SOUTH EAST LONDON CANCER NETWORK

UROLOGY

DIAGNOSTIC AND TREATMENT GUIDELINES

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The South East London Cancer Network (SELCN) serves a local resident population of 1.5 million although for specialist and less common cancers it has a larger catchment population. The Network oversees the strategic development of cancer services, the setting, implementation and monitoring of evidence based protocols as well as the establishment of network wide policies and systems, communication and high quality network wide research and development.

The South East London Cancer Network (SELCN) comprises six hospital Trusts (in alphabetical order):

- Guy’s & St Thomas’ Hospital
- Kings College Hospital
- Princess Royal University Hospital
- Queen Elizabeth Hospital
- Queen Mary Hospital
- University Hospital Lewisham

Key to implementing the NICE Urological Improving Outcomes Guidance (IOG) is the centralisation of all major surgery for any form of urological malignancy. Within the South East London Cancer Network, collaboration between Guy’s and St. Thomas’ Hospital (GSTT), King’s College Hospital (KCH), Queen Elizabeth Hospital, Woolwich (QUEH) and Princess Royal
University Hospital Bromley, (PRUH) (PRUH and QEH are now functionally South London Healthcare-SLHC as of 2011) has created a single Network-wide specialist multidisciplinary team (SMDT) and the agreed centralisation of radical prostate surgery and radical bladder surgery centralised at GSTT.

In September 2005 the Network Board agreed the centralisation of prostate and bladder urological surgery within the Joint Cancer Centre (JCC) at Guy’s, St Thomas and Kings Hospitals. Since 2009 cystectomy has been centralized on the Guy’s site and from June 2012 radical prostatectomy also. Penile cancers continue to be referred to St George’s Hospital, Tooting. Testicular cancer would be managed through a supra network specialist team based on SE London, West Anglia and NE London.

To support implementation of the IOG the Network Urological Cancer Tumour Working Group has produced these guidelines on the referral, diagnosis, treatment and follow up of prostate, bladder and renal cancers in SE London. The guidelines should be read in conjunction with the Networks Operational Policy for Urological Cancer.

**Primary referral of all urological cancer patients**

Patients, in whom a diagnosis of urological cancer is suspected, are referred by their General Practitioner via the standard form or by letter. The fax form highlights the National Guidelines for referral under the 2-Week Wait (2ww)(see page 5).

Patients are booked to the appropriate clinic depending upon their suspected cancer and the defined hospital of referral. At KCH patients are seen at a designated haematuria clinic or rapid access clinic. 2ww/urgent patients at SLHC are seen in rapid access clinics. At GSTT 2ww and suspected cancer patients are prioritised to be seen in the one stop clinics (OSC) which occur 4 times per week.

Following diagnosis all patients will be discussed at the Local multidisciplinary team (LMDT) meetings (see unit operational policies for details).
SOUTH EAST LONDON CANCER NETWORK
Urology Urgent Suspected Cancer Referral

Please tick the box of the hospital clinic you are referring to and fax this form to the relevant Urgent Referral Team within 24 hours. Guidelines are on the reverse side.

- **Princess Royal**
  - Fax: 01689 863187
  - Tel: 01689 865676

- **Queen Elizabeth**
  - Fax: 020 8836 4035
  - Tel: 020 8836 5964/5

- **Guy’s & St Thomas’**
  - Fax: 020 7188 0923
  - Tel: 020 7188 0902

- **King’s College**
  - Fax: 020 3299 1515
  - Tel: 020 3299 1516

**SECTION 1 – PATIENT INFORMATION.** PLEASE COMPLETE IN BLOCK CAPITALS.

<table>
<thead>
<tr>
<th>SURNAME</th>
<th>Patient visited this hospital Y / N before?</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST NAME</td>
<td>NHS Hospital Number</td>
</tr>
<tr>
<td>Gender</td>
<td>D.O.B.</td>
</tr>
<tr>
<td>Address</td>
<td>First language</td>
</tr>
<tr>
<td>Post Code</td>
<td>Interpreter required? Y / N</td>
</tr>
<tr>
<td>Daytime Telephone</td>
<td>Home Telephone (if different) / Mobile No.</td>
</tr>
<tr>
<td>Transit required? Y / N</td>
<td></td>
</tr>
</tbody>
</table>

**SECTION 2 – PRACTICE INFORMATION.** USE PRACTICE STAMP IF AVAILABLE.

| Referring GP | Date of referral |
| Practice Address | Telephone |
| Post Code | Fax |

**SECTION 3 – CLINICAL INFORMATION.** PLEASE TICK THE RELEVANT BOXES.

- **Cancer suspected**
  - [ ] Prostate
  - [ ] Kidney
  - [ ] Bladder
  - [ ] Testis
  - [ ] Penis

- **Symptoms**
  - [ ] Microscopic haematuria
  - [ ] Symptomatic
  - [ ] Asymptomatic
  - [ ] Painless macroscopic haematuria
  - [ ] Loin pain
  - [ ] Bone pain
  - [ ] Lower urinary tract symptoms (e.g. hesitancy, poor stream)
  - [ ] Other (please list)

- **Clinical Examination**
  - [ ] Renal mass
  - [ ] Prostate feels malignant on rectal examination
  - [ ] Pyrexia
  - [ ] Swelling in body of testis
  - [ ] Lesion on penis
  - [ ] Other (please list)
### Results of Investigations

<table>
<thead>
<tr>
<th>Haematology</th>
<th>Biochemistry</th>
<th>Radiology (if relevant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>PSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatinine</td>
<td></td>
</tr>
</tbody>
</table>

**Additional information** - Attach patient computer record summary if available. Continue on separate sheet if required.
SOUTH EAST LONDON CANCER NETWORK
Information to support Urology referrals

Refer urgently patients with:

- Painless macroscopic haematuria in adults.
- Recurrent or persistent urinary tract infection associated with haematuria in patients aged over 40 years.
- Unexplained microscopic haematuria in patients aged over 50 years.
- An abdominal mass identified clinically or radiologically that is thought to arise from the urinary tract.
- Swellings in the body of the testis.
- Symptoms or signs of penile cancer, including progressive ulceration or a mass in the glans or prepuce or involving the skin of the penile shaft.
- Raised or rising age-specific PSA (in men with other co-morbidities or life expectancy <10 years, consider discussion with patient/carers and/or a specialist before urgent referral).
- Clinically malignant prostate on DRE. Prostate-specific antigen (PSA) should be measured and the result should accompany the referral.

Use this proforma to refer urgently (2 Week Wait)

Refer non-urgently:

Patients under 50 years of age with microscopic haematuria should have proteinuria and serum creatinine levels measured. Those with proteinuria or raised serum creatinine should be referred to a renal physician. If there is no proteinuria and serum creatinine is normal, a non-urgent referral to a urologist should be made.

Use Choose & Book or a letter to refer non-urgently

Investigations in Primary Care:

- In an asymptomatic male with a borderline level of PSA, repeat the PSA test after 1 to 3 months. If the PSA level is rising, refer the patient urgently.
- A digital rectal examination and a PSA test (after counseling) are recommended for patients with any of the following unexplained symptoms:
  - inflammatory or obstructive lower urinary tract symptoms
  - erectile dysfunction
  - haematuria
  - lower back pain
  - bone pain
  - weight loss, especially in the elderly.
- Exclude urinary infection before PSA testing. Postpone the PSA test for at least 1 month after treatment of a proven urinary infection.
- PSA age specific reference range: 50-59 years ≤ 3.0ng/ml; 60-69 years ≤ 4.0ng/ml; 70+ ≤ 5ng/ml.
- In male or female patients with symptoms suggestive of a urinary infection and macroscopic haematuria, diagnose and treat the infection before considering referral. If
infection is not confirmed, refer them urgently.

**Patient information and support:**
Consider the information and support needs of patients and the people who care for them while they are waiting for the referral appointment. Resources for GPs to use are available from the Cancer Network on 020 7593 0160, or visit our website [www.selcn.nhs.uk](http://www.selcn.nhs.uk).

*Approved by the South East London Cancer Network in June 2012.*
For comments or additional copies contact the Network on Tel 020 7188 7090 / Fax 020 7188 7120, or visit our website [www.selcn.nhs.uk](http://www.selcn.nhs.uk).
Referral to Specialist MDT
All patients with newly diagnosed prostate, bladder or renal cancer are discussed at the Local multidisciplinary team (LMDT) meetings. The LMDT will determine if the patient fits the criteria for referral to the Network Specialist multidisciplinary team (SMDT) meetings. For details of the process and contact details please refer to the section on each individual tumour type or Network operational policy.

Each Urology unit has a Clinical Nurse Specialist to support the patient throughout their pathway as follows:

Clinical Nurse Specialist (CNS) Referral Pathway

1. Referrals for CNS support can be made via: telephone, email or fax.

2. Referrals are either self-referrals or can be made with the consent of the patient via:
   - Relative/carer
   - Medical staff
   - Nursing staff
   - Primary care
   - Professions Allied to Medicine (P.A.M.’s)

3. Appropriate criteria for referral include:
   - New diagnosis of cancer
   - Recurrent or new metastatic disease

4. Information to include in referral:
   - Patient contact details
   - Name
   - Age
   - Hospital number
   - Diagnosis or suspected diagnosis
   - Reason for referral

5. Seamless Network Wide CNS support
   The Centre and Unit CNS’s will work jointly to support patients who have a diagnosis of urological malignancy. Primary responsibility, whilst patients are receiving active treatment at the Centre, will be with Centre CNS’s, unless otherwise arranged and agreed with Unit CNS. Patients will be informed which CNS’s are responsible for them.

6. CNS Documentation
   CNS’s will write in the medical notes summaries of information given, assessment of identified needs and plan for follow-up. Also any information needs to be shared with the team in order to support the way in which patients wish to be treated. CNS’s will also keep their own CNS notes, to document telephone conversations or confidential matters (see below).

7. Patient Confidentiality
   CNS discussions with the patients are confidential. Current patient needs should be discussed with the whole team to achieve consistent care. All patients will be told that we document
interactions in the medical notes. When patients request confidentiality between us, we will respect this as long as we feel it does not compromise the patients’ safety.

Dear Patient,

Coming into hospital and having investigations, surgery or treatments can be a challenging and uncertain time for you and those close to you. It is important to us that you receive the best care and support possible.

As experienced nurses who work closely with the doctors, nurses and support staff involved in your urological care, we are often in a good position to provide you with additional support and information.

We can offer help with the following:

- Answering any questions
- Explaining procedures or diagnosis
- Advising on symptom control
- By organising counselling or putting you in touch with someone trained in giving emotional support
- Providing you with printed information and details of support groups
- Assisting you in getting extra support at home
- Finding you support with financial worries/ benefits advice
- At your request, offer support to friends, relatives and partners
- Referring you for complementary therapy and nutritional advice

There may be nothing on this list, which you feel applies to you, but perhaps you would just like to have someone to talk to about your feelings.

Your local Clinical Nurse Specialist (CNS) is:

Thank you
SELCN
Clinical Nurse Specialists
South East London Cancer Network

SECTION A

GUIDELINES FOR THE MANAGEMENT OF PROSTATE CANCER

June 2012
Prostate Cancer Guidelines

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1. Introduction

The aim of the SE urological Network is to develop and further an integrated service with the aim to offer all network patients equal access to urological cancer services. This document has been agreed by members of the tumour working group and Specialist Prostate Cancer Group.

The majority of prostate cancer patients will be managed locally with active surveillance, hormone ablation and postoperative or post-radiotherapy follow-up. Patients with end stage disease will be managed locally by Urologists and palliative care team and oncologists as appropriate.

All patients with newly diagnosed prostate cancer are discussed at the LMDT meeting, where a member of the SMDT is present. Patients that fit the criteria of referral to the Network SMDT will be either discussed at the next available SMDT meeting or will be referred to the SMDT after all required investigations have been completed. The SMDT will discuss treatment plans and give treatment recommendations to ensure that patients are managed according to the SELCN guidelines.

2. Specialist multidisciplinary team (SMDT) referral criteria

The following patients should be discussed at the SMDT meeting:

- Early or advanced prostate cancer
- Advanced or metastatic prostate cancer after failed first line treatment
- Prostate cancer patients which are considered for inclusion into cancer studies

All patients will have access to appropriate information, offered a hand-held Patient Record and will be allocated a Keyworker who they can contact for help and information during their patient journey.

3. Organisation and Frequency of Specialist MDT

- The prostate SMDT will be held on a weekly basis. This is at the moment in the form of a combined meeting as bladder, prostate and kidney SMDT on Tuesday Mornings at 0800.
- The timing and structure of the SMDT might have to change in the future depending on clinical needs and feasibility.
- The meeting is video-linked with the main hub at KCH
4. Referrals to SMDT

All referrals to SMDT should be made via the Urology Coordinators. Details should be forwarded via confidential e-mail, by fax to the SMDT coordinator or via the electronic patient record system (EPR). This should ideally be no later then 2 clinical working days prior to the meeting (referrals should be submitted on Thursdays for the SMDT the following Tuesday).

5. Referrals from outside the network and 2\textsuperscript{nd} opinions

Patients that have been referred to the joint cancer center from outside the network will be reviewed at the specialist SMDT if clinically appropriate.

Second opinions should be directly referred to a named Consultant who will be responsible to bring the patients to the SMDT if clinically appropriate.

6. Documentation of SMDT outcome

Every patient that has been discussed at the SMDT will have their treatment recommendation documented in form of an individual treatment plan. This plan will be part of each patient's notes. The plan should contain the following information:
- Patient identity
- Diagnosis and staging
- SMDT treatment plan
- Date of SMDT

7. Communication of SMDT outcome

After the SMDT Meeting, the recommended treatment options will be discussed with the patient at their next outpatient appointment. All patients are offered a written record of the discussion in the form of a copy of the letter that is sent to their GP (in keeping with guidelines).

8. Background

Cancer of the prostate (CaP) is now recognised as one of the principal medical problems facing the male population. The discrepancy between clinical incidence and pathological prevalence is a major issue.

9. Classification

The 2009 TNM (Tumour Node Metastasis) classification for CaP is shown in Table 1.

