Sherwood Forest Hospitals
NHS Foundation Trust

TITLE: Investigation, management and follow up of prostate, kidney and bladder cancer guideline

(Adapted from Nottingham City Hospital & East Midland Cancer Network Guidelines)

Document Category:	**CLINICAL**
Document Type:	**GUIDELINE**

Keywords:	Renal; urology; urological; referral; diagnosis; staging; treatment;

Version:	**Issue Date:**	**Review Date:**
2.2 (formal approval not required)	27th July 2023	September 2023

Supersedes:	v2.1, Issued 30th April 2021 to Review Date Sept 2023		
Approved by (committee/group):	v2.0, Urology Clinical Governance Meeting v2.1, Urology Clinical Governance Meeting v2.2, Formal approval not required	**Date Approved:**	Sept 2020 April 2021 July 2023

Scope/ Target Audience: (delete as applicable / describe)	**Specialty/ Department** • **Urology**

Evidence Base/ References:	See Section 6

Lead Division:	Surgery
Lead Specialty:	Urology
Lead Author:	Tom Walton – Cancer Lead for Urology NUH Miss Frances Burge – Urology SFH Mr Ashok Bhojwani,– Urology, SFH
Sponsor:	Mr Ashok Bhojwani, Head of Service – Urology – SFH Steve Jenkins, Divisional General Manager - SFH Mr Menon, Surgery Division Clinical Chair – SFH

	Name the documents here or record not applicable
Associated Policy	n/a
Associated Procedure(s)	n/a
Associated Pathway(s)	n/a
Associated Standard Operating Procedure(s)	n/a
Other associated documents e.g. documentation/ forms	n/a

Consultation Undertaken:	v2.0 • Urology Clinical Governance Meeting • Urology Consultant Meeting v2.1 • Urology Team

	v2.2 • Not Applicable

Template control:	v1.4 November 2019

Amendments from previous version(s)

Version	Issue Date	Section(s) involved	Amendment
2.2	July 2023	2.1, table bottom of page 4	• In line with NICE guidance, age parameter of 70+yrs changed to 70-79yrs and >79yrs and PSA thresholds for referral for all age ranges changed except 40-49.
2.1	April 2021	4.5.2.3, page 38	• BCG administration scheduled updated

CONTENTS

1 INTRODUCTION / BACKGROUND

The purpose of this guideline is to define an agreed departmental policy for the investigation, management and follow up of patients with prostate, kidney and bladder cancer at Sherwood Forest Hospitals NHS Foundation Trust (SFH). Network guideline for testis and penile cancer fall under the remit of the East Midlands Cancer Network and are available online and elsewhere. These guidelines are not meant to be exhaustive: more comprehensive sources including British Association of Urological Surgeons (BAUS); National Institute of Health and Care Excellence (NICE); European Association of Urology (EAU); and American Urological Association (AUA) are available for this purpose. Rather the information collated herein is meant to address key areas where significant departmental heterogeneity exists, in order to promote a consistent and efficient approach to the provision of cancer care for urology patients at SFH.

The guidelines have been agreed at Departmental and Multi-Disciplinary Team level, and where possible represent the best evidence currently available. It is recognised however that guidance often changes over time, and as such the current version will be subject to review every two years. It is also acknowledged that situations arise where it is impractical or inappropriate to rigidly apply the guidelines, this is inevitable and part of the art of consultation. Nevertheless, it is hoped that this document will provide a working framework to aid healthcare professionals interacting with urology cancer patients at SFH.

2 PROSTATE GUIDELINES

We agree to follow the prostate cancer risk management guidelines for referral of men with suspected prostate cancer.

2.1 Referral for Investigation

The East Midlands Cancer Advisory Group (ECAG) guidelines for referral of men with suspected prostate cancer are shown below:

- **Clinically malignant (firm, hard or craggy) prostate on DRE**
- **Raised age-adjusted PSA**
- **Patients 80 yrs and over with PSA ≥ 20**
- **Clinical or radiological suspicion of prostate cancer bone metastases**

Age specific PSA threshold levels for referral	
40-49 yrs	≥ 2.5 ng/ml
50-59 yrs	≥ 3.5 ng/ml
60-69 yrs	≥ 4.5 ng/ml
70-79 yrs	≥ 6.5 ng/ml
>79 yrs	Use clinical judgement
**There are no age specific reference ranges for men over 80 years. Nearly all men of this age have at least a focus of cancer in their prostate. Prostate cancer only needs to be diagnosed in this age group if it is likely to need palliative treatment.	

Locally mandated information for 2WW referral should include demographics, investigation results (PSA, UE/eGFR, urine dipstick (+MSU) and DRE), performance status, weight, BMI, medication, anticoagulant history, and MRI scanning exclusion criteria.

The updated SFH urological cancer 2WW guidelines also emphasise that men do not necessarily require referral if they have significant comorbidities, performance status ≥3 or a life expectancy <10 years. To assist primary care colleagues a ready reckoner has been included in the 2WW form, as shown below.

Average UK Male expectancy in years*	
Age 70 years	14.4 years remaining
72	13.1
74	11.7
76	10.5
78	9.3
80	8.2
82	7.1
86	5.4
88	4.7
90	4.1
*As a ready reckoner, for patients in best quartile of health, add 50% to years remaining; for those in the worst quartile of health, substract 50%; for average patients, do not adjust	

2.2 Diagnosis

2.2.1 2WW Triage:

Patients fulfilling the above criteria are referred to SFH and referrals are triaged by clinicians daily. Rather than leading to an outpatient appointment 2WW referral slots now map to a ghost clinic.

The benefit of radical treatment over observation for men with newly diagnosed localised prostate cancer is not proven for men with a life expectancy <10 years.

Men 78 years and over are triaged as follows:

- PSA < 20 Review in consultant clinic. Recommend PSA observation alone, do not biopsy.
- PSA≥ 20 Book bone scan and review in consultant clinic

All patients fulfilling the eligibility criteria are referred to a straight to test (STT) multiparametric MRI (mpMRI).

MRI compatibility:

SFH do not currently MRI patients with cardiac pacemakers, irrespective of compatibility. Patients with pacemakers or non-compatible intravascular prostheses or clips should be booked for conventional 12-core TRUS biopsy.

Anticoagulation:
Anticoagulated men requiring a biopsy following mpMRI should be discussed with the responsible consultant and managed according to SFH perioperative management of anticoagulation.

Triage of mpMRI results
All mpMRI results should explicitly describe the calculated prostate volume and be reported according to current standards (Likert scale/PIRADS v2 or above). Results are reviewed in a virtual clinic by a Consultant Urologist / Cancer nurse specialist and triaged according to the following guidelines:

When to biopsy:
Do not biopsy MRI score 1/2, or MRI score 3 with PSA density < 0.12.

Offer biopsy to MRI score 3 and PSAD >/= 0.12 *or* Afro-Caribbean/African status *or* positive family history (one or more first degree relatives with prostate cancer), and all MRI score 4/5 lesions.

Men with no indication for biopsy

(i) *If PSA density <0.12, discharge to GP*. Recommend annual PSA testing and re-referral if PSA value breaches a threshold value of >/= 0.12 [i.e. 0.12 x prostate volume]. Re-referred patients should undergo repeat mp-MRI scanning

(ii) *If PSA density >/= 0.12 and <0.2, discharge to GP*. Recommend annual PSA testing and re-referral if PSA value breaches a threshold value based on a PSA kinetics increase of 20% [i.e. 1.2 x baseline PSA value]. Re-referred patients should undergo repeat mp-MRI scanning.

(iii) *If PSA density >/= 0.2, retain in secondary care*. Check PSA at 3 months and 6 months. See in consultant clinic at 6 months with results. If PSAD remains elevated, consider transperineal template-guided mapping prostate biopsies (TTMPB) after explaining the risks*.

* Transperineal template-guided mapping prostate biopsies (TTMPB) are associated with the following risks: bleeding (common), infection (1%), urinary retention (10%) and temporary erectile dysfunction (up to 20%).

2.2.2 Biopsy technique

Posterior lesions should be targeted by a 6-core TRUS biopsy of the affected prostate lobe (LA) or transperineal MR-US fusion biopsy (LA) depending on availability.

Anterior lesions should be targeted either by cognitive-directed transperineal biopsy (GA), or image-guided transperineal fusion (LA/GA) depending on availability.

For men </= 70 years of age who are suitable for nerve-sparing robotic prostatectomy, limited systematic prostate sampling of the contralateral prostate is mandated.

For men undergoing TRUS biopsy this essentially means a standard 12-core TRUS biopsy. For men undergoing cognitive targeted transperineal biopsy or MR-US guided fusion biopsies, the recommended biopsy schedule is shown in
Appendix C.

For men > 70 years of age or those unsuitable for nerve-sparing robotic prostatectomy perform targeted biopsies only.

Formal transperineal template-guided mapping biopsies should only be used in select cases (e.g. rising PSA and previous negative mp-MRI +/- biopsy).

- Men with no requirement for biopsy will be contacted by a Cancer Nurse Specialist (CNS) and a routine appointment in a Consultant clinic is made.
- Men needing TRUS biopsy are contacted by the CNS team, counselled and offered an urgent appointment in TRUS clinic. Appropriate antibiotic prescriptions are sent to the patient.
- Men requiring Transperineal biopsy are offered an urgent appointment in a Consultant Clinic.
- **Men with mpMRI showing cT3a/b *or* N1 *or* M1 require a bonescan which should be booked at the time of the virtual clinic or biopsy.**

2.2.3 What to do about a single negative biopsy:

i. ASAP & HGPIN 4 or more positive cores both have an approximate 40% risk of cancer on a second set of transrectal biopsies. Therefore consider offering an immediate second set of 12 core transrectal biopsies.
ii. If 3 or fewer cores of HGPIN, manage as per benign
iii. If completely benign, calculate PSA density;

(i) If MRI score 3 and PSA density >/= 0.12 and <0.2, discharge to GP. Recommend annual PSA testing and re-referral if PSA value breaches a threshold value based on a PSA kinetics increase of 20% [i.e. 1.2 x baseline PSA value]. Re-referred patients should undergo repeat mp-MRI scanning.

(ii) If MRI score 3 and PSA density >/= 0.2, retain in secondary care. Check PSA at 3 months and 6 months. See in consultant clinic at 6 months with results. If PSAD remains elevated, consider transperineal template-guided sectoral biopsies after explaining the risks*.

(iii) If MRI score 4/5, retain in secondary care. **Re-review mp-MRI and histopathology in MDT**. If no evidence of atypia or inflammation consider immediate transperineal template-guided mapping biopsies after explaining the risks*.

Alternatively commence PSA surveillance (at 3 months and 6 months) with repeat mp-MRI scanning at 6 months.

* Transperineal template-guided prostate biopsies are associated with the following risks: bleeding (common), infection (1%), urinary retention (10%) and temporary erectile dysfunction (up to 20%).

2.3 Staging

NICE guidelines Recommend the use of D'Amico criteria for risk stratification, which is subtly different from the criteria recommended by BAUS. We will follow the D'Amico/NICE criteria as shown below:

Table 1 Risk stratification for men with localised prostate cancer

Level of risk	**PSA**		**Gleason score**		**Clinical stage**
Low risk	<10 ng/ml	and	<6	and	T1-T2a
Intermediate risk	10-20 ng/ml	or	7	or	T2b
High risk	>20 ng/ml	or	8-10	or	>T2c
High-risk localised prostate cancer is also included in the definition of locally advanced prostate cancer.					

Immediate staging investigations at SFH are based on risk category:

Low risk	No staging required
Intermediate risk	staging MRI pelvis only
High risk	staging MRI pelvis and bone scan
Choline-PET/ PSMA-PET	Should not be routinely performed for primary CaP staging. They may be considered in certain men with primary and recurrent disease following discussion at the MDT meeting.

2.4 Treatment

2.4.1 New diagnoses

All new diagnoses of prostate cancer are discussed at a weekly Uro-oncology MDT meeting. Management options are reviewed in light of disease characteristics and patient co-morbidities, and treatment recommendations made. Sometimes a single management option is advised by the MDT (e.g. active surveillance or ADT +/- docetaxel). Commonly however a patient may be eligible for multiple treatment options (e.g active surveillance vs. radical surgery vs. radical radiotherapy). Careful counselling is thus required, both by clinicians and by the CNS team. Patients should either be seen in a joint urology-oncology clinic, or be offered a separate referral to the Oncology team for additional counselling, and receive adequate time to make a treatment decision.

2.4.2 Active surveillance

Indications for active surveillance (AS) have been relaxed in the last few years. Previously there were strict criteria for entry into AS protocols. However, accumulating evidence suggests that AS is a safe option for the vast majority of men with low-risk disease, an approach supported by current NICE guidelines. **Appropriate risk stratification at initial diagnosis is essential however**. For example it is well established that approximately 30-40% of men with Gleason 3+3 disease on TRUS biopsy actually harbour higher grade disease on mapping transperineal template-guided prostate biopsies. The findings on pre-biopsy mp-MRI and knowledge of PSA density can modify the likelihood of significant upgrading, and have therefore been incorporated into current SFH AS protocols.

AS is recommended as first line for all men with low-risk prostate cancer, assuming appropriate risk stratification at initial diagnosis. AS may also be considered in selected men with low-volume Gleason 3+4 disease.

The SFH protocol for active surveillance in men with newly diagnosed low-risk prostate cancer is outlined in Section 2 Appendix. Specific points are outlined below:

- A pre-biopsy mp-MRI as part of the prostate cancer assessment pathway (PCAP).
- For those who have undergone primary TRUS biopsies, or with incidental findings at TURP, mp-MRI scanning should be deferred for 3 months to allow haemorrhage/inflammation to subside.
- Offer transperineal template-guided prostate biopsies for stratification to the following patients:
  - MRI score ≥ 3
  PSA density ≥ 0.12
  - Persistent haemorrhage on post-biopsy mpMRI (if performed)
  - Gleason 3+4 on initial biopsy
  - Age 70 or less
- Refer appropriately risk-stratified patients to the nurse-led surveillance clinic for 6 monthly PSA tests (regular DRE is not required).
- Scheduled mp-MRI scans are performed at 1 year after stratification (i.e after diagnosis or after template biopsies if required) then every 2 years thereafter (1,3,5,7 etc.) until the patient is not considered a candidate for radical treatment*, or until treatment is indicated. Surveillance mp-MRI scan results are reviewed in the virtual clinic or by the patient's responsible consultant for decision-making. A Template letter for satable appreaences is available (Appendix D).
- Consider a non-scheduled mp-MRI scan if the PSA (checked on 2 separate occasions) rises by ≥ 50% over a 12 month period.
- Evidence of radiological progression on mp-MRI mandates targeted rebiopsy, as outlined in section 2.2.2

* Current national actuarial data indicate that average male life expectancy falls below 10 years at 77 years of age.

