes

In these cases, FNA cytology or core-needle biopsy should be considered. If negative it may be repeated or excision biopsy should be done. In positive cases or concern over palpable nodes, a standard lymphadenectomy should be undertaken

Contra-lateral inguinal regions with no palpable nodes should be assessed as in 4.2.1.

If more than two nodes are found to be positive in one groin or there is extra capsular disease, then the risk of pelvic nodal disease is up to 40%. In this group five-year survival may be very poor. A pelvic/abdominal MR/CT scan should be undertaken. In cases where no pelvic nodes are identified then pelvic lymphadenectomy (ipsilateral) should be considered. Pelvic radiotherapy can be considered as an alternative.

Inguinal radiotherapy may be considered in N2-3 patients. In selected patients' adjuvant EBRT/ChemoRT or Chemotherapy may be offered.

If positive nodes are found at pelvic lymphadenectomy, or obvious radiological involvement then adjuvant chemotherapy may be considered, preferably within the trial setting.

In cases of fixed inguinal nodes chemotherapy can be considered followed by lymphadenectomy. Chemotherapy, radiotherapy or

chemoradiotherapy may be offered, preferably within the trial setting.

In cases of palpable nodes noted during follow-up then treatment should be directed as above. If there has been a long interval then unilateral lymphadenectomy can be considered, although the risk of bilateral disease can be as high as 30%.

4.3 Distant metastasis

Chemotherapy can be considered and should be case dependent. Treatment within a trial setting is encouraged. In some cases, radiotherapy or chemoradiation may be considered, again this is preferable within the trial setting.

5.0 Follow up

All patients require follow up. This can initially be undertaken at the Supra Network Centre but where facilities are in place, to have integrated follow up at local specialist centres (e.g., Arrowe Park).

5.1 Primary Tumour

5.1.1 Conservative surgery

Should be as per nodal status – see below

5.1.2 Partial Penectomy/Radical Penectomy

Should be as per nodal status – see below

5.2 Nodes

5.2.1 cN0

for Low-Risk disease as 5.1.1

3 monthly for year 1
4 monthly for year 2
6 monthly for years 3 – 4
Annually there after

for Intermediate Risk & High Risk (after sentinel node biopsy or surveillance):

3 monthly for year 1
4 monthly for year 2
6 monthly for years 3 - 4
Then annually

Length of follow up should be:

For low risk, at least 5 years
for intermediate risk, at least 5 years
for high risk, at least 5 years

5.2.2 cN+

This should be guided by the individual patients' risks & co-morbidities. Some patients may be followed up as part of a trial protocol.

5.2.2 CIS

In patients where CIS has been found on circumcision and clinical follow-up is indicated this should be on a 3 monthly basis for 12 months. After 12 months with no evidence of disease, patients can be discharged with instructions to self-examine.

6 SUPRANETWORK MDT CORE MEMBERSHIP

6.1 The group of people comprising the Core Membership are the surgeons operating on the named hospital sites together with

the health professionals who work in the MDT membership roles with them.

	Christie	**Wirral**
Urological Surgeons*	Mr Vijay Sangar Mr Maurice Lau Mr Arie Parnham	Mr Arie Parnham
Clinical Oncologists	Dr Tony Elliott Dr. Anna Tran	Dr. Isabel Syndikus
Medical Oncologists	Prof. Silke Gillesen	
Histopathologists	Dr Jonathan Shanks Dr Pedro Oliviera	Dr Ranjala Seneviratine
Radiologists	Dr Ben Taylor Dr Hans-Ulrich Laasch Dr Jon Bell Dr Thomas Hanbrook Dr Pavan Najran Dr. Sean Tenant Dr. Philip Borg	Dr David Hughes
Urology Nurse Specialists	Jane Booker Sharon Capper Stephen Booth Helen Johnson Cath Pettersen	Beverley Rogers
MDT coordinator	Daniel Bird Ben Hill-de-Vries	Rowan Davies
EXTENDED MEMBERS		
Urologist	Mr. Vijay Ramani	Mr. Nigel Parr
Palliative Care representative	Richard Berman Carole Mula	
Plastic/reconstructive surgeon	David Mowatt Dimesh Oudit	
Psycho-oncologist & Psycho-sexual counselling	Tarnya Hawthorne Josie Butcher	Geraldine Swift

**Any consultant in the supranetwork catchment area of the MDT who is responsible for performing lymph node dissections and/or penile reconstruction should be a core member of the supranetwork penile cancer team*.