<table>
<thead>
<tr>
<th>T</th>
<th>Primary tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Clinically inapparent tumour not palpable or visible by imaging</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour incidental histological finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour incidental histological finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen level)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour confined within the prostate(^1)</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour involves one half of one lobe or less</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour involves more than one half of one lobe but not both lobes</td>
</tr>
<tr>
<td>T2c</td>
<td>Tumour involves both lobes</td>
</tr>
</tbody>
</table>
T3 Tumour extends through the prostatic capsule
T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b Tumour invades seminal vesicle(s)
T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator ani and/or pelvic wall

N Regional lymph nodes
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M Distant metastasis
M0 No distant metastasis
M1 Distant metastasis
M1a Non-regional lymph node(s)
M1b Bone(s)
M1c Other site(s)

1 Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1C
2 Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as T3, but as T2.
3 The regional lymph nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. Laterality does not affect the N classification.
4 When more than one site of metastasis is present, the most advanced category should be used.

10. Treatments available

The following treatments are available for cancer of the prostate within SELCN.

- Active surveillance
- Watchful waiting
- Hormone monotherapy
- Radical prostatectomy- open, laparoscopic and robotic
- Brachytherapy
- External beam radiotherapy
- External beam radiotherapy with a brachytherapy boost
- Cryotherapy
- Chemotherapy

11. Referrals for suspected prostate cancer

Patients in whom a diagnosis of prostate cancer is suspected should be referred by their GP via the standard network proforma according to the national guidelines for referrals under the 2 week wait rule by fax or post although a clinical letter from a GP will be accepted.

Patients can be referred by letter/phone call from other clinical specialities and wards
A prostate biopsy if required will be booked directly from the clinic and the histology will be available 7 to 10 days after the prostate biopsy. The patient is given an outpatient appointment 1-2 weeks after the biopsy. This appointment should be made after the patients histology and case has been discussed at the LMDT.

12. Prostate biopsy

Prostate biopsies will be performed as systematic TRUS-guided biopsies. The prostate cancer group has agreed on a protocol of a 5 region pattern with 10 to 12 prostate cores being taken. This has in recent studies shown to give the best cancer yield.

Regions of tissue sampling include lateral and mid peripheral zone of prostate base, middle and apex additional TZ biopsies are taken if clinically indicated.

Each area should be sampled and sent for histology separately. To improve Patient tolerance of the procedure LA should be given as per recent BAUS Guidance document.

Standardised prostate biopsy across the Network is recommended to allow better histological work up and comparison and therefore better prognostic data.

The following features should be recorded for each prostate biopsy:
1. site
2. number of cores collected
3. presence of carcinoma and high grade PIN
4. no. of cores involved by carcinoma, length of carcinoma and Gleason score
5. invasion of nerves, striated muscle and seminal vesicles
6. other pathology e.g acute prostatitis

The first repeat biopsy can be done locally
If a patient requires further repeat biopsy he should be referred for templated saturation biopsies to the centre at either KCH or GSTT.

Special circumstances may dictate that a patient would be more suitable for a primary transperineal prostate biopsy instead of a TRUS biopsy.

13. Diagnosis

A histopathological diagnosis of prostate cancer should be made in all cases unless the general condition and co-morbidities of the patient does not allow a biopsy or the patient declines a biopsy or in view selected cases where reconfirmation by biopsy is deemed unnecessary (very high PSA with widespread bony metastases in frail patients).

All patients should have a physical examination including DRE, PSA and a flow test with post void residual if they have additional LUTS.

14. Staging tests

Bone scan:
- in moderate to high risk cases if PSA>20
- If patient is symptomatic
- Gleason grade >4+3

MRI pelvis:
- Most patients will have an MRI prior to a prostate biopsy where possible.
Otherwise
- PSA>10 in clinically organ-confined disease
- Gleason grade >4+3 if considered for radical treatment
- T3 disease if radical treatment is considered
- Any patient where the clinician feels it will help management

15. Guidelines on diagnosis and staging
   a. abnormal DRE and/or elevated serum PSA may indicate CaP
   b. the diagnosis of CaP usually depends on histopathological confirmation unless a biopsy is contraindicated
   c. Local staging T staging is based on findings from DRE. Further information is provided by imaging and the number and sites of positive biopsy cores and tumour grading
   d. N staging should only be performed if treatment with curative intent is planned. MRI maybe useful in recognising large lymphnodes. This could help avoiding operative procedures Accurate lymph node staging can only be determined by bilateral lymphadenectomy.
   e. M staging for skeletal metastasis is best assessed by bone scan. This may not be indicated in asymptomatic patients if PSA is <10ng/ml or in the presence of well and moderately differentiated tumours.

16. Deferred treatment or Active surveillance

This term is used to describe a treatment that includes an active stand point to postpone treatment until required.

Indications

In presumed localized disease(N0, Nx M0)
- T1a well and moderately differentiated disease. In younger patients with Life expectancy over 10 years re-evaluation with PSA follow up and transperineal template biopsy is recommended
- T1b all patients with a life expectancy of>10 years or good performance status should have PSA monitoring and transperineal template guided after 3-6 months.
- T2 disease well and moderately differentiated with life expectancy of<10 years and asymptomatic with an early transperineal template biopsy to corroborate the disease state.
- Presumed localized disease all staging and gradings if patient is unwilling to accept side effects of active treatment at that time.

Watchful waiting

- Locally advanced disease(T3-T4). Asymptomatic patients with well or moderately differentiated tumours and short life expectancy in metastatic disease.
- Patients with disease for which treatment has been recommended but are unwilling to undergo treatment

Deferred treatment for metastatic disease is only acceptable in asymptomatic patients with a strong wish to avoid treatment related side effects. The MRC trial has highlighted the risk of developing symptoms (pathological fractures and spinal chord compression) without receiving the possible benefit from hormonal treatment. These patients need close follow up.
17. Radical treatment options

All patients considered for Radical treatment must be discussed at the SMDT meeting. All patients should be counselled and seen by a urological surgeon, oncologist and specialist nurse to enable them to make an informed choice.

All patients will be allocated a Keyworker and offered a patient held record.

18. Radical Prostatectomy

The following range of operative options is available in the SE urological network and if radical prostatectomy is chosen by the patient all operative options should be discussed with the patient.

- open retropubic radical prostatectomy
- laparoscopic radical prostatectomy
- robotic assisted radical prostatectomy

**Indications**

presumably curable patients with a life expectancy >10 years
- T1a if high grade Gleason or life expectancy >15 years
- T1b,T2
- T1c when not insignificant according to staging and grading
- T3 when there is limited extracapsular extension i.e. it is operable and in the absence of metastatic disease with the understanding that it is likely to be part of multimodality treatment.

**Contraindications**

- When no survival benefit is expected
- When there is a low probability of cure

- Patients requiring radical prostatectomy will be referred to the network centre either at Kings College Hospital or at Guys Hospital. From June 2012 all radical prostatectomies will be booked for surgery at Guy’s centralising the prostate specialists from KCH and GSTT.
- Surgical treatment will be carried out by a member of the prostate team.
- Where possible the referring team will be responsible for the treatment of their own patients.
- First 2 follow ups will be by the operating surgeon either at the centre or the local unit.
- Further follow ups can be done locally by the referring SMDT member.

19. Radiotherapy with curative intent

All external beam radiation is planned and delivered at St Thomas’ Hospital by one of the radiation oncologist members of the SMDT.

20. External beam radiation

Radiation therapy is performed in the network at St Thomas Hospital. The use of state of the art 3 dimensional conformal radiation therapy (3D-CRT) is recommended, which allows
tailoring the prescription dose to target volumes and therefore reducing toxicity while delivering higher doses of radiation to the regions of interest.

Neoadjuvant androgen deprivation is used in the majority of patients over a period of at least 3 months to reduce the pre-radiotherapy target volume. This allows a decrease in the dose delivered to adjacent tissue thereby minimizing the risk of morbidity from high dose radiotherapy.

Patients should continue on anti-androgen ablation for 3 years after radiotherapy. It is almost universally accepted that this improves treatment outcome in patients with locally advanced disease. This adjuvant treatment is under periodic review depending on new research.

21. Salvage radiotherapy after failed radical prostatectomy

Patients with positive surgical margins and seminal vesicle involvement at the time of surgery are at a high risk of local disease recurrence. Estimated local failure rate is between 25-68% in these cases. Although postoperative radiotherapy appears to reduce local recurrence rates and PSA levels, the impact on survival remains unproven and further studies are needed.

Follow up

The patient will be seen by the radiation oncologist in the early post-treatment phase and will then be referred back after 6 months to the local SMDT urologists for follow up per protocol.

22. Interstitial radiotherapy (brachytherapy)

Brachytherapy treatment is available at Guys Hospital in form of a LDR single session procedure. Permanent radioactive seeds are implanted under TRUS guidance (iodine 125 half-life 60 days). The operative procedure takes 1-2 hours and may be performed in an outpatient setting.

Brachytherapy can be considered a safe and effective treatment for organ-confined CaP with stage T1c-T2a disease and a well to moderately differentiated tumours and PSA<10ng/ml.

23. Hormonal Treatment

All units across the network treat patients with all forms of 1st line and most 2nd line hormonal treatment. Patients with failed treatment are discussed at SMDT.

As testosterone is essential to the perpetuation of CaP, any treatment that reduces the level of testosterone either in the serum or at the prostate level is called hormonal therapy. Major categories of hormonal therapy include:

- Surgical castration
- LHRH analogues
- Oestrogens
- Antiandrogens

Indications

Patients with locally advanced or metastatic disease

There is evolving evidence that early treatment is superior to delayed treatment in patients with metastatic disease.
Optional

Patients who are symptomatic with localized CaP who are not fit for curative treatment.

- T1a no option
- T1b-T2 symptomatic patients unfit for curative treatment
- T3-T4 standard therapy
- N+/M+ standard therapy

24. Taxanes and Novel Therapies and Trials

Patients that are to be considered for the treatment with Taxanes and other novel treatments or that are to be considered for the inclusion into trials and research studies should be discussed at SMDT level.

25. Follow up

After treatment with curative intent

Reasons for follow up are good responsible patient care, possibility of 2nd line treatment, possibility of early hormonal therapy after failure, part of study protocol.

1. In asymptomatic patients a disease specific history and serum PSA supplemented by DRE are the recommended tests for routine follow up. These should be performed at 3,6,12 months, then every 6 months until 3 years and then annually.
2. After radical prostatectomy a serum PSA of more than 0.2 ng/ml is mostly associated with residual or disease recurrence
3. After radiation therapy a rising PSA level rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease.
4. Both a palpable nodule and rising serum PSA can be signs of a local recurrence.
5. Detection of local recurrence by TRUS and biopsy is recommended if it will affect the treatment plan.
6. Metastasis may be detected by abdominal/pelvic CT/MRI or bone scan.
7. If the patient has bone pain, a bone scan should be considered irrespective of the PSA level.

After Hormonal Therapy

The main objective is to monitor the response to treatment, o ensure compliance, to detect possible complications and to guide the modalities of palliative symptomatic treatment at the time of hormone escape..

Follow up should include physical examination, PSA, U&E's, FBC, liver function. AP(in M1 disease) is a bone specific marker for patients with M1 disease and has the advantage not to be influenced by hormonal therapy compared with PSA

In cases where there is a suspicion of disease progression other tests like US, bone scan, C-XR.

1. In asymptomatic patients a disease specific history and serum PSA supplemented by DRE are the recommended tests for routine follow up. These should be performed at 3,6,12 months, then every 6 months until 3 years and then annually.
2. After radical prostatectomy a serum PSA of more than 0.2 ng/ml is mostly associated with residual or disease recurrence.
3. After radiation therapy a rising PSA level rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease.
4. Both a palpable nodule and rising serum PSA can be signs of a local recurrence.
5. Detection of local recurrence by TRUS and biopsy is recommended if it will affect the treatment plan.
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7. If the patient has bone pain, a bone scan should be considered irrespective of the PSA level.
South East London Cancer Network

SECTION B

GUIDELINES FOR THE MANAGEMENT OF BLADDER CANCER

August 2012

Review date: Aug 2013
Bladder Cancer Guidelines

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5. Transurethral Resection of tumours and Biopsies-Template for recording findings
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7. How to manage high risk NMIBC if BCG is not available
8. Follow up schedule in NMIBC
9. Muscle invasive Bladder Cancer (MIBC)
10. Treatment of muscle invasive bladder cancer
   a) Radical Surgery
   b) Bladder Sparing Protocols
   c) External beam radiotherapy
   d) Chemotherapy
10) Metastatic Disease
11) Follow-up after Radical Cystectomy
12) Follow-up schedule after orthotopic urinary reconstruction

1. Introduction
The aim of the SE Network Urologists is to develop an integrated service for the network patients such that all patients are offered equal access to urological cancer services. This document has been agreed by members of the Tumour Working Group and the Specialist Bladder Cancer Group. Diagnostic and treatment guidelines are based on the European Association of Urology guidelines on bladder cancer (www.uroweb.org).

The majority of bladder cancers will be managed locally with endoscopic surgery and intravesical chemotherapy. Patients with end stage disease will be managed locally by Urologists and Palliative Care services with input from the Oncologists as appropriate (appendix 2 – Palliative Care Guidelines).

All patients will be discussed at local MDTs and the designated intermediate and high risk cases will be discussed at the Specialist MDT (see SMDT Operational Policy). Patients suitable for radical surgical treatment will undergo this at the Network Centre at Guy’s Hospital. Specialist Surgeons from each Network hospital will operate on patients requiring radical surgery at the centre. Specialist Surgeons will care for other patients with intermediate and high risk bladder cancer locally, these cases will be referred to the members of the SMDT at their local MDT meetings.

All patients will have access to appropriate information and will be allocated a Key Worker as their point of contact for information and help during their diagnosis and treatment (see appendix 4 - Network key worker policy).

2. Referral

Patients, in whom a diagnosis of urological cancer is suspected, are referred by their General Practitioner via the standard network fax form or by letter. The fax form highlights the National Guidelines for referral under the 2-Week Wait (see appendix 1).

