5.1 INTRODUCTION

5.1.1 Allied Health Professionals work with all age groups and conditions, and are trained in assessing, diagnosing, treating and rehabilitating people with health and social care needs. They work in a range of settings including hospital, community, education, housing, independent and voluntary sectors. This guidance provides an administrative framework to support the management of patients waiting for AHP services.

5.1.2 Although it is written primarily for services provided in Trusts, it is recognised that there are a number of AHPs who provide services for children with physical and learning disabilities within special schools and with special educational needs within mainstream schools. Operational practices in these settings should be in line with the principles of the IEAP and provide consistency and equity for patients. Trusts should collaborate with colleagues within the Department of Education and the relevant schools to harmonise practices and ensure that children are able to access services equitably and within the maximum waiting time guarantees. A robust monitoring process will be required.

5.1.3 For the purposes of this section of the protocol, the generic term ‘clinic’ will be used to reflect AHP activity undertaken in hospital, community or domiciliary settings as it is recognised that AHPs provide patient care in a variety of care locations.

5.2 KEY PRINCIPLES

5.2.1 Trusts should ensure that there is a systematic approach to modernising AHP services which will help to improve access to services and quality of care for patients. This section should be read within the overall context of both the IEAP and the specific section governing the management of hospital outpatient services.

5.2.2 When looking at the experience of the patient it is important to consider the whole of their journey, with both the care and administrative pathways designed to support the patient's needs at each stage. The wait to receive outpatient therapy is likely to be one of many they experience in different parts of the system. It is the responsibility of all those involved to ensure that the patient wastes as little time as possible waiting and is seen by the right person as quickly as possible.

5.2.3 Booking will enable patients to have an opportunity to contact the hospital and agree a convenient time for their appointment. As outlined in paragraph 4.1.4, booking strategies should be developed in line with these Booking Principles. In the interim period, while fixed appointments are being issued, Trusts should ensure that the regional guidance is followed in the management of patients.

5.3 CALCULATION OF THE WAITING TIME

5.3.1 The waiting time clock for an AHP referral commences on the date the referral letter is received by the AHP service within the Trust. All referral letters, including faxed, emailed and electronically received referrals, will be date stamped on the date received.

5.3.2 The waiting time clock stops when the first definitive AHP treatment has commenced or when a decision is made that treatment is not required. Further information on definitions and sample patient pathways is contained in the Data Definitions and Guidance Document for AHP Waiting Times and can be found in **Appendix 12.**

5.3.3 As booking systems are introduced, patients should be made a reasonable offer, where clinically possible. Patients who refuse a reasonable offer of treatment, or fail to attend an AHP appointment, will have their waiting time clock re-set to the date the service was informed of the cancellation (CNAs) or the date the patient failed to attend (DNAs).

5.4 NEW REFERRALS

5.4.1 All AHP referrals will be registered on the relevant information system within 1 working day of receipt.

5.4.2 Trusts should work towards a system whereby all AHP referrals sent to the Trust are received at a dedicated registration function (s). Trusts should ensure that adequate systems are in place to deal with multiple referrals for the same patient regarding the same condition from a number of sources.

5.4.3 All referrals must be triaged or assessed to make a clear decision on the next step of a referral and clinical urgency (urgent or routine) clearly identified and recorded. All referrals will be prioritised and returned to the registration point with 3 working days.

5.4.4 Trusts must ensure that protocols are in place to prevent unnecessary delay from date stamping / logging of referrals to forwarding to the AHP department responsible for referral triage and/or initiation of treatment. It will be the responsibility of the relevant manager to monitor this performance indicator.

5.4.5 A robust system should be in place to ensure that cover is provided for referrals to be read and prioritised during practitioners' absence. A designated officer should oversee this and a protocol will be required for each service.

5.4.6 Where referrals can be reviewed less frequently than weekly, a process must be put in place and agreed with AHPs whereby the referrer's prioritisation is accepted in order to proceed with booking patients.

5.4.7 Following prioritisation, referrals must be updated on the relevant information system and appropriate correspondence issued to patients within 1 working day. Where there is insufficient information for the AHP to make a decision, they should contact the originating referrer in the first instance to access the

necessary information. If this cannot be gained, the referral should be returned to the referral source.

5.4.8 Trusts will work towards a system whereby the location of all letters can be tracked at all times through the referral and appointment system, and that letters sent to be prioritised and letters which are not returned can be identified.

5.4.9 If at the referral stage the patient / client is identified as being clinically or socially unfit to receive the necessary service the referral should not be accepted (not added to a waiting list) and returned to the originating referrer with a request that they re-refer the patient / client when they are clinically or socially fit to be treated.

5.5 URGENT AND ROUTINE APPOINTMENTS

5.5.1 All routine patients should be appointed within the maximum waiting time guarantee. Urgent patients must be booked within locally agreed maximum waits from the date of receipt. Local booking process should be based upon the principles outlined in Section 1.7.

5.5.2 For routine waiting list patients, an acknowledgement letter will be sent to patients within 5 working days of receipt of the referral, which should provide information to patients on their anticipated length of wait and details of the booking process.

5.5.3 A minimum of three weeks' notice should be provided for all routine patients. This does not prevent patients being offered an earlier appointment. Patients refusing short notice appointments (i.e. less than three weeks notice) will not have their waiting time clock reset, in line with guidance on reasonable offers.

5.5.4 Trusts must ensure that all communication to patients is clear, easily understood and complies with all relevant legislation.

5.6 CHRONOLOGICAL MANAGEMENT

5.6.1 Patients, within each clinical priority category, should be selected for booking in chronological order, i.e. based on the date the referral was received. Trusts should ensure that local administrative systems have the capability and functionality to effectively operate a referral management and booking system that is chronologically based.

5.7 CAPACITY PLANNING AND ESCALATION

5.7.1 It is important for AHP services to understand their baseline capacity, the make-up of the cohort of patients waiting to be treated and the likely changes in demand that will impact on their ability to initiate treatment and meet the maximum waiting time guarantees for patients.

5.7.2 Trusts should ensure that robust prospective capacity planning arrangements are in place, with clear escalation procedures to facilitate capacity gaps to be identified and solutions found in a timely manner to support operational booking processes and delivery of the targets.

5.8 REASONABLE OFFERS

5.8.1 As booking systems are introduced, patients should be offered reasonable notice, where clinically possible. A reasonable offer is defined as an offer of appointment, irrespective of provider, that gives the patient a minimum of three weeks notice and two appointments. If a reasonable offer is made to a patient, which is then refused, the waiting time will be recalculated from the date the reasonable offer was refused. To ensure a verbal booking process is auditable, the Trust should make and cancel an appointment using the date of the second appointment date offered and refused for this transaction.

5.8.2 If the patient is offered an appointment within a shorter notice period and it is refused, the waiting time cannot be recalculated.

5.8.3 If the patient accepts an appointment at short notice, but then cancels the appointment, the waiting time can be recalculated from the date of cancellation as the patient has entered into an agreement with the Trust.

5.8.3 It is essential that Trusts have robust audit procedures in place to demonstrate compliance with the above.

5.9 AHP SERVICE INITIATED CANCELLATIONS

5.9.1 No patent should have his or her appointment cancelled. If Trusts cancel a patient's appointment, the waiting time clock will not be re-set and the patient will be offered an alternative reasonable appointment date, ideally at the time of cancellation, and no more than 6 weeks in advance. The Trust must ensure that the new appointment date is within the maximum waiting time guarantee.

5.9.2 The patient should be informed of the reason for the cancellation and the date of the new appointment. This should include an explanation and an apology on behalf of the Trust.

5.9.3 Trusts will make best efforts to ensure that a patient's appointment is not cancelled a second time for non-clinical reasons.

5.9.4 AHP service initiated cancellations will be recorded and reported to the relevant department on a monthly basis. Where patients are cancelled on the day of appointment as a result of AHP service initiated reasons, i.e. equipment failure, staff sickness, a new appointment should, where possible, be agreed with the patient prior to the patient leaving the department.

5.10 MAXIMUM WAITING TIME GUARANTEE

5.10.1 If a patient requests an appointment date that is beyond the maximum waiting time guarantee, the patient will be discharged and advised to revisit their referrer when they are ready to be seen. This will ensure that all patients waiting for an AHP appointment / treatment are fit and ready to be seen.

5.10.2 There will undoubtedly be occasions and instances where local discretion is required and sensitivity should be applied when short periods of time are involved; for example, if patients are requesting dates up to a week over their breach date. Trusts should ensure that reasonableness is complied with to facilitate re-calculation of the patient's waiting time, and to facilitate booking the patient into the date they requested.

5.11 COMPLIANCE WITH LEAVE PROTOCOL

5.11.1 Capacity lost due to cancelled or reduced clinics or visits at short notice has negative consequences for patients and on the Trust's ability to successfully implement robust booking processes. Clinic cancellation and rebooking of appointments is an extremely inefficient way to use such valuable resources.

5.11.2 It is therefore essential that AHP practitioners and other clinical planned leave or absence is organised in line with an agreed Trust Human Resources (HR) protocol. Thus it is necessary for Trusts to have robust local HR policies and procedures in place that minimise the cancellation/reduction of AHP clinics and the work associated with rebooking patient appointments. There should be clear practitioner agreement and commitment to this HR policy. Where cancelling and rebooking is unavoidable the procedures used must be equitable, efficient and comply with clinical governance principles.

5.11.3 The protocol should require a minimum of six weeks' notification of planned leave, in line with locally agreed HR policies.

5.11.4 A designated member of staff should have responsibility for monitoring compliance with the notification of leave protocol, with clear routes for escalation, reporting and audit.

5.12 CLINIC OUTCOME MANAGEMENT

5.12.1 All patients will have their attendance recorded or registered on the relevant information system upon arrival for their appointment. The patient must verify their demographic details on every visit. The verified information must be cross-checked on information system and the patient records. Any changes must be recorded and updated in the patient record on the date of the clinic.

5.12.2 When the assessment/treatment has been completed, and where there is a clear decision made on the next step, patient outcomes must be recorded on the date of clinic.

5.13 REVIEW APPOINTMENTS

5.13.1 All review appointments must be made within the time frame specified by the practitioner. If a review appointment cannot be given at the specified time due to the unavailability of a clinic appointment slot, a timeframe either side of this date should be agreed with the practitioner. Where there are linked interventions, discussions on a suitable review date should be discussed and agreed with the practitioner.