2.4.3 Robot-assisted radical prostatectomy (RARP)

Men electing to undergo RARP are required to perform pre-op baseline functional studies, which comprise a **UCIQ urinary function score and IEEF erectile function score.** Forms are available in clinic and are recorded by the CNS team, who also arrange pre-op continence and andrology referrals prior to surgery.

2.4.3.1 Who requires a pelvic lymphadenectomy at the time of RARP?

There is currently an absence of level one evidence supporting a specific survival benefit for pelvic lymphadenectomy in men with localised prostate cancer. In addition, the use of supersensitive PSA at SFH means that biochemical relapse may be identified early, thereby avoiding some of the complications of ePLND, such as DVT, lymphocoele formation and lymphoedema.

Nevertheless, there is evidence to suggest that some patients with low volume LN mets and favourable local pathology experience long-term biochemical recurrence-free survival after RARP and ePLND (Touijier 2014).

As such, extended pelvic lymph node dissection should be considered in all men with intermediate/high-risk disease undergoing radical prostatectomy.

2.4.3.2 Follow-up protocols after RARP

The average number of OPAs for men receiving prostatectomy is 12. CQIN funding agreements for robotic prostatectomy are predicated on a reduction in OPAs. A nurse-led prostatectomy follow-up schedule has been introduced to achieve this for men undergoing robotic prostatectomy. A schedule, which include regular assessment of continence (UCIQ score) and erectile function (IEEF score) recovery is shown in Section 2 Appendix.

Penile rehabilitation remains controversial with limited evidence to support its benefit. The Area Prescribing Group does not currently support the use of once daily tadalafil for penile rehabilitation. Generic sildenafil is supported however. Current recommendations for post-prostatectomy penile rehabilitation are outlined below:

Non nerve-sparing (NNS) prostatectomy Vacuum tumescence device (VTD) +/- intracavernosal injection therapy (ICI)

Bilateral/unilateral NS prostatectomy* Sildenafil 100mg three times per week +/- VTD. Consider ICI if no response to sildenafil after 6 months

* Patients should be counselled that spontaneous regeneration of erectile function can occur up to 24 months after surgery and that regular blood flow into the penis following surgery (via VTD etc.) is crucial preserve the chances of recovery.

2.4.4 Initiation of androgen deprivation therapy (ADT)

The current recommended schedule for initiation of ADT is as follows:

50mg bicalutamide od for 28 days*

11.25mg triptorelin (decapeptyl) im at 2 weeks

* This is substantially cheaper than cyproterone acetate (£2.69 vs. £56.76 for 28 days as per BNF) with equivalent side-effect profile and efficacy (Sugiono 2005)

All further LHRH analogue injections to be administered by the patient's GP practice. The Area Prescribing Committee (APC) currently recommends either 3-monthly or 6-monthly triptorelin for ongoing LHRH therapy.

For men with **prostate cancer spinal metastases *and* established or impending spinal cord compression** in whom rapid control of testosterone is desirable, the LHRH antagonist degarelix may be considered. The dose of degarelix is as follows:

240mg degarelix (firmagon) sc immediately
80mg degarelix sc monthly thereafter*
* To be administered by the patient's GP practice

Bilateral orchidectomy remains an alternative to luteinising hormone-releasing hormone (LHRH) agonist *and* antagonist therapy for all men with metastatic prostate cancer as per NICE NG 131 May 2019.

2.4.5 Castrate-refractory prostate cancer (CRPC)

The EAU definition of castrate-refractory prostate cancer is as follows:
Castrate serum levels of testosterone (testosterone < 50 ng/dL or < 1.7 nmol/L) plus either:

- Three consecutive PSA rises, 1 week apart, resulting in two 50% increases over the nadir, with a PSA >2 ng/mL.
- Radiological progression: the appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours).

2.4.5.1 Treatment options

Currently the key to the management of CRPC is to determine the presence or absence of metastatic disease, and to assess performance status. There are essentially 3 groups (see below):

- **Men with metastatic disease at original presentation who received ADT and subsequently develop CRPC** - these men are eligible for second-line treatment (docetaxel/abiraterone/enzalutamide etc.) Refer all men to Oncology with performance status 0-2.*
- **Men with non-metastatic disease at original presentation, who subsequently develop CRPC and new radiologically confirmed metastases** - these men are eligible for second-line treatment (docetaxel/abiraterone/enzalutamide etc.) Refer all men to Oncology with performance status 0-2.*

- M**en with non-metastatic disease at original presentation, who subsequently develop CRPC without metastases -** these men are not currently eligible for second-line treatment (although SPARTAN and PROSPER trials have shown a survival benefit for apalutamide and enzalutamide respectively and may receive future approval). It is important to diagnose metastases as early as possible. Therefore perform choline-PET when PSA ≥5. If no metastatic disease commence PSA surveillance 3 monthly and repeat choline-PET at every PSA doubling. For those with confirmed non-metastatic CRPC options remain limited:
  (i) PSA surveillance alone
  (ii) Consider 50mg bicalutamide (no survival benefit but PSA response in up to 50%). If PSA rises on bicalutamide withdraw (approx. 30% will have PSA response)
  (iii) Dexamethasone 0.5mg od (50% PSA response)

* If performance status 3 or more, manage expectantly. Discuss end-of life options, specifically attitudes to nephrostomy insertion, and document in notes. Consider dexamethasone 0.5mg od and refer to community Macmillan service or hospital palliative care team if symptomatic.

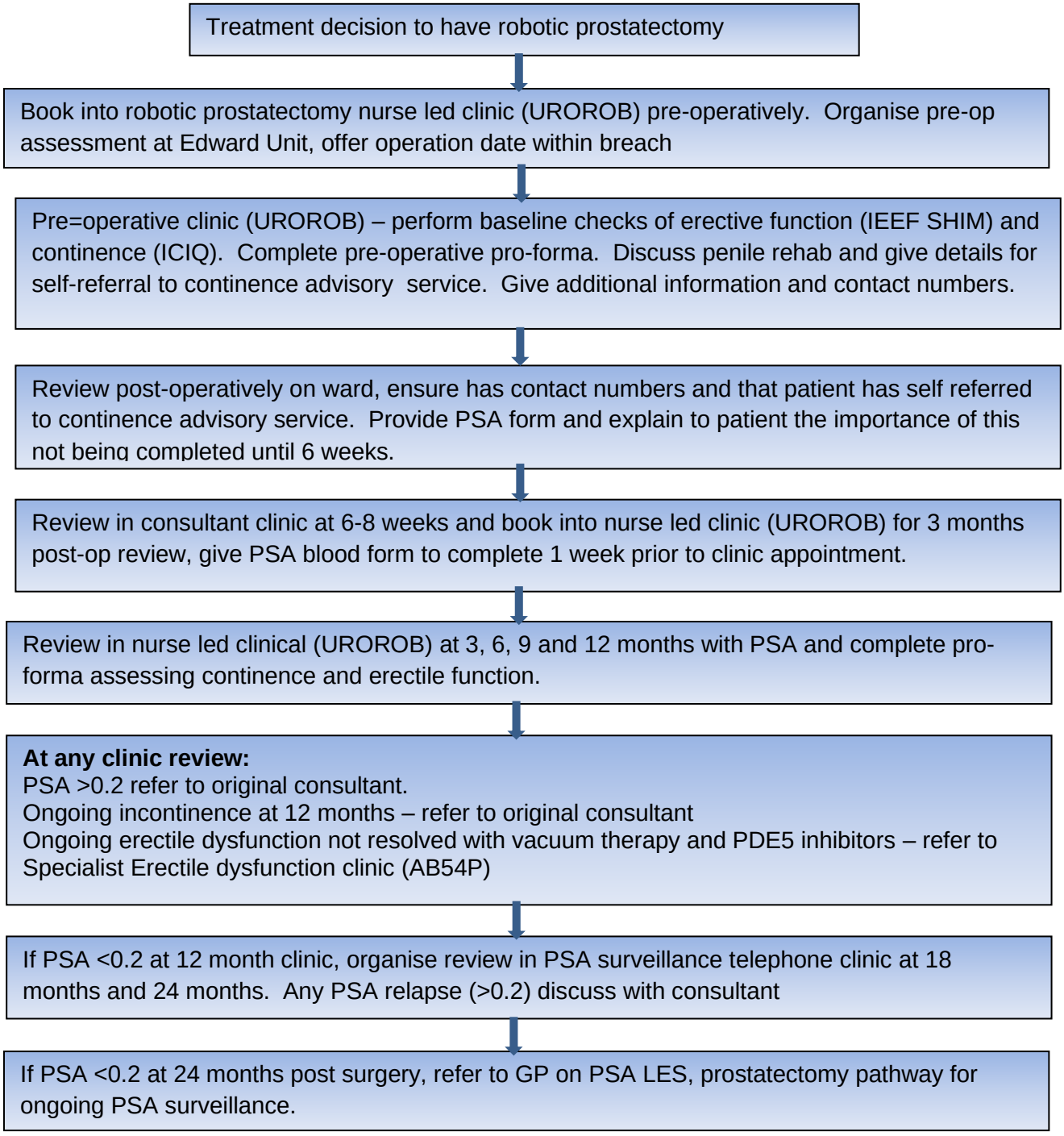
2.5 Discharge of prostate cancer patients into the community

Pathways are shown in Section 2 Appendix. General considerations:

- **Watchful waiting**: The monitoring of asymptomatic patients with prostate cancer with a view to palliative therapy including hormone therapy:
  - Referral to GP with clearly stated PSA threshold for re-referral.
  - GP to repeat ALP and PSA 6 monthly lifelong.
  - Refer back if abnormal ALP/bone pain or threshold breached.
- **Patients on hormonal therapy:**
  - All patients assessed in clinic after 3 months:
  - Responders discharged to GP follow up,
  - Non-responders followed up in clinic and continue to have GnRH in primary care.
  - ALP and PSA and symptoms to be assessed 6 monthly.
  - Refer back if nadir <10 and rises >10 or if nadir >10 and increases by >20%.
    - If bone pain/raised ALP for bone scan and review,
    - If raised PSA needs testosterone at time of referral.
- **Following RALP:**
  - Discharged 2 yrs after prostatectomy
  - GP to check PSA 6 monthly for 3 years and yearly for life
  - Refer back if PSA >0.1 ng/ml or symptoms
- **Following radical radiotherapy**
  - Patient discharged after completing adjuvant hormone therapy
  - PSA and testosterone 6 monthly for 3 years then annually for life
  - Refer back if PSA >2 ng/ml on 2 occasions 1 month apart
    - Or concerns over urinary/rectal toxicity.

NB: in patients with severe comorbidity routine PSA checks can be discontinued or reserved for symptomatic progression only.

Appendix A: Nurse led prostatectomy flowchart (for use at NUH)



Appendix B – PSA pathway guidance for Community Monitoring of Patients with Stable Prostate Cancer

Contents

Pathway colours

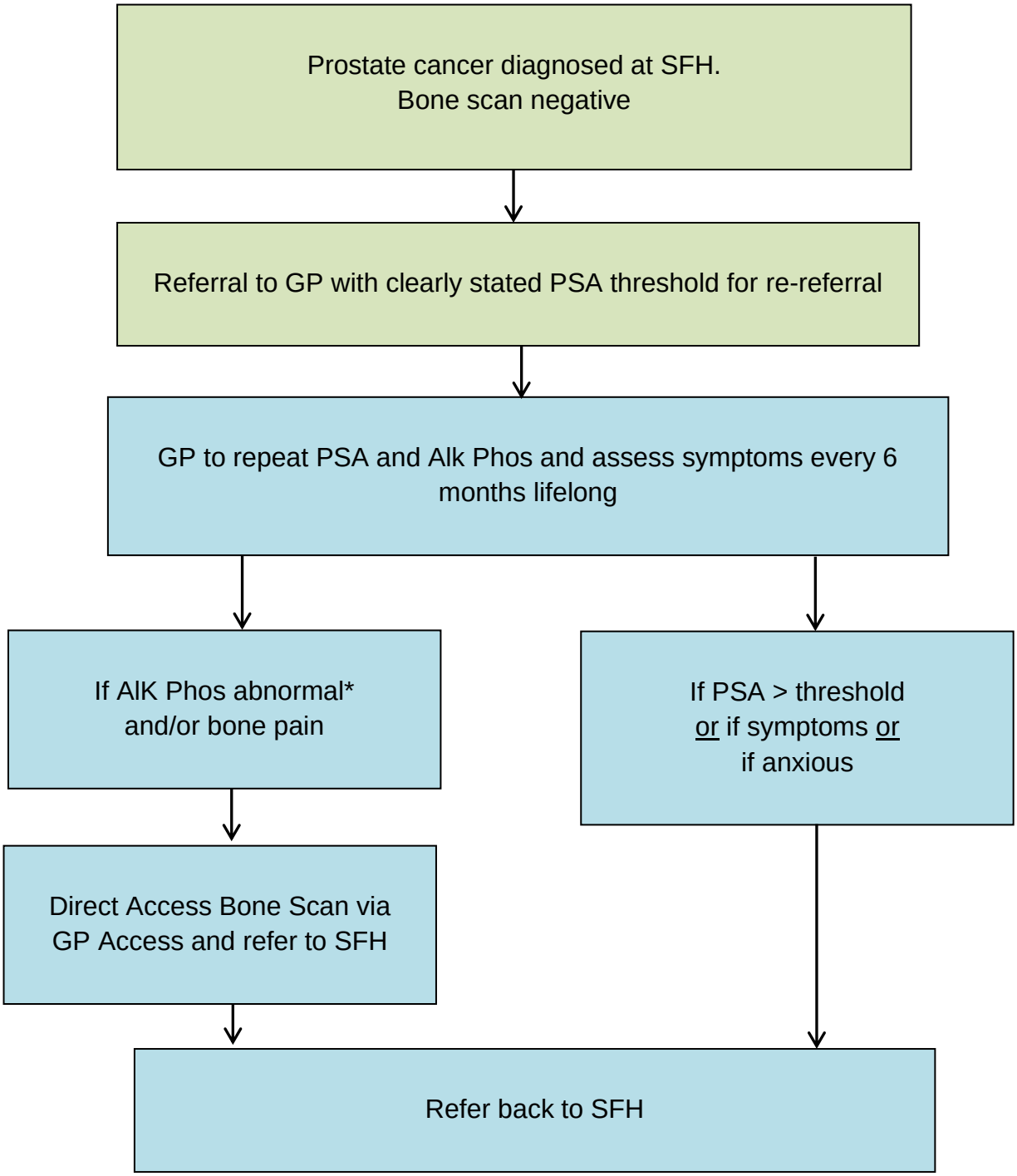
 – SFH Secondary Care action

 – GP action

These guidelines cover follow up for confirmed diagnoses of carcinoma of the prostate. For referral guidelines please refer to NICE Guideline CG27. In particular we would like to remind clinicians to postpone PSA testing for 4-6 weeks after a proven UTI.