Patients referred with suspicion of bladder cancer i.e., frank/microscopic haematuria as defined in the guidelines will be:

a) Referred on a 2-week wait proforma faxed to the local Trust (see attached)
b) Referred by letter from the General Practitioner
c) Referred by letter/telephone call from other specialist clinic and wards.
This may be carried out in dedicated one stop clinics (Kings, PRUH Guy’s/QEH) or by ring-fenced appointments for 2-WW patients in existing clinics (QEH).

**Referral from other teams**

Physicians from other specialities can refer patients to these clinics by letter/proforma.

3. **Haematuria Clinic**

Assessment in the Haematuria clinic will include full history and examination including Digital Rectal Examination (DRE) and pelvis, urinalysis, urine cytology, Cystoscopy and urinary tract ultrasound.

Patients arriving in other clinics because of referrals or when haematuria is an incidental finding may be referred to the haematuria clinic or have Cystoscopy and imaging arranged separately depending upon local services. Flexible cystoscopy should include following information to achieve standardisation across the network.

**Mandatory Evaluations**
- Physical examination (including digital rectal and pelvic examination)
- Urinalysis +/- MC&S
- Urinary cytology
- Renal and bladder ultrasonography and/or CT Urogram/IVP
4: Flexible Cystoscopy

<table>
<thead>
<tr>
<th>Initial or Follow Up</th>
<th>Tumour Found Y / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour Type</td>
<td></td>
</tr>
<tr>
<td>Number of Tumours</td>
<td></td>
</tr>
<tr>
<td>Description of Tumour</td>
<td></td>
</tr>
</tbody>
</table>

**TUMOUR**

Flexible Cystoscopy Date:

Diagram To be Completed Manually

Trans-urethral Resection of the Bladder Tumours: Patients with proven bladder tumour on flexible cystoscopy or obvious tumour on imaging will be admitted for Cystoscopy, resection of tumour with biopsy of the underlying tissue at the tumour base. Random biopsies will be obtained from any visibly suspicious areas and in those patients who have positive cytology but
no visible tumour (Base, Right lateral wall, left lateral wall, dome of the bladder anterior and posterior walls) and sent in separate containers.

It is best to use this template for recording the findings at TURBT:

Loop biopsies from the prostatic urethra should be obtained:
a) Carcinoma in situ of the bladder  
b) Tumours at the trigone/bladder neck  
c) Positive cytology without evidence of tumour in the bladder  
d) Potential candidates for orthotopic bladder reconstruction.

Fluorescence guided cystoscopy and resection of bladder tumours will be undertaken in the following clinical situations where the facility exists. Units where this is not available patients will be referred to the regional centre.

a) Multifocal primary or recurrent tumours  
b) Positive urine cytology and no visible tumour

Post-Resection: Following adequate resection patients will be administered intra-vesical Mitomycin-C 40 mg in 50 mls normal saline within 6-24 hours of resection. Exceptions to this will include:

a) Suspected / obvious bladder perforation at resection  
b) Large solid tumours requiring radical treatment.

Pathology: All newly diagnosed tumours will be discussed in local and/or Specialist MDT. Pathologists are expected to provide following information pertaining to the resected tumours:

a) Histological type of tumour  
b) Grade of the tumour  
c) Stage (depth) of the tumour  
d) Presence or absence of CIS  
e) Presence or absence of muscle in the specimen  
f) Presence of lymphovascular invasion

A second resection will be carried out within 2-6 weeks if:

a) Initial resection was incomplete  
b) Absence of muscle in pathological specimen particularly if the tumour is of higher grade (>G1)  
c) High grade T1 tumour (G3pT1)

Risk Stratification in NMIBC

In order to rationalize the management of NIMBC, tumours will be risk stratified as per EAU recommendations into low, intermediate and high risk groups.
Table 6: Weighting used to calculate recurrence and progression scores

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recurrence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tumours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥ 8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Tumour diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 cm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥ 3 cm</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Prior recurrence rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≤ 1 recurrence/year</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 1 recurrence/year</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ta</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Concurrent CIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Grade (WHO 1973)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>G3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Total score</td>
<td>0-17</td>
<td>0-23</td>
</tr>
</tbody>
</table>

CIS = carcinoma in situ; WHO = World Health Organization.

Table 7: Probability of recurrence and progression according to total score

<table>
<thead>
<tr>
<th>Recurrence score</th>
<th>Probability of recurrence at 1 year</th>
<th>Probability of recurrence at 5 years</th>
<th>Recurrence risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15 (10-10)</td>
<td>31 (24-37)</td>
<td>Low risk</td>
</tr>
<tr>
<td>1-4</td>
<td>24 (21-26)</td>
<td>46 (42-49)</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>5-9</td>
<td>38 (35-41)</td>
<td>62 (58-65)</td>
<td></td>
</tr>
<tr>
<td>10-17</td>
<td>61 (55-67)</td>
<td>78 (73-84)</td>
<td>High risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression score</th>
<th>Probability of progression at 1 year</th>
<th>Probability of progression at 5 years</th>
<th>Progression risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.2 (0-0.7)</td>
<td>0.8 (0-1.7)</td>
<td>Low risk</td>
</tr>
<tr>
<td>2-6</td>
<td>1 (0.4-1.6)</td>
<td>6 (5-8)</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>7-13</td>
<td>5 (4-7)</td>
<td>17 (14-20)</td>
<td>High risk</td>
</tr>
<tr>
<td>14-23</td>
<td>17 (10-24)</td>
<td>45 (35-55)</td>
<td></td>
</tr>
</tbody>
</table>
**Low Risk:** This group includes: single, Ta, G1, <3cm diameter

Management of these will entail transurethral resection followed by single instillation of Mitomycin-C. Follow up cystoscopy at 3 months and if clear annually.

**Intermediate Risk:** Ta-T1, G1-G2, multi-focal, >3cm diameter (low risk Ta-T1, G1 >3cm diameter multi-focal)

These will be treated with transurethral resection followed by immediate singe instillation of MMC. Further management will be stratified according to the grade and stage:-

*Low grade G2pTa* - 6 weekly instillations of MMC. Followed by 3 monthly check cystoscopy for 2 years, 6 monthly for next two years and then annually thereafter if no recurrence.

*High grade G2 pTa/T1* BCG will be used preferentially initially as six weeks course followed by maintenance for one year.

**High Risk:** G3pTa, G3 pT1 with or without CIS

Conservative treatment for high risk NMIBC may be appropriate in patients who have:

a) Single tumours <3cm
b) No CIS away from the main tumour
c) Compliant patient

Such cases should be managed with intravesical immunotherapy (BCG) or combination of MMC and BCG (Di Stasi Regimen). If there is residual disease or recurrence after initial course patients should be strongly recommended radical surgery. In case of good response maintenance BCG should be continued for up to 3 years either as per Donald Lamb regimen or given modified dose schedule according to the individual patient’s tolerability.

**Radical surgery should be strongly recommended:**

a) Multifocal tumours
b) CIS away from the main tumour
c) Patients with significant irritative bladder symptoms
d) Immuno-compromised patients
e) Poorly compliant
f) Recurrence of tumours in spite of treatment
g) Poor tolerance of BCG/ Complications from BCG

**Guidelines for managing high risk NMIBC while BCG is unavailable**

Due to difficulties at the manufacturing plant, production of BCG (ImmuCyst) has been suspended by the company Sanofi Pasteur. It has not, so far, been made clear what the production difficulties are, but the
company do not think that Immucyst production will recommence until the end of 2013. This clearly presents a problem for urological teams and their patients. Another type of BCG called ‘OncoTICE’ (manufactured by MSD) is an alternative choice but, currently, their supplies are very limited. MSD is confident that some supplies of OncoTICE will be available at the end of August 2012 but not in sufficient amounts to meet the full requirements for BCG in the UK.

Urological teams are very aware of the potential worry and distress this will cause patients. To this end, The British Association of Urological Surgeons (BAUS) have produced some guidance for urologists so that patients can be looked after safely and to a consistent standard across the country. This guidance can be read by clicking here and this link also provides access to the Department of Health website, for information provided by the National Clinical Director for Cancer, Sir Mike Richards.

The lack of BCG does mean that patients will need to consider alternative strategies for looking after their bladders.

For patients with newly-diagnosed, high-risk, non-muscle invasive bladder cancer who have not yet started any treatment after an initial transurethral resection of the bladder tumour (TURBT). (These cancers are called T1 G3, Ta G3 and CIS cancers.)

Some patients with this type of bladder cancer already receive a recommendation to undergo radical cystectomy (bladder removal) as this is undoubtedly the best curative treatment; better even than BCG. All patients considered fit and strong enough to undergo major surgery will have this option discussed with them.

Radical cystectomy is not suitable for everyone, for a number of reasons, and, if this is the case, the Bladder Cancer Team will discuss alternatives. For many patients, the best alternative will probably be intra-vesical chemotherapy. Intravesical (into the bladder) chemotherapy in these situations is not thought to be as effective as BCG but can work to reduce the risk of cancer recurrence. Chemotherapy is delivered via a catheter placed in the bladder and is usually administered weekly for 6 weeks.

There are a number of different methods of administering the chemotherapy. The exact one recommended by bladder cancer teams will differ according to local availability:

a) Mitomycin or other chemotherapy drugs (e.g. epirubicin /gemcitabine) given weekly over 6 consecutive weeks

b) EMDA (Electromotive drug administration) Mitomycin given weekly over 6 consecutive weeks

c) Hyperthermic Mitomycin (Synergo) given weekly over 6 consecutive weeks

Patients should be aware that data on the effectiveness of EMDA and Synergo in this setting is limited.

Urologists will recommend a "second look" cystoscopy for many patients, prior to them starting any intra-vesical treatment. This is to be as certain as possible that the bladder is clear of cancer before starting the intravesical chemotherapy.

Approximately 6 weeks after a course of chemotherapy, patients would undergo a check cystoscopy to determine if there has been a complete response to treatment.

If the bladder cancer has not fully cleared, then radical cystectomy should be considered if the patient is considered fit and strong enough to undergo major surgery. For patients still undergoing their first course of BCG, whose treatment has been interrupted by lack of supplies of BCG

Patients who have started BCG induction will not be able to complete the full induction course of six doses due to lack of supplies. Clearly this is a difficult situation.

For many patients who have received the majority of the doses (4 or more), the simplest solution may be to undergo their planned check cystoscopy to see if the bladder is clear of disease. For other patients, who have only just started their course of treatment, alternative treatment may need to be offered. This
alternative treatment could be with major surgery (radical cystectomy) to remove the bladder or with intravesical chemotherapy. If chemotherapy is chosen, the number of doses will be dependent on how much of the induction course was completed.

The chemotherapy options below may be offered according to local availability:

Mitomycin or other chemotherapy drugs (e.g. epirubicin /gemcitabine) given weekly over 6 consecutive weeks  
EMDA Mitomycin given weekly over 6 consecutive weeks  
Hyperthermic Mitomycin (Synergo) given weekly over 6 consecutive weeks

For patients who have completed an induction (first course) but have not completed the first year of treatment

Many patients who have undergone their first 6 dose treatment with BCG, and who have been found to be clear of disease at their first check cystoscopy, will be offered further treatment with intravesical chemotherapy. The treatment schedule will involve treatment once a month, for up to one year, with regular check cystoscopies and urine testing for cancer. Chemotherapy is not a tried and tested treatment in this setting but probably offers the best chance of keeping the bladder free of disease until more BCG becomes available.

If the bladder cancer has not fully cleared then radical cystectomy should be considered, if the patient is considered fit and strong enough to undergo major surgery.

For patients who are currently receiving maintenance BCG courses beyond the first year of treatment

BCG maintenance therapy for these patients will need to be discontinued. The risk from discontinuing treatment is small. For those patients who never had carcinoma in situ in their bladder, recent research suggests that the risk from discontinuing treatment may be negligible. Given the low risk of problems, alternative treatment with chemotherapy is probably not required and the best policy will almost certainly be one of careful surveillance.

The surveillance would be with 6-monthly check cystoscopies and urine tests for bladder cancer (urine cytology tests).

If surveillance is performed diligently, we think the risk to patients in this situation is small. Once BCG supplies are restored, there is no reason, of course, why a patient could not re-start their maintenance BCG schedule.

**Follow up after TUR in NMIBC**

Cystoscopy is still the best way to follow-up patients with bladder cancer and in the majority of patients this can be achieved using a flexible Cystoscope in dedicated cystoscopy clinics. First check Cystoscopy will be at 3 months in all cases. The frequency of later Cystoscopies is adapted to the prognosis of the individual tumours (See follow-up protocol sheet).

Recurrence of superficial bladder cancer continues but reduces with time. Generally recurrences continue to appear during follow-up for 10-12 years. Patients developing regular recurrences will continue to do so until death or Cystectomy. Patients developing recurrences during the first 4 years after TUR will continue to have lifelong recurrence. Therefore follow-up should continue for 12 years if free of disease. Lifelong if recurrence occurs in first 4 years after TUR.
Follow-up with urine cytology has little value in low grade superficial bladder cancer because the samples often fail to show abnormalities. Upper tract tumours are very rare and need for upper tract imaging can be adjusted to the pattern of bladder tumours recurrence. Upper tract imaging should be considered in patient with multifocal and frequent recurrences every 2 years.

4. Recommended Follow-up for Bladder Cancer

**Cystoscopy**

<table>
<thead>
<tr>
<th>TaG1 &lt;3cm</th>
<th>1st check 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No recurrence – Cystoscopy at 9 months</td>
</tr>
</tbody>
</table>

**Low Risk**

<table>
<thead>
<tr>
<th>Ta – T1</th>
<th>G1 G2 multifocal</th>
<th>Or &gt;3cm diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No recurrence – 3 monthly for 2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No recurrence – 6 monthly for 3 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No recurrence – annually</td>
<td></td>
</tr>
</tbody>
</table>

**Intermediate Risk**

<table>
<thead>
<tr>
<th>T1 G3</th>
<th>Multi-focal</th>
<th>Highly recurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st check at 3 months after re-resection at 4-6 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 monthly for 2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 monthly in 3rd year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 months for 5 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annually.</td>
<td></td>
</tr>
</tbody>
</table>

*Patients with CIS have cytology checked at each visit.*

Any recurrent disease or positive cytology requires admission for GA Cystoscopy and resection, biopsy. These patients will be discussed at the local MDT. Intermediate and high risk patients will go on to SMDT.