5.13.2 Review patients who require an appointment within six weeks will negotiate the date and time of the appointment before leaving the service and PAS / information system updated. Patients requiring an appointment outside six weeks should be managed on a review waiting list, with the indicative date recorded when appointment is required and booked in line with the booking principles outlined.

5.13.3 If domiciliary review appointment is required within 6 weeks, the appointment date should be agreed with the patient and confirmed in writing by the booking office. Where a domiciliary review appointment is required outside 6 weeks, the patient should be managed on a review waiting list, within the indicative date recorded, and booking in line with the booking principles outlined.

5.14 CLINIC TEMPLATE MANAGEMENT

5.14.1 Clinic templates should be agreed between the practitioner and service manager. These should reflect the commissioning volumes associated with that service area in the Service and Budget Agreement.

5.14.2 Templates will identify the number of slots available for new urgent, new routine and follow up appointments; specify the time each clinic is scheduled to start and finish; and identify the length of time allocated for each appointment slot.

5.14.3 All requests for template and temporary clinic rule changes will only be accepted in writing to the relevant service manager. A minimum of six weeks notice will be provided for clinic template changes.

5.14.4 All requests for permanent and temporary template changes should be discussed with the appropriate service or general manager.

5.15 ROBUSTNESS OF DATA / VALIDATION

5.15.1 A continuous process of data quality validation should be in place to ensure data accuracy at all times. This should be undertaken as a minimum on a weekly basis and continually reviewed as waiting times reduce. This is essential to ensure Primary Targeting Lists are accurate and robust at all times.

5.15.2 As booking processes are implemented and waiting times reduce, there is no longer the need to validate patients by letter.

5.15.3 For patients in AHP services that are not yet booked, they will be contacted to establish whether they will still require their appointment.

SECTION 6 PROTOCOL GUIDANCE FOR MANAGEMENT OF ELECTIVE ADMISSIONS

6.1 INTRODUCTION

6.1.1 The following protocol is based on nationally recommended good practice guidelines to assist staff with the effective management of elective waiting lists.

6.1.2 The administration and management of elective admissions within and across Trusts must be consistent, easily understood, patient focused, and responsive to clinical decision-making.

6.2 COMPUTER SYSTEMS

6.2.1 To ensure consistency and the standardisation of reporting with Commissioners and the Department, all waiting lists are to be maintained in the PAS system.

6.2.2 Details of patients must be entered on to the computer system within two working days of the decision to admit being made. Failure to do this will lead to incorrect assessment of waiting list size when the daily / weekly downloads are taken.

6.2.3 As a minimum 3 digit OPCS codes should be included when adding a patient to a waiting list. Trusts should work towards expanding this to 4 digit codes.

6.3 CALCULATION OF THE WAITING TIME

6.3.1 The starting point for the waiting time of an inpatient is the date the consultant agrees with the patient that a procedure will be pursued as an active treatment or diagnostic intervention, and that the patient is medically fit to undergo such a procedure.

6.3.2 The waiting time for each inpatient on the elective admission list is calculated as the time period between the original decision to admit date and the date

at the end of the applicable period for the waiting list return. If the patient has been suspended at all during this time, the period(s) of suspension will be automatically subtracted from the total waiting time.

6.3.3 Patients who refuse a reasonable offer of treatment, or fail to attend an offer of admission, will have their waiting time reset to the date the hospital was informed of the cancellation (CNAs) or the date the patient failed to attend (DNAs). Any periods of suspension are subtracted from the patients overall waiting time.

6.4 STRUCTURE OF WAITING LISTS

6.4.1 To aid both the clinical and administrative management of the waiting list, lists should be sub-divided into a limited number of smaller lists, differentiating between active waiting lists, planned lists and suspended patients.

6.4.2 Priorities must be identified for each patient on the active waiting list, allocated according to urgency of the treatment. The current priorities are urgent and routine.

6.5 INPATIENT AND DAY CASE ACTIVE WAITING LISTS

6.5.1 Inpatient care should be the exception in the majority of elective procedures. Trusts should move away from initially asking “is this patient suitable for day case treatment?” towards a default position where they ask “what is the justification for admitting this patient?” The Trust’s systems, processes and physical space should be redesigned and organized on this basis.

6.5.2 Patients who are added to the active waiting list must be clinically and socially ready for admission on the day of the decision to admit, i.e. if there was a bed available tomorrow in which to admit a patient they are fit, ready, and able to come in.

6.5.3 All decisions to admit will be recorded on PAS within two working days of the decision to admit being taken.

6.5.4 Robust booking and scheduling systems will be developed to support patients having a say in the date and time of their admission. Further guidance will be provided on this.

6.5.5 Where a decision to admit depends on the outcome of diagnostic investigation, patients should not be added to an elective waiting list until the outcome of this investigation is known. There must be clear processes in place to ensure the result of the investigation is timely and in accordance with the clinical urgency required to admit the patient.

6.5.6 The statements above apply to all decisions to admit, irrespective of the decision route, i.e. direct access patients or decisions to directly list patients without outpatient consultation.

6.6 COMPLIANCE WITH TRUST HR LEAVE PROTOCOL

6.6.1 Trusts should have in place a robust protocol for the notification and management of medical and clinical leave and other absence. This protocol should include a proforma for completion by or on behalf of the consultant with a clear process for notifying the theatre scheduler of leave / absence.

6.6.2 The protocol should require a minimum of six weeks' notification of intended leave, in line with locally agreed consultant's contracts.

6.6.3 A designated member of staff should have responsibility for monitoring compliance with the notification of leave protocol, with clear routes for escalation, reporting and audit.

6.7 TO COME IN (TCI) OFFERS OF TREATMENT

6.7.1 The patient should be advised of their expected waiting time during the consultation between themselves and the health care provider/practitioner and confirmed in writing.

6.7.2 Patients should be made reasonable offers to come in on the basis of clinical priority. Within clinical priority groups offers should then be made on the basis of the patient's chronological wait.

6.7.3 All patients must be offered reasonable notice. A reasonable offer is defined as an offer of admission, irrespective of provider, that gives the patient a minimum of three weeks' notice and two TCI dates. If a reasonable offer is made to a patient, which is then refused, the waiting time will be recalculated from the date of the refused admission.

6.7.4 If the patient is offered an admission within a shorter notice period and it is refused, the waiting time cannot be recalculated.

6.7.5 If the patient however accepts an admission at short notice, but then cancels the admission, the waiting time can be recalculated from the date of that admission as the patient has entered into an agreement with the Trust.

6.7.6 It is essential that Trusts have robust audit procedures in place to demonstrate compliance with the above.

6.8 SUSPENDED PATIENTS

6.8.1 A period of suspension is defined as:

- A patient suspended from the active waiting list for medical reasons, or unavailable for admission for a specified period because of family commitments, holidays, or other reasons i.e. a patient may be suspended during any periods when they are unavailable for treatment for social or

medical reasons (but not for reasons such as the consultant being unavailable, beds being unavailable etc).

- A maximum period not exceeding 3 months.

6.8.2 At any time a consultant is likely to have a number of patients who are unsuitable for admission for clinical or social reasons. These patients should be suspended from the active waiting list until they are ready for admission. All patients who require a period of suspension will have a personal treatment plan agreed by the consultant with relevant healthcare professionals. One month prior to the end of the suspension period, these plans should be reviewed and actions taken to review patients where required.

6.8.3 Every effort will be made to minimise the number of patients on the suspended waiting list, and the length of time patients are on the suspended waiting list.

6.8.4 Should there be any exceptions to the above, advice should be sought from the lead director or appropriate clinician.

6.8.5 Suspended patients will not count as waiting for statistical purposes. Any periods of suspension will be automatically subtracted from the patient's total time on the waiting list for central statistical returns.

6.8.6 No patient added to a waiting list should be immediately suspended. Patients should be recorded as suspended on the same day as the decision was taken that the patient was unfit or unavailable for surgery.

6.8.7 No patient should be suspended from the waiting list without a review date. All review dates must be 1st of the month to allow sufficient time for the patient to be treated in-month to avoid breaching waiting times targets.

6.8.8 No more than 5% of patients should be suspended from the waiting list at any time. This indicator should be regularly monitored.

6.8.9 Trusts should ensure that due regard is given to the guidance on reasonableness in their management of suspended patients.

6.9 PLANNED PATIENTS

6.9.1 Planned patients are those who are waiting to be recalled to hospital for a further stage in their course of treatment or surgical investigation within specific timescales. This is usually part of a planned sequence of clinical care determined on clinical criteria (e.g. check cystoscopy).

6.9.2 These patients are not actively waiting for treatment, but for planned continuation of treatment. A patient is planned if there are clinical reasons that determine the patient must wait set periods of time between interventions. They will not be classified as being on a waiting list for statistical purposes.

6.9.3 Trusts should be able to demonstrate consistency in the way planned patients are treated and that patients are being treated in line with the clinical constraints. Planned patients should have a clearly identified month of treatment in which it can be shown that the patients are actually being treated.

6.9.4 Ideally, children should be kept under outpatient review and only listed when they reach an age when they are ready for surgery. However, where a child has been added to a list with explicit clinical instructions that they cannot have surgery until they reach the optimum age, this patient can be classed as planned. The Implementation Procedure for Planned Patients can be found in **Appendix 13.**

6.10 CANCELLATIONS AND DNA'S

6.10.1 Patient Initiated Cancellations

Patients who cancel a reasonable offer will be given a second opportunity to book an admission, which should be within six weeks of the original admission date. If a second admission offer is cancelled, the patient will not normally be offered a third opportunity and will be referred back to their referring clinician.

6.10.2 Patients who DNA

If a patient DNAs their first admission date, the following process must be implemented:

- Where a patient has had an opportunity to agree the date and time of their admission, they will not normally be offered a second admission date.

- Under exceptional circumstances a clinician may decide that a patient should be offered a second admission. The second admission date must be agreed with the patient.

6.10.3 In a period of transition where fixed TCIs are still being issued, patients should have two opportunities to attend.

6.10.4 Following discharge patients will be added to the waiting list at the written request of the referring GP and within a four week period from date of discharge. Patients should be added to the waiting list at the date of the written request is received.