6.2 The MDT will nominate one of the members of the core or extended team as the person responsible for ensuring that service improvement is integrated into the functions of the MDT.

6.3 A member of the Core Penile Cancer Team will be an extended member of the Skin MDT.

7 AUDIT AND DATA COLLECTION

7.1 During the year prior to the peer review visit the penile cancer team with all its referring teams should have carried out, as one of the agreed network audit projects, the following:

7.2 An audit of cases over the previous year, diagnosed with penile cancer by its referring teams, and its own cases.

7.3 Cases referred for specialist care and Supranetwork care should be audited for consistency with the network penile cancer guidelines (defining specialist and Supranetwork care for the network). The audit should also ascertain whether all cases diagnosed with penile cancer were discussed with the Supranetwork team prior to referral or to proposed specialist care.

7.4 The Supranetwork MDT will provide the total number of the following procedures performed for penile cancer by the team and by individual surgeons during the year prior to being reviewed.

i) Penile reconstruction procedures.
ii) Lymphadenectomies.

These will be presented at an annual meeting of the Supranetwork MDT.

8 ANNUAL MEETING

8.1 During the year prior to peer review, the Supranetwork penile cancer MDT will have held a meeting at which at least one core member of the team met with at least one core member of each of its referring teams to review all the cases during the previous year diagnosed as having penile cancer by its referring teams, and its own cases. At the meeting they should have ascertained:

- whether all cases were discussed with them prior to referral or to proposed specialist care and
- whether referrals for specialist and Supranetwork care were consistent with the network guidelines

8.2 The Annual Meeting will also be used to discuss, review, agree and record operational policies.

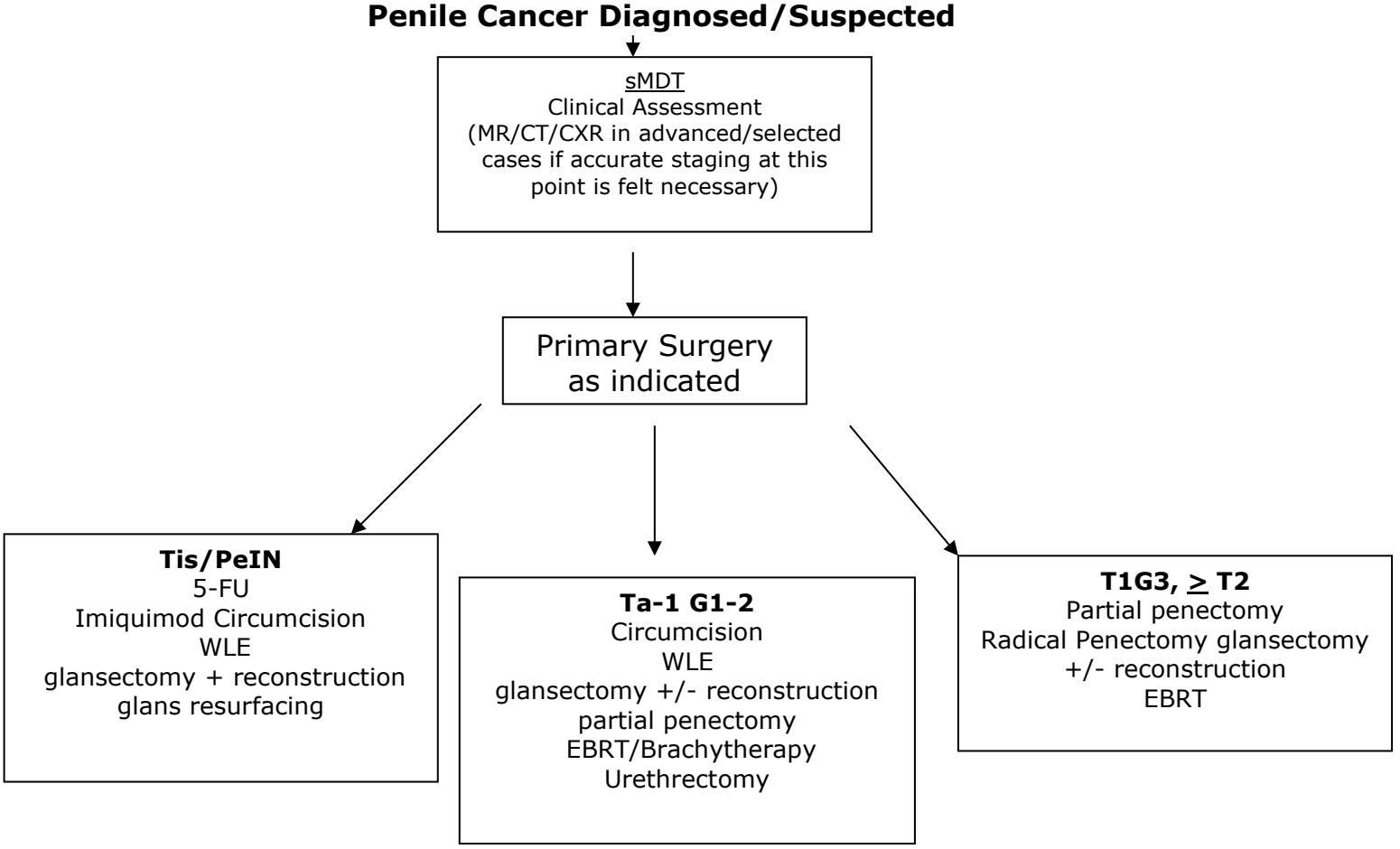
8.3 The Supranetwork penile cancer team may arrange more regular meetings (4 – 6 monthly) to facilitate research and audit.