Patients on maintenance BCG will be followed up by cystoscopy and cytology.

5. Muscle invasive Bladder Cancer

Muscle invasive bladder cancer may be suspected at Cystoscopy but is confirmed by histology. Patients with this finding require further staging investigations.

**CT Scan Chest, Abdomen & Pelvis**
PET CT Scan in selected cases

The gold standard treatment for muscle invasive bladder cancer is radical Cystectomy. This may also be the recommended treatment for high risk superficial disease T1 G3 large volume and BCG resistant CIS and highly recurrent extensive papillary disease.

All patients suitable for both Radical radiotherapy and Cystectomy should have both options discussed with them in a single multidisciplinary outpatient clinic. Radical cystectomy is the preferred option in the following circumstances:

- Multifocal disease,
- Large volume tumours (>7cm maximum diameter),
- Presence of CIS
- Poor bladder function
- Previous pelvic radiotherapy,
- Pre-existing hydronephrosis
- Poor compliance
- Active inflammatory bowel disease
- Bowel adhesions,
- Bilateral hip prostheses

Radical Cystectomy consists of removal of the bladder and neighbouring organs (prostate and seminal vesicles in men, urterus and adenxa in women, the distal ureters and the urethra if CIS is present). Pelvic lymph node dissection is also carried out to various levels according to the individual patient pathology and performance status. Urinary diversion into an ileal conduit, neo bladder, or continent diversion is offered as an open, laparoscopic or robotic assisted procedure.

6-Bladder Preservation Schedules

Bladder preservation in suitable patients may be achieved by combination(s) of Chemotherapy, Radiotherapy and in few cases by partial Cystectomy. There is no randomised data comparing the results of radical radiotherapy (with salvage surgery if required) to those of surgery alone. It is likely that survival is related to the presence or absence of metastases at the time of local therapy rather than the modality chosen for local control. The aim for patients treated with radical radiotherapy is to achieve local tumour control and cure whilst preserving normal
bladder function and minimising the toxicity to neighbouring structures. The best candidates for bladder preservation include those who have:

- Early T stage (pT2)
- Size <5cm
- T0 after resection
- No CIS
- Transitional cell histology
- Good renal function
- Good bladder function
- No upper tract obstruction

All patients should initially undergo resection of as much gross tumour as possible. This may require a repeat TURBT. For patients in whom there is equipoise regarding the choice of definitive local management Blue-light cystoscopy can assist in the selection of the most appropriate option.

All patients receiving radical radiotherapy must be willing to comply with regular cystoscopic follow-up (in addition to imaging). Female patients who are sexually active should be counselled about the risk of vaginal dryness and stenosis before starting radiotherapy and offered treatment with vaginal dilators.

The use of neoadjuvant platinum-based chemotherapy is recommended for all suitable patients.

a) **External Beam Radiotherapy**

Consent for Radical Radiotherapy should be performed following the Guy’s & St. Thomas’ NHS Trust Radiotherapy Department guidelines, using a Department of Health consent form and local information booklets. The radiotherapy planning CT scan should be acquired using a helical CT scanner with a flat-top couch. The Clinical Target Volume is the entire bladder with an additional 0.5cm margin around and extra-vesical extension. An additional 1.5cm margin is added to form a Planning Target Volume. The CTV-PTV margin can be individualised for the patient if an adaptive radiotherapy strategy is employed. The following Organs at Risk should also be segmented on the planning CT scan to ensure the dose received is within predicted toxicity tolerances: Rectum, Femoral heads, Small bowel.
Radical external beam radiotherapy delivers 64Gy in 32 fractions over 45 days; or 50-55Gy in 20 fractions over 28 days depending on the schedule chosen. A cone-beam CT based off-line image-guidance protocol is used to verify treatment delivery. Patients are assessed weekly during treatment by a specialist Uro-oncology radiographer, and are seen in their consultant’s outpatient clinic during the last week of treatment, or earlier if required. Patients will be follow-up by the Specialist Bladder Cancer Team according to the follow-up protocol. This will include either flexible cystoscopy at 3 months rigid if an abnormality is seen?), then 3/12ly flexible cystoscopies until 24 months, then 6 monthly thereafter. CT we’ve been doing at 3 months, then every 6 months till 24months, then annually.

There has been interest in the concomitant delivery of other agents with radical radiotherapy with the intention of improving efficacy. The BC2001 study compared radiotherapy alone with radiotherapy plus concomitant systemic chemotherapy (mitomycin-C and 5FU). Only 1/3 of subjects received neoadjuvant chemotherapy. Local control was improved with concomitant therapy (67% v 54% 2 year local control) although there was no overall survival benefit. Late toxicity was equal, although there was a 3-fold increase in acute GI toxicity in the group who received chemotherapy. A phase 3 randomised controlled study has also been conducted to assess the impact of concomitant nicotinamide (oral) and Carbogen (98% oxygen, 2% carbon dioxide) with radiotherapy. A significant increase in 3 year overall survival was found (59% v 46%) with no increase in acute or late toxicity. However, carbogan and nicotinamide are unlicensed for this indication and there are technical challenges concerning the delivery of carbogen in a linear accelerator bunker.

The choice of palliative external beam radiotherapy schedule depends on the indication, patient’s performance status, and patient / doctor preference. The following schedules are in use:

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Fractions</th>
<th>Duration (days)</th>
<th>Planning</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1</td>
<td>1</td>
<td>Virtual simulation</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>7</td>
<td>Virtual simulation</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>12</td>
<td>Virtual simulation</td>
</tr>
<tr>
<td>21</td>
<td>3</td>
<td>15</td>
<td>Conformal planning</td>
</tr>
<tr>
<td>36</td>
<td>6</td>
<td>36</td>
<td>Conformal planning</td>
</tr>
</tbody>
</table>

b) **Systemic Chemotherapy**
Up to 50% of patients with muscle invasive bladder cancer will develop metastatic disease within 2 years of surgery: 25% develop disease confined to the pelvis; 75% develop distant metastases. Cisplatin-based combination chemotherapy regimens give response rates of 40-70%, and can be used in the neo-adjuvant, adjuvant, and metastatic settings. All systemic therapy for transitional cell bladder cancer is delivered at Guy’s Hospital.

c) Neo-adjuvant Chemotherapy

Neo-adjuvant chemotherapy for bladder cancer has been extensively studied. It is associated with potential advantages and disadvantages which should be considered when deciding on whether to recommend its use.

Potential advantages:
1. Improved control of systemic disease. Chemotherapy is given at the earliest point when the burden of micrometastatic disease is lowest.
2. Tolerability of chemotherapy is better than after cystectomy.
3. In vivo sensitivity to chemotherapy is tested.
4. Access to treated tumour tissue. The cystectomy sample will allow evaluation of molecular mechanisms of response and resistance to the drugs used.
5. Reduction of primary tumour. This may be particularly useful in patients with large/complicated lesions.

Potential disadvantages:
1. Delayed cystectomy may compromise surgery in those who are resistant to chemotherapy.
2. Side-effects of chemotherapy may delay surgery.
3. Staging with CT/MRI may over and under-stage patients with possible over treatment.

A meta-analysis evaluating data from more than 3,000 patients provides level 1 evidence for cisplatin-based neo-adjuvant chemotherapy. Compared with surgery alone cisplatin-based combination chemotherapy was associated with a significant increase in disease-free survival and overall survival (HR=0.86, 95% CI 0.77-0.95; p = 0.003) that translated into a 5% absolute improvement at 5 years. Two trials dominated the data upon which this analysis is based. An EORTC trial randomised patients with T2 to T4a Nx disease to receive either 3 cycles of neoadjuvant cisplatin, methotrexate and vinblastine or no chemotherapy. At a median follow up of 7 years, a significant improvement in survival favouring chemotherapy was seen (p =0.048). The second trial was from a U.S. intergroup trial that randomised 317 patients with T2 to T4a
disease to either 3 cycles of neoadjuvant MVAC followed by cystectomy or cystectomy alone (5). At 8.7 years median follow-up both median survival (77 vs. 46 months) and 5 year survival (57% versus 43%) were superior in the MVAC arm. In both trials chemotherapy was well tolerated with no negative effects on surgery.

Neoadjuvant chemotherapy should be considered for all patients with a performance status of 0-1, and T2-4 N0-1 M0 bladder tumours. Clinical features that preclude neoadjuvant chemotherapy include uncontrolled severe haematuria, ureteric obstruction that cannot be easily stented, severe urinary symptoms, significant poorly controlled medical co-morbidities, and histological features predicting chemo-resistance. Two cisplatin-based regimens are available for use in the neoadjuvant setting: 3 cycles of Gemcitabine and Cisplatin; or 3 cycles of Accelerated MVAC (Cisplatin, Methotrexate, Vinblastine, Doxorubicin). These regimens have been selected for efficacy, ease of administration, and lower rates of toxicity than earlier generation treatments. In patients with impaired renal function (EDTA measured GFR <50ml/min), carboplatin is substituted for cisplatin.

It is extremely important that these patients are monitored very closely to ensure that subsequent surgery / radiotherapy is not compromised. The Specialist Bladder Cancer Team must be kept updated throughout the neoadjuvant treatment schedule. A restaging CT scan should be performed between cycles 2 and 3 to detect poor responders so they can proceed straight to definitive local therapy rather than continuing neoadjuvant treatment.

d) Adjuvant Chemotherapy

The role for adjuvant chemotherapy after radical cystectomy remains controversial. The potential benefits of chemotherapy in this setting include:

1. Chemotherapy is administered after accurate pathological staging.
2. Over treatment in patients at low risk of metastatic disease is avoided.
3. No delay in definitive surgery, especially in patients who are chemo-resistant.

The potential disadvantages include:

1. Delay or intolerance of chemotherapy due to post-operative morbidity.
2. Assessment of in vivo chemosenstivity is not possible.

The trials of adjuvant chemotherapy have been suboptimal with deficiencies in design, chemotherapy regimens used and analysis. The data are not convincing enough to give unequivocal recommendations at present. The one meta-analysis to date, with individual data
from six trials and a total of only 491 patients, provides some support for the use of adjuvant chemotherapy with an overall hazard ratio for survival of 0.75 (95% CI 0.60-0.96, p=0.019). However, the power of this meta-analysis is clearly limited due to its size and concerns with the quality of the data.

Adjuvant chemotherapy may be considered for patients with a performance status of 0-1, and T3-4 N0-3 M0 bladder tumours. However patients should be informed of the scare evidence available to support this treatment. Ideally these patients should be enrolled into clinical trials whenever possible. Two cisplatin-based regimens are available for use in the adjuvant setting: 4-6 cycles of Gemcitabine and Cisplatin; or 4-6 cycles of Accelerated MVAC (Cisplatin, Methotrexate, Vinblastine, Doxorubicin). These regimens have been selected for efficacy, ease of administration, and lower rates of toxicity than earlier generation treatments. In patients with impaired renal function (EDTA measured GFR <50ml/min), carboplatin is substituted for cisplatin.

e) Palliative Chemotherapy

Urothelial cancers are sensitive to cisplatin-based chemotherapy in the first-line metastatic setting with response rates around 45-50%. Two regimens are available for use in this setting: 6 cycles of Gemcitabine and Cisplatin; or 6 cycles of Accelerated MVAC (Cisplatin, Methotrexate, Vinblastine, Doxorubicin). These regimens have been selected for efficacy, ease of administration, and lower rates of toxicity than earlier generation treatments. In patients with impaired renal function (EDTA measured GFR <50ml/min), carboplatin is substituted for cisplatin.

There is no standard second-line therapy for stage 4 urothelial cancer, and where possible patients should be offered entry into clinical trials. For ineligible patients, and those who decline entry, if they have achieved 6 months progression-free survival following a cisplatin-based regimen, they can be re-challenged with the same or an alternative cisplatin-based regimen. Vinflunine has EMEA approval for use in the second-line setting (despite not demonstrating definitive superiority over best supportive care), but received a negative cost-effectiveness evaluation by NICE. Finally, a survey of UK oncologists revealed that Paclitaxel would be their second-line therapy of choice, based on encouraging Phase II study data. However access to funding for this treatment varies across the UK.
6. Metastatic Disease

Patients with metastatic disease after radical surgery or radiotherapy will be discussed at SMDT and those fit for chemotherapy treatment will be referred to Guys Medical Oncology team as before.

7. Follow-up after Radical Cystectomy

Follow-up needs to address the risks of recurrent disease and the complications of the reconstructive surgery. The risk of disease progression depends upon the tumour stage e.g.,

\[
\begin{align*}
pT1 & \quad G3 \quad 50\% \\
pT4 & \quad N2 \quad 90+\% \\
\end{align*}
\]

Recurrence may develop in the pelvis or distantly and new tumours may occur in the remaining ureothelium of the upper tracts and male urethra if not removed. The risk of recurrence is highest in the first 2 years after Cystectomy and reduced in the 3rd year to a low level after 3 years.

Disease developing in the upper tracts occurs in 5-15% of cases and 50% of these develop in the first 12 months after Cystectomy. The most common site of new urothelial tumour occurrence is the male urethra if it has not been removed; the incidence is 5-13%. The risk of new urothelial tumours developing does not reduce with time, therefore lifelong follow-up and surveillance is required.

Urinary diversions are associated with mechanical problems due to the re-implantation of the ureters and monitoring needs to assess reflux, stenosis and associated renal problems.

**Incidence of reflux and ureteral stenosis associated with urethral stenosis**

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Reflux (%)</th>
<th>Ureteral stenosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileum conduit</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>Colon conduit</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Ureterosigmoidostomy</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pouch:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileum</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mixed ileum/colon</td>
<td>0-7</td>
<td>8</td>
</tr>
<tr>
<td>Orthotopic bladder (ileum)</td>
<td>0-3</td>
<td>25</td>
</tr>
</tbody>
</table>
Problems also occur associated with the stoma and hernia development and in continence diversions with the continence mechanism.