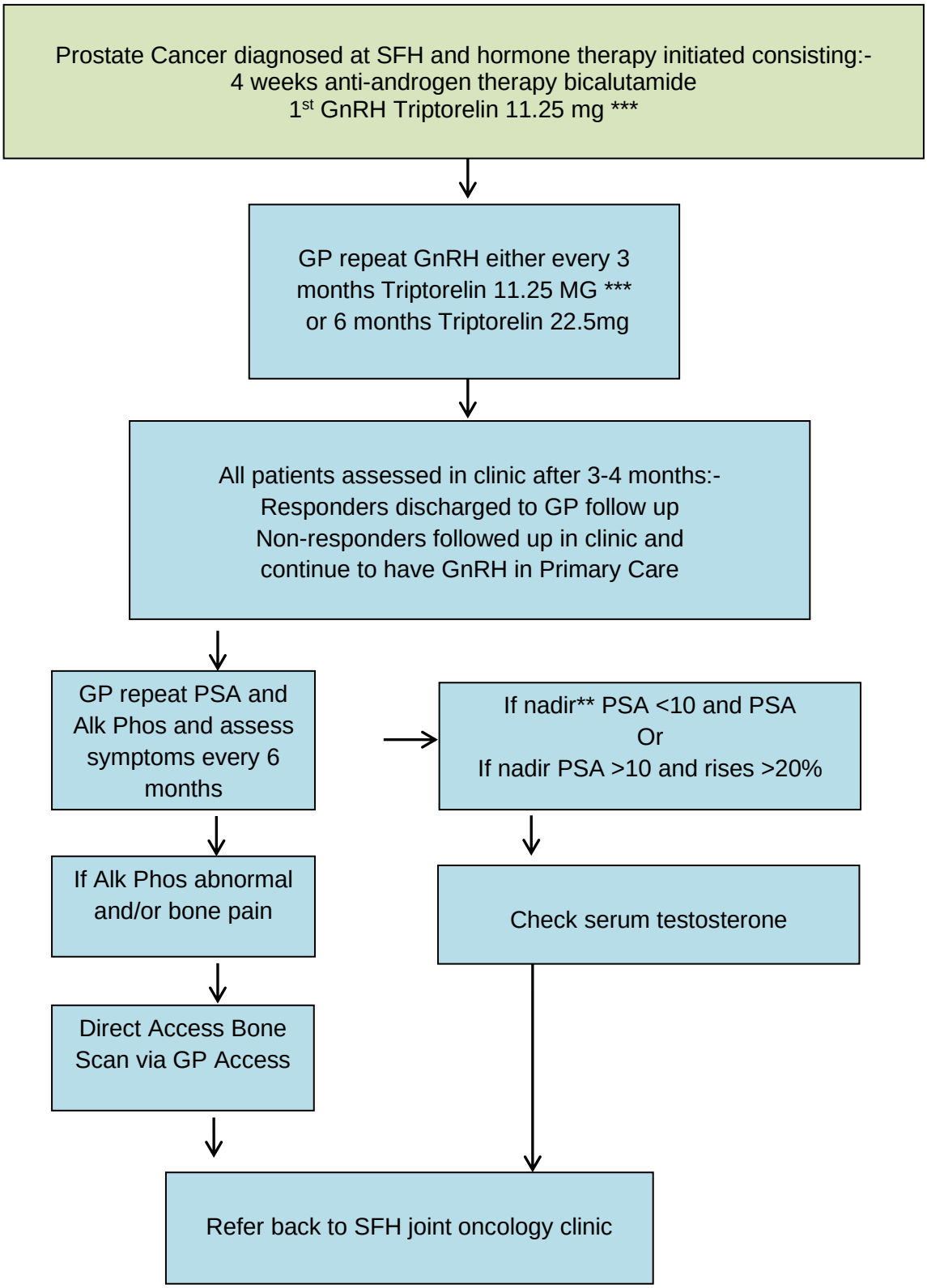
1. Watchful waiting

Patients who are deemed to be watchful waiting, defined as the monitoring of patients with asymptomatic prostate cancer with a view to palliative therapy including hormone therapy, if symptoms develop.



*NB consider other causes of raised AlK Phos e.g liver disease

2. Administration and monitoring of patients on Hormonal Therapy GnRH



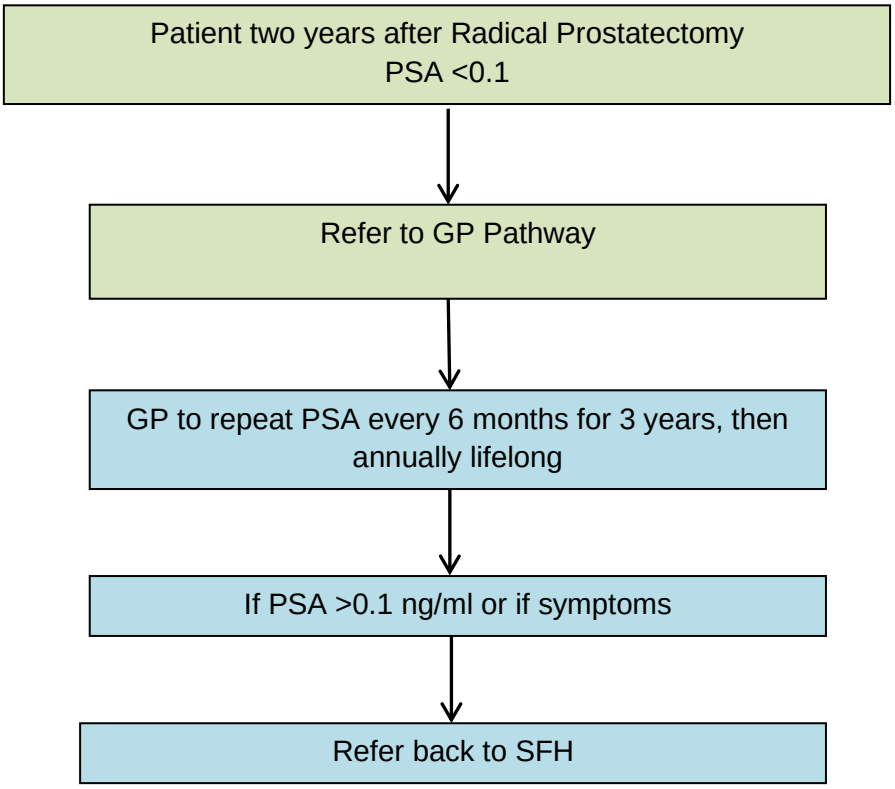
* All patients whether responders or non-responders will be referred back to GP for GnRH injections and can all be included in register

** Nadir PSA = lowest PSA level following diagnosis

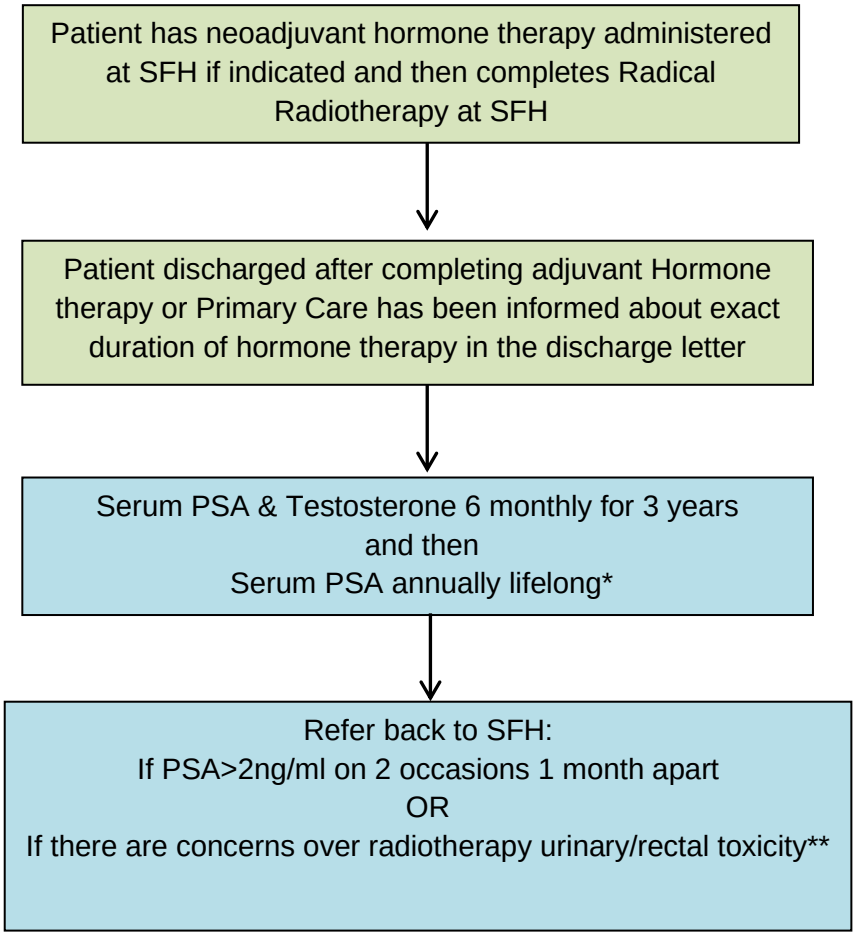
*** Triptorelin is currently recommended by the Area Prescribing Committee APC

3. Monitoring patients discharged 2 years after Radical Prostatectomy

NICE guidelines recommends that all patients without on-going problems should be discharged 2 years after radical prostatectomy



4. Monitoring after Radical Radiotherapy/Brachytherapy



*Please consider referring patients in whom the serum testosterone remains persistently low >12 months after completing hormone therapy. In patients with severe co-morbidity, routine PSA checks may be stopped altogether, with PSA tests reserved for symptomatic progression only.

**NICE guidelines recommend referral for full investigations, including flexible sigmoidoscopy, in men who have symptoms of radiation-induced enteropathy, colicky abdominal pain, diarrhoea, rectal bleeding, tenesmus

5. Active surveillance

Active surveillance is defined as the active monitoring of patients with prostate cancer, with a view to treatment with curative intent if there are signs of progression.
*Note - patients in this group will continue to be followed up in secondary care.

6. Reference ranges

PSA Levels

Age matched reference range after prostate cancer diagnosis is not important. Trends in PSA levels give a better indication of treatment efficacy – refer back as per the agreed pathways.

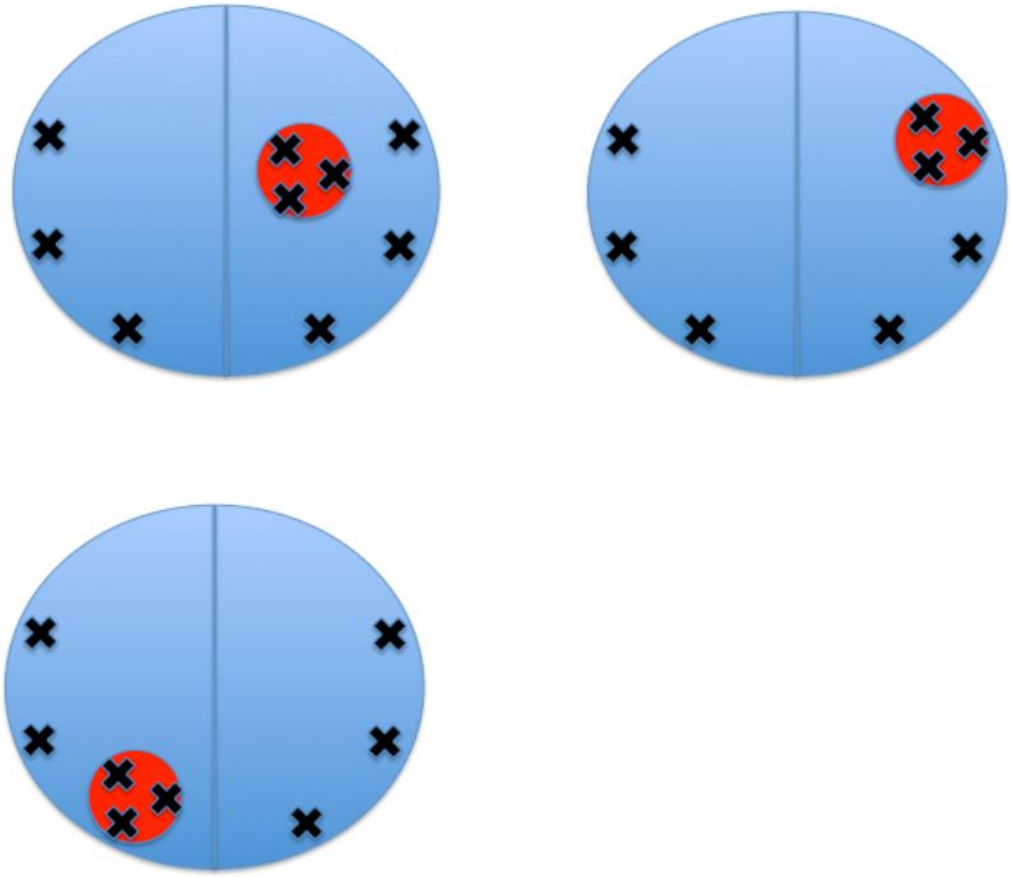
Alkaline Phosphatase

40-130 normal range. Also consider hepatic causes for increased level.

Testosterone

If >2.0nmmol/litre, consider treatment failure and refer to SFH as per the agreed pathways.