6.10.5 It is acknowledged that there may be exceptional circumstances for those patients identified as being ‘at risk’ (children, vulnerable adults).

6.10.6 No patient should have his or her operation cancelled prior to admission. If Trusts cancel a patient’s admission/operation in advance of the anticipated TCI date, the waiting time clock (based on the original date to admit) will not be reset and the patient will be offered an alternative reasonable guaranteed future date within a maximum of 28 days.

6.10.7 Trusts should aim to have processes in place to have the new proposed admission date arranged before the patient is informed of the cancellation.

6.10.8 The patient should be informed in writing of the reason for the cancellation and the date of the new admission. The correspondence should include an explanation and an apology on behalf of the Trust.

6.10.9 Trusts will make best efforts to ensure that a patient's operation is not cancelled a second time for non clinical reasons.

6.10.10 Where patients are cancelled on the day of surgery as a result of not being fit for surgery / high anaesthetic risk, they will be suspended, pending a clinical review of their condition either by the consultant in outpatients or by their GP. The patient should be fully informed of this process.

6.10.11 Hospital-initiated cancellations will be recorded and reported to the relevant department on a monthly basis.

6.11 PERSONAL TREATMENT PLAN

6.11.1 A personal treatment plan must be put in place when a confirmed TCI date has been cancelled by the hospital, a patient has been suspended or is simply a potential breach. The plan should:

- Be agreed with the patient
- Be recorded in the patient's notes
- Be monitored by the appropriate person responsible for ensuring that the treatment plan is delivered.

6.11.2 The listing clinician will be responsible for implementing the personal treatment plan.

6.12 CHRONOLOGICAL MANAGEMENT

6.12.1 The process of selecting patients for admission and subsequent treatment is a complex activity. It entails balancing the needs and priorities of the patient and the Trust against the available resources of theatre time and staffed beds.

6.12.2 The Booking Principles outlined in Section 1.7 should underpin the development of booking systems to ensure a system of management and monitoring that is chronologically as opposed to statistically based.

6.12.3 It is expected that Trusts will work towards reducing the number of prioritisation categories to urgent and routine.

6.13 PRE-OPERATIVE ASSESSMENT

6.13.1 All patients undergoing an elective procedure (including endoscopy procedures) must undergo a pre-operative assessment. This can be provided using a variety of methods including telephone, postal or face to face assessment. Please refer to the Design and Deliver Guide 2007 for further reference.

6.13.2 Pre operative assessment will include an anaesthetic assessment. It will be the responsibility of the pre-operative assessment team, in accordance with protocols developed by surgeons and anaesthetists, to authorise fitness for surgery.

6.13.3 If a patient is unfit for their operation, their date will be cancelled and decision taken as to the appropriate next action.

6.13.4 Only those patients that are deemed fit for surgery may be offered a firm TCI date.

6.13.5 Pre-operative services should be supported by a robust booking system.

6.14 PATIENTS WHO DNA THEIR PRE OPERATIVE ASSESSMENT

6.14.1 Please refer to the guidance outlined in the Outpatient section.

6.15 VALIDATION OF WAITING LISTS

6.15.1 A continuous process of data quality validation should be in place to ensure data accuracy at all times. This should be undertaken as a minimum on a monthly basis, and ideally on a weekly basis as waiting times reduce. This is essential to ensure the efficiency of the elective pathway at all times.

6.15.2 As booking processes are implemented and waiting times reduce, there will no longer be the need to validate patients by letter. For patients in specialties that are not yet booked, they will be contacted to establish whether they will still require their admission.

6.15.3 Involvement of clinicians in the validation process is essential to ensure that waiting lists are robust from a clinical perspective. Trusts should ensure an ongoing process of clinical validation and audit is in place.

6.16 PATIENTS LISTED FOR MORE THAN ONE PROCEDURE

6.16.1 Where the same clinician is performing more than one procedure at one time, the first procedure should be added to the waiting list with additional procedures noted.

6.16.2 Where different clinicians working together will perform more than one procedure at one time the patient should be added to the waiting list of the clinician for the priority procedure with additional clinician procedures noted.

6.16.3 Where a patient requires more than one procedure performed on separate occasions or bilateral procedures by different (or the same) clinician, the patient should be placed on the active waiting list for the first procedure and the planned waiting list for any subsequent procedures.

6.17 TRANSFERS BETWEEN HOSPITALS or to INDEPENDENT SECTOR

6.17.1 Effective planning on the basis of available capacity should minimise the need to transfer patients between hospitals or to Independent Sector Providers. Transfers should not be a feature of an effective scheduled system.

6.17.2 Transfers to alternative providers must always be with the consent of the patient and the receiving consultant. Administrative speed and good communication are very important to ensure this process runs smoothly. The Implementation Procedure and Technical Guidance for Handling Inpatient Transfers can be found in **Appendix 15b.**

Datix

Carly Connolly

SHSCT GOVERNANCE TEAM (IR2) Form -NEW June 2018

Incident Details
ID & Status

Incident Reference ID	121045
Submitted time (hh:mm)	12:59

Incident IR1 details

Notification email ID number	W116553
Incident date (dd/MM/yyyy)	31/10/2019
Time (hh:mm)	16:00
Does this incident involve a patient under the age of 16 within a Hospital setting (inpatient or ED)	No
Does this incident involve a Staff Member?	Yes
Description Enter facts, not opinions. Do not enter names of people	Diagnosed with locally advanced prostate cancer August 2019. MDM 31st October 2019 recommended ADT and refer for EBRT. Not referred for EBRT and hormone treatment not as per guidance. March 2020 rising PSA and local progression (urinary retention). Re-staged June 2020 and developed metastatic disease.
Action taken Enter action taken at the time of the incident	Patient and family have been seen in outpatients and the diagnosis and future management plan discussed. Family asked if earlier treatment with EBRT would have changed the course and I have advised them that the care would be looked into.
Learning Initial	Concern MDM outcome not followed and patient has subsequently developed progression of disease.
Reported (dd/MM/yyyy)	14/07/2020
Reporter's full name	[redacted]
Reporter's SHSCT Email Address	[redacted]
Opened date (dd/MM/yyyy)	22/07/2020
Were restrictive practices used?	
Name This will auto-populate with the patient/client's name if the person-affected details have been entered for this incident.	[redacted]

Location of Incident

Site	Craigavon Area Hospital
Loc (Type)	Outpatient Clinic
Loc (Exact)	Thorndale Unit
Directorate	Acute Services
Division	Surgery and Elective Care
Service Area	General Surgery
Speciality / Team	Urology Surgery

Staff initially notified upon submission

Management of Incident

Reasons for Rejection - History

No records to display.

Linked records

No Linked Records.

Coding

Datix Common Classification System (CCS)

Category	Treatment, procedure
Sub Category	
Detail	

Datix CCS2

Type	Patient Incidents
Category	Administrative Processes (Excluding Documentation)
Sub-Category	Referrals
Detail	Referral delayed
Is this a Haemovigilance /Blood Transfusion or Labs-related Incident?	No
Is this an incident relating to confidentiality? This may include inappropriate access / disclosure, loss or theft of records etc	No

SAI / RIDDOR / NIAIC?
Click here To Help you determine whether or not an incident constitutes an SAI please refer to the Regional SAI reporting criteria by clicking here.

SAI?

Click To help you determine whether or not an incident constitutes an SAI please refer to the Regional SAI reporting criteria by clicking here.

Is this incident RIDDOR reportable?

Below are the 5 categories which qualify a RIDDOR Reportable incident (click on blue links for further definition):
1. Employee or self-employed person working on Trust premises is killed or suffers a major injury
2. A member of the public on Trust premises is killed or taken to hospital
3. An incident connected with the Trust where an employee, or self-employed person working on Trust premises, suffers an "over 3 day injury (being incapacitated to do their normal duties for more than three consecutive days (not counting the day of the accident but including weekends and rest days). Incapacitation means that the member of staff is absent or unable to do their normal work e.g. placed on lighter duties which are not part of their normal work)
4. Dangerous Occurence attributable to the work of the Trust
5. A doctor has notified you in writing that a Trust employee suffers from a reportable work-related disease

Is this a NIAIC Incident

NIAIC (Northern Ireland Adverse Incident Centre) incidents relate to medical devices. If a medical device is involved in an incident consider the list below to identify if the incident is NIAIC reportable;
- design or manufacturing problems
- inadequate servicing and maintenance
- inappropriate local modifications
- unsuitable storage and use conditions
- selection of the incorrect device for the purpose
- inappropriate management procedures
- poor user instructions or training (which may result in incorrect user practice

[redacted]

Investigation

Investigator

Date started (dd/MM/yyyy)

[redacted]

Actual Impact/Harm

Catastrophic

This has been populated by the reporter. To be quality assured by the investigating manager.

Risk grading

Click here
When the incident has a Severity (actualimpact/harm, grading of insignificant to moderate, you need to plot on the matrix oppositethe Potential impact/harm. Deciding what are the chances of the incidenthappening againunder similar circumstances. (Likelihod) and multiply that by the potential impact if it were to reoccur (consequence) The overall risk grading for the event will be determined by plotting: consequence multiplied by likelihood = risk grading. Refer to impact table here:

	Consequence				
Likelihood of recurrence	Insignificant	Minor	Moderate	Major	Catastrophic
Almost certain (Expected to occur daily)	O	O	O	O	O
Likely (Expected to occur weekly)	O	O	O	O	O
Possible (Expected to occur monthly)	O	O	O	O	O
Unlikely (Expected to occur annually)	O	O	O	O	O
Rare (NOT expected to occur for years)	O	O	O	O	O
	Grade:				

Action taken on review

Enter here any actions you have taken as a result of the incident occurring; e.g. communicating with staff / update care plan / review risk assessment (corrective and preventative action)

Action Plan Required?

A formal action plan is required for all Moderate to Catstrophic incidents. If you tick yes an "Action plan" section will appear below. Use this to create your action plan.

Action Plan

No actions.