9 TRIALS

9.1 The Supranetwork MDT will maintain a list of approved trials to which each Network agrees to enter patients.

9.2 The Supranetwork MDT will ensure that mechanisms are in place to support entry of eligible patients into clinical trials, subject to patients giving fully informed consent.

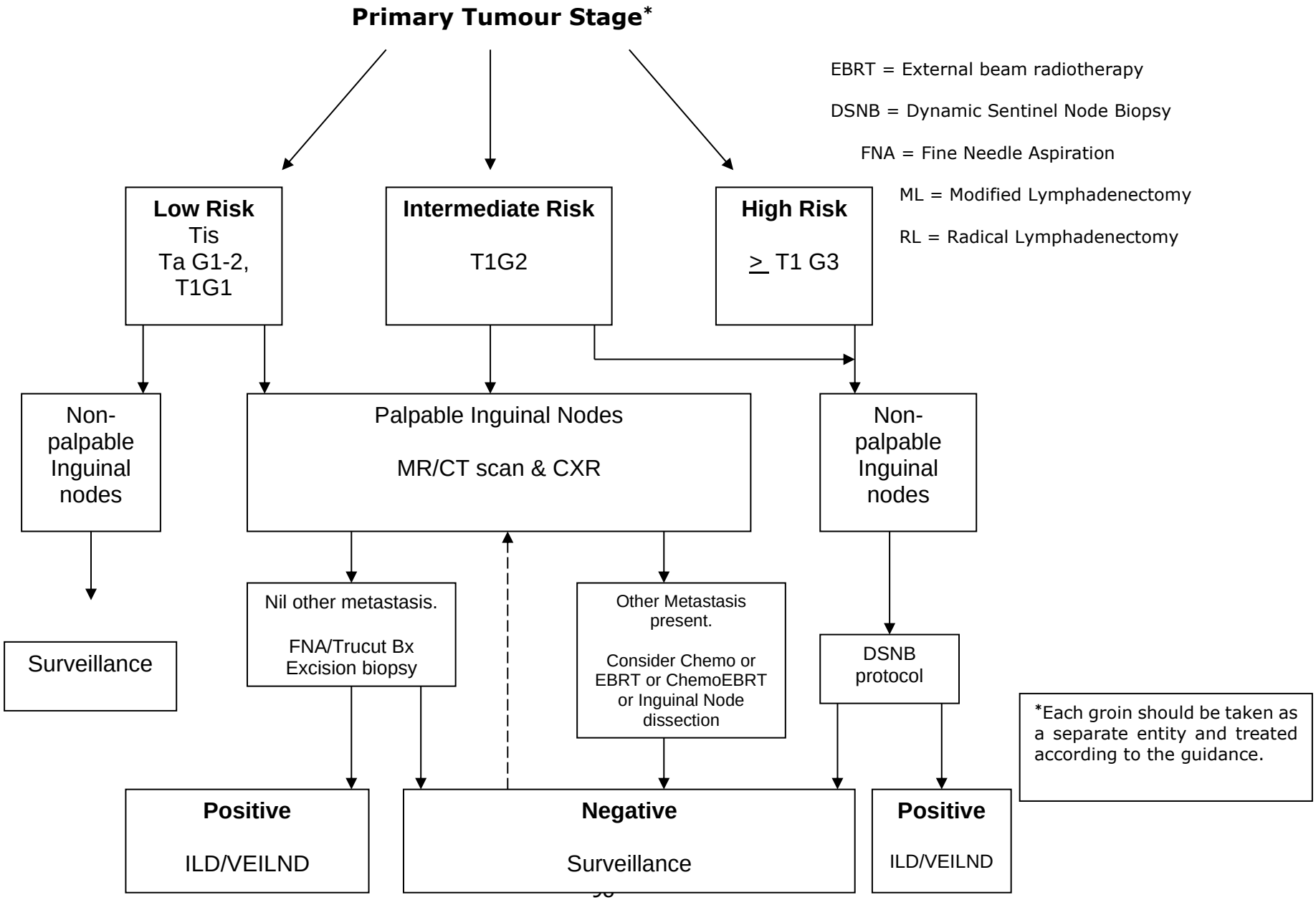
Appendix A – Penile Cancer Primary Treatment