Appendix C - Diagram



Appendix 4. Cognitive transperineal/ MR-US fusion targeted and limited sampling technique for different lesion locations. [Required for men >/= 70 years of age eligible and willing to undergo robotic-assisted radical prostatectomy. 3 sample pots should be sent; targeted (minimum 4 cores), left posterolateral, right posterolateral]

Appendix D – Example Standard Prostate Cancer Letter Template

Sherwood Forest Hospitals
NHS Foundation Trust

Please ask for:
Mr Bhojwani's Secretary

NHS Number: nhs
Ref: AGB/JL/ id

DATE (today)

King's Mill Hospital
Mansfield Road
Sutton in Ashfield
Nottinghamshire
NG17 4JL

Tel: 01623 622515 ext 3753

TITLE FORENAME SURNAME
Addr1
Addr2
Addr3
Addr4
Post Code

Dear TITLE SURNAME

Thank you for coming in for your recent MRI scan. I am very pleased to report that there was no evidence to suggest progression of your known low-risk prostate cancer. As such, I would recommend that we continue on an active surveillance policy. I have arranged for you to come back to our Nurse Led Telephone Clinic for 6 monthly PSA tests. You will require a further MRI scan in two years' time, which we will arrange for you nearer the time.

Kind regards

Yours sincerely

Mr A G Bhojwani FRCS Urol
Consultant Urological Surgeon

Cc GP_TITLE GP_INITS GP_SURNAME
GP_PRACTICE
GP_ADDR1
GP_ADDR2
GP_ADDR3
GP_ADDR4

Clinical Nurse Specialist

3 RENAL CANCER GUIDELINES

3.1 Referral for investigation (also see Section 1)

Refer people urgently using a suspected cancer pathway referral (2WW) if:

- **Aged 45 yrs and over with visible haematuria (VH) which is unexplained or persists/recurs after treatment of UTI***
- **Aged 60 yrs and over with non-visible haematuria (NVH) and either dysuria or a raised serum white cell count****
- **Radiological imaging is suspicious for kidney/bladder malignancy**

** Consider non-urgent referral for patients <45 yrs with visible haematuria which is unexplained or persists/recurs after treatment of UTI.*
*** Consider non-urgent referral for patients ≥60 yrs with either persistent NVH or recurrent/persistent urinary tract infection.*

Locally mandated information for 2 week-wait referral should include demographics, investigation results (PSA, U&E/ eGFR, urine dipstick (+ MSU result if dipstick positive), and DRE), performance status, weight and BMI, medication, anticoagulant history, and MRI scanning exclusion criteria (see Section 1).

3.2 Staging

- FBC, U+E, LFT Albumin and ALP, CRP and ESR
- CT of chest, abdomen and pelvis with IV contract
- Bone scan: if bone pain or elevated ALP (NB Stauffer's syndrome)
- DMSA- if imperative or elective partial nephrectomy is being considered or if differential function is suspected to be asymmetric
- MR abdomen: if clarification of venous involvement is required (ensure repeat ideally within one week of surgical intervention)
- Renal mass biopsy (RMB): not normally required in the context of an enhancing mass on CT where surgery is planned (EAU guidelines) but should be considered in the following circumstances:
    i. Diagnostic uncertainty
    ii. Renal tumour and extra-renal malignancy
    iii. Small renal mass lesions considered for active surveillance
    iv. Prior to renal ablative treatment
    v. Cases where the patient is unsuitable or unwilling to undergo surgery, and where biological treatment is indicated TKIs etc
- Brain CT - only if symptoms of cerebral metastases
- 3D CT reconstruction may be considered for nephron sparing surgery or in cases with abnormal anatomy i.e. horseshoe kidney etc

3.3 Treatment

3.3.1 General considerations

All renal tumours should be discussed at the local MDT meeting. Complex cases to be discussed in detail include small renal masses suitable for active surveillance or partial nephrectomy, T3 tumours with venous extension, radiological N+ disease, bilateral tumours, patients requiring renal support, and those with inherited renal tumour predisposition syndromes e.g. vHL disease etc.

3.3.2 Small renal masses (pT1a ≤ 4cm)

The incidence of small renal masses is increasing secondary to the widespread use of abdominal USS and cross-sectional imaging. Often cases are referred to the Departmental X-ray meeting and Uro-Oncology MDT meetings without appropriate initial investigation. Frequently the findings of a well-performed formal renal characterisation scan guide decision-making without the need for further discussion.

3.3.2.1 Renal mass characterisation

- All incidentally-found small renal masses require a formal triple-phase CT abdomen/pelvis for characterisation prior to treatment planning. Thoracic imaging should not be routinely performed at this stage according to accepted ALARA principles.
- If the CT abdomen and pelvis demonstrates an enhancing mass lesion or Bosniak 3/4 cyst a CT thorax should be arranged and the patient referred to the Uro-oncology MDT for discussion.

3.3.2.2 Imaging in patients with renal impairment

Current SFH guidelines allow for the administration of IV contrast to patients with an eGFR of 30ml/min or more. Patients with an eGFR < 30ml/min who require further characterisation may be suitable for either a contrast-enhanced USS, a plain CT abdomen/pelvis or alternatively a non-contrast MRI renal scan dependent of previous tests. Specific cases should be discussed directly with the Uro-Radiology team to ensure the most appropriate next investigation.

3.3.2.3 Benign renal tumours

(i) Bosniak cystic lesions

- Bosniak 1 and 2 renal cysts - discharge with no further imaging.
- Bosniak 2F renal cysts - there is a lack of quality evidence on the subject but the best available evidence (Hindman 2014) suggests approximately 11% patients progress, of which 90% are malignant, and all progress within 4 years. Therefore all patients should be scanned annually for 4 years (CT or MRI) and if no progression may be discharged.

- Bosniak 3 and 4 cysts - manage as for malignancy. Perform CT thorax and refer to the Uro-Oncology MDT.

(ii) Sporadic renal angiomyolipoma (AML)

AMLs are usually diagnosed incidentally and the evidence base for surveillance/treatment is limited. However, based on the best available evidence (Bhatt 2016, Flum 2016), once formally diagnosed on renal characterisation CT, the following management is recommended:

- Perform annual community USS in all men and pre-menopausal women (women no longer require surveillance after the menopause). Refer to Urology if ≥ 4cm or symptomatic (pain/haematuria).
- Perform USS renal 3 monthly during pregnancy. Refer to Urology if ≥ 4cm or symptomatic (pain/haematuria).

It should be noted not all patients with AMLs ≥ 4cm require embolisation, although size, a growth rate of > 0.25cm/yr, or a large angiogenic component are associated with a higher risk of bleeding complications.

3.3.2.4 Active surveillance

Accumulating evidence suggests that active surveillance may be a viable alternative to surgery in some patients with small renal masses. It is generally accepted that metastasis at presentation with an SRM is rare (<1%), growth rates for tumours <3cm are slow (0.1 to 0.3cm per year – Jewett et al 2011; Chawla et al 2006) and the development of metastases whilst on active surveillance is uncommon (1-2% per year). While the routine use of active surveillance in younger, fitter patients cannot yet be recommended, the publication of the large Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) study demonstrated CSS of 99% and 100% at 5 years in those patients with SRM under 4cm treated with radical treatment and active surveillance respectively.

Active surveillance should be considered an option in the following patient groups:

- Elderly patients
- Patients with significant coexistent co-morbidity
- Severe underlying renal dysfunction
- Informed younger patients who are unwilling to consider extirpative surgery and accept a risk of disease progression whilst on active surveillance

Active surveillance should be differentiated from palliative management in patients who are clearly unfit for surgical intervention, and should be reserved for patients in whom surgery would be feasible should they demonstrate signs of progression.

3.3.2.5 Renal mass biopsy

In a recent meta-analysis renal mass percutaneous core biopsy demonstrated a diagnostic rate of 92%, with a sensitivity and specificity of over 99%. (Marconi et al. 2016 Eur Urol). Renal mass biopsy (RMB) should be considered in all patients entering an active

surveillance programme as approximately 30% of lesions under 3 cm are benign and certain histological features might prompt a recommendation for immediate surgical treatment. Specific adverse biopsy features include the following:

- Type 2 papillary renal cell carcinoma
- Grade 3/4 clear cell renal cell carcinoma
- Sarcomatoid differentiation
- Urothelial carcinoma

There is no role for renal biopsy in the assessment of cystic lesions.

3.3.3 Partial nephrectomy

The oncological safety of nephron sparing surgery has been established and should be considered for all patients with T1 tumours. Minimally invasive partial nephrectomy laparoscopic or robotic should be considered for all of these patients although remains a technically challenging procedure. Open partial nephrectomy with/without intraoperative cooling remains an alternative in carefully counselled patients.

Absolute indications for partial nephrectomy

- Solitary kidney
- Bilateral synchronous tumours
- Metachronous tumours (vHL)

Relative indications

- Tumour <7cm with normal contralateral kidney
- Established renal impairment
- Systemic disease that may affect renal function e.g. diabetes

Contraindications to partial nephrectomy

- Insufficient volume of remaining parenchyma to maintain proper organ function
- Renal vein thrombosis
- Unfavourable tumour location e.g. adherence to the renal vessels
- Use of anticoagulants

3.3.4 Radical Nephrectomy

This may be approached via open surgery or a laparoscopic approach depending on tumour characteristics and surgical factors. A laparoscopic approach is generally preferred for patient recovery.

3.3.4.1 Adrenalectomy

Adrenalectomy is not mandatory. The only definite indication is evidence of direct invasion of the ipsilateral adrenal on pre-operative imaging.

3.3.4.2 Lymphadenectomy

Lymphadenectomy offers more accurate staging and associated prognostic information, but historically has not been shown to improve survival in patients with clinical N0 disease pre-operatively. A recent meta-analysis demonstrated no survival benefit in M0 and M1 patients undergoing lymph node dissection (Bhindi

et al, BJUI 2018). In patients with suspected N1 disease pre-operatively LND is recommended (although the evidence base is extremely poor), as surgery remains the only curative option and approximately 20-30% of patients will survive 10 years. The extent of lymphadenectomy remains controversial.

3.3.4.3 Metastatic disease cytoreductive nephrectomy

The evidence for nephrectomy in the presence of metastases remains unclear in the era of oncological treatment with targeted systemic therapies. Attempts have been made to risk stratify patients with metastatic RCC into prognostic groups which in turn are used to determine recommendation for cytoreductive nephrectomy. The most notable risk calculator is based on the Heng (IMDC) criteria.

Heng Criteria:

- Karnofsky performance score <80 % = 1 point
- < 1 year from diagnosis to systemic therapy = 1 point*
- Haemoglobin <120g/L = 1 point
- Calcium > 10.2mg/dL = 1 point
- Neutrophils >7x109/L = 1 point
- Platelets >400,000 = 1 point

Interpretation:

- Good prognosis group = 0 points
- Intermediate prognosis group = 1-2 points
- Poor prognosis group = 3 or more points

* this is not relevant for patients with metastases at primary presentation and should be disregarded when calculating a **Modified Heng Score** to decide on CNx

Based on the best available evidence – CARMENA (No overall survival benefit from surgery, but almost all patients were intermediate or poor prognosis groups), SURTIME (poorly recruited but favouring systemic therapy prior to surgery) and a recent meta-analysis (Bhindi et al. Eur Urol 2019) we recommend the following:

- Offer up front cytoreductive nephrectomy to good prognosis patients, provided they have a they have a favourable primary:metastatic ratio and no bony/visceral organ mets.
- Offer up front systemic therapy followed by re-staging in intermediate prognosis patients. Those that demonstrate a stable or improved disease burden could be offered cytoreductive nephrectomy provided they have a they have a favourable primary:metastatic ratio and no bony/visceral organ mets.
- Do not offer surgery to poor prognosis patients.

*Any decision to perform cytoreductive surgery should be fully discussed at the SMDT and with a carefully counselled patient. All clinicians referring patients with metastatic RCC to the

SMDT should include Karnofsky performance score and results of necessary blood tests to allow the SMDT to calculate a Modified Heng/IMDC score.

There is little or no role for palliative nephrectomy. Renal embolisation is an option for patients with troublesome bleeding who are not surgical candidates, and should be performed by specialist vascular interventional radiologists. In patients with metastatic RCC who are unsuitable for cytoreductive nephrectomy, a biopsy should be performed to confirm the diagnosis prior to oncological treatment. All patients should be referred to oncology for consideration of systemic treatment regardless of performance status and tumour subtype.

3.4 Follow Up

Most of the literature regarding follow-up of renal cancer relates to biological behaviour of the clear-cell subtype. In this regard, the Leibovich score appears to discriminate the likelihood of recurrence, as shown below. Recurrences to the thorax are usually asymptomatic, those to bone and brain symptomatic, those to abdomen equivocal.

Leibovich Risk Group	**Year 1 %**	**Year 3 %**	**Year 5 %**	**Year 10 %**
Low O-2	0.5	2.1	2.9	7.5
Intermediate 3-5	9.6	20.2	26.2	35.7
High >6	42.3	62.9	68.8	76.4

The following guidelines have been agreed for all patients undergoing radical/partial nephrectomy follow-up, provided surgical margins are clear.

- Low risk (0-2) — Discharge to GP at first post-operative review
  Annual CXR by GP for 10 years
- Intermediate risk (3-5) — CT chest/abdomen/pelvis 6,12,24,36 mo.
  Then annual CXR & USS abdomen by GP to 10 years
- High risk >6 — CT chest/abdomen/pelvis 6,12,24,36,48,60 mo.
  Then annual CXR & USS abdomen by GP to 10 years

Oncocytoma	Not cancer. Discharge to GP
Chromophobe	Follow-up as for low-risk
Papillary	Follow-up as for intermediate risk
Other Subtype	Follow-up as per EAU risk stratification (see EAU guidelines)

VHL patients – combination of MRI/CT as recommended by MDT for detailed followup. Intervention to be based on radiological appearances and planned when the largest lesion reaches 3cm or undergoes rapid growth. Surgery for vHL is not considered curative and is aimed at preventing metastasis. Any intervention must balance the risk of metastasis against the morbidity of intervention.

3.5 Recurrent Disease

Distant: All cases to be discussed at SMDT
Consider period of observation to determine disease cadence and then consider excision if isolated recurrence
Widespread recurrence is not an indication for surgical intervention

Local: All cases to be discussed at SMDT
Consider excision if disease cadence is favourable and isolated

3.6 Management of upper urinary tract urothelial carcinoma (UTUC)

Radical nephroureterectomy (RNU) with formal excision of an ipsilateral bladder cuff is considered gold standard treatment for upper tract urothelial cancer. However kidney preserving treatment may be considered in all patients with pathologically confirmed low-risk disease (see EAU guidelines). It may also be considered following MDT review in the following patients with high-risk disease, provided survival is not significantly compromised.