Lessons learned

Notepad

Communication

Medication details

Falls Information
Please Quality Assure all information as part of your investigation

Pressure Ulcers

Equipment details

Documents added

People Affected

Employees

No Employees

Other Contacts

No Other Contacts

Datix

Carly Connolly

SHSCT GOVERNANCE TEAM (IR2) Form -NEW June 2018

Incident Details
ID & Status

Incident Reference ID	121851
Submitted time (hh:mm)	14:08

Incident IR1 details

Notification email ID number	W117359
Incident date (dd/MM/yyyy)	31/10/2019
Time (hh:mm)	15:00
Does this incident involve a patient under the age of 16 within a Hospital setting (inpatient or ED)	No
Does this incident involve a Staff Member?	Yes
Description Enter facts, not opinions. Do not enter names of people	Initial assessment May 2019. Clinically felt to have a malignant prostate. Commenced on Bicalutamide 50mg OD, TURP arranged (Benign pathology). Reviewed in outpatients in July 2019. Planned for repeat PSA and further review. Emergency Department attendance May 2020 resulting in catheterization. Rectal mas investigated and diagnosed as locally advanced prostate cancer. Commenced on Hormone treatment July 2020 and staging investigations arranged.
Action taken Enter action taken at the time of the incident	Discussed at MDM and prompt Outpatient review and commencement of treatment arranged.
Learning Initial	Concern TURP is not a diagnostic investigation for suspected prostate cancer and no prostate biopsies were performed despite clinical suspicion of locally advanced prostate cancer. Dose of bicalutamide patient commenced on below dose for standard antiandrogen monotherapy and no plan to utilize at this dose as cover for commencement of LHRHa therapy. No additional staging investigations arranged despite clinical impression of locally advanced prostate cancer. Patient subsequently re-presented with complications of local progression of untreated prostate cancer.
Reported (dd/MM/yyyy)	28/07/2020
Reporter's full name	[redacted]
Reporter's SHSCT Email Address	[redacted]
Opened date (dd/MM/yyyy)	30/07/2020
Were restrictive practices used?	
Name This will auto-populate with the patient/client's name if the person-affected details have been entered for this incident.	[redacted]

Location of Incident

Site	Craigavon Area Hospital
Loc (Type)	Outpatient Clinic
Loc (Exact)	Urology Clinic
Directorate	Acute Services
Division	Surgery and Elective Care
Service Area	General Surgery
Speciality / Team	Urology Surgery

Staff initially notified upon submission

Management of Incident

Reasons for Rejection - History

Linked records

Coding

Datix Common Classification System (CCS)

Datix CCS2

SAI / RIDDOR / NIAIC?
Click here To Help you determine whether or not an incident constitutes an SAI please refer to the Regional SAI reporting criteria by clicking here.

SAI?

Click To help you determine whether or not an incident constitutes an SAI please refer to the Regional SAI reporting criteria by clicking here.

Is this incident RIDDOR reportable?

Below are the 5 categories which qualify a RIDDOR Reportable incident (click on blue links for further definition):
1. Employee or self-employed person working on Trust premises is killed or suffers a major injury
2. A member of the public on Trust premises is killed or taken to hospital
3. An incident connected with the Trust where an employee, or self-employed person working on Trust premises, suffers an "over 3 day injury (being incapacitated to do their normal duties for more than three consecutive days (not counting the day of the accident but including

weekends and rest days). Incapacitation means that the member of staff is absent or unable to do their normal work e.g. placed on lighter duties which are not part of their normal work)
4. Dangerous Occurence attributable to the work of the Trust
5. A doctor has notified you in writing that a Trust employee suffers from a reportable work-related disease

Is this a NIAIC Incident

NIAIC (Northern Ireland Adverse Incident Centre) incidents relate to medical devices. If a medical device is involved in an incident consider the list below to identify if the incident is NIAIC reportable;
- design or manufacturing problems
- inadequate servicing and maintenance
- inappropriate local modifications
- unsuitable storage and use conditions
- selection of the incorrect device for the purpose
- inappropriate management procedures
- poor user instructions or training (which may result in incorrect user practice

Investigation

Investigator

Date started (dd/MM/yyyy)

Actual Impact/Harm: Major

This has been populated by the reporter. To be quality assured by the investigating manager.

Risk grading

Click here
When the incident has a Severity (actualimpact/harm, grading of insignificant to moderate, you need to plot on the matrix oppositethe Potential Impact/harm. Deciding what are the chances of the incidenthappening againunder similar circumstances. (Likelihod) and multiply that by the potential impact if it were to reoccur (consequence) The overall risk grading for the event will be determined by plotting: consequence multiplied by likelihood = risk grading. Refer to impact table here:

	Consequence				
Likelihood of recurrence	Insignificant	Minor	Moderate	Major	Catastrophic
Almost certain (Expected to occur daily)	O	O	O	O	O
Likely (Expected to occur weekly)	O	O	O	O	O
Possible (Expected to occur monthly)	O	O	O	O	O
Unlikely (Expected to occur annually)	O	O	O	O	O
Rare (NOT expected to occur for years)	O	O	O	O	O

Grade: [redacted]

Action taken on review

Enter here any actions you have taken as a result of the incident occurring; e.g. communicating with staff / update care plan / review risk assessment (corrective and preventative action)

Action Plan Required?

A formal action plan is required for all Moderate to Catstrophic incidents. If you tick yes an "Action plan" section will appear below. Use this to create your action plan.

Action Plan

No actions.

Lessons learned

Lessons learned

If you think there are any lessons from an incident which could be shared with other teams please record here. If not please type "none".

Date investigation completed (dd/MM/yyyy)

Was any person involved in the incident? No

Was any equipment involved in the incident? No

Notepad

Communication

Medication details

Falls Information
Please Quality Assure all information as part of your investigation

Pressure Ulcers

Equipment details

Documents added

People Affected

Employees

Other Contacts

Contact information urology SAI

Name	Contact Details	Date contacted	Details of conversation	GP
Patient 1 (RIP) Personal Information redacted by USI	NOK Patient 1's Daughter Personal Information redacted by USI	Informed 26/10/2020	I spoke to Mr Patient 1 daughter and offered my sincere condolences on the death of her father. I advised that Mr Haynes had spoken to her and her father at the clinic appointment in July and advised the Trust would be reviewing your care. I advised that this review will include of a small group of people. There has been some media coverage and did not want to distress her or her mother about the review. I advised on the chair appointed and he will want to meet with all the families to participate in the review. Patient's Daughter is Personal Information redacted by USI but has zoom and will be happy to meet with the chair via zoom. I will follow up with a letter.	
Patient 9 Personal Information redacted by USI Personal Information redacted by USI	Personal Information redacted by USI NOK Personal Information redacted by USI	Informed 26/10/2020	Introductions advised Mr O'Donaghue spoke to you in the clinic on 6 July 2020 and advised we would be reviewing your care. Mr Patient 9 was not aware of this discussion taking place. I apologised as I thought he was contacted. Advised about the SAI review and that it also include a small number of people and the chair will be in contact with you by letter to invite you to participate in it. Thanked me for the call.	

Patient 7 Personal Information redacted by the USI	Personal Information redacted by the USI NOK Daughter Personal Information redacted by the USI	Informed on 26/10/2020 PK	Apologised for the call. Advised we wanted to address this with you face to face at appointment on 2/11/2020 at 3pm but pre-empted by press release. Advised he has an appointment with Mr Glackin this afternoon at 3pm Advised about the SAI process and that will involve other patients and that I will follow up a letter in next few days. Contact number given. Patient 7 's daughter Personal Information redacted by the USI rang to advise about the review and to understand what has happened. She wanted to know if the doctor was suspended and I advised he no longer worked for the Trust.	Olivia Morgan
Patient 3 Personal Information redacted by the USI	Personal Information redacted by the USI Nok Personal Information redacted by the USI (Wife)	Contacted 27/10/2020	I phoned Patient 3 and advised of the SAI review in relation to the press release. He advised that he was more that happy with his care in Southern Trust and that his consultant was particularly attendance and give him a very high standard of care.	
Patient 2 Personal Information redacted by the USI	Personal Information redacted by the USI	26/10/2020	I phoned Patient 2 today and apologised for informing him of the SAI review but in view of media coverage have had to discuss over the phone. I advised that the review will be to review his pathway to the cancer services and how that compares with good practice. This will be part of a bigger review involving other patients.	

			I offered him a clinic appointment to discuss this further with Mr Haynes on 2 Nov at 3pm. The oncology team asked us to look into your pathway of care regarding delay in referral for oncologist review.	
Patient 5 Personal Information redacted by the USI Personal Information redacted by the USI	Personal Information redacted by the USI Nok Daughter Personal Information redacted by the USI Personal Information redacted by the USI Personal Information redacted by the USI Personal Information redacted by the USI	Contact PK 26/10/2020	Mr Haynes had spoken to you at the clinic and advised the Trust would be reviewing your care. This review will include of a small group of people. There has been some media coverage about a patient recall. Will not need to be recalled but will be part of a group of people in an SAI. There will be an opportunity to participate in the review and will be contact by letter with invitation.	
Patient 6 Personal Information redacted by the USI Personal Information redacted by the USI	Phone Personal Information redacted by the USI (home)	Contact PK 26/10/20	I spoke to Patient 6 and advised Mr Haynes had spoken to you at the clinic and advised the Trust would be reviewing your care. There has been some media coverage about There has been some media coverage about a patient recall. Will not need to be recalled but will be part of a group of people in an SAI. There will be an opportunity to participate in the review and will be contact by letter with invitation	Dr Hicks and Partners
Patient 8 Personal Information redacted by the USI	Personal Information redacted by the USI Personal Information redacted by the USI (Wife)	26/10/2020 Informed by PK	I spoke to Patient 8 and advised that Mr Haynes had spoken to you at the clinic 11 August and advised the Trust would be reviewing your care. This review will include of a small group of people. There has been some media coverage about a patient recall on the urology services. I want to advise you that you will be	

			part of an SAI which will involve a small group of people.	
Patient 4 Personal Information redacted by the USI Personal Information redacted by the USI	Deceased Personal Information redacted by the USI Daughter Personal Information redacted by the USI	26/10/2020 by PK	Daughter informed – Personal Information redacted by the USI I apologised for the call and offered condolences. I advised that the Trust is undertaking a SAI incident review into her father's care.	