In all Surgical Cases reconstruction should always be considered at the time of surgery.
In radical penectomy delayed phalloplasty should be an option.

WLE = wide local excision; EBRT = external beam radiotherapy; 5-FU= 5-fluorouracil

Appendix B - Lymph Node Assessment & Treatment



Appendix C

Trusts included within MDT	Local MDT Name & Hospital Base of MDT	Specialist MDT Name and Hospital Base	Catchment Population
Pennine Acute Trust	**Pennine Acute** Royal Oldham Hosp	**North East Sector Urological Cancer Specialist MDT** **Hospital base to be confirmed**	**744,000**
Central Manchester and Manchester Children's Trust	**Central Manchester and Manchester Children's** Manchester Royal Infirmary		**225,000**
Bolton Hospitals NHS Trust	**Bolton Hospitals** Bolton Hospital	**Salford Urological Cancer Specialist MDT** **Salford Royal Hospital** **Salford NHS Foundation Trust**	**276,000**
Wrightington, Wigan and Leigh NHS Trust	**Wrightington, Wigan and Leigh** Royal Albert Edward Infirmary		**302,000**
Salford Hospitals NHS Trust	**Salford Hospitals** Hope Hospital		**243,000**
South Manchester University Hospital NHS Trust Trafford Healthcare NHS Trust	**South Manchester University Hospital** Wythenshawe Hospital	**South Manchester Urological Cancer Specialist MDT** **Wythenshawe Hospital**	146,000 + 224,000 **Total = 370,000**

Stockport Foundation Trust Tameside & Glossop Trust	**Stockport Foundation Trust -** Stepping Hill Hospital	**University Hospitals South Manchester NHS Foundation Trust**	290,000 + 233,000 **Total = 523,000**
East Cheshire Trust	**East Cheshire** Macclesfield General		**196,000**
Mid Cheshire Trust	**Mid Cheshire** Leighton Hospital		**246,000**

Local MDT Name & Hospital Base of MDT	Catchment Population	Penile Cancer Specialist MDT	Total Catchment Population
Greater Manchester & Cheshire Cancer Network Local urology MDTs	**3.125m**	Christie Hospitals NHS Trust*	**7,725,000**
Merseyside & Cheshire Cancer Network	**2.3m**		
Lancashire & Cumbria Cancer Network Local MDTs	**1.7m**		
North Wales Local Urology MDTs	**0.6m**		

***Joint, single Supranetwork MDT with Wirral Hospitals NHS Trust. Operating site at Christie**

All hospitals within the Penile Cancer Network are listed below:

Organisation	Address
Pennine Acute Hospitals NHS Trust (North East)	Westhulme Avenue Oldham Lancashire OL1 2PN
Pennine Acute Hospitals NHS Trust	As above
Pennine Care NHS Trust	225 Old Street Ashton-under-Lyne OL6 7SR
Pennine Care NHS Trust	As above
Bolton, Salford & Trafford Mental Health NHS Trust	Bury New Road Prestwich Manchester M25 3BL
Bolton, Salford & Trafford Mental Health NHS Trust	As above
Bolton Hospitals NHS Trust	Royal Bolton Hospital Minerva Road Farnworth Bolton BL4 0JR
Bolton Hospitals NHS Trust	As above
Stockport NHS Foundation Trust	Oak House Stepping Hill Hospital Poplar Grove Stockport SK2 7JE
Stockport NHS Foundation Trust	As above
North West Ambulance Service NHS Trust	Ambulance Service HQ Ladybridge Hall Chorley New Road Heaton Bolton BL1 5DD
North West Ambulance Service NHS Trust	As above
North West Ambulance Service NHS Trust Cheshire & Mersey Area Office	Elm House Belmont Grove Liverpool L6 4EG