- Isolated distal ureteric tumour
- Solitary functioning kidney
- Severe renal insufficiency
- Significant co-morbidity

3.6.1 Adjuvant chemotherapy following RNU

The POUT trial has shown that adjuvant chemotherapy is associated with a significant survival advantage following radical nephroureterectomy. Whilst the greatest benefit was seen for cisplatin combination therapy, carboplatin (reserved for patients with a postoperative eGFR 30-59 ml/min) also showed benefit. Therefore **all patients with T2-4 N0-3 M0 disease after nephroureterectomy and an eGFR ≥ 30 should be referred** for consideration of adjuvant chemotherapy.

3.6. Surveillance protocol after radical nephroureterectomy

Compared with equivalent stage and grade bladder cancer UTUC has a higher rate of recurrence and death. In addition - although not considered a distant recurrence from an oncological perspective - bladder recurrences occur in up to 50% of patients.
Recommended follow-up schedules are shown below:

Non-muscle invasive UTUC (Tis/Ta/T1)

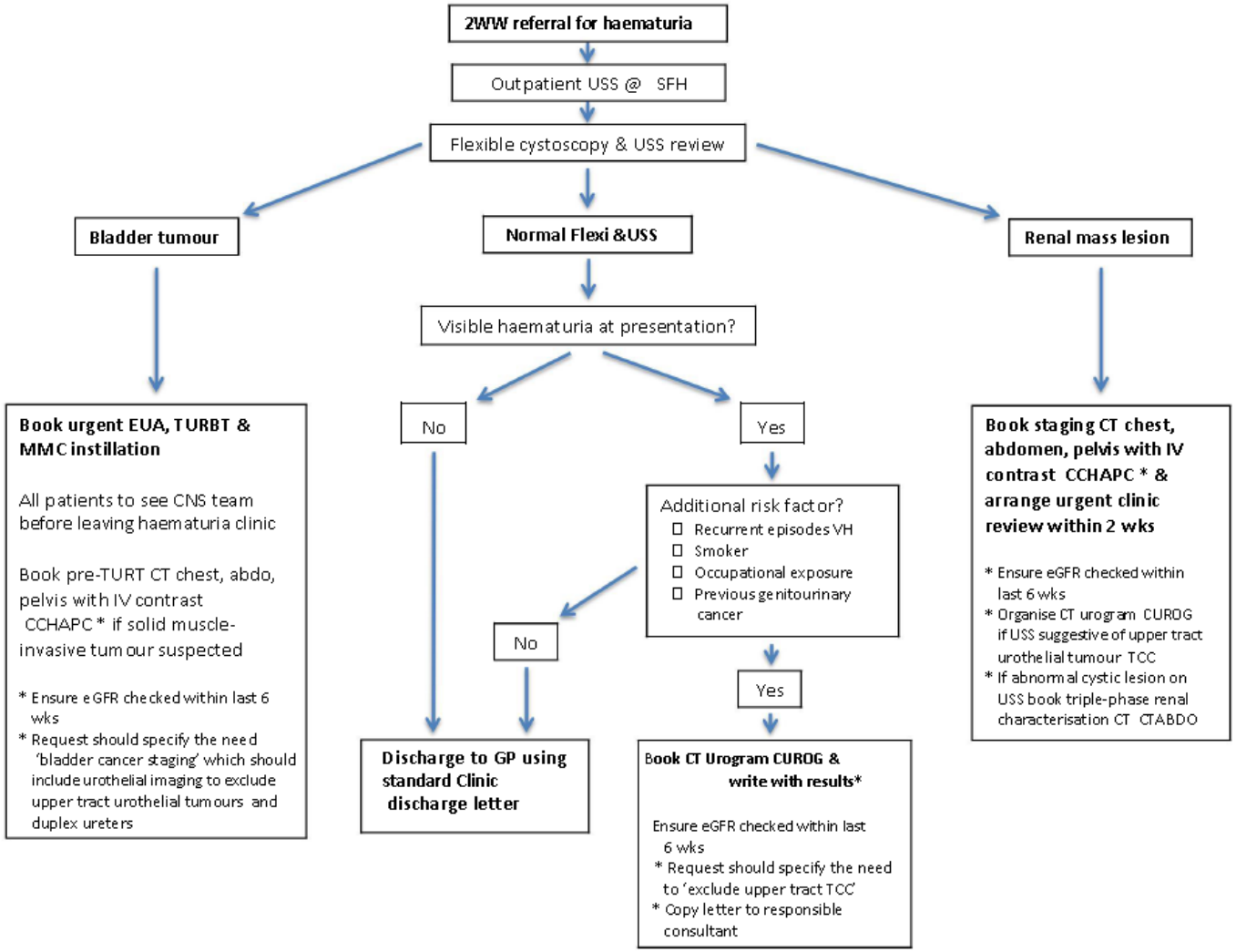
CT urogram and CT chest at 12 & 24 months
Then annual CTU to 5 years
Flexible cystoscopy 3 monthly for 2 years, 6 monthly for 3 years, then annually for 5 years
Discharge at 10 years

Muscle-invasive UTUC (T2+)

CT urogram and CT chest at 6, 12, 24 and 36 months

Then annual CTU to 5 years
Flexible cystoscopy 3 monthly for 2 years, 6 monthly for 3 years, then annually for 5 years
Discharge at 10 years

Appendix E – 2WW referral for haematuria (flowchart)



Appendix F – Example Letter Regarding Recent Investigations

Sherwood Forest Hospitals
NHS Foundation Trust

Please ask for:
Secretary to…….

King's Mill Hospital
Mansfield Road
Sutton in Ashfield
Nottinghamshire
NG17 4JL

Tel: 01623 622515 ext 3753

NHS Number: nhs
Ref: / id

DATE (today)

TITLE FORENAME SURNAME
Addr1
Addr2
Addr3
Addr4
Post Code

Dear TITLE SURNAME

The purpose of this letter is to confirm that **your recent investigations blood in the urine were normal**. As such, you do not need any further investigation or follow up at this time. Very occasionally blood in the urine can predict kidney problems in the future. For this reason, we recommend that you have your blood pressure, kidney function and urine tested at your GPs once a year. If you have further blood on dipstick testing we would not necessarily need to see you again, but **if you see blood in the urine on more than one occasion, further investigations may be necessary**. If this is the case, we would ask that you see your GP to arrange for further referral to be made.

Yours sincerely

Urology Department

Cc GP_TITLE GP_INITS GP_SURNAME
GP_PRACTICE
GP_ADDR1
GP_ADDR2
GP_ADDR3
GP_ADDR4

Attention for GP. NICE guidelines CG73 recommends that patients with persistent non-visible haematuria be followed up 'annually with repeat testing for haematuria, proteinuria/albuminuria, GFR and blood pressure monitoring for as long as the haematuria persists.'

4 BLADDER CANCER GUIDELINES

4.1 Referral for Investigation

Refer people urgently using a suspected cancer pathway referral (2WW) if:

- **Aged 45 yrs and over with visible haematuria (VH) which is unexplained or persists/recurs after treatment of UTI***
- **Aged 60 yrs and over with non-visible haematuria (NVH) and either dysuria or a raised serum white cell count****
- **Radiological imaging is suspicious for kidney/bladder malignancy**

** Consider non-urgent referral for patients <45 yrs with visible haematuria which is unexplained or persists/recurs after treatment of UTI.*

*** Consider non-urgent referral for patients ≥60 yrs with either persistent NVH or recurrent/persistent urinary tract infection.*

Locally mandated information for 2 week-wait referral should include demographics, investigation results (PSA, U&E/ eGFR, urine dipstick (+ MSU result if dipstick positive), and DRE), performance status, weight and BMI, medication, anticoagulant history, and MRI scanning exclusion criteria.

An algorithm for the investigation of 2WW patients with haematuria, and a sample haematuria discharge letter are shown in Appendix E&F.

General considerations:

- 'Trace' of blood on urinalysis = insignificant
- NVH: >/= 1 + blood on urinalysis. Confirmation via microscopy not required
- Persistent NVH = 2/3 urinalyses with >/= 1+ blood

4.2 Investigations for Haematuria

Patient fulfilling the above 2WW criteria for investigation are booked for a direct-to-test renal tract ultrasound scan followed by flexible cystoscopy. Where possible, if UEs and risk factors are known a CT Urogram may be booked as a primary investigation for visible haematuria.
General considerations:

- If a solid bladder tumour is suspected at flexible cystoscopy request a CT chest, abdomen and pelvis with IV contrast prior to TURBT. The request should indicate the need for 'bladder cancer staging', including urothelial imaging to identify co-existing upper tract urothelial tumours and duplex ureters.
- Request a CT urogram after a normal Flexi/USS in patients with visible haematuria and one or more additional risk factors (see below):
  - **Recurrent episodic visible haematuria**
  - **Current or ex-smoker**
  - **Occupational risk (rubbers, dyes, benzenes etc.)**

- **History of genitourinary cancer**
- **Previous pelvic irradiation**

- Request a CT urogram if the USS is suggestive of an upper tract urothelial tumour (UTUC).
- Request a renal characterisation CT abdomen/pelvis for patients with small renal tumours ≤4cm or atypical cysts on renal USS
- Request a staging CT chest, abdomen and pelvis with IV contrast for patients with renal mass lesions > 4cm on renal USS

4.2.1 Outcome of Haemauria work-up

(i) Negative investigations

For patients with a normal flexible cystoscopy/renal tract USS without further indication for investigation, discharge to GP using a standard haematuria clinic discharge letter (see section 3). For those patients with outstanding investigations, do not bring patients back to clinic if the results are normal. Write with results and discharge to GP using a standard haematuria clinic discharge letter.

Patients should be referred for further investigation if they develop episodic visible haematuria.

(ii) Bladder tumour identified

Ensure all patients are seen by the CNS team for counselling prior to leaving the haematuria clinic. If direct access to the CNS team is not possible ensure patient details are left with the CNS team for further contact. Record the number, size and location of tumour(s) and list for an urgent EUA, TURBT and MMC instillation.*

*Whilst MMC instillation is not beneficial for patients with muscle-invasive bladder cancer, the decision to omit MMC should be taken by the operating surgeon at the time of TURBT, based on the pre-operative imaging and intraoperative assessment (see 4.3 below).

4.3 Initial TURBT

The quality of transurethral resection has a substantial impact on patient outcome. The following are considered to be minimum requirements for the performance of TURBT at SFH.

- All TURBTs should be performed with narrow band imaging if available.
- Initial TURBT should be performed under GA with muscle paralysis unless there are significant contraindications. Lateral tumours/tumours occupying a large area of the bladder have the highest risk of obturator kick and subsequent bladder perforation.
- The operative note and histopathology form should specify the following:
    - Previous bladder cancer history and treatment
    - Pre and post-resection EUA
    - Anterior urethral abnormalities/prostatic urethral abnormalities
    - Location/size/multifocality of tumour(s) within the bladder
    - Whether the tumour has been completely resected or not

        - Every attempt should be made to obtain detrusor muscle in the resection specimen, as a failure to do so may adversely impact on subsequent treatment and prognosis. Following initial specimen resection, cold cut or loop biopsies of the tumour base should be taken and sent separately for histopathological analysis.
    - Avoid excessive cauterisation during TURBT to avoid tissue deterioration.
    - An attempt to fully resect the intravesical tumour component should be made in all cases.
    - Mitomycin C (MMC) should be given immediately following TURBT* (or within 6 hours if a tumour is identified unexpectedly), except in the following circumstances:
        - There is concern regarding bladder perforation (due to risk of extravasation).
        - There is concern regarding haematuria (due to risk of systemic absorption).
        - Muscle invasive bladder cancer is suspected.
        - EORTC recurrence score is confirmed to be > 5** (See scoring below; there is no evidence for the routine use of MMC in these patients.)
    - Biopsies of the prostatic urethra should be performed in men with a trigonal or bladder neck tumour, an abnormal prostatic urethra or in the presence of CIS. Biopsies should be taken from from the precollicular area (between the 5 and 7 o'clock position) using a resection loop.
    - Random biopsies of normal urothelium are not routinely required, but should be considered in patients with abnormal urine cytology in whom no other plausible explanation has been found.

* Several large meta-analyses have shown that a single post-operative instillation of MMC after TURBT significantly reduces the recurrence rate compared to TURBT alone (absolute reduction 14%; from 59% to 45%; number needed to treat (NNT) to prevent one recurrence within five yrs = 7).

**For patients with recurrent tumours, only those with a prior recurrence rate of less than or equal to one recurrence per year and those with an EORTC recurrence score < 5 will benefit from repeat single instillation of MMC.

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3	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
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total Score	**0-17**	**0-23**

Table: EORTC recurrence and progression score calculator

4.4 MDT Review

All patients with bladder cancer should be discussed at the MDT. Minimum reporting requirements for MDT discussion include:

- Primary or recurrent tumour
- Previous treatment history
- Number and size of tumours and whether completely resected
- Presence of urethral involvement
- Stage, grade and risk stratification of of resected tumour
- Presence/absence of detrusor muscle
- Presence/absence of additional CIS
- Co-morbidity/performance status/fitness for further surgery.

4.5 Non muscle invasive bladder cancer (NMIBC)

All patients with non-muscle invasive bladder cancer should be assigned a risk stratification according to the following table, to inform the need for adjuvant intravesical therapy & define subsequent surveillance protocols (see below). Following TURBT and discussion at the MDT patients will attend a nurse-led bladder tumour follow-up clinic to discuss adjuvant treatment/cystoscopic follow-up and to provide/document smoking cessation advice where indicated. Consultant outpatients review is reserved for patients in whom radical cystectomy being considered high-risk superficial/BCG refractory disease.

Low Risk

Urothelial cancer with any of:

- solitary pTaG1 ≤ 3 cm
- solitary pTaG2 (low grade) ≤ 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 > 3cm
- multifocal pTaG1
- solitary pTaG2 (low grade) > 3cm
- 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, plasmacystoid, large component sarcomatoid or nested variants

4.5.1 CT Urography

Carry out assessment for synchronous upper tract urothelial cancer if:

- High grade urothelial carcinoma

Also consider if:

- Multifocal tumour
- Trigonal location

4.5.2 Re-resection

Re-resection TURBT should be performed between 2 to 6 weeks* for:

- All T1 tumours (unless primary cystectomy is indicated)
- High grade urothelial tumours
- Incomplete primary resection

*High-grade pT1 bladder cancer patients at very high risk of understaging following initital TURBT (ie. large palpable mass on initial TURBT, suspicion of MIBC on imaging, upper tract obstruction, lymphadenopathy on imaging) should undergo reresection **as soon as feasible**

(i.e. 2 weeks following MDT discussion). An alternative option is consideration of immediate primary cystectomy following MDT discusssion.