Independent review

Patient 16 Personal Information redacted by the USI	NOK daughter Personal Information redacted by the USI Personal Information redacted by the USI	26/10/2020 PK	You may have seen some press coverage about our urology services, just to let you know that your father's case whilst it won't be reviewed again, it will be looked at again as part of the wider review to ensure learning has been implemented. Previous review of care.
Index Case.			
Patient 10 Personal Information redacted by the USI Personal Information redacted by the USI	Personal Information redacted by the USI / Personal Information redacted by the USI	26/10/2020 PK	I rang Patient 10 and advised that as part of the new SAI into the urology services that the previous SAI will be made available to the review team.
Patient 14 Personal Information redacted by the USI	Personal Information redacted by the USI (mobile	26/10/2020 PK	Informed about media coverage and will result in relooking at the SAI conducted previously. Will not impact on his case. Just letting him know that the report will be made

Personal Information redacted by the USI			available to look at overall service.
Personal Information redacted by the USI	Now deceased		Never told
Patient 13 Personal Information redacted by the USI	Personal Information redacted by the USI (mobile)		Previous review of care – will be discussed in this look back. Examine the learning. Patient 13 would like to have a discussion about the review. He has concerns that his health has been compromised and that he was on cyclophasamide which has known side of bladder cancer I will arrange for Mark to see him to discuss the report.
Patient 11 Personal Information redacted by the USI	Personal Information redacted by the USI (home) Personal Information redacted by the USI (mobile)	26/10/2020	I spoke to Patient 11 and advised about the media outbreak and how this may cause him some concern. I referred to the previous review that he received a letter recently to advise that there was no impact on his care. But did advise that the review conducted in 2017 will be made available to new review of care. He said he understood but wanted to advise that he had an appointment for a bone scan which he cancelled as he was afraid of covid. I will get someone to resend an appointment. He would prefer to be seen in Belfast. I shared this with Martina Corrigan.
Patient 12 Personal Information redacted by the USI	Personal Information redacted by the USI (home)	26/10/2020	Patient 12 doing very well. Advised re:media release and he will not be part of that call back. Previous review of care – will be discussed in this look back. Examine the learning.

King, Dawn

From: Kingsnorth, Patricia [redacted]
Sent: 12 January 2021 15:37
To: Andrew Anthony
Subject: RE: your Client [TS-Live.FID694915]
Attachments: 11 January 2021 - Letter to Solicitor.docx; Questions for Mr O.docx; Level 3 SAI review draft Terms of Reference for HSCB.docx

Dear Mr Anthony
Apologies for the delay.

Please see letter attached from Dr Hughes and Questions he would like addressed. He has asked that he receives a response before **29 January 2021.**

We have sent the copies of notes for Mr O'Brien to review to your office via recorded delivery. As requested they have the used the same initial as previously sent from DLS. Apologies but I do not have the manpower to paginate the records at this time.
However, they are in order as filed. Please can I ask that the patient information sent is treated confidentially and that when you are concluded with them that they are either returned to the Trust for safe disposal or that the information is disposed of in the appropriate confidential waste by your office.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
[redacted]

From: Andrew Anthony [redacted]
Sent: 07 January 2021 18:44
To: Kingsnorth, Patricia
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Thanks for your email. Can you please send the records to my office – address below?

I assume you will be forwarding notes for each of the patients whose care is being considered under the SAI processes.

If the notes are to be anonymised can you please ensure that we have an identification for each patient by letters or a number. The DLS have corresponded with me and provided brief summaries in relation to the various SAI's being investigated. Can you please relate the patient letter/name to the summary as that will assist in considering the records. Can I also suggest that the records are paginated and that the Trust keep a copy of the paginated records as that may assist in further communications.

Can you email me when the records are in the post in order that I can keep an eye out for them?

Kind regards,

Andrew

ANDREW ANTHONY
Partner
Andrew.Anthony@tughans.com
T: Personal Information redacted by the USI
M
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia Personal Information redacted by the USI
Sent: 06 January 2021 17:47
To: Andrew Anthony Personal Information redacted by the USI
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
They will be sent via recorded delivery post.
Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
Personal Information redacted by the USI

From: Andrew Anthony Personal Information redacted by the USI
Sent: 06 January 2021 17:46
To: Kingsnorth, Patricia
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Can you let me know how you propose to send them – hard or soft copies or both? I will then take instruction on where they should be sent.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
Andrew.Anthony@tughans.com
T: Personal Information redacted by the USI
M:
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia Personal Information redacted by the USI
Sent: 05 January 2021 17:26
To: Andrew Anthony Personal Information redacted by the USI
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
I am arranging for copies of patient's notes to be made available to your client Mr Aidan O'Brien
Can you advised where I should send them please?

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
Personal Information redacted by the USI

From: Andrew Anthony Personal Information redacted by the USI
Sent: 23 December 2020 17:34
To: Kingsnorth, Patricia
Subject: FW: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Further to our previous correspondence please see the attached which I would be grateful if you would provide to Dr Hughes.

Kind regards,

Andrew

Andrew Anthony
Partner
Personal Information redacted by the USI
T: Personal Information redacted by the USI

M Personal Information redacted by the USI
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Andrew Anthony Personal Information redacted by the USI
Sent: 17 December 2020 10:42
To: Kingsnorth, Patricia <Patricia.King

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Southern Health & Social Care Trust archive all Email (sent & received) for the purpose of ensuring compliance with the Trust 'IT Security Policy', Corporate Governance and to facilitate FOI requests.

Southern Health & Social Care Trust IT Department Personal Information redacted by the USI

11 January 2021 **Our Ref:**

Private & Confidential

Dear Mr Anthony

As requested, please see attached questions for Mr O'Brien. I have arranged for copies of the notes for each patient to be sent to your offices. They will be sent recorded delivery.

I have attached the terms of reference and review methodology as requested
I have also enclosed a brief description with the questions. Unfortunately I can't paginate all the pages, but have put them into order for you.

As we are facing time constraints from the HSCB, I would ask that we receive the answers to my questions by close of play 29 January 2021.

The remaining requests you have asked for will need to be submitted by the Trust as they are beyond my remit as chair.

Yours faithfully

Dermot Hughes

Dr Dermot Hughes
Chair of the SAI Panel

Dr Dermot F C Hughes MB BCH BAO FRCPath Dip Med Ed

Questions for Mr O'Brien

Service User A
A Patient diagnosed with prostatic cancer (Gleason 4+3)

- Can you advise why the recommendation from the MDM (31.10.2019) was not followed regarding commencement of androgen deprivation according to regional NICAN guidance (2016)?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was unable to avail himself of this service?
- Why did you prescribe bicalutamide 50mgs?

Servicer user B
A Patient diagnosed with advanced prostate cancer when he presented in ED CAH in March 2020 despite benign pathology in June 2019.

- In a patient with biochemical and clinical evidence of prostate cancer- why was a TURP sample of 2g taken to indicate the absence of cancer?
- Why was the NICAN urology clinical guidance pathway for diagnosis not followed?
- If there was a clinical assumption of cancer, why was bicalutamide prescribed instead of adhering to the NICAN regional guidance regarding androgen deprivation therapy?
- The patient had no allocated specialist nurse to support his complex and difficult journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was not able to avail himself of this service?

Service User C
A Patient diagnosed with a renal tumour. He had a CT scan on 17 December 2019. The scan result was not followed up despite being abnormal.

- Can you advise why his CT scan result was not followed up in December 2019?
- Can you advise why the patient was not allocated a specialist nurse despite peer review and annual report documents indicating that these were available to all patients?

Service User D
A Patient diagnosed with prostate cancer (Gleason 5+5)

- Why was this patient not referred to oncology?
- When his disease progressed, why was he not re-referred to the MDT?
- Why wasn't he prescribed ADT as per protocol?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this was unable to avail himself of this service?

Service User E
A Patient diagnosed with testicular cancer. A recommendation was made at MDM on 25 July 2019 to refer patient to oncology. This didn't happy until 25 September 2019. Oncology intervention was time critical and a delay has impacted on the patient's care.

- Can you explain the reason for the delay?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was unable to avail himself of this service?

Service User F
A patient diagnosed with prostate cancer. At the MDM (8 August 20) the diagnosis of intermediate risk but organ confined prostate cancer was agreed management by surveillance or active treatment with curative intent was recommended.

- Why did you prescribe bicalutamide 50mgs?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this was this patient unable to avail himself of this service?

Service User G
The patient was on long term surveillance for a small lesion and was considered for partial nephrectomy.

- Can you advise why this patient was not referred to the regional small renal mass MDM for additional expert input accordance to guidance?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was unable to avail himself of this service?

Service User H
A Patient diagnosed with penile cancer and managed in CAH outside of guidance?

- Regional guidance states that penile cancers can be diagnosed initially in a cancer unit. Additional investigations and therapies were carried out in CAH. Why was the NICAN regional guidance for penile cancer not followed?
- The patient had no allocated specialist nurse to support his complex and difficult journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this was patient was unable to avail himself of this service?

Service User I
A Patient was diagnosed with prostate cancer on 29.1.2020, but was not informed of cancer diagnosis until August 2020.

- Why wasn't he advised about his diagnosis, referred to the MDT and offered the support of a specialised nurse?

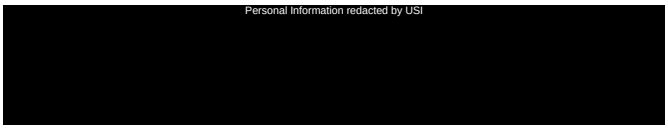
Southern Health and Social Care Trust

Quality Care - for you, with you

Level 3 Serious Adverse Incident Review

Urology Services

Datix numbers



Date 16th October 2020

PURPOSE OF PAPER

This paper seeks to provide a framework within to conduct a Level 3 Serious Adverse Incident Review regarding the treatment and care provided by a Urology Consultant (Doctor 1) who is no longer employed by Health and Social Care Services (Northern Ireland).

This paper will address the following:

- Proposed draft terms of reference for the review
- Confirmation of review panel
- Proposed timeline for conducting the review
- Outlining the process for engagement with families throughout the review

Draft Terms of Reference

Introduction

The core values of the Southern Health and Social Care Services (Northern Ireland) are of openness, honesty, respect and compassion. In keeping with these values, the Director of Acute Service has commissioned a level 3 SAI review to address the issues referenced above. The draft terms of reference may be amended pending engagement with all affected patients and families.

Purpose of Review

The purpose of the review is to consider the quality of treatment and the care provided by Doctor 1 and to understand if actual or potential harm occurred. The review findings will be used to promote learning, to understand system wide strengths and weaknesses and to improve the quality and safety of care and treatment provided.