There are also metabolic consequences of urine diversion:
- Vitamin 12 deficiency developing in 3-5 years
- Hyperchloraemic acidosis (less common with ileal diversions)
- Mild acidosis associated with ammonia absorption occurs with ileal diversions
- Increased incidence of stones
- Reduced renal function

Recommendations for follow-up are as follows:

### 8. Follow-up scheme after urinary diversion

<table>
<thead>
<tr>
<th>Metabolic checks</th>
<th>Disease recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year 1: at 3-4 monthly intervals</strong></td>
<td>CT Abdomen and pelvis with CXR-6m, Urethroscopy (or urethral cytology), Urine cytology-annual</td>
</tr>
<tr>
<td>USS—Upper Tract/Residual</td>
<td></td>
</tr>
<tr>
<td>Electrolytes, creatinine levels and alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>Base excess</td>
<td></td>
</tr>
<tr>
<td><strong>Year 2-3: at 6 monthly intervals</strong></td>
<td>CT Abdomen and pelvis with CXR, Urethroscopy (or urethral cytology), Urine cytology-Annually</td>
</tr>
<tr>
<td>• Ultrasound of the kidneys and reservoir</td>
<td></td>
</tr>
<tr>
<td>• Electrolytes, creatinine levels and alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>• Base excess</td>
<td></td>
</tr>
<tr>
<td><strong>Year 4: at yearly intervals</strong></td>
<td>CT Abdomen and pelvis and CXR annually, 12 monthly Urethroscopy (or washout cytology), urine cytology</td>
</tr>
<tr>
<td>• Ultrasound of the kidneys and reservoir</td>
<td></td>
</tr>
<tr>
<td>• Electrolytes and creatinine levels</td>
<td></td>
</tr>
<tr>
<td>• Base excess</td>
<td></td>
</tr>
<tr>
<td>• Vitamin B12 levels</td>
<td></td>
</tr>
<tr>
<td><strong>Year 5 and thereafter: at yearly intervals</strong></td>
<td>Annual Urethroscopy (or washout cytology, urine cytology)</td>
</tr>
<tr>
<td>• Ultrasound of kidneys and reservoir</td>
<td></td>
</tr>
<tr>
<td>• Electrolytes and creatinine level</td>
<td></td>
</tr>
<tr>
<td>• Base excess</td>
<td></td>
</tr>
<tr>
<td>• Vitamin B12 level</td>
<td></td>
</tr>
<tr>
<td>• Colonoscopy in patients with Ureterosigmoidostomy</td>
<td></td>
</tr>
</tbody>
</table>

Patients who have undergone radical radiotherapy or bladder preservation combined therapy should follow the same protocol but omitting the ultrasound to assess upper tract dilatation and residual urine in reconstruction and the base excess estimation and including regular cystoscopy.
An Algorithm for bladder cancer patient management is given here:

Findings - Tumour
Solid / Papillary / Flat / Other

Flexible Cystoscopy

TURBT

Clinic ➔ MDM ➔ Histology

Existing Initial Assessment?

NMIBC

Low Intermediate High

MMC MMC / BCG

Cystectomy BCG MMC & BCG Re-Resection

MMC & BCG Cystectomy

Follow Up Cystoscopy

Clear Progression Recurrence

Maintenance BCG Cystectomy

Follow Up Cystoscopy

Follow Up Flexi Cystoscopy (3 Months Then Annual)

MIBC

Unfit Fit

Symptomatic Treatment Neo-Adjuvant Chemotherapy

Chemotherapy + Radiotherapy

Cystectomy Follow Up Cystoscopy

Unfit

MMC / BCG Maintenance

Follow Up Cystoscopy

Low Intermediate High

MMC MMC / BCG

Cystectomy BCG MMC & BCG Re-Resection

MMC & BCG Cystectomy

Follow Up Cystoscopy

Clear Progression Recurrence

Maintenance BCG Cystectomy

Follow Up Cystoscopy

Follow Up Flexi Cystoscopy (3 Months Then Annual)
**Aims**

The aim of the SE Network Urologists is to develop an integrated service for the network patients such that all patients are offered equal access to urological cancer services. This document has been agreed by members of the Tumour Working Group and the Specialist Renal Cancer Group.

The majority of localised renal cancers will be managed locally with surgery – open or laparoscopic. Patients for minimally invasive therapies such as cryo or RFA will be referred to the team with the appropriate expertise within the network. Patients with advanced disease such as IVC/cardiac involvement will be managed jointly between urologists and hepatobiliary/cardiothoracic surgeons within the Cancer centre. Patients with metastatic disease will be referred to the network oncologists for consideration of systemic therapy.

All patients will be discussed at local MDTs and the designated intermediate and high risk cases will be discussed at the Specialist MDT.

All patients will have access to appropriate information and will be allocated a Key Worker as their point of contact for information and help during their diagnosis and treatment.
1 INTRODUCTION

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2.2 Recommendation
2.3 References

3 DIAGNOSIS AND STAGING

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3.1.1 Physical examination
3.1.2 Laboratory findings
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5.1.3.1 Conclusion
5.1.3.2 Recommendation
5.1.4 Partial laparoscopic nephrectomy
5.1.4.1 Conclusion
5.1.4.2 Recommendation
5.2 Alternative treatment
5.2.1 Conclusion
5.2.2 Recommendation
5.3 Adjuvant therapy
5.3.1 Conclusion
5.3.2 Recommendation
5.4 Surgical treatment of metastatic RCC (tumour nephrectomy)
5.4.1 Conclusion
5.4.2 Recommendation
5.5 Resection of metastases
5.5.1 Conclusion
5.5.2 Recommendation
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5.6.1 Conclusion
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6.1.1 Conclusion
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6.2 Immunotherapy
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6.2.1.1 Conclusion
6.2.1.2 Recommendation
6.2.2 Interleukin-2
6.2.2.1 Conclusion
6.2.2.2 Recommendation
6.2.3 Combinations
6.2.3.1 Conclusion
6.2.3.1 Recommendation
6.3 Angiogenesis inhibitor drugs
6.3.1 Conclusion
6.3.2 Recommendation
6.4 References

7 SURVEILLANCE FOLLOWING RADICAL SURGERY FOR RCC

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7.2 Which investigations for which patient, and when?
7.3 Imaging modalities
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8 ABBREVIATIONS USED IN THE TEXT
1. INTRODUCTION
The EAU Guideline Group for renal cell carcinoma (RCC) have prepared this guideline to help urologists assess the evidence-based management of RCC and to incorporate the guideline recommendations into their clinical practice. Publications concerning RCC are mostly based on retrospective analysis, including some larger multicentre studies and well-designed controlled studies. Only a few randomized studies are available, so that it is difficult to obtain qualified evidence-based data.

The recommendations provided in the current guideline are based on a systemic literature search using Medline, the Cochrane Central Register of Controlled Trials, and reference lists in publications and review articles. The level of evidence available for the information given in this guideline (an update of the EAU guidelines on RCC published in 2002) is listed below.

There is clearly a need for continuous re-evaluation of the information inherent in the current guideline at regular intervals by the RCC Guideline Group. It has to be emphasized that the current guideline contains information for the treatment of an individual patient according to a standardized general approach. The information should be considered as providing recommendations without legal implications.

Table 1: Levels of evidence and grade of guideline recommendations as used by EAU (1)

<table>
<thead>
<tr>
<th>Level Type of evidence:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a Evidence obtained from meta-analysis of randomized trials</td>
</tr>
<tr>
<td>1b Evidence obtained from at least one randomized trial</td>
</tr>
<tr>
<td>2a Evidence obtained from one well-designed controlled study without randomization</td>
</tr>
<tr>
<td>2b Evidence obtained from at least one other type of well-designed quasi-experimental study</td>
</tr>
<tr>
<td>3 Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports</td>
</tr>
<tr>
<td>4 Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade Nature of recommendations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial</td>
</tr>
<tr>
<td>B Based on well-conducted clinical studies, but without randomized clinical trials</td>
</tr>
<tr>
<td>C Made despite the absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>

2. BACKGROUND:
EPIDEMIOLOGY AND AETIOLOGY
Renal cell carcinoma represents 2-3% of all cancers (2), with the highest incidence occurring in the more developed countries. The worldwide and European annual increase in incidence is approximately 2%, though in Denmark and Sweden a continuing decrease has been observed during the last two decades (3). In 1998, about 30,000 patients were diagnosed with kidney cancer within the EU and approximately 15,000 died of the disease (4).

Renal cell carcinoma is the most frequently occurring solid lesion within the kidney and comprises different RCC types with specific histopathological and genetic characteristics (5). There is a 1.5:1 predominance of men over women, with peak incidence occurring between 60
and 70 years of age. Aetiological factors include lifestyle factors, such as smoking, obesity and antihypertensive therapy (3,6,7). The most effective prophylaxis is to avoid cigarette smoking.

Due to the increased detection of tumours by the use of imaging techniques such as ultrasound and computerized tomography (CT), an increasing number of incidentally diagnosed RCCs are found. These tumours are more often smaller and of lower stage (8-10). Despite the increased incidental detection rate, the mortality from RCC has remained unaffected and parallel to the incidence.

2.1 Conclusion
A number of aetiological factors have been identified including smoking, obesity and antihypertensive drugs. Cigarette smoking is a definite risk factor for RCC (level of evidence: 2a). The roles of obesity and prolonged intake of antihypertensive medication as risk factors for RCC remain to be definitively clarified (level of evidence: 2a).

2.2 Recommendation
The most important primary prevention for RCC is to eliminate cigarette smoking and to avoid obesity (grade B recommendation).

3. DIAGNOSIS AND STAGING
3.1 Symptoms
Many renal masses remain asymptomatic and non-palpable until late in the natural course of the disease (1) (level of evidence: 4). Today, more than 50% of RCCs are detected incidentally using non-invasive imaging for the evaluation of a variety of non-specific symptom complexes (1) (level of evidence: 4). The classic triad of flank pain, gross haematuria and palpable abdominal mass is now rarely found (6-10%) (2,3) (level of evidence: 3).

Paraneoplastic syndromes are found in around 30% of patients with symptomatic RCC. The most common of these are: hypertension, cachexia, weight loss, pyrexia, neuromyopathy, amyloidosis, elevated erythrocyte sedimentation rate, anaemia, abnormal liver function, hypercalcaemia, polycythaemia, etc. (1) (level of evidence: 4).

A minority of patients present with symptoms directly caused by metastatic disease, such as bone pain or persistent cough (1) (level of evidence: 4). Still, 20-30% of patients are diagnosed due to symptoms associated with metastatic disease.

3.1.1 Physical examination
Physical examination has a limited role in diagnosing RCC, but it may be valuable in some cases such as palpable abdominal mass, palpable cervical lymphadenopathy, non-reducing varicocele or bilateral lower extremity oedema, which suggests venous involvement. These findings should initiate radiological examinations.

3.1.2 Laboratory findings
The most commonly assessed laboratory parameters are haemoglobin, erythrocyte sedimentation rate, alkaline phosphatase and serum calcium (1,4) (level of evidence: 4).

3.2 Radiological investigations
The majority of renal tumours are diagnosed by abdominal ultrasound (US) and CT performed for various reasons (level of evidence: 4). Detection of a solid renal mass with US should be further investigated with a high-quality CT scan using contrast medium. It serves to verify the diagnosis of RCC and provides information on the function and morphology of the contralateral kidney (5) (level of evidence: 3). Abdominal CT assesses primary tumour extension with extrarenal spread and provides information on venous involvement, enlargement of locoregional lymph nodes, and condition of adrenal glands and the liver (level of evidence: 3). Chest CT is the most accurate investigation for chest staging (6-13) (level of evidence: 3), but at least routine chest radiography, as a less accurate alternative, must be done for metastatic evaluation (level of evidence: 3).
Magnetic resonance imaging (MRI) can be reserved primarily for patients with locally advanced malignancy, possible venous involvement, renal insufficiency or allergy to intravenous contrast (14-18) (level of evidence: 3). Magnetic resonance imaging is also an option for the evaluation of inferior vena cava tumour thrombus extension and the evaluation of unclassified renal masses (level of evidence: 3). Evaluation of the tumour thrombus can also be performed with Doppler US in such cases (19) (level of evidence: 3).

There is consensus that most bone and brain metastases are symptomatic at the time of diagnosis and that routine bone scan or brain CT are not generally indicated (20,21). If indicated by clinical or laboratory signs and symptoms, other diagnostic procedures may be applied, such as bone scan, brain CT or MRI (level of evidence: 3). Renal arteriography, inferior venacavography or fine-needle biopsy (22-24) have only a limited role in the clinical work-up of patients with RCC, but may be considered in selected cases (level of evidence: 3).

3.3 Conclusion
Although incidentally detected renal masses are increasingly common, in Europe, some patients with RCC are still diagnosed due to clinical symptoms, such as palpable mass and haematuria, paraneoplastic and metastatic symptoms (level of evidence: 3). Accurate staging of RCC with abdominal and chest CT or MRI is obligatory (level of evidence: 3). Chest CT is the most sensitive approach for chest staging. There is no role for routine bone scan or CT of the brain in the standard clinical work-up of asymptomatic patients. There is an increasing role for fine-needle biopsy (level of evidence: 3) which is being used in selected cases of renal masses, or other indeterminate lesions.

3.4 Recommendation
In a patient with one or more of these laboratory or physical findings, the possible presence of RCC should be suspected. A plain chest X-ray can be sufficient for assessment of the lung in low-risk patients but chest CT is most sensitive. Abdominal CT and MRI are recommended for the work-up of patients with RCC and are the most appropriate imaging modalities for TNM classification prior to surgery. In high-risk patients for bone metastases (raised alkaline phosphatase or bone pain), further evaluation utilizing an imaging approach should be done (grade A recommendation).

4. CLASSIFICATION AND PROGNOSTIC FACTORS
4.1 Classification
The 2002 TNM stage classification system was previously recommended for clinical and scientific use (1). It is unclear whether the current TNM classification is optimal for the prediction of survival in patients with RCC and might be a subject for re-classification. The pT1 substratification, introduced in 2002 (1), has been validated by a number of studies (2-4) (level of evidence: 3).