Management options for NMIBC

4.5.2.1 Low-risk NMIBC

Transurethral resection followed by immediate intravesical MMC.
Surveillance flexible cystoscopy at 3,12,24 and 36 months
Discharge after 3 years without recurrence

Laser fulguration for low-risk tumours

In patients with a history of low-risk NMIBC who have low volume tumour recurrence consider outpatient biopsy and laser fulguration.

4.5.2.2 Intermediate-risk NMIBC

Transurethral resection followed by immediate intravesical MMC.
Consider additional intravesical MMC x 6
Surveillance flexible cystoscopy at 3,6,12,18,24,36,48,60 months
Discharge after 5 years without recurrence

Laser fulguration for intermediate-risk tumours

In patients with a history of intermediate risk NMIBC who have low volume tumour recurrence consider outpatient biopsy and laser fulguration.

Additional intravesical therapy for intermediate-risk disease

Consider mitomycin-C x 6 instillations (13-14% absolute reduction in recurrences). Bacillus Calmette Guerrin (BCG) instillations further reduce recurrence and modify progression risk but with additional toxicity. Consider if recurrences occur despite MMC x 6. Device-assisted MMC may also be considered as an alternative to BCG.

4.5.2.3 High-Risk NMIBC (5 year risk of progression = up to 45%)

Transurethral resection followed by immediate intravesical MMC
Arrange upper tract CT urography and perform re-resection where indicated
Offer the choice of intravesical BCG or radical cystectomy*

*this should be done by an urologist who performs radical cystectomy (see below).

Primary cystectomy for NMIBC

There are several reasons to consider immediate radical cystectomy (RC) for selected patients with NMIBC:

- The staging accuracy of TURBT for T1 disease is low (27-51% of patients are upstaged to muscle-invasive disease after cystectomy (especially those with residual disease on re-resection).

- Some patients with NMIBC progress to muscle-invasive disease despite intravesical treatment.
- Patients who progress to muscle-invasive disease have a worse prognosis than those who present with 'primary' muscle-invasive disease.

The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life. It is reasonable to propose immediate RC in those patients with NMIBC who are at highest risk of disease progression including:

- Incompletely resected high-grade disease not amenable to further endoscopic management
- pT1G3 tumour within a diverticulum (absent muscle layer)
- Tumours with adverse histopathological features:
    - Multiple/large (> 3 cm) pT1G3 tumours
    - pT1G3 with concurrent CIS (in bladder/urethra)
    - Recurrent high-grade (G3) tumours following radiotherapy
    - Recurrent high-grade (G3) tumour following BCG therapy (see later)
    - Residual high-grade T1 disease on re-resection
    - pT1G3 with lymphovascular invasion
    - Micropapillary, nested, plasmacystoid variants
    - Extensive non-urothelial differentiation (squamous/sarcomatoid)
    - Non-TCC T1 tumours (SCC, non-urachal adenocarincoma, small cell)

BCG therapy

BCG therapy should be administered according to the following schedules (unless enrolled in a clinical trial):

- **Primary/recurrent pT1/Ta G3/High grade TCC +/- CIS**: Induction BCG x6, followed by maintenance BCG x 3 at 3, 6, 12, 18 and 24 months. All patients should aim to complete 2 years if tolerated.
- **Primary CIS:** Induction BCG x 6, followed by maintenance BCG x3 at 3, 6, 12, 18 and 24 months. All patients should aim to complete 2 years if tolerated.
- **Recurrent intermediate risk bladder cancer despite MMC x6:** Induction BCG x 6, followed by maintenance BCG x3 at 3, 6, 12, 18 and 24 months. In this group the aim should be to complete 2 years, but it would be reasonable to consider stopping at 12 months if they are experiencing side effects.

Endoscopic Surveillance after BCG therapy

Perform the first post-induction BCG cystoscopy under GA (so that bladder sampling can be obtained) in the following patients:

Residual high-grade disease at re-resection
Primary CIS
pT1G3 +/- CIS

In other patients, perform flexible cystoscopy after 6 instillations with immediate GA cystoscopy/re-biopsy if mucosa remains abnormal. Proceed if clear with further **flexible cystoscopy 3 monthly for 2 years, 6 monthly until 5 years and then annually for 5 years. Discharge after 10 years without recurrence.**

4.5.3 Management of BCG failure / intolerance

Definitions

BCG Failure
Whenever a muscle-invasive tumour is detected during follow up
BCG-refractory tumour:
1. If a high grade, non-muscle invasive papillary tumour is present at 3 months (206). Further conservative treatment with BCG is associated with increased risk or progression (134, 207) (LE:3)
2. If CIS (without concomitant papillary tumour) is present at both 3 and 6 months. In patients with CIS present at 3 months, an additional BCG course can achieve a complete response in >50% of cases (48) (LE:3)
3. If high grade tumour appears during BCG therapy
High grade recurrence after BCG. Recurrence of high grade/grade 3 (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response (208) (LE:3)
BCG intolerance
Severe side effects that prevent further BCG instillation before completing induction (191)

BCG failure is associated with poorer oncological outcomes when compared with primary radical cystectomy. It should be identified as early as possible and managed aggressively, according to the following recommendations:

- **Muscle-invasive disease**: NAC and radical treatment (cystectomy/EBRT)
- **High-grade recurrence**: Unlikely to respond to further BCG*, and not considered radiosensitive. **Radical cystectomy is therefore the preferred option**. Other bladder preservation strategies (further intravesical immunotherapy, intravesical chemotherapy, device-assisted therapy and combination therapy) may be considered in those unfit or unwilling to consider cystectomy, but are considered oncologically inferior to surgery.

* The presence of CIS at the first post-induction GA cystoscopy is not considered to be BCG-failure as a further induction course of BCG is associated with a further response in >50% cases. Patients with low-grade NMIBC recurrences should receive TURBT and continue BCG therapy as tolerated.

4.6 Muscle-invasive bladder cancer (MIBC)

Minimum requirements for staging:

- FBC, U+Es, LFTs and calcium
- CT chest/abdomen/pelvis (CT scan requests should explicitly indicate the need for excretory phase images to delineate pelvicalyceal and ureteric anatomy and to exclude concomitant UTUC)
- Pelvic MRI may assist local assessment of T-stage in selected cases, as directed by the MDT
- Consider fluorodeoxyglucose positron emission tomography (FDG PET)-CT for people with MIBC or high-risk NMIBC before radical treatment if there are

indeterminate findings on CT or MRI, or a high risk of metastatic disease Following MDT discussion patients considered fit for radical surgery are seen urgently by a cystectomy surgeon and CNS team for counselling and treatment discussion. General considerations:

T2-4a N0 M0 urothelial carcinoma

- Identify adverse clinico-pathological risk factors for surgical vs. radiotherapy outcome (see below*)
- The survival benefit associated with neoadjuvant chemotherapy (NAC) is now believed to be 8% at 5 years for patients receiving cisplatin combination therapies. Therefore **consider referral for NAC prior to radical treatment in all patients with a performance status 0-2 and an eGFR ≥ 60ml/min**. Repeat cross sectional imaging and arrange MDT review after 2 cycles. (Ensure patients who are scheduled for radical cystectomy have appropriate urology follow-up arranged).
- Referral to clinical nurse specialist for further discussion/support.
- Provide/document smoking cessation advice.

*__Factors favouring surgery__; upper urinary tract obstruction, concomitant CIS, widespread multifocal tumour, requirement for urethrectomy, failure of endoscopic management, tumour within a diverticulum, non-urothelial TCC (adenocarcinoma and SCC are not radiosensitive), small capacity symptomatic bladder, previous pelvic radiotherapy, active inflammatory bowel disease, bilateral hip replacements, pregnancy.

*__Factors favouring radiotherapy__: small solitary tumour adequately debulked at TURBT, preference for bladder/sexual preservation, severe comorbidity. [when offering radiotherapy patients should be counselled that up to a 1/3rd patients experience local relapse necessitating salvage cystectomy]

Indications for urethrectomy at cystectomy

- Anterior urethral disease
- Extensive prostatic infiltration
- Bladder neck/urethral tumour in women
- Positive frozen section histology (if performed) at level of urethral dissection

Squamous cell carcinoma

Muscle-invasive SCC is considered a chemoresistant disease. Radical radiotherapy has previously been associated with poor outcomes. **Radical cystectomy and urinary diversion is therefore recommended as standard treatment.** Partial cystectomy does not have a role.

Primary bladder adenocarcinoma

In cases of bladder adenocarcinoma metastasis from a non-urological primary site should be excluded. Primary bladder adenocarcinoma typically presents with muscle-invasive disease, and is characterised by high rates of local recurrence (30%) and early metastasis. It is considered chemoresistant, and the role of radiotherapy remains to be defined. **Radical cystectomy and urinary diversion is therefore recommended as standard treatment.** Urachal adenocarcinoma accounts for approximately 10% of adenocarcinoma cases and is characterised by its location at the dome of the bladder. Urachal tumours are traditionally managed with umbilectomy, urachectomy and partial cystectomy.

Small cell/neuroendocrine tumours

Small cell bladder cancer is rare, but carries a high likelihood of tumour dissemination at presentation. Consider FDG PET routinely in such patients. Patients require immediate systemic chemotherapy, typically with cisplatin/etoposide followed by local radical treatment in the absence of metastatic disease.

4.7 Follow-up after Radical Cystectomy

Recurrence-free survival after cystectomy ranges from 61.7% to 76% at 5 years and 55.2% to 73% at 10 years. Recurrence may be local or distant, but generally confers poor prognosis. General considerations:

4.7.1 Local recurrence

Local pelvic recurrence occurs in 5-15% patients following cystectomy, typically within the first 24 months. Risk factors include pathological stage, LN involvement, limited LN yield and positive margins. Patients generally have a poor prognosis after the diagnosis of pelvic recurrence: **even with treatment median survival ranges from 4-8 months**. Treatment typically involves a multimodality strategy comprising chemotherapy radiation and surgery.

4.7.2 Metastatic disease

Most patients who recur after radical cystectomy do so with distant metastatic disease, typically to LNs, lungs, liver and bone. Risk factors include increasing pathological stage and positive LNs. Distant recurrence is most common in the first 2 years after cystectomy, with 90% developing within 3 years. **Median survival with platinum-based chemotherapy is 9-26 months**.

4.7.3 Urethral recurrence

Recurrent urothelial carcinoma in the retained urethra following cystectomy occurs in 4-6% of patients, with a lower incidence in continent diversions. Risk factors include prostatic urethra/prostate involvement, bladder neck disease in women and positive urethral margins. Urethral recurrences occur at a median range of 1.5 to 2.2 years, average survival is 28-38 months following urethral recurrence, and 50% will develop systemic disease. **A survival advantage in men with asymptomatic vs. symptomatic urethral recurrence mandates annual surveillance**

4.7.4 Upper tract recurrence

The risk of upper urinary tract recurrence after cystectomy is relatively low (1-9%), partly due to high mortality rates after treated MIBC, and partly as upper urinary tract recurrence is a delayed event. Patients with NMIBC are more likely to have UTUC than patients with invasive disease. Evidence that routine surveillance for UTUC confers a survival advantage is lacking; however it is generally accepted that earlier detection improves outcome.

4.7.5 Surveillance protocol after radical cystectomy

IVU/USS renal	6 weeks
Bloods (FBC, UE, LFT, Ca, bicarb, chloride)	6 months
CT Chest/Abdomen/Pelvis (with urography)	
High risk NMIBC	12,24 months, then annual CTU to 5 yrs Discharge at 5 years
MIBC	6, 12, 24 and 36 months, then annual CTU to 5 yrs Discharge at 5 years
Urethroscopy (where applicable)	Annually for 5 years

4.8 Surveillance protocol after radical radiotherapy

Following radical radiotherapy:

- Perform rigid cystoscopy 3 months after radiotherapy has been completed if patient fit for salvage cystectomy, followed by either or flexible cystoscopy:
    - every 3 months for the first 2 years **then**
    - every 6 months for 3 years **then**
    - annually for 5 years
- **CT chest,abdomen and pelvis (with urography) at 6,12,24 and 36 months, then annual CT urogram (CTU) to 5 years.**
- Discharge at 10 years

4.9 Metastatic bladder cancer

Systemic chemotherapy is associated with significant response rates and improved survival in patients with metastatic bladder cancer. Whilst cisplatin-combination remains first-line, immune checkpoint inhibitors (eg pembrolizumab, atezolizumab) also show good activity in cisplatin-ineligible patients. Therefore consider oncology referral following MDT discussion in all patients with metastatic bladder cancer and a performance status 0-2.