Scope of Review

As part of an internal review of patients under the care of Doctor 1, a number of patients have been identified as possibly been exposed to increased or unnecessary risk.

Review Team

The proposed review team is as follows:

Chairperson / Lead Reviewer	Dr Dermot Hughes
Independent Consultant Urologist	Mr Hugh Gilbert
Cancer Services Lead	Mrs Fiona Reddick
Clinical Nurse Specialist	Ms Patricia Thompson
Clinical Governance Facilitator	Mrs Patricia Kingsnorth

Review Aims and Objectives

The aims and objectives of this review are to:

- To carry out a systematic multidisciplinary review of the process used in the diagnosis, multidisciplinary team decision making and subsequent follow up and treatment provided for each patient identified, using a Root Cause Analysis (RCA) Methodology.
- To review individually the quality of treatment and care provided to each patient identified and consider any factors that may have adversely influenced or contributed to subsequent clinical outcomes.

- To engage with patients / families to ensure where possible questions presented to the review team or concerns are addressed within the review.
- To develop recommendations to establish what lessons are to be learned and how our systems can be strengthened regarding the delivery of safe, high quality care.
- Examine any areas of good practice and opportunities for sharing learning from the incidents

Review Team Access Arrangements

Through the Review Commissioner, the Review Team will:

- Be afforded the assistance of all relevant staff and other relevant personnel.
- Have access to all relevant files and records (subject to any necessary consent/data protection requirements, where necessary).

Should immediate safety concerns arise, the Lead Reviewer will convey the details of these concerns to the Director of Acute Services / Trust Board (known as Review Commissioner) as soon as possible.

Review Methodology

The review will follow a review methodology as per the Regional Serious Adverse Incident Framework (2016) and will be cognisant of the rights of all involved to privacy and confidentiality and will follow fair procedures. The review will commence in October 2020 and will be expected to last for a period of 4 months approximately, provided unforeseen circumstances do not arise. Following completion of the review, an anonymised draft report will be prepared by the review team outlining the chronology, findings and recommendations. All who participated in the review will have an opportunity to provide input to the extracts from the report relevant to them to ensure that they are factually accurate and fair from their perspective.

Prior to finalising the report, the Lead Reviewer will ensure that the Review Team apply Trust quality assurance processes to ensure compliance of the review process with regional guidance prior to delivery of the final report to the Review Commissioner. The Review Commissioner will seek assurance that the quality assurance process has been completed.

Recommendations and Implementation

The report, when finalised, will be presented to the Review Commissioner. The Review Commissioner is responsible for ensuring that the local managers responsible for the service where the incident occurred will implement the recommendations of the review report. The Review

Commissioner is responsible for communicating regionally applicable recommendations to the relevant services for wider implementation.

Stinson, Emma M

From: McClements, Melanie
Sent: 06 March 2021 11:49
To: Devlin, Shane
Subject: FW: Timeline to Tughan requesting input from consultant
Attachments: Timeline to Tughan requesting input from consultant.docx

fyi Shane

From: Kingsnorth, Patricia
Sent: 06 March 2021 11:30
To: Wallace, Stephen
Cc: McClements, Melanie; OKane, Maria
Subject: Timeline to Tughan requesting input from consultant

Stephen
Apologies for the delay. See attached as requested.
Please let me know if there is anything else I can do.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
Personal Information redacted by the USI

Timeline to Tughan's request involvement in SAI review

Date	Email trail	Contents of email
11 December 2020	Email to Tughan's Solicitor	Letter from Chair Inviting AOB to participate in the review  Letter to Mr O' Brien inviting to participate
23 December 2020	Letter from Tughans	To Chair requesting the following  letter to Dr Hughes 23_12_2020.pdf
30 December 2020	Just returned from annual leave. Response to Tughan's advising I had forwarded questions to Chair.	 RE your Client TS-Live.FID694915 3
5 January 2021	Letter to solicitors to advise notes will be forward notes and requesting contact address	 5.1.2021.msg
6 January 2021	Email from Tughan's requesting how the notes will be sent	
6 January 2021	Response back to say posted to the required contact address	 6 January 2021 - letter.docx
7 January 2021	Email from Tughan's , Contact to his office advising we use the same user ID as previous contacts to avoid confusion.	This required the team to identify each patient as Service User A, B C etc All notes need to be redacted and identification allocated to each patient as above. Extensive man hours required. Unable to paginate as requested by solicitor.  RE your Client TS-Live.FID694915 ti
12 January.2021	Letter from Dr Hughes with questions for each patient. Send TOR and	 Questions for Mr O.docx

	copies of notes sent but not paginated. Response required 29/1/2020	
13 January 2021	Email to say that Tughan's had not received the notes	
13 January 2021	Response to advise they were sent first class recorded delivery on 12.1.2021	
18 January 2021	Email from solicitor to request a word document is forwarded on each of the timeline previously provided.	Response unable to provide due to lack of manpower
19 January 2021	Email to say that Mr AOB had suffered a bereavement and will not be responding this week and will update next week	
19 January 2021	Email response offering condolences on behalf of Chair and review team.	 RE your Client TS-Live.FID694915 α
22 January 2021	Email from Solicitor- not received went straight to junk email.	
27 January 2021	Resent email from Tughan's with letter to chair requesting NICAN / NICE/ peer review/ SAI regional guidelines and approved TOR along will an extensive list of questions including a request for all NIECR records pertaining to each patient to be sent.	 Dr Dermot Hughes 20 01 21 EMAIL (4) m
27 January 2021	Letter forwarded to the chair	As attachment above
27 January 2021	Acknowledgement email sent and apology for not receiving the email on 22.1. 2021 as gone into to junk email.	 RE Mr Aidan O'Brien Strictly Private and C

28 January 2021	email to Vivienne/ Maria advising the Chair would like to speak to legal team before providing response to the email.	
4 February 2021	Document – guidelines forwarded via email Advised solicitors that redacted NIECR records are sent recorded delivery.	 FW Requested documents 4.2.2021.
9 February 2021	Email with Datix sent as requested.	 9.2.2021 Datix.msg
10 February 2021	Meeting planned with June Turkington.	 legal advice to the TrustSAI panel - privil
10 February 2021	Email with attached response to questions for Tughan's from Chair	 Response from Dr Hughes to Tughans S
19.2.2021	Email sent to Tughan's from PK as no response received to previous email sent on 10 Feb.	 19.2.2021 response from Tughans.msg
No further correspondence		

11 December 2020 **Our Ref:**

Private & Confidential

Dear Aidan

As you may be aware, I am the External Chair of the SAI processes into 9 patients who were previously under your care.

As part of the normal SAI process we have been carrying out interviews with all relevant members of staff who have been involved in these patients' care.
The interviews are based on the patient's journey and are aimed at identifying learning and making recommendations for future care.

We would be keen to have your input into this process and would like to agree an appropriate time (in person/ zoom/ telephone).
I would be grateful for a prompt response.

Yours sincerely

Dermot

Dr Dermot Hughes
Chair of the SAI Panel

Dr Dermot F C Hughes MB BCH BAO FRCPath Dip Med Ed

Tughans

tughans.com

Dr Dermot Hughes
Co SHSCT

Our Ref: AFA/

Your Ref:

Date: 23 December 2020

By email to; Kingsnorth, Patricia [redacted]

Dear Dr Hughes

SAI's
Mr Aidan O'Brien

I have been instructed by the Medical Protection Society on behalf of Mr Aidan O'Brien. Your letter to Mr O'Brien of 11 December 2020 has been passed to me. I have already explained to Miss Kingsnorth that our energies were diverted in relation to dealing with an Interim Orders Application before the Medical Practitioners Tribunal this week, hence the delay in responding to you. Mr O'Brien has also been unwell which has contributed to the delay in me receiving instructions.

Your letter has advised that you are the External Chair of a panel appointed to review Serious Adverse Incidents concerning nine patients previously under the care of Mr. O'Brien. You have invited Mr O'Brien's input into the process of your review. However, your letter is unclear in relation to what input you shall be requesting. It would be helpful if you could provide clarification.

If you are requesting information from Mr O'Brien in relation to the clinical care he has provided to the patients it will be necessary for him to be provided with:

1. The terms of reference;
2. The review methodology;

Tughans
Marlborough House
30 Victoria Street
Belfast BT1 3GG

T [redacted]
F [redacted]
DX [redacted]
E law@tughans.com

Tughans

tughans.com

3. A description of the incident/case;
4. The timeline drafted by the SAI group;
5. The threshold criteria for each SAI engaged;
6. Specific issues which you are inviting Mr O'Brien to address on a case-by-case basis;
7. Complete photocopies of hard copy records and complete data available on NIECR for each patient. To date Mr O'Brien has received only copies of the hard copy data in relation to 2 patients who appear to be the subject of the SAI's (referred to by the Trust as Service Users A and B) however in those cases he has not been provided with the NIECR records which are required to understand the complete chronology.

I look forward to hearing from you. Can you please let me have your response by no later than the 8th of January?

Yours sincerely

Andrew Anthony

_____

ANDREW ANTHONY

Personal Information redacted by the USI

Tughans
Marlborough House
30 Victoria Street
Belfast BT1 3GG

T Personal Information redacted by the USI
F Personal Information redacted by the USI
DX Personal Information redacted by the USI
E law@tughans.com

Stinson, Emma M

From: Kingsnorth, Patricia [redacted]
Sent: 30 December 2020 09:09
To: Andrew Anthony
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
Apologies for delay to respond as I have just returned from leave.

I acknowledge receipt of your email. I can confirm I have forwarded to Dr Hughes for his consideration.

Kind regards
Patricia.

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
[redacted]

From: Andrew Anthony [redacted]
Sent: 23 December 2020 17:34
To: Kingsnorth, Patricia
Subject: FW: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Further to our previous correspondence please see the attached which I would be grateful if you would provide to Dr Hughes.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
[redacted]
T: [redacted]
M:+[redacted]
D: [redacted]

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Andrew Anthony [redacted]
Sent: 17 December 2020 10:42

To: Kingsnorth, Patricia [redacted]
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Thank you for your email. I apologise for the slight delay in replying. I have been heavily engaged in preparation for and attendance at the Interim Orders Tribunal of the MPT which occurred on Tuesday. I was out of the office all day yesterday at another pre-existing work commitment.