North West Ambulance Service Great Manchester Area Offices	Bury Old Road Whitefield Road Manchester M45 6AQ
Cumbria & Lancashire Area Office	Lancashire Area Office 449 – 451 Garstang Road Broughton Preston Lancs PR3 5LN
Calderstones NHS Trust	Mitton Road Whalley Clitheroe Lancs BB7 9PE
Calderstones NHS Trust	As above
Lancashire Teaching Hospital NHS Foundation Trust	Royal Preston Hospital Sharoe Green Lane Fulwood PRESTON PR2 9HT
Lancashire Teaching Hospital NHS Foundation Trust	As above
Trafford Healthcare NHS Trust	Moorside Road Urmston Manchester M41 5SL
Trafford Healthcare NHS Trust	As above
Wrightington, Wigan & Leigh NHS Trust	The Elms Royal Albert Edward Infirmary Wigan Lane Wigan WN1 2NN
Wrightington, Wigan & Leigh NHS Trust	As above
Salford Royal Hospitals NHS Trust	E2, Hope Hospital Stott Lane Salford M6 8HD
Salford Royal Hospitals NHS Trust	As above

Central Manchester & Manchester Children's University Hospitals NHS Trust	Cobbett House Manchester Royal Infirmary Oxford Road Manchester M13 9WL
Central Manchester & Manchester Children's University Hospitals NHS Trust	As above
Tameside & Glossop Acute Services NHS Trust	1st Floor, Darnton Building, Darnton Road Ashton under Lyne OL6 9RW
Tameside & Glossop Acute Services NHS Trust	As above
University Hospital of South Manchester NHS Foundation Trust	Wythenshawe Hospital Southmoor Road Wythenshawe Manchester M23 9LT
University Hospital of South Manchester NHS Foundation Trust	As above
Manchester Mental Health & Social Care NHS Trust	Chorlton House 70 Manchester Road Chorlton Manchester M21 9UN
Manchester Mental Health & Social Care Trust	As above
Christie Hospital NHS Trust	Wilmslow Road Withington Manchester M20 4BX
Christie Hospital NHS Trust	As above
Royal Liverpool & Broadgreen University Hospital NHS Trust	Prescot Street Liverpool L7 8XP
Royal Liverpool & Broadgreen University Hospital NHS Trust	As above
Aintree University Hospitals NHS Foundation Trust	Aintree House Longmoor Lane Liverpool Merseyside L9 7AL
Aintree University Hospitals NHS Foundation Trust	As above

Mersey Care NHS Trust	8 Princes Parade Princes Dock St Nicholas Place Liverpool L3 1DL
Mersey Care NHS Trust	As above
Wirral Hospital NHS Trust	Arrowe Park Arrowe Park Road Upton Wirral CH49 5PE
Wirral Hospital NHS Trust	As above
Cheshire & Wirral Partnership NHS Trust	Trust Board Offices Upton Lea Resource Centre 1st Floor Liverpool Road Chester CH2 1BQ
Cheshire & Wirral Partnership NHS Trust	As above
Countess of Chester NHS Foundation Trust Hospital	Health Park Liverpool Road Chester CH2 1UL
Countess of Chester NHS Foundation Trust Hospital	As above
Clatterbridge Centre for Oncology NHS Trust	Clatterbridge Road Bebington Wirral CH63 4JY
Clatterbridge Centre for Oncology NHS Trust	As above
Walton Centre for Neurology & Neurosurgery NHS Trust	Lower Lane Fazakerley Liverpool L9 7PJ
Walton Centre for Neurology & Neurosurgery NHS Trust	As above
The Cardiothoracic Centre Liverpool NHS Trust	Thomas Drive Liverpool L14 3PE