However, refinements remain to be performed for pT3 tumours. Firstly, for renal sinus fat invasion only, it has not been established whether this carries the same prognostic information as does perinephric fat invasion (5,6). Secondly, many studies have suggested that adrenal invasion represents a very poor prognostic group. It has been suggested that these RCCs should be classified as T4 tumours (7,8). Furthermore, it is still not clear whether the stratification of RCCs with venous invasion in T3b and T3c is accurate. Additional studies are required to investigate the independent prognostic value of vena caval invasion compared with renal vein invasion (9). More recently, the accuracy of the N1-N2 subclassification has been questioned (10). For adequate M-staging of patients with RCC, an accurate pre-operative imaging procedure, which is currently chest and abdominal CT, should be performed (11,12).

This system was revised in 2010, and is supported by both the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) [50]. These TNM criteria define the anatomic extent of disease and stage and have been shown to correlate with prognosis. (See "Prognostic factors in patients with renal cell carcinoma".)
The 2010 version of the TNM system is shown in the following table (table 2). In this system, tumors limited to the kidney are classified as T1 or T2 based upon size. T3 tumors extend into the renal vein or perinephric tissues but not beyond Gerota’s fascia, while T4 tumors extend beyond Gerota’s fascia, including direct extension into the ipsilateral adrenal gland. Nodal and distant metastases are simply classified as absent or present.

Differences from the 2002 version of the TNM system include:

- T2 lesions have been subdivided into T2a and T2b, based upon a size criterion (>7 but ≤10 cm versus >10 cm)
- Ipsilateral adrenal involvement is reclassified as T4 if contiguous invasion and M1 if not contiguous
- Renal vein involvement is reclassified as T3a rather than T3b
- Nodal involvement is simplified to present or absent (N0 versus N1)

4.2 Prognostic factors
Factors influencing prognosis can be classified into: anatomical, histological, clinical and molecular (13).

4.2.1 Anatomical factors
Anatomical factors include tumour size, venous invasion, renal capsule invasion, adrenal involvement, and lymph node and distant metastasis. These factors are commonly gathered together in the universally used 2002 TNM staging classification system.

**Table 2: The 2002 TNM staging classification system**

<table>
<thead>
<tr>
<th>T - Primary tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0 No evidence of primary tumour</td>
</tr>
<tr>
<td>T1 Tumour &lt; 7 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T1a Tumour &lt; 4 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T1b Tumour &gt; 4 cm but &lt; 7 cm in greatest dimension, but not more than 7 cm</td>
</tr>
<tr>
<td>T2 Tumour &gt; 7 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T3 Tumour extends into major veins or directly invades adrenal gland or perinephric tissues but not beyond Gerota’s fascia</td>
</tr>
<tr>
<td>T3a Tumour directly invades adrenal gland or perinephric tissues (1) but not beyond Gerota’s fascia</td>
</tr>
<tr>
<td>T3b Tumour grossly extends into renal vein (2) or its segmental branches, or the vena cava below the diaphragm</td>
</tr>
<tr>
<td>T3c Tumour grossly extends into vena cava or its wall above diaphragm</td>
</tr>
<tr>
<td>T4 Tumour directly invades beyond Gerota’s fascia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N - Regional lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0 No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1 Metastasis in a single regional lymph node</td>
</tr>
<tr>
<td>N2 Metastasis in more than 1 regional lymph node</td>
</tr>
</tbody>
</table>
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

1. Includes renal sinus (prepelvic fat).
2. Includes segmental (muscle-containing branches).
A help desk for specific questions about TNM classification is available at http://www.uicc.org/tnm

4.2.2 Histological factors
Histological factors include Fuhrman grade, histological subtype, presence of sarcomatoid features, microvascular invasion, tumour necrosis and collecting system invasion. Fuhrman nuclear grade is the most widely accepted histological grading system in RCC (14). Although it is subject to intra- and inter-observer discrepancies, it remains an independent prognostic factor (15) (level of evidence: 3).

According to the WHO classification (16), three major histological subtypes of RCC exist: conventional (clear cell) (80-90%), papillary (10-15%) and chromophobe (4-5%) (level of evidence: 4). Many studies have shown a trend towards a better prognosis for patients with chromophobe, papillary and conventional (clear cell) RCCs, respectively (17,18). However, the prognostic information of the RCC subtype is lost when stratified to tumour stage (18).

Among papillary RCCs, two subgroups with different outcomes have been identified (19). Type I are low-grade tumours with a chromophilic cytoplasm and a favourable prognosis. Type II are mostly high-grade tumours with an eosinophilic cytoplasm and a great propensity for developing metastases (level of evidence: 3). The RCC type subclassification has been confirmed at the molecular level by cytogenetic and genetic analyses (20-22).

4.2.3 Clinical factors
Clinical factors include patient performance status, localized symptoms, cachexia, anaemia, platelet count (23-27) (level of evidence: 3).

4.2.4 Molecular factors
There are numerous molecular markers being investigated including: carbonic anhydrase IX (CaIX), vascular endothelial growth factor (VEGF), hypoxia inducible factor (HIF), Ki67 (proliferation), p53, PTEN (cell cycle), Ecadherin, abd CD44 (cell adhesion) (21,22) (level of evidence: 3). As yet, these markers are not in widespread use. Recently, gene expression profiling has identified 259 genes, which predict survival independent of clinical prognostic factors in conventional RCCs, indicating that genetic information will improve prognostication (28).

4.2.5 Prognostic systems and nomograms
Prognostic systems and nomograms that combine independent prognostic factors have been recently developed. It has been suggested that these systems are more accurate than TNM stage or Fuhrman grade alone for predicting survival (29-32) (level of evidence: 3).

4.3 Conclusion
In patients with RCC, TNM stage, nuclear grade according to Fuhrman and RCC subtype (WHO 2004) should be performed because they contribute important prognostic information (level of evidence: 2). There are currently no prognostic integrated systems or molecular markers recommended for routine clinical use. Prognostic systems or nomograms can be useful for the stratified inclusion of patients into clinical trials (level of evidence: 2).

4.4 Recommendations for classification and prognosis
The current TNM classification system is recommended since it has consequences for prognosis and therapy. Fuhrman grading system and classification of RCC subtype should be used. The use of integrated prognostic systems or nomograms is not routinely recommended, although these systems provide a rationale for a prognostic prediction useful for including patients in clinical trials. No molecular prognostic marker is currently recommended for utilization in the clinical routine (grade B recommendation).

5. TREATMENT OF LOCALISED DISEASE
5.1 Surgery
Radical nephrectomy that includes the removal of the tumour-bearing kidney remains the gold standard curative therapy for patients with localized RCC and offers a reasonable chance of curing the disease (1).

Except in the case of a large upper pole tumour, which is associated with a risk of direct invasion of the adrenal gland, or a tumour of > 7 cm maximum diameter, which is associated with a higher risk of intra-adrenal metastatic spread, there is evidence that a routine adrenalectomy is unnecessary during the surgical treatment of RCC, provided the pre-operative imaging procedures for tumour staging (CT, MRI) reveal negative findings.

5.1.1 Embolization
Indications for tumour embolization include patients with gross haematuria who are not fit for surgical intervention and prior to surgical resection of large paravertebral metastases. There is no benefit in performing tumour embolization before routine radical nephrectomy (level of evidence: 3) (2-8).

5.1.1.1 Conclusion
Radical nephrectomy according to Robson is no longer the gold standard treatment for smaller renal tumours (level of evidence: 2b). Adrenalectomy is not recommended provided the adrenal is normal on pre-operative CT scan (level of evidence: 3). About half of adrenal metastases develop from larger upper pole tumours (level of evidence: 3). Lymphadenectomy should be restricted to the perihilar tissue for staging purposes since extended lymphadenectomy does not improve survival (level of evidence: 2b). Renal cell carcinomas with tumour thrombi have a higher stage and grade (level of evidence: 2b). Distant or lymph node metastases are twice as common (level of evidence: 3). This increased biological aggressiveness determines the clinical prognosis more than the presence or the cranial extension of intracaval thrombosis (level of evidence: 3) (9-22).

5.1.1.2 Recommendation
Surgical therapy is the only curative approach for the treatment of RCC. In some selected cases with lymph node disease limited to the retroperitoneal space, extended lymphadenectomy might improve a patient's clinical prognosis. In general, extended lymphadenectomy cannot be considered to be the therapeutic standard. Adrenalectomy together with nephrectomy, except in the case of large upper pole tumours where direct invasion of the adrenal gland is likely, can be spared in the majority of patients (grade B recommendation). Embolization as a palliative approach can be beneficial in patients unfit for surgery with massive haematuria or profound local pain (grade C recommendation).

5.1.2 Nephron-sparing surgery
Standard indications for nephron-sparing surgery are divided into the following categories:
• absolute (anatomical or functional solitary kidney)
• relative (functioning opposite kidney that is affected by a condition that might impair renal function in future). Relative indications also include patients with hereditary forms of RCC, who are at high risk of developing a tumour in the contralateral kidney in the future.
• elective (localized unilateral RCC with a healthy contralateral kidney).

5.1.2.1 Conclusion
Nephron-sparing surgery for RCC, when performed in patients with a solitary tumour less than < 4 cm maximum diameter, provides recurrence-free and long-term survival rates similar to those observed after a radical surgical procedure (level of evidence: 2b) (23-25). After nephron-sparing surgery for absolute indications compared with elective indications, both the complication rate and the risk of developing locally recurrent disease appear to be elevated, probably due to the larger tumour size (level of evidence: 3) (26,27). There is some evidence that patients subjected to radical nephrectomy compared with nephron-sparing surgery for RCC have an increased risk of impaired renal function, resulting in chronic renal insufficiency and proteinuria (level of evidence: 3) (28-30).
In a few series, even patients with a tumour diameter up to 7 cm have been subjected to nephron-sparing surgery, delivering oncological results equivalent to those observed after a radical approach. If the tumour is completely resected, the thickness of the surgical margin does not impact on the likelihood for local recurrence (level of evidence: 3).

5.1.2.2 Recommendation
Nephron-sparing surgery is an established curative approach for the treatment of patients with RCC. Nephron-sparing surgery for the treatment of tumours more than 4-7 cm maximum diameter can be performed in centres with expertise in appropriate cases. A minimal tumour-free surgical margin following partial resection of kidney cancer appears appropriate to avoid the increased risk of local recurrence. If tumours of larger size are treated with nephron-sparing surgery, the follow-up should be intensified due to an increased risk of intrarenal recurrences (grade B recommendation).

5.1.3 Laparoscopic nephrectomy
Since its introduction, laparoscopic nephrectomy for RCC has become an established surgical procedure worldwide. Whether done retro- or trans-peritoneally, the laparoscopic approach has to duplicate established open surgical oncological principles, i.e. early control of the renal vessels before tumour manipulation, wide specimen mobilization external to Gerota’s fascia, avoidance of specimen traumatization or rupture, and intact specimen extraction.
In the hands of experienced laparoscopic urological surgeons, and with adherence to the above-mentioned principles of open radical nephrectomy, laparoscopic radical nephrectomy may now be considered a standard of care for patients with T1-2 RCCs. Intermediate outcome data indicate equivalent cancer-free survival rates when compared with open radical nephrectomy.

5.1.3.1 Conclusion
Laparoscopy for radical nephrectomy has a lower morbidity when compared with open surgery (level of evidence: 3). Tumour control rates appear equivalent for T1-2 and possible T3a tumours in experienced hands (level of evidence: 3).

5.1.3.2 Recommendation
Laparoscopic tumour nephrectomy should be performed in centres with laparoscopic expertise. Laparoscopic tumour nephrectomy can be expected to become a widely distributed treatment option and should be promoted in centres treating kidney tumours (grade B recommendation).

5.1.4 Partial laparoscopic nephrectomy
In experienced hands, laparoscopic partial nephrectomy might be an alternative to open nephron-sparing surgery for selected patients (31-34). The optimal indication for laparoscopic nephron-sparing surgery is a relatively small and peripheral renal tumour. Although the
oncological outcome following laparoscopic partial nephrectomy has been suggested to duplicate 
that of open techniques of nephron-sparing surgery (35,36), larger studies that would reveal 
reliable long-term equivalence are not available at present. Suggested disadvantages of the 
laparoscopic approach are the longer warm ischaemia time and increased intra-operative and 
post-operative complications when compared with open surgery (37-39).

5.1.4.1 Conclusion
Partial nephrectomy by laparoscopic surgery is technically feasible (level of evidence: 2b).

5.1.4.2 Recommendation
Open partial nephrectomy currently remains the standard of care. Laparoscopic partial 
nephrectomy should be limited to experienced centres (grade C recommendation).

5.2 Minimally invasive alternative treatments
Image-guided percutaneous and minimally invasive techniques, e.g. percutaneous 
radiofrequency (RF) ablation (40,41), cryoablation (42), microwave ablation, laser ablation and 
high-intensity focused ultrasound ablation (HIFU) have been suggested as alternatives to the 
surgical treatment of RCC (level of evidence: 2b) (43). Potential advantages of these and other 
techniques might include reduced morbidity, outpatient therapy, and the ability to treat high-risk 
surgical candidates (level of evidence: 2b).

Indications for minimally invasive techniques including RF ablation include small, incidentally 
found, renal cortical lesions in elderly patients, patients with genetic predisposition to multiple 
tumours, or patients with a solitary kidney, or bilateral tumours (level of evidence: 2b).

Contraindications to the above-mentioned procedures include a poor life expectancy of < 1 year, 
multiple metastases, or difficulty for successful treatment due to size or location of tumour. In 
general, tumours > 5 cm or tumours in the hilum, the proximal ureter or central collecting system 
are not typically recommended for RF ablation (44). Absolute contraindications include 
irreversible coagulopathies or severe medical instability, such as sepsis.

Although, even in high-risk patients, the reported complication rates are low, greater multicentre 
experience is required to define the oncological success and complications after use of these 
procedures as an alternative to open or laparoscopic surgery.

5.2.1 Conclusion
The formerly mentioned, minimally invasive approaches currently have the status of experimental 
treatment options for kidney cancer. Their efficacy should be further evaluated within clinical 
trials. Their disadvantage is a lack of adequate histopathological evaluation. However, their 
advantage is decreased invasiveness enabling 
treatment of patients with reduced health condition, who are otherwise not fit for conventional 
surgery (level of evidence: 3).