I will take instructions and get back to Dr Hughes in the near future.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
[redacted]
T: [redacted]
M:
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia [redacted]
Sent: 11 December 2020 12:56
To: Andrew Anthony [redacted]
Subject: your Client

Dear Mr Anthony

I have been asked to forward this letter to your client Mr Aidan O'Brien from the external Chair of the Urology SAI review.
I understand Mr O'Brien has suffered a [redacted] and appreciate you will know the appropriate timing of this letter.

I will await your response.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
[redacted]

Stinson, Emma M

From: Kingsnorth, Patricia [redacted]
Sent: 12 January 2021 15:37
To: Andrew Anthony
Subject: RE: your Client [TS-Live.FID694915]
Attachments: 11 January 2021 - Letter to Solicitor.docx; Questions for Mr O.docx; Level 3 SAI review draft Terms of Reference for HSCB.docx

Dear Mr Anthony
Apologies for the delay.

Please see letter attached from Dr Hughes and Questions he would like addressed. He has asked that he receives a response before **29 January 2021.**

We have sent the copies of notes for Mr O'Brien to review to your office via recorded delivery. As requested they have the used the same initial as previously sent from DLS. Apologies but I do not have the manpower to paginate the records at this time.
However, they are in order as filed. Please can I ask that the patient information sent is treated confidentially and that when you are concluded with them that they are either returned to the Trust for safe disposal or that the information is disposed of in the appropriate confidential waste by your office.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
[redacted]

From: Andrew Anthony [redacted]
Sent: 07 January 2021 18:44
To: Kingsnorth, Patricia
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Thanks for your email. Can you please send the records to my office – address below?

I assume you will be forwarding notes for each of the patients whose care is being considered under the SAI processes.

If the notes are to be anonymised can you please ensure that we have an identification for each patient by letters or a number. The DLS have corresponded with me and provided brief summaries in relation to the various SAI's being investigated. Can you please relate the patient letter/name to the summary as that will assist in considering the records. Can I also suggest that the records are paginated and that the Trust keep a copy of the paginated records as that may assist in further communications.

Can you email me when the records are in the post in order that I can keep an eye out for them?

Kind regards,

Andrew

ANDREW ANTHONY
Partner
Personal Information redacted by the USI
T: Personal Information redacted by the USI
M:
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia Personal Information redacted by the USI
Sent: 06 January 2021 17:47
To: Andrew Anthony Personal Information redacted by the USI
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
They will be sent via recorded delivery post.
Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
Personal Information redacted by the USI

From: Andrew Anthony Personal Information redacted by the USI
Sent: 06 January 2021 17:46
To: Kingsnorth, Patricia
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Can you let me know how you propose to send them – hard or soft copies or both? I will then take instruction on where they should be sent.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
Personal Information redacted by the USI
T: Personal Information redacted by the USI
M:
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia Personal Information redacted by the USI
Sent: 05 January 2021 17:26
To: Andrew Anthony Personal Information redacted by the USI
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
I am arranging for copies of patient's notes to be made available to your client Mr Aidan O'Brien
Can you advised where I should send them please?

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
Personal Information redacted by the USI

From: Andrew Anthony Personal Information redacted by the USI
Sent: 23 December 2020 17:34
To: Kingsnorth, Patricia
Subject: FW: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Further to our previous correspondence please see the attached which I would be grateful if you would provide to Dr Hughes.

Kind regards,

Andrew

Andrew Anthony
Partner
Personal Information redacted by the USI
T:+ Personal Information redacted by the USI

M: Personal Information redacted by the USI
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Andrew Anthony Personal Information redacted by the USI
Sent: 17 December 2020 10:42
To: Kingsnorth, Patricia <Patricia.King

The Information and the Material transmitted is intended only for the person or entity to which it is addressed and may be Confidential/Privileged Information and/or copyright material.

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Southern Health & Social Care Trust archive all Email (sent & received) for the purpose of ensuring compliance with the Trust 'IT Security Policy', Corporate Governance and to facilitate FOI requests.

Southern Health & Social Care Trust IT Department Personal Information redacted by the USI

11 January 2021 **Our Ref:**

Private & Confidential

Dear Mr Anthony

As requested, please see attached questions for Mr O'Brien. I have arranged for copies of the notes for each patient to be sent to your offices. They will be sent recorded delivery.

I have attached the terms of reference and review methodology as requested
I have also enclosed a brief description with the questions. Unfortunately I can't paginate all the pages, but have put them into order for you.

As we are facing time constraints from the HSCB, I would ask that we receive the answers to my questions by close of play 29 January 2021.

The remaining requests you have asked for will need to be submitted by the Trust as they are beyond my remit as chair.

Yours faithfully

Dermot Hughes

Dr Dermot Hughes
Chair of the SAI Panel

Dr Dermot F C Hughes MB BCH BAO FRCPath Dip Med Ed

Questions for Mr O'Brien

Service User A
A Patient diagnosed with prostatic cancer (Gleason 4+3)

- Can you advise why the recommendation from the MDM (31.10.2019) was not followed regarding commencement of androgen deprivation according to regional NICAN guidance (2016)?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was unable to avail himself of this service?
- Why did you prescribe bicalutamide 50mgs?

Servicer user B
A Patient diagnosed with advanced prostate cancer when he presented in ED CAH in March 2020 despite benign pathology in June 2019.

- In a patient with biochemical and clinical evidence of prostate cancer- why was a TURP sample of 2g taken to indicate the absence of cancer?
- Why was the NICAN urology clinical guidance pathway for diagnosis not followed?
- If there was a clinical assumption of cancer, why was bicalutamide prescribed instead of adhering to the NICAN regional guidance regarding androgen deprivation therapy?
- The patient had no allocated specialist nurse to support his complex and difficult journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was not able to avail himself of this service?

Service User C
A Patient diagnosed with a renal tumour. He had a CT scan on 17 December 2019. The scan result was not followed up despite being abnormal.

- Can you advise why his CT scan result was not followed up in December 2019?
- Can you advise why the patient was not allocated a specialist nurse despite peer review and annual report documents indicating that these were available to all patients?

Service User D
A Patient diagnosed with prostate cancer (Gleason 5+5)

- Why was this patient not referred to oncology?
- When his disease progressed, why was he not re-referred to the MDT?
- Why wasn't he prescribed ADT as per protocol?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this was unable to avail himself of this service?

Service User E
A Patient diagnosed with testicular cancer. A recommendation was made at MDM on 25 July 2019 to refer patient to oncology. This didn't happy until 25 September 2019. Oncology intervention was time critical and a delay has impacted on the patient's care.

- Can you explain the reason for the delay?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was unable to avail himself of this service?

Service User F
A patient diagnosed with prostate cancer. At the MDM (8 August 20) the diagnosis of intermediate risk but organ confined prostate cancer was agreed management by surveillance or active treatment with curative intent was recommended.

- Why did you prescribe bicalutamide 50mgs?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this was this patient unable to avail himself of this service?

Service User G
The patient was on long term surveillance for a small lesion and was considered for partial nephrectomy.

- Can you advise why this patient was not referred to the regional small renal mass MDM for additional expert input accordance to guidance?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was unable to avail himself of this service?

Service User H
A Patient diagnosed with penile cancer and managed in CAH outside of guidance?

- Regional guidance states that penile cancers can be diagnosed initially in a cancer unit. Additional investigations and therapies were carried out in CAH. Why was the NICAN regional guidance for penile cancer not followed?
- The patient had no allocated specialist nurse to support his complex and difficult journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this was patient was unable to avail himself of this service?

Service User I
A Patient was diagnosed with prostate cancer on 29.1.2020, but was not informed of cancer diagnosis until August 2020.

- Why wasn't he advised about his diagnosis, referred to the MDT and offered the support of a specialised nurse?

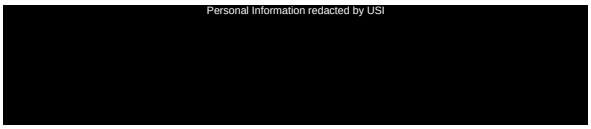
Southern Health and Social Care Trust

Quality Care - for you, with you

Level 3 Serious Adverse Incident Review

Urology Services

Datix numbers



Date 16th October 2020

PURPOSE OF PAPER

This paper seeks to provide a framework within to conduct a Level 3 Serious Adverse Incident Review regarding the treatment and care provided by a Urology Consultant (Doctor 1) who is no longer employed by Health and Social Care Services (Northern Ireland).

This paper will address the following:

- Proposed draft terms of reference for the review
- Confirmation of review panel
- Proposed timeline for conducting the review
- Outlining the process for engagement with families throughout the review

Draft Terms of Reference

Introduction

The core values of the Southern Health and Social Care Services (Northern Ireland) are of openness, honesty, respect and compassion. In keeping with these values, the Director of Acute Service has commissioned a level 3 SAI review to address the issues referenced above. The draft terms of reference may be amended pending engagement with all affected patients and families.

Purpose of Review

The purpose of the review is to consider the quality of treatment and the care provided by Doctor 1 and to understand if actual or potential harm occurred. The review findings will be used to promote learning, to understand system wide strengths and weaknesses and to improve the quality and safety of care and treatment provided.

Scope of Review

As part of an internal review of patients under the care of Doctor 1, a number of patients have been identified as possibly been exposed to increased or unnecessary risk.

Review Team

The proposed review team is as follows:

Chairperson / Lead Reviewer	Dr Dermot Hughes
Independent Consultant Urologist	Mr Hugh Gilbert
Cancer Services Lead	Mrs Fiona Reddick
Clinical Nurse Specialist	Ms Patricia Thompson
Clinical Governance Facilitator	Mrs Patricia Kingsnorth

Review Aims and Objectives

The aims and objectives of this review are to:

- To carry out a systematic multidisciplinary review of the process used in the diagnosis, multidisciplinary team decision making and subsequent follow up and treatment provided for each patient identified, using a Root Cause Analysis (RCA) Methodology.
- To review individually the quality of treatment and care provided to each patient identified and consider any factors that may have adversely influenced or contributed to subsequent clinical outcomes.

- To engage with patients / families to ensure where possible questions presented to the review team or concerns are addressed within the review.
- To develop recommendations to establish what lessons are to be learned and how our systems can be strengthened regarding the delivery of safe, high quality care.
- Examine any areas of good practice and opportunities for sharing learning from the incidents

Review Team Access Arrangements

Through the Review Commissioner, the Review Team will:

- Be afforded the assistance of all relevant staff and other relevant personnel.
- Have access to all relevant files and records (subject to any necessary consent/data protection requirements, where necessary).