4.9.1 Managing symptoms of incurable locally advanced or metastatic bladder cancer

(i) Persistent/intractable haematuria

- Consider debulking palliative TURBT (also consider for severe storage symptoms)
- Palliative radiotherapy
- Angioembolisation

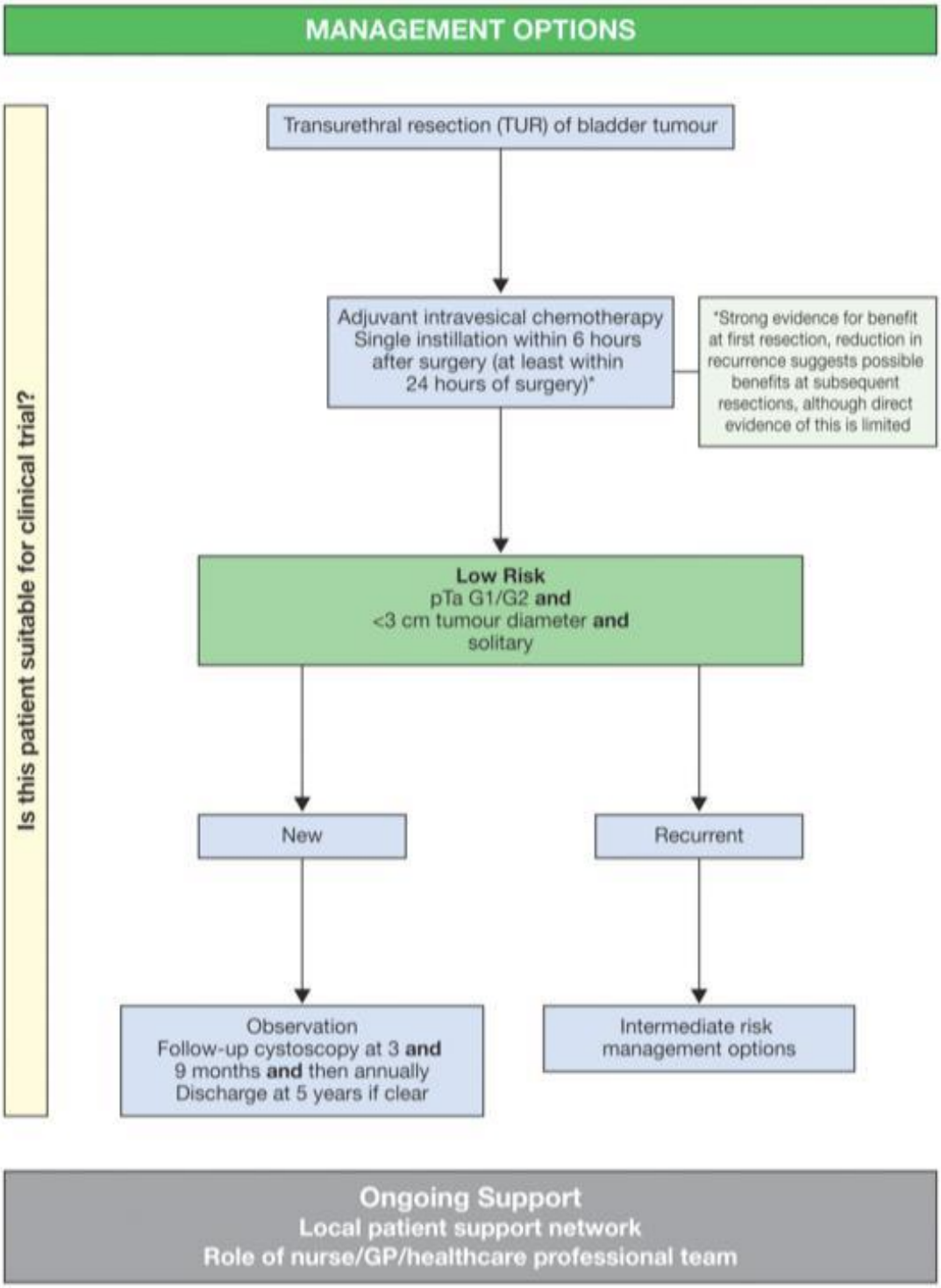
- Radical surgery - palliative cystectomy with urinary diversion carries the greatest morbidity and should be only considered in a fit patient for symptom relief of a non-curable cancer if there are no other options.

(ii) ***Loin pain and symptoms of renal failure***

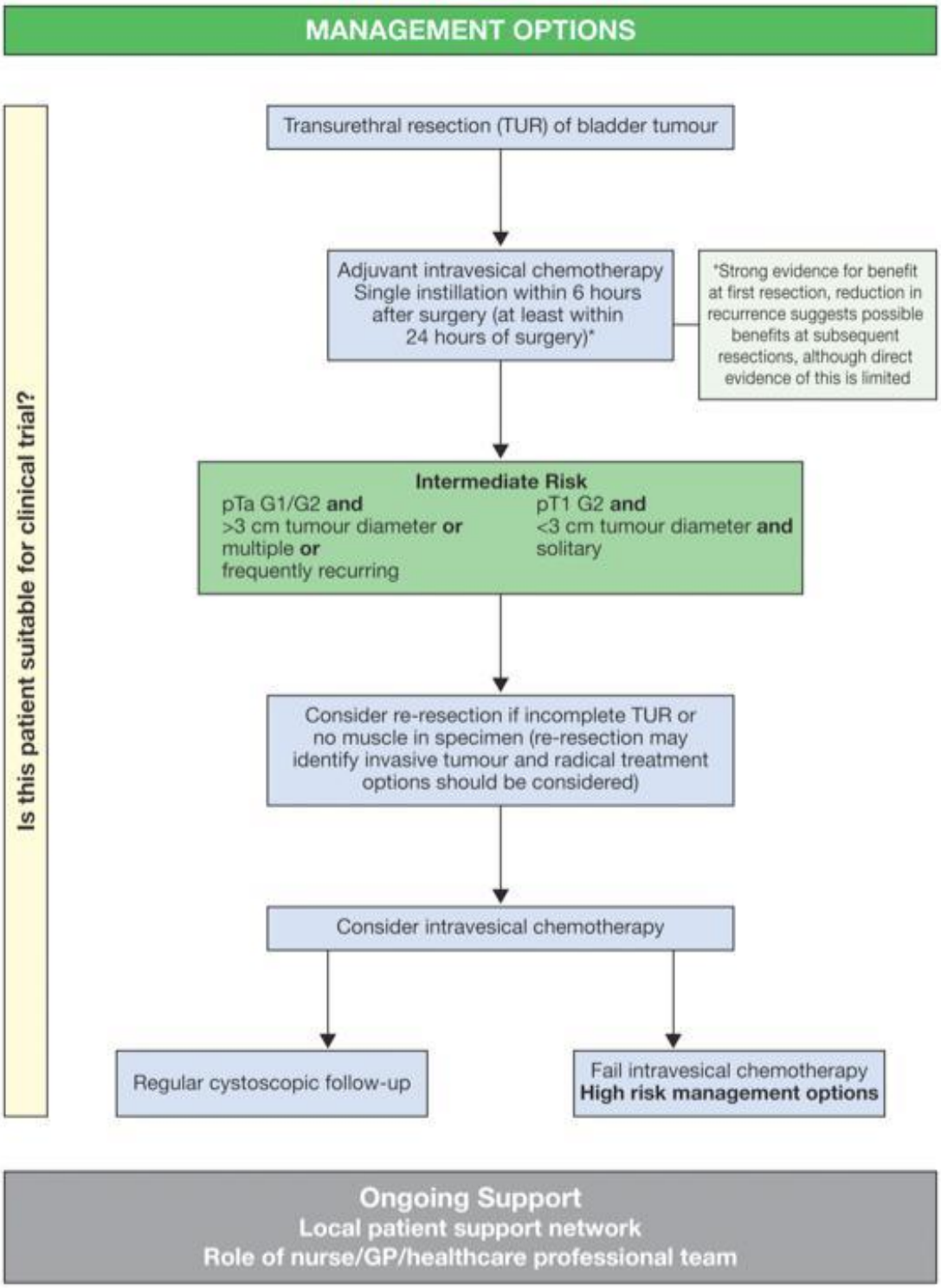
Consider percutaneous nephrostomy (single best kidney) or retrograde stenting (if technically feasible) for people with locally advanced or metastatic bladder cancer and ureteric obstruction who need treatment to relieve pain, treat acute kidney injury or improve renal function before further treatment. **In many cases, nephrostomy insertion will be preferred as it offers more reliable drainage** and avoids the need for general anaesthesia.

Low risk	Urothelial cancer with any of: • solitary pTaG1 ≤ 3 cm • solitary pTaG2 (low grade) ≤ 3 cm • any papillary urothelial neoplasm of low malignant potential **Flexible cystoscopy at 3,12,24,36 months** **Discharge when recurrence-free for 3 years**
Intermediate risk	Urothelial cancer that is not low risk or high risk, including: • solitary pTaG1 > 3cm • multifocal pTaG1 • solitary pTaG2 (low grade) > 3cm • 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 **Flexible cystoscopy at 3,6,12,18,24 months, then annually to 5 years** **Discharge when recurrence-free for 5 years**
High risk	Urothelial cancer with any of: • pTaG3 • pT1G2 • pT1G3 • pTis (CIS) • aggressive variants of urothelial carcinoma, for example micropapillary, plasmacystoid, large component sarcomatoid or nested variants Perform the first post-induction BCG cystoscopy under GA (so that bladder sampling can be obtained) in the following patients: • **Residual high-grade disease at re-resection** • **Primary CIS** • **pT1G3 +/- CIS** In other patients, perform flexible cystoscopy after 6 instillations with immediate GA cystoscopy/re-biopsy if mucosa remains abnormal. **Flexible cystoscopy at 3 monthly for 2 years, 6 monthly for 3 years, then annually for 5 years.** **Discharge at 10 years**

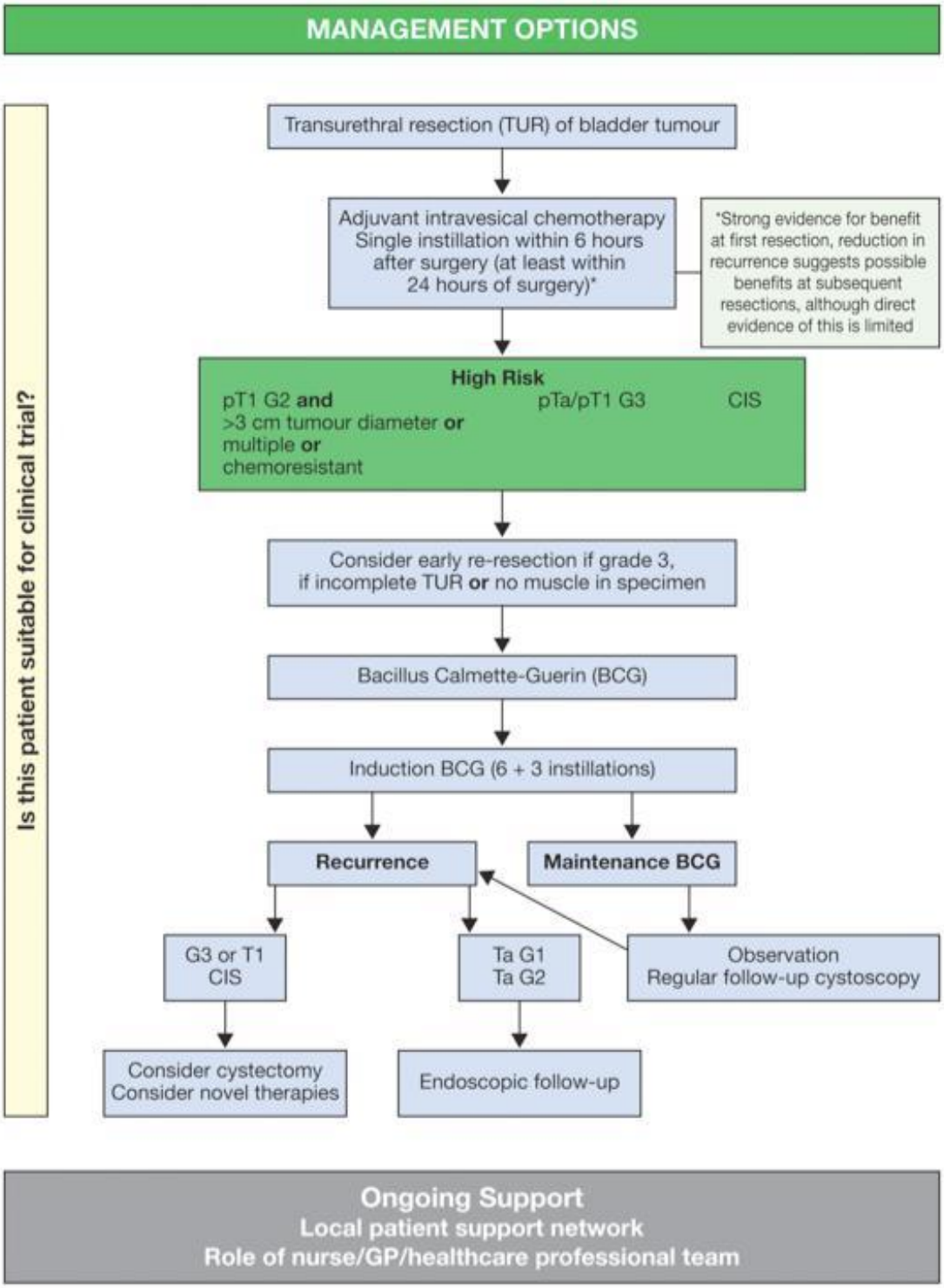
Appendix G – Algorithm for the Management of Low-Risk NMIBC



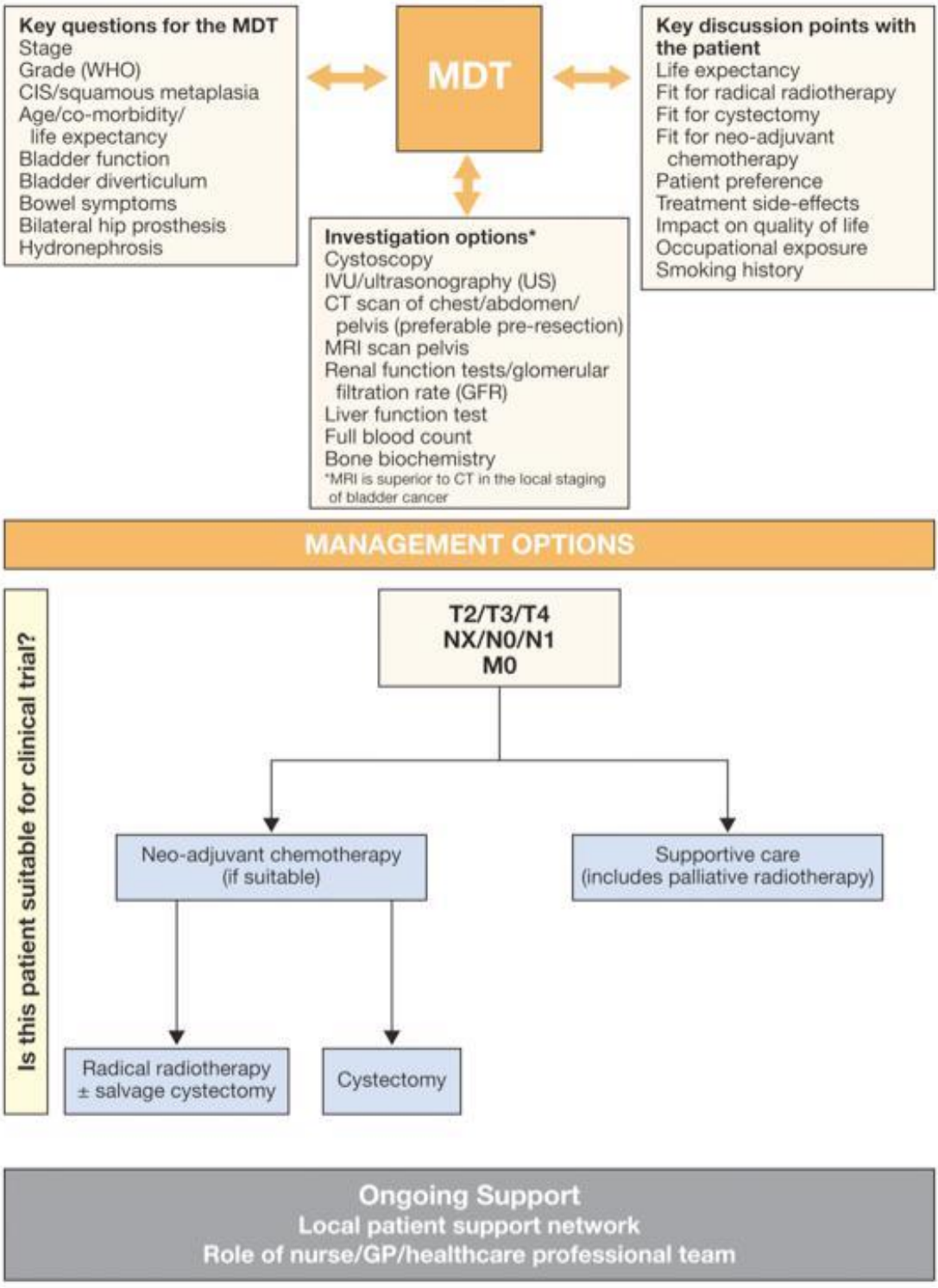
Appendix H – Algorithm for the Management of Intermediate-Risk NMIBC