5.2.2 Recommendation
Currently, patients not suitable for open or laparoscopic surgery due to poor performance status 
with smaller peripheral tumours should be considered for the above-mentioned techniques for 
RCC treatment (grade B recommendation).

5.3 Adjuvant therapy
Current evidence that adjuvant tumour vaccination might improve the duration of the progression-
free survival of selected subgroups of patients undergoing nephrectomy for T3 renal carcinomas 
needs further confirmation regarding the impact on overall survival (level of evidence: 1b) (45-
49). At present the standard of care for patients post-nephrectomy is entry into a clinical trial or 
close surveillance. At the current time SELCRN are participating in the PROTECT study of 
adjuvant pazopanib for high risk resected clear cell carcinomas.
5.3.1 Conclusion
Adjuvant therapy with cytokines does not improve survival after nephrectomy (level of evidence: 1b).

5.3.2 Recommendation
Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery (grade A recommendation).

5.4 Surgical treatment of metastatic RCC (tumour nephrectomy)
Nephrectomy is curative only if surgery can excise all tumour deposits. For the majority of patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and other systemic treatments are necessary. In a meta-analysis of two randomised studies, comparing nephrectomy combined with immunotherapy versus immunotherapy only, an increased long-term survival was found in patients who had nephrectomy (50). CN in patients with metastatic disease is indicated for patients who are both suitable for surgery and have good performance status (51). All patients are discussed at the kidney cancer MDM to decide if surgery is appropriate. Potential exclusions to surgery include large volume of metastatic disease and liver or CNS metastases.

Recent improvements in our understanding of the molecular biology of renal cell carcinoma have identified multiple pathways associated with its' pathogenesis and have led to the development of molecularly targeted therapies. These include vascular endothelial growth factor (VEGF) neutralising antibodies, tyrosine kinase receptor inhibitors and mammalian target of rapamycin (mTOR) inhibitors that have shown unprecedented response rates in both the primary tumour and metastases.

These dramatic improvements in the treatment of metastatic RCC has meant that the need for and benefit of CN has reemerged as a clinically relevant question. At present there is not a phase III study comparing the survival of patients treated by CN plus targeted therapy versus targeted therapy alone and thus an empirical approach is needed. The majority of patients enrolled in the pivotal phase III studies had undergone nephrectomy, (Table 1) prior to initiation of targeted therapy. Thus, the benefits of these drugs have largely been demonstrated in a nephrectomised population. Our practice, outside of a clinical trial, is that in appropriately selected patients CN should precede initiation of targeted therapy.

5.4.1 Conclusion
Cytoreductive nephrectomy in combination with interferon-alpha (IFN-alpha) improves the survival of patients with metastatic RCC (mRCC) and good performance status (level of evidence: 2b). Systemic therapy is no longer with immunotherapy except in highly selected cases. Our practice, outside of a clinical trial, is that in appropriately selected patients CN should precede initiation of targeted therapy.

5.4.2 Recommendation
Cytoreductive nephrectomy is recommended for metastatic RCC patients with good performance status (grade A recommendation).

5.5 Resection of metastases
Complete removal of metastatic lesions contributes to an improvement of clinical prognosis. Systemic therapy, where there has been complete resection of metastatic lesions or isolated local recurrences, is not known to contribute to an improvement in clinical prognosis (level of evidence: 2b) (51-55). Our practice, outside of a clinical trial, is that in appropriately selected patients CN should precede initiation of targeted therapy.

5.5.1 Conclusion
There is a definite role for metastasectomy in patients with RCC in order to improve the clinical prognosis (level of evidence: 3).

5.5.2 Recommendation
In patients with synchronous metastatic spread, metastasectomy should be performed where disease is resectable and the patient has a good performance status. The clinical prognosis is worse in patients who have surgery for metachronous metastases. Metastasectomy should be performed in patients with residual and resectable metastatic lesions previously responding to systemic therapy and/or a limited (solitary lesion) number of metachronous metastases in order to improve the patient’s prognosis (grade B recommendation).

5.6 Radiotherapy for metastases in RCC
Radiotherapy can be used for selected symptomatic patients with non-resectable brain or osseous lesions who do not respond to other conservative treatment approaches (56,57).

5.6.1 Conclusion
Radiotherapy of metastases from renal cell cancer can induce a significant relief from symptoms with pain reduction, e.g. a single bony deposit (level of evidence: 2b).

5.6.2 Recommendation
In individual cases, radiotherapy for the treatment of brain metastases (whole brain irradiation or stereotactic approach) and osseous lesions can induce a relief from symptoms due to mRCC (grade B recommendation) (58,59).

6. SYSTEMIC THERAPY FOR METASTATIC RCC
6.1 Chemotherapy
Since RCCs develop from the proximal tubules, they have high levels of expression of the multiple-drug resistance protein P-glycoprotein and are therefore resistant to most chemotherapy. There is no role for the use of chemotherapy in the treatment of clear cell RCC. It may be used for selected patients with non-clear cell variants such as collecting duct carcinomas.

6.1.1 Conclusion
Chemotherapy does not have a role in the treatment of clear cell mRCC (level of evidence: 3).

6.1.2 Recommendation
Chemotherapy as monotherapy should not be considered effective in patients with mRCC (grade B recommendation).

6.2 Immunotherapy
6.2.1 Interferon-alpha
In randomized studies, IFN-alpha has proven superiority for survival over hormonal therapy in patients with mRCC (2). The studies were done using the regimen of IFN-alpha, 10MU, three times per week for 12 weeks. The patients who benefited were of good WHO status (0-1) and were treated for at least 12 weeks and up to 1 year.

6.2.1.1 Conclusion
Immunotherapy with INF-alpha seems beneficial for mRCC patients with a good performance status with an improved survival of several months (level of evidence: 1b). This treatment has been superseded by the new class of targeted therapy.

6.2.1. Recommendation
Interferon-alpha can be considered as a possible treatment option in mRCC patients who have failed tyrosine kinase inhibitor and everolimus.

6.2.2 Interleukin-2
Interleukin-2 (IL-2) has been used in mRCC since 1985. Several studies have shown responses ranging from 7-27% (3-5). The optimal IL-2 regimen is not clear, but long-term (> 10 years)
complete responders have been achieved with high-dose bolus IL-2 (6). However, no randomized study has been done against best supportive care. The toxicity of IL-2 is substantially higher than that of IFN-alpha. It seems that only clear cell type RCC responds to immunotherapy. There is a small group of patients who achieve durable complete responses and consideration should be given to its’ use in highly selected patients. These include those who are very fit without significant co-morbidities and with lymph node and pulmonary disease. These patients are referred to the medical oncology unit at St Bartholomew’s hospital.

6.2.2.1 Conclusion
Interleukin-2 has more side-effects than INF-alpha. High-dose IL-2 gives durable complete responders in a limited number of patients. To date, no superiority has been seen for either INF-alpha or IL-2 treatment in mRCC patients (level of evidence: 1b). Consideration for referral for high dose IL-2 as outlined above.

6.2.2. Recommendation
Only patients with mRCC, good performance status and with clear cell subtype histology can be treated with immunotherapy IL-2 or IFN-alpha (grade B recommendation).

6.2.3 Combinations
Several randomized studies have been performed to investigate the efficacy of combinations of cytokines. Patient survival was not better than survival achieved with monotherapy regimens (7). No other combinations with cis-retinoic acid or 5FU have shown a clinical significant benefit(8,9).

6.2.3.1 Conclusion
To date, combination therapy has not shown any clinical benefit for mRCC patients (level of evidence: 1b).

6.2.3. Recommendation
The results from the MRC/EORTC study comparing INF-alpha versus INF-alpha/IL-2/5FU showed no benefit for the treatment of RCC using combination treatment.

6.3 Angiogenesis inhibitor drugs
Recent improvements in our understanding of the molecular biology of renal cell carcinoma have identified multiple pathways associated with its’ pathogenesis and have led to the development of molecularly targeted therapies. Due to the high expression of angiogenesis proteins in clear cell RCC, clinical efficacy has been observed with antibody inhibition to one of these proteins known as vascular epithelial growth factor (VEGF) (10). In addition, inhibition of downstream tyrosine kinases has shown clinical efficacy (11,12). These studies have shown significant clinical benefit in both clinical response rate and survival. The new agents include vascular endothelial growth factor (VEGF) neutralising antibodies, tyrosine kinase receptor inhibitors and mammalian target of rapamycin (mTOR) inhibitors that have shown unprecedented response rates in both the primary tumour and metastases.

In a randomised study Sunitinib as first-line monotherapy showed a significant improvement in progression free survival (11 months) compared with IFN alpha (5 months). This study has established sunitinib as the new standard first-line systemic therapy for metastatic RCC. More recently pazopanib, another VEGF TKI, has been approved by NICE for the first line treatment of metastatic RCC. Both sunitinib and pazopanib are used as first line systemic therapy for metastatic RCC in our network.

Temsirolimus is a specific inhibitor of mammalian target of rapamycin (mTOR). A phase III trial demonstrated increased overall survival in poor risk patients with Temsirolimus monotherapy compared with IFN alpha. Everolimus, an oral mTOR inhibitor, has shown a significant improvement in progression free survival for patients failing sunitinib and/or sorafenib (level of evidence:1b) It can be applied for via the cancer drugs fund.

6.3.1 Conclusion
Tyrosine kinase inhibitors have proven efficacy in mRCC patients for response and survival (level of evidence: 1b).

**6.3.2 Recommendation**

Sunitinib or pazopanib should be considered as the standard first-line treatment for mRCC patients. Everolimus is a suitable option for second-line therapy and may be applied for via the cancer drugs fund.

7. **SURVEILLANCE FOLLOWING RADICAL SURGERY FOR RCC**

7.1 **Introduction**

Surveillance after radical surgery allows the urologist to monitor or identify:
- post-operative complications
- renal function
- local recurrence
- recurrence in the contralateral kidney
- development of metastases.

The method and timing of investigation has been the subject of many publications. There is no consensus on surveillance after radical surgery of the kidney. Post-operative complications and renal function are readily assessed by history, physical examination and measurement of serum creatinine. Repeated long-term monitoring of creatinine levels is indicated if there is impaired renal function before surgery or a post-operative significant increase in the serum creatinine level (1).

Local recurrence is rare (1.8%), but early diagnosis is useful since the most effective treatment is cytoreductive surgery (2,3). Recurrence in the contralateral kidney is also rare (1.2%) and is related to positive margins, multifocality and grade (4).

The reason for surveillance is to identify metastases early. This is because more extended tumour growth can reduce the possibility of surgical resection, which is considered the standard therapy in cases of resectable and preferably solitary metastatic lesions. In addition, within clinical trials, an early diagnosis of tumour recurrence might enhance the efficacy of a systemic treatment if the tumour burden is low.

7.2 **Which investigations for which patients, and when?**

Repeated intensive radiological surveillance for all patients is unnecessary because, for example, the outcome after surgery for small, well-differentiated tumours is almost always excellent. It is therefore reasonable to modify follow-up, taking into account the risk of developing recurrence or metastases. No randomized evidence exists, but there are large studies with long follow-up from which some conclusions can be drawn (level of evidence: 4).

Factors influencing prognosis can be classified into: anatomical, histological, clinical and molecular (5,6). Anatomical factors include: tumour size, stage, venous invasion, adrenal involvement and lymph node status. Histological factors include: grade, presence of sarcoma, necrosis and collecting system invasion. Clinical factors include: patient performance status, anaemia, platelet count and cachexia.

There are also numerous molecular markers that are being investigated with respect to future treatments. These markers include immunotherapy, vaccine, gene and angiogenesis techniques, but as yet none of these are in widespread use.

7.3 **Imaging modalities**

Where the likelihood of relapse is low, chest X-ray and US are appropriate. Where the risk is intermediate or high, CT of chest and abdomen is the investigation of choice, though the significant morbidity of radiation dose with repeated CT scans should be taken into account (7).

Dependent on the availability of new effective treatments more strict follow-up schedules may be required. Another problematic issue is the optimal duration of the follow-up. One may argue the
follow-up by imaging is not cost effective after 5 years (8). Late metastases are more frequently solitary and these justify more aggressive therapy with curative intent. Also patients with tumors that develop in the contralateral kidney (2-3%) can be treated with nephron-sparing surgery when detected with a small size. Furthermore, for tumors <4cm there seems to be no obvious difference in recurrence in the follow-up after partial or radical nephrectomy (9).

Using many of these variables, several groups have designed scoring systems and algorithms to stratify patients into low-, intermediate- and high-risk groups for developing tumour recurrence or metastases. The frequency and type of investigation are different for each group (10-13). Examples of these scoring systems are shown in Tables 3 and 4.

Table 3: Scoring algorithm to predict metastases after nephrectomy in patients with clear cell renal cell carcinoma according to the Mayo Scoring System (13)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor / T-stage</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>0</td>
</tr>
<tr>
<td>pT1b</td>
<td>2</td>
</tr>
<tr>
<td>pT2</td>
<td>3</td>
</tr>
<tr>
<td>pT3 - pT4</td>
<td>4</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
</tr>
<tr>
<td>&lt;10cm</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10cm</td>
<td>1</td>
</tr>
<tr>
<td>Regional Lymph Node status</td>
<td></td>
</tr>
<tr>
<td>pNx/pN0</td>
<td>0</td>
</tr>
<tr>
<td>pN1 - pN2</td>
<td>2</td>
</tr>
<tr>
<td>Nuclear grade</td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3</td>
</tr>
<tr>
<td>Tumor necrosis</td>
<td></td>
</tr>
<tr>
<td>No necrosis</td>
<td>0</td>
</tr>
<tr>
<td>Necrosis</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Table 4: Accumulated risk of metastases (%) after nephrectomy in patients with clear cell renal cell carcinoma as defined in risk groups according to the Mayo Scoring System (13)

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Year 1</th>
<th>Year 3</th>
<th>Year 5</th>
<th>Year 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.5</td>
<td>2.1</td>
<td>2.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Intermediate</td>
<td>9.6</td>
<td>20.2</td>
<td>26.2</td>
<td>35.7</td>
</tr>
<tr>
<td>High</td>
<td>42.3</td>
<td>62.9</td>
<td>68.8</td>
<td>76.4</td>
</tr>
</tbody>
</table>

The use of these scoring systems allows the urologist to be selective in the use of imaging and to appropriately target those patients most in need of intensive surveillance.