The Cardiothoracic Centre Liverpool NHS Trust	As above
Royal Liverpool Children's NHS Trust	Alder Hey Hospital Eaton Road Liverpool L12 2AP
Royal Liverpool Children's NHS Trust	As above
Southport & Ormskirk Hospital NHS Trust	Southport & Formby District General Hospital Town Lane Kew Southport
Southport & Ormskirk NHS Trust	As above
Blackpool, Fylde & Wyre Hospitals Trust	Blackpool Victoria Hospital Whinney Heys Road Blackpool FY3 8NR
Blackpool, Fylde & Wyre Hospitals Trust	As above
University Hospitals of Morecambe Bay	Westmorland General Hospital Burton Road Kendal LA9 RG
University Hospitals of Morecambe Bay	As above
North Cumbria Acute Hospitals NHS Trust	Cumberland Infirmary Carlisle CA2 7HY
North Cumbria Acute Hospitals NHS Trust	As above
Cumbria Partnership NHS Trust	The Carleton Clinic Cumwhinton Drive Carlisle CA1 3SX
Cumbria Partnership NHS Trust	As above
East Lancashire Hospitals NHS Trust	The Royal Blackburn Hospital Haslingden Road Blackburn Lancashire BB2 3HH
East Lancashire Hospitals NHS Trust	As above
Mid Cheshire Hospitals NHS Trust	Leighton Hospital Middlewich Road Crew CW1 4QJ

Mid Cheshire Hospitals NHS Trust	As above
East Cheshire NHS Trust	Macclesfield District General Hospital Victoria Road Macclesfield SK10 3BL
East Cheshire NHS Trust	As above
North Cheshire Hospital Trust	Lovely Lane Warrington Cheshire WA5 1QG
North Cheshire Hospital Trust	As above
St Helens & Knowsley Hospitals NHS Trust	Whiston Hospital Prescot Merseyside L35 5DR
St Helens & Knowsley Hospital Trust	As above
5 Boroughs Partnership NHS Trust	Hollins Park House Hollins Lane Winwick Warrington WA2 8WA
5 Boroughs Partnership NHS Trust	As above
Liverpool Women's NHS Foundation Trust	Crown Street Liverpool L8 7SS
Liverpool Women's Hospital Foundation NHS Trust	As above
Wrexham Maelor Hospital	Croesnewydd Road Wrexham LL13 7TD
Bangor Community Hospital	Castle Street Bangor BT20 4TA
North West Wales NHS Trust	Ysbyty Gwynedd Penrhosgarnedd Bangor Gwynedd LL57 2PW

Appendix 4
Superficial (NMIBC) Risk Stratification and follow up Guidelines

EAU Risk Stratification

EAU risk factors

Risk group	
Low Risk	A primary, single, Ta/T1 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 (see above*)
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 T1 G1, no CIS with all 3 risk factors Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors T1 G2 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 T1 G2 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

Clinical risk factors are: -

- Age>70
- Multiple tumours
- Tumour >3cm

NICE risk categories 2015

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

NCCN (AUA) risk categories

Low risk	• PUNLMP • LG, pTa AND <3c AND solitary

Intermediate	• **LG**
	  ○ **T1 or**
	  ○ **>3cm or**
	  ○ **Multifocal or**
	  ○ **Recurrence within 1 year**
	• **HG**
	  ○ **pTa AND <3cm AND solitary**

High risk	• **HG**
	  ○ **Cis or**
	  ○ **pT1 or**
	  ○ **>3cm or**
	  ○ **multifocal**

Very High Risk	• **BCG unresponsive** • **Variant Histologies** • **LVI** • **Prostatic Urethral Invasion**

Follow up Protocols

1 Low risk – cystoscopy only

Year	1	2	3	4	5	>5years
EAU	3 + 12 months	Annual	annual	annual	annual	As clinically indicated
NICE	12/12					
NCCN	3 + 12 months	annual	annual	annual	annual	As clinically indicated

Discharge at 5 years (1 year according to NICE) if no recurrence, only do flexi if symptoms thereafter

2 Intermediate Risk

Year	1	2	3	4	5	>5
EAU	3/12	NS	NS	NS	NS	As clinically indicated
NICE	3 + 9 months	18/12	annual	annual	annual	As clinically indicated
NCCN	3, 6, 12 months	18 and 24 montrhs	annual	annual	annual	As clinically indicated

NS – not specified

3 High and Very High-Risk Cystoscopy

Year	1	2	3	4	5	5-10 years	>10 years
EAU	3 monthly	3 monthly	6 monthly	6 monthly	6 monthly	annual	As clinically indicated
NICE	3 monthly	3 monthly	6 monthly	6 monthly	annual	annual	As clinically indicated
NCCN	3 monthly	3 monthly	6 monthly	6 monthly	6 monthly	annual	As clinically indicated

Includes Urine Cytology at each check

Imaging

EAU – Annual CTU

NCCN – CTU at 12 months then every 1-2 ye