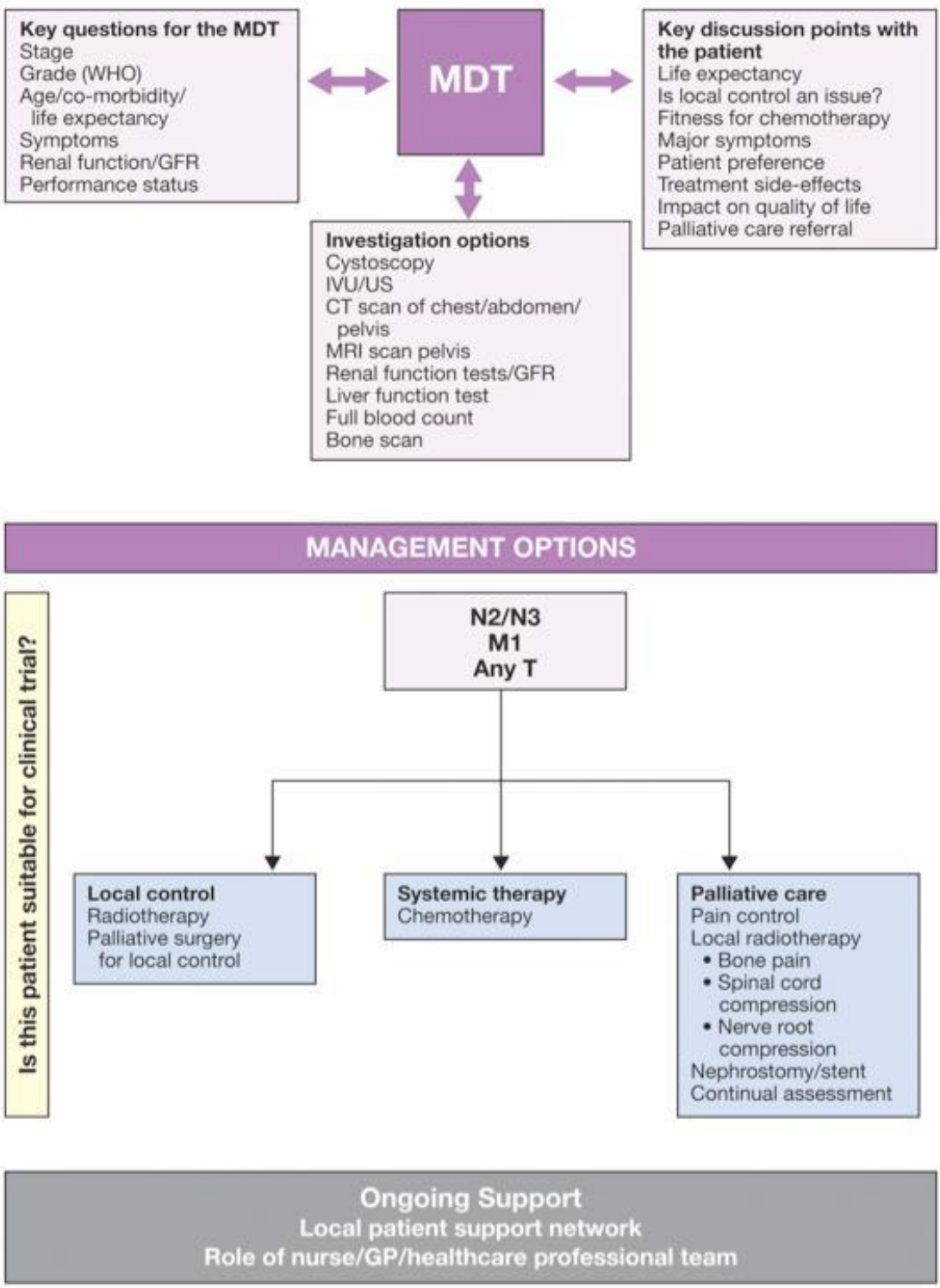
Appendix I – Algorithm for the Management of High-Risk NMIBC



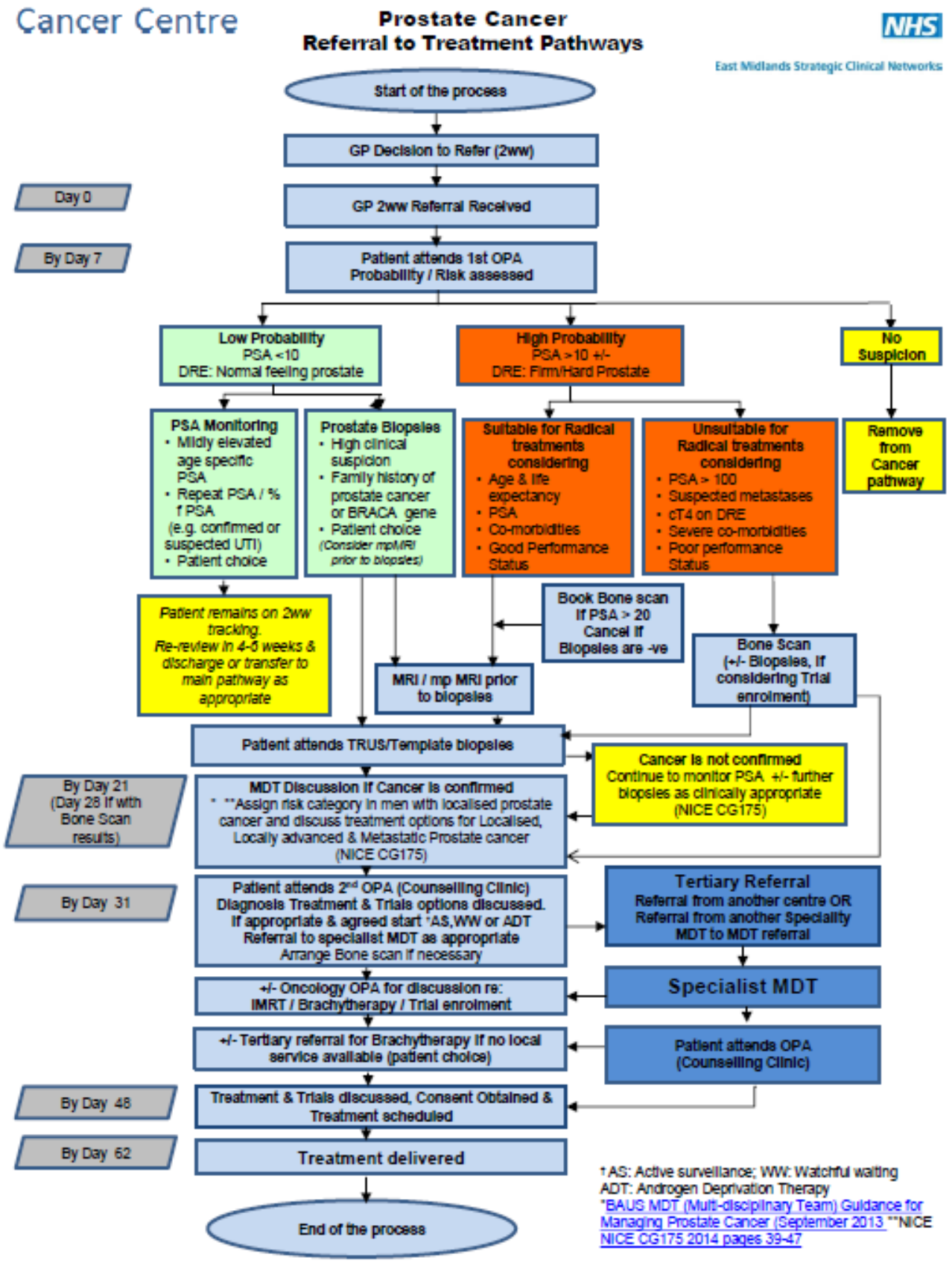
Appendix J – Algorithm for the Management of Organ-confined MIBC



Appendix K – Algorithm for the Management of Metastatic Bladder Cancer



Appendix L – Prostate Cancer Referral to Treatment Pathways and Risk Stratification of Newly Diagnosed Prostate Cancer Patients



Risk Stratification of Newly Diagnosed Prostate Cancer Patients

Level of risk	PSA		Gleason score		Clinical stage
Low risk	<10 ng/ml	&	≤6	&	T1–T2a
Intermediate risk	10–20 ng/ml	or	7	or	T2b
High risk[1]	>20 ng/ml	or	8 10	or	≥T2c
[1]High-risk localised prostate cancer is also included in the definition of locally advanced prostate cancer.					

*Risk stratification for men with localised prostate cancer (*NICE Clinical Guideline 175. Prostate cancer: diagnosis and treatment (January 2014)

5 DEFINITIONS AND/ OR ABBREVIATIONS

SFH	Sherwood Forest Hospitals NHS Foundation Trust
BAUS	British Association of Urological Surgeons
NICE	National Institute of Health and Care Excellence
EAU	European Associate of Urology
AUA	American Urological Association
PSA	Prostate Specific Antigen
2WW	2 week wait
TRUS	Trans Rectal Ultrasound
PROMIS	Prostate MRI Imaging Study
ASAP	Atypical small acinar proliferation
HGPIN	High grade Intraepithelial neoplasia
ePLND	Extended pelvic lymph node dissection
OPA	Outpatient appointment
CQIN	Commissioning for Quality and Innovation
LES	
ADT	Androgen deprivation therapy
CRPC	Castrate resistant prostate cancer
LHRH	Leutenising hormone releasing hormone

6 EVIDENCE BASE/ REFERENCES

- D'Amico, A et al The combination of preoperative prostate specific antigen and postoperative pathological findings to predictPSA outcome in clinically localised prostate cancer, J Urol 1998. Dec.160(6)1.2096-2101
- NICE May 2019 NG 131: Prostate cancer: diagnosis and management
- Small, E. et al Apultamide and overall survival in non-metastatic castration-resistant prostate cancer. Ann Oncol.2019 Nov;30(11):1813-1820 (SPARTAN TRIAL)
- Hussain, M et al. Enzalutamide in men with non-metastatic, castration resistant Prostate cancer. NEJM 2018;378:2465-2474
- NICE June 2005 CG27 Referral Guidelines for Suspected Cancer
- NICE Jan 2014 CG 175 Prostate Cancer: Diagnosis and Management
- NICE July 2014 CG73 Chronic kidney disease in adults: assessment and management (last updated Jan 2015)
- NICE June 2015 NG12 Suspected Cancer: Recognition and Referral (last updated July 2017)
- Bhatt, J et al. Natural history of renal AML: most patients with large AMLs>4cm can be offered Active surveillance as an initial Management strategy Eur Urol 2016 Jul;70(1):85-90

- Flum A et al. Update on the diagnosis and management of renal angiomyolipoma. J Urol.2016 Apr;195(4 pt 1):834-46
- Jewett, M et al. Active surveillance of small renal masses:progression patterns of early stage kidney cancer. Eur Urol.2011 Jul;60(1):39-44
- Chawla et al The natural history of observed enhancing renal masses:meta-analysis and review of the world literature. J Urol 2006. 175(2) 425-431
- Pierorazio P et al Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renam masses: the DISSRM registry. Eur Urol 2015 Sept;68(3):408-15
- Marconi et al Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. Eur Urol 2016 Apr;69(4)660-673
- WHO 2004 G1 1973 Classification
- EAU guidelines: https://uroweb.org/individual-guidelines/oncology-guidelines/
- AUA guidelines: https://www.auanet.org/guidelines

7 EQUALITY IMPACT ASSESSMENT

Equality Impact Assessment (EqIA) Form (please complete all sections)

- Guidance on how to complete an Equality Impact Assessment
- Sample completed form

Name of service/policy/procedure being reviewed: Investigation, management and follow-up of prostate, kidney and bladder cancer			
New or existing service/policy/procedure: Existing			
Date of Assessment: 18/8/2020			
For the service/policy/procedure and its implementation answer the questions a – c below against each characteristic (if relevant consider breaking the policy or implementation down into areas)			
Protected Characteristic	a) Using data and supporting information, what issues, needs or barriers could the protected characteristic groups' experience? For example, are there any known health inequality or access issues to consider?	b) What is already in place in the policy or its implementation to address any inequalities or barriers to access including under representation at clinics, screening?	c) Please state any barriers that still need to be addressed and any proposed actions to eliminate inequality
The area of policy or its implementation being assessed:			
Race and Ethnicity:	Afro-carribean/African ethnicity is a risk factor for prostate cancer	Threshold to biopsy prostate is expanded to include all PIRADS 3 lesions	none
Gender:	none	none	none
Age:	none	none	none
Religion:	none	none	none

Disability:	none	none	none
Sexuality:	none	none	none
Pregnancy and Maternity:	none	none	none
Gender Reassignment:	none	none	none
Marriage and Civil Partnership:	none	none	none
Socio-Economic Factors (i.e. living in a poorer neighbourhood / social deprivation):	none	none	none

What consultation with protected characteristic groups including patient groups have you carried out?

- none

What data or information did you use in support of this EqIA?

- Powell, I.Epidemiology and pathophysiology of prostate cancer in African American men. J Urol 2007 Feb:177(2):444-9

As far as you are aware are there any Human Rights issues be taken into account such as arising from surveys, questionnaires, comments, concerns, complaints or compliments?

- No

Level of impact

From the information provided above and following EqIA guidance document please indicate the perceived level of impact:

Low Level of Impact

For high or medium levels of impact, please forward a copy of this form to the HR Secretaries for inclusion at the next Diversity and Inclusivity meeting.

Name of Responsible Person undertaking this assessment:

Frances Burge

Signature:

Date:

18/8/2020