7.4 Conclusion
In cases where there is a very low risk for tumour recurrence or systemic tumour progression, CT scans can be omitted as routine follow-up examinations. In these patients, a CT scan is only justified in cases of possible tumour-associated symptoms. In the intermediate-risk group, an intensified follow-up that includes CT scans at regular time intervals should be performed according to a risk-stratified nomogram. In high-risk patients, the follow-up examinations should include routine CT scans (level of evidence: 4).
7.5 Recommendation
The intensity of the follow-up programme for an individual patient should be adapted according to
the risk of tumour recurrence or systemic tumour progression, as determined by a risk nomogram
developed for risk stratification (grade C recommendation).
<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diane Nurse</td>
<td>Consultant Urologist – Chair</td>
<td>Princess Royal University Hospital</td>
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<td>Munir Ahmed</td>
<td>Consultant Urologist</td>
<td>Princess Royal University Hospital</td>
</tr>
<tr>
<td>Maureen Baldwin</td>
<td>Divisional Manager</td>
<td>Princess Royal University Hospital</td>
</tr>
<tr>
<td>Sophie Baugh</td>
<td>Service Manager – General Surgery, Urology &amp; Audiology</td>
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</tr>
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<td>Ronald Beaney</td>
<td>Consultant Clinical Oncologist</td>
<td>Guys &amp; St Thomas' Hospital</td>
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<td>Guys &amp; St Thomas' Hospital</td>
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<tr>
<td>Kirstie Black</td>
<td>Service General Manager</td>
<td>Guys &amp; St Thomas' Hospital</td>
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<tr>
<td>Cathy Burton</td>
<td>Associate Director – Primary Care</td>
<td>SELCN</td>
</tr>
<tr>
<td>Declan Cahill</td>
<td>Consultant Urologist – Vice Chair</td>
<td>Guys &amp; St Thomas' Hospital</td>
</tr>
<tr>
<td>Penny Champion</td>
<td>CNS – Renal &amp; Testicular</td>
<td>Guys &amp; St Thomas' Hospital</td>
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<td>Ashish Chandra</td>
<td>Consultant Histopathologist</td>
<td>Guys &amp; St Thomas' Hospital</td>
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</tr>
<tr>
<td>David Landau</td>
<td>Consultant Clinical Oncologist</td>
<td>Guys &amp; St Thomas’ Hospital</td>
</tr>
<tr>
<td>Julie Lees</td>
<td>Trust Cancer Manager</td>
<td>Queen Elizabeth Hospital</td>
</tr>
<tr>
<td>Elaine McDonald</td>
<td>Trust Cancer Manager</td>
<td>Kings College Hospital</td>
</tr>
<tr>
<td>Naheed Mir</td>
<td>Trust Clinical Lead</td>
<td>University Hospital Lewisham</td>
</tr>
<tr>
<td>Gordon Muir</td>
<td>Consultant Urologist</td>
<td>Kings College Hospital</td>
</tr>
<tr>
<td>Janette Nichol</td>
<td>Clinical Nurse Specialist</td>
<td>Guys &amp; St Thomas’ Hospital</td>
</tr>
<tr>
<td>Ramon Neikrash</td>
<td>Consultant Urologist</td>
<td>Queen Elizabeth Hospital</td>
</tr>
<tr>
<td>Tim O’Brien</td>
<td>Consultant Urologist</td>
<td>Guys &amp; St Thomas’ Hospital</td>
</tr>
<tr>
<td>Patrick O’Donnell</td>
<td>Consultant Histopathologist</td>
<td>Guys &amp; St Thomas’ Hospital</td>
</tr>
<tr>
<td>Rick Popert</td>
<td>Consultant Urologist</td>
<td>Guys &amp; St Thomas’ Hospital</td>
</tr>
<tr>
<td>David Porbert</td>
<td>Deputy Divisional Director</td>
<td>Guys &amp; St Thomas’ Hospital</td>
</tr>
<tr>
<td>Reena Seunath</td>
<td>Clinical Nurse Specialist</td>
<td>Queen Elizabeth Hospital</td>
</tr>
<tr>
<td>Peter Thompson</td>
<td>Consultant Urologist</td>
<td>Kings College London</td>
</tr>
<tr>
<td>Gordon Kooiman</td>
<td>Consultant Urologist</td>
<td>Kings College London</td>
</tr>
<tr>
<td>Alastair Whittington</td>
<td>Network Director</td>
<td>SELCN</td>
</tr>
<tr>
<td>Angelika Zang</td>
<td>Consultant Urologist</td>
<td>Princess Royal University Hospital</td>
</tr>
<tr>
<td>Vacant</td>
<td>Ass Director Service Improvement</td>
<td>SELCN</td>
</tr>
</tbody>
</table>
Patient meets Criteria for Referral*
If URGENT contact Specialist Palliative Care Team Directly

Hospital
- In Patient
- Out Patient
- Urgent
  - Referral to Hospital Palliative Care Team (HPCT)

Home/Nursing home
- Referral to Community Palliative Care Team (CPCT)

Referral to Specialist Palliative Care Inpatient Unit/Hospice, +/- Day Care
Routine referrals will be contacted within 2 working days to arrange an assessment. For urgent referrals, direct contact with the palliative care team is needed to discuss each situation individually.

**Criteria for Referral**

Most patients will have an advanced, progressive disease, where the focus of care will have changed from curative to palliative and the prognosis is limited. Some patients, who have complex specialist needs, can be referred at an earlier stage, from diagnosis onwards. Patients may be discharged if their condition stabilises.

A demonstrable need for specialist palliative care services must be established. Appropriate reasons for referral may include potential / existing difficulties with the following:

- Pain and Symptom management
- Meeting the psycho-social needs of the patient & their family, and/or significant others
- Terminal Care/Dying
- Where possible, the patient, and if not, the carer, should be informed and in agreement with the referral
- Any Health Care Professional can refer to the Specialist Palliative Care Team, but acceptance must be with the agreement of the GP or inpatient Consultant

**Criteria for Urgent Referral: needing advice/assessment within 1-2 working days.**

- Difficult psychological/physical symptoms causing distress and not responding to current management
- Rapidly deteriorating condition

**Mechanisms of Referral**

**Hospital Palliative Care Teams**

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Contact Details</th>
<th>Method of Referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>King’s College Hospital</td>
<td>Telephone 020 7346 4060 Fax 020 7346 4713</td>
<td>Telephone</td>
</tr>
<tr>
<td>GSTT</td>
<td>St Thomas': 020 7188 4755 Fax 020 7188 4720 Guy's 020 7188 4754 Fax 020 7188 4748</td>
<td>Referral form</td>
</tr>
<tr>
<td>Queen Elizabeth Hospital, Woolwich</td>
<td>020 8836 5442 Fax 020 8836 5428</td>
<td>Telephone</td>
</tr>
<tr>
<td>Queen Mary’s Hospital, Sidcup</td>
<td>020 8308 3295 Fax 020 8308 3168</td>
<td>Telephone</td>
</tr>
<tr>
<td>Princess Royal University Hospital</td>
<td>01689 825755 Fax 01689 892999 PRUH hospital Bleep 745/629</td>
<td>Telephone</td>
</tr>
<tr>
<td>Lewisham Hospital</td>
<td>020 8333 3017 Fax 020 8333 3270</td>
<td>Referral form</td>
</tr>
</tbody>
</table>

**Community Palliative Care Teams**

Copies of recent medical correspondence, a list of current medication and relevant investigation results should accompany all referrals.
<table>
<thead>
<tr>
<th>Name of Team</th>
<th>Catchment area</th>
<th>Contact details</th>
<th>Method of referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>St Christopher's at Home</td>
<td>Parts of LSL, North Bromley</td>
<td>020 8776 5656 Fax 020 8776 5798</td>
<td>Referral form</td>
</tr>
<tr>
<td>Ellenor Foundation</td>
<td>North Bexley</td>
<td>020 8310 4100 Fax 8312 2115</td>
<td>Referral form</td>
</tr>
<tr>
<td></td>
<td>South Bexley</td>
<td>020 8308 3014 Fax 020 8308 3168</td>
<td></td>
</tr>
<tr>
<td>Greenwich Community Team</td>
<td>Greenwich</td>
<td>020 8312 1166 Fax 020 8312 2266</td>
<td>Referral form</td>
</tr>
<tr>
<td>Lewisham Macmillan Team</td>
<td>Lewisham</td>
<td>020 8333 3017 Fax 020 8333 3270</td>
<td>Referral form</td>
</tr>
<tr>
<td>St Thomas' PCT</td>
<td>North and West Lambeth</td>
<td>020 7188 4755 Fax 020 7188 4720</td>
<td>Referral form</td>
</tr>
<tr>
<td>Guy's PCT</td>
<td>North Southwark</td>
<td>020 7188 8178 Fax 020 7188 4748</td>
<td>Referral form</td>
</tr>
<tr>
<td>Harris HospisCare</td>
<td>South Bromley</td>
<td>01689 825755 Fax 01689 892999</td>
<td>Referral form</td>
</tr>
</tbody>
</table>

**Specialist Palliative Care Units/Hospices (inpatient and day care)**

All referrals made using appropriate referral form. Copies of recent medical correspondence, current medication and relevant investigation results should accompany all referrals.

<table>
<thead>
<tr>
<th>Name of Unit</th>
<th>Catchment Area</th>
<th>Contact details</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>St Christopher's Hospice</td>
<td>All of SELCN</td>
<td>020 8768 4500</td>
<td>Inpatient and day centre</td>
</tr>
<tr>
<td>Greenwich and Bexley Cottage Hospice</td>
<td>Greenwich and Bexley</td>
<td>020 8312 2244</td>
<td>Inpatient and day centre</td>
</tr>
<tr>
<td>Trinity Hospice</td>
<td>LSL</td>
<td>020 7787 1000</td>
<td>Inpatient and day centre</td>
</tr>
<tr>
<td>Harris HospisCare</td>
<td>South Bromley</td>
<td>01689 605300 Fax 01689 605303</td>
<td>Day centre</td>
</tr>
<tr>
<td>Richard Dimbleby Cancer Information and Support Service</td>
<td>All of SELCN</td>
<td>020 7188 5918</td>
<td>Information centre and psychological support service</td>
</tr>
</tbody>
</table>

**Symptom Control Guidelines**

South East London Cancer Network Palliative Care Coordinating Group have developed guidelines for management of common symptoms within the hospital or community setting. These guidelines are available from your local Specialist Palliative Care Team or by contacting Sharon Peirson at SELCN on 020 7188 7090
LEAD HISTOPATHOLOGISTS

<table>
<thead>
<tr>
<th>Lead Histopathologist (Prostate)</th>
<th>Dr Patrick O’Donnell</th>
<th>GSTFT</th>
<th>Patrick.O’<a href="mailto:Donnell@gstt.nhs.uk">Donnell@gstt.nhs.uk</a></th>
<th>020 7188 2919</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead Histopathologist (Bladder &amp; Renal)</td>
<td>Dr Ashish Chandra</td>
<td>GSTFT</td>
<td><a href="mailto:Ashish.Chandra@gstt.nhs.uk">Ashish.Chandra@gstt.nhs.uk</a></td>
<td>0207 188 2946</td>
</tr>
</tbody>
</table>

COVER ARRANGEMENTS

<table>
<thead>
<tr>
<th>Prostate histopathology</th>
<th>Dr Catherine Horsfield</th>
<th>GSTFT</th>
<th><a href="mailto:Catherine.Horsfield@gstt.nhs.uk">Catherine.Horsfield@gstt.nhs.uk</a></th>
<th>0207 188 2907</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder &amp; Renal histopathology</td>
<td>Dr Fahim Tungekar</td>
<td>GSTFT</td>
<td><a href="mailto:Fahim.Tungekar@gstt.nhs.uk">Fahim.Tungekar@gstt.nhs.uk</a></td>
<td>0207 188 2940</td>
</tr>
</tbody>
</table>

THE LEAD HISTOPATHOLOGISTS:

- Coordinate the histopathology team to ensure timely reporting of specimens to be discussed at the MDM, including external cases once they have been received in the Centre as per MDM SOP
- Are responsible for ensuring that all external histopathology has been reviewed by at least two histopathologists before presentation at the MDM and that pathology reports show the agreed diagnosis
- Ensure that relevant information from the Royal College of Pathologists minimum dataset is included in the final histopathology report
- Are the main point of contact for the MDM chairman for any complaint or other issue relating to the quality, timeliness or content of the histopathology report
- Ensure that the referring unit histopathology sections and blocks are appropriately stored and returned once they have been reviewed
- Are members of the SELCN Urology Tumour Working Group (TWG)

REVIEW OF EXTERNAL CASES

- Pathology material will be requested from external pathology services by the urology MDM co-ordinator and sent to the histopathology department (Ms Marilyn Murphy, St. Thomas’ Hospital, London SE1 7EH).
- Details of all previous malignant disease and pathology samples are required.
• The reporting histopathologists will review and report all external histology for new patients referred to MDM, subject to availability, in the same way as for internal cases.

• For external pathology review, a report will be issued on the pathology system under the patient unit number and histology number and the report sent to the requesting or current clinical consultant(s).

• The reporting pathologist at the external hospital will be informed of the review in the form of a copy of the report.

• The slides and/or blocks will be returned to the external hospital after a suitable period of retention in case further pathology discussion is required during treatment. This period will vary depending on the patient’s treatment schedule and the need to refer slides on for specific tumour types or referral to another MDT. Normally, slides will be returned within one week of reporting or MDM discussion, whichever is the later. When slides are not returned within this timescale, the external consultant will be informed by letter.

• A record of the number of slides, blocks and reports received and returned is maintained with an audit trail.

• Where there is disparity between Unit diagnosis and Centre diagnosis, the Centre histopathology report, with any necessary external opinion, will be final.