Should immediate safety concerns arise, the Lead Reviewer will convey the details of these concerns to the Director of Acute Services / Trust Board (known as Review Commissioner) as soon as possible.

Review Methodology

The review will follow a review methodology as per the Regional Serious Adverse Incident Framework (2016) and will be cognisant of the rights of all involved to privacy and confidentiality and will follow fair procedures. The review will commence in October 2020 and will be expected to last for a period of 4 months approximately, provided unforeseen circumstances do not arise. Following completion of the review, an anonymised draft report will be prepared by the review team outlining the chronology, findings and recommendations. All who participated in the review will have an opportunity to provide input to the extracts from the report relevant to them to ensure that they are factually accurate and fair from their perspective.

Prior to finalising the report, the Lead Reviewer will ensure that the Review Team apply Trust quality assurance processes to ensure compliance of the review process with regional guidance prior to delivery of the final report to the Review Commissioner. The Review Commissioner will seek assurance that the quality assurance process has been completed.

Recommendations and Implementation

The report, when finalised, will be presented to the Review Commissioner. The Review Commissioner is responsible for ensuring that the local managers responsible for the service where the incident occurred will implement the recommendations of the review report. The Review

Commissioner is responsible for communicating regionally applicable recommendations to the relevant services for wider implementation.

6 January 2021 **Our Ref:**

Private & Confidential

Dear Mr Anthony

Please see attached questions for Mr O'Brien. I have arranged for copies of the notes for each patient to be sent to your offices. They will be sent recorded delivery.

I have attached the terms of reference and review methodology as requested
I have also enclosed a brief description with the questions I would like answered by close of play 22 January 2021. The remaining requests will need to be submitted by the Trust as they are beyond my remit as chair.

Yours faithfully

Dermot Hughes

Dr Dermot Hughes
Chair of the SAI Panel

Dr Dermot F C Hughes MB BCH BAO FRCPath Dip Med Ed

Stinson, Emma M

From: Kingsnorth, Patricia
Sent: 28 January 2021 17:45
To: 'Andrew Anthony'
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
Apologies for the delay to respond. I am sorry I cannot provide a word version as I wouldn't have the capacity to redact all the documents you require.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
Personal Information redacted by the USI

From: Andrew Anthony Personal Information redacted by the USI
Sent: 18 January 2021 17:03
To: Kingsnorth, Patricia
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

I note at the start of each set of patient records there is a chronology. It would assist with my review of the records if you could let me know if it is possible for those to be provided as word documents? If so the sooner the better as that should assist with me preparations.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
Personal Information redacted by the USI
T: Personal Information redacted by the USI
M
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia [redacted]
Sent: 13 January 2021 16:16
To: Andrew Anthony [redacted]
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
I can confirm they were sent yesterday morning first class.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
[redacted]

From: Andrew Anthony [redacted]
Sent: 13 January 2021 10:11
To: Kingsnorth, Patricia
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

I have not as yet received the records – can you let me know when they were sent. I have asked our reception staff to keep an eye out for them.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
[redacted]
T: [redacted]
M
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia [redacted]
Sent: 12 January 2021 15:37
To: Andrew Anthony [redacted]
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
Apologies for the delay.

Please see letter attached from Dr Hughes and Questions he would like addressed. He has asked that he receives a response before **29 January 2021.**

We have sent the copies of notes for Mr O'Brien to review to your office via recorded delivery. As requested they have the used the same initial as previously sent from DLS. Apologies but I do not have the manpower to paginate the records at this time.
However, they are in order as filed. Please can I ask that the patient information sent is treated confidentially and that when you are concluded with them that they are either returned to the Trust for safe disposal or that the information is disposed of in the appropriate confidential waste by your office.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
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Personal Information redacted by the USI

From: Andrew Anthony Personal Information redacted by the USI
Sent: 07 January 2021 18:44
To: Kingsnorth, Patricia
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Dear Ms Kingsnorth,

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I assume you will be forwarding notes for each of the patients whose care is being considered under the SAI processes.

If the notes are to be anonymised can you please ensure that we have an identification for each patient by letters or a number. The DLS have corresponded with me and provided brief summaries in relation to the various SAI's being investigated. Can you please relate the patient letter/name to the summary as that will assist in considering the records. Can I also suggest that the records are paginated and that the Trust keep a copy of the paginated records as that may assist in further communications.

Can you email me when the records are in the post in order that I can keep an eye out for them?

Kind regards,

Andrew

ANDREW ANTHONY
Partner
Personal Information redacted by the USI
T: Personal Information redacted by the USI
M
D

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia [redacted]
Sent: 06 January 2021 17:47
To: Andrew Anthony [redacted]
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
They will be sent via recorded delivery post.
Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
[redacted]

From: Andrew Anthony [redacted]
Sent: 06 January 2021 17:46
To: Kingsnorth, Patricia
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Can you let me know how you propose to send them – hard or soft copies or both? I will then take instruction on where they should be sent.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
[redacted]
T: [redacted]
M:
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia [redacted]
Sent: 05 January 2021 17:26
To: Andrew Anthony [redacted]
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
I am arranging for copies of patient's notes to be made available to your client Mr Aidan O'Brien
Can you advised where I should send them please?

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
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From: Andrew Anthony Personal Information redacted by the USI
Sent: 23 December 2020 17:34
To: Kingsnorth, Patricia
Subject: FW: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Further to our previous correspondence please see the attached which I would be grateful if you would provide to Dr Hughes.

Kind regards,

Andrew

Andrew Anthony
Partner
Personal Information redacted by the USI
T Personal Information redacted by the USI
M
D

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Andrew Anthony Personal Information redacted by the USI
Sent: 17 December 2020 10:42
To: Kingsnorth, Patricia <Patricia.King

Questions for Mr O'Brien

Service User A
A Patient diagnosed with prostatic cancer (Gleason 4+3)

- Can you advise why the recommendation from the MDM (31.10.2019) was not followed regarding commencement of androgen deprivation according to regional NICAN guidance (2016)?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was unable to avail himself of this service?
- Why did you prescribe bicalutamide 50mgs?

Servicer user B
A Patient diagnosed with advanced prostate cancer when he presented in ED CAH in March 2020 despite benign pathology in June 2019.

- In a patient with biochemical and clinical evidence of prostate cancer- why was a TURP sample of 2g taken to indicate the absence of cancer?
- Why was the NICAN urology clinical guidance pathway for diagnosis not followed?
- If there was a clinical assumption of cancer, why was bicalutamide prescribed instead of adhering to the NICAN regional guidance regarding androgen deprivation therapy?
- The patient had no allocated specialist nurse to support his complex and difficult journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was not able to avail himself of this service?

Service User C
A Patient diagnosed with a renal tumour. He had a CT scan on 17 December 2019. The scan result was not followed up despite being abnormal.

- Can you advise why his CT scan result was not followed up in December 2019?
- Can you advise why the patient was not allocated a specialist nurse despite peer review and annual report documents indicating that these were available to all patients?

Service User D
A Patient diagnosed with prostate cancer (Gleason 5+5)

- Why was this patient not referred to oncology?
- When his disease progressed, why was he not re-referred to the MDT?
- Why wasn't he prescribed ADT as per protocol?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this was unable to avail himself of this service?

Service User E
A Patient diagnosed with testicular cancer. A recommendation was made at MDM on 25 July 2019 to refer patient to oncology. This didn't happy until 25 September 2019. Oncology intervention was time critical and a delay has impacted on the patient's care.

- Can you explain the reason for the delay?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was unable to avail himself of this service?

Service User F
A patient diagnosed with prostate cancer. At the MDM (8 August 20) the diagnosis of intermediate risk but organ confined prostate cancer was agreed management by surveillance or active treatment with curative intent was recommended.

- Why did you prescribe bicalutamide 50mgs?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this was this patient unable to avail himself of this service?

Service User G
The patient was on long term surveillance for a small lesion and was considered for partial nephrectomy.

- Can you advise why this patient was not referred to the regional small renal mass MDM for additional expert input accordance to guidance?
- The patient had no allocated specialist nurse to support his journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this patient was unable to avail himself of this service?

Service User H
A Patient diagnosed with penile cancer and managed in CAH outside of guidance?

- Regional guidance states that penile cancers can be diagnosed initially in a cancer unit. Additional investigations and therapies were carried out in CAH. Why was the NICAN regional guidance for penile cancer not followed?
- The patient had no allocated specialist nurse to support his complex and difficult journey despite peer review and annual report documents indicating that these were available to all patients. Can you advise why this was patient was unable to avail himself of this service?

Service User I
A Patient was diagnosed with prostate cancer on 29.1.2020, but was not informed of cancer diagnosis until August 2020.

- Why wasn't he advised about his diagnosis, referred to the MDT and offered the support of a specialised nurse?

Stinson, Emma M

From: Kingsnorth, Patricia
Sent: 19 January 2021 17:21
To: 'Andrew Anthony'
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
I am very sorry to hear that. Please pass on our condolences to Mr O'Brien and his family.
I will update Dr Hughes and look forward to hearing your update next week.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
Personal Information redacted by the USI

From: Andrew Anthony Personal Information redacted by the USI
Sent: 19 January 2021 13:37
To: Kingsnorth, Patricia
Subject: FW: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

This is just to let you know that Mr O'Brien's mother in law passed away last night. He has another relative in hospital and another unwell but not hospitalised as a result of the pandemic. He had another family bereavement to cope with shortly before Christmas (unrelated to the pandemic).

In the circumstances I will not be taking any instructions from Mr O'Brien this week.

I will review the position next week and update you then. However we will not be able to respond within the timetable suggested by Dr Hughes.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
Personal Information redacted by the USI
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M:
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Andrew Anthony [redacted]
Sent: 18 January 2021 17:03
To: Kingsnorth, Patricia [redacted]
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

I note at the start of each set of patient records there is a chronology. It would assist with my review of the records if you could let me know if it is possible for those to be provided as word documents? If so the sooner the better as that should assist with me preparations.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
[redacted]
T: [redacted]
M:
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia [redacted]
Sent: 13 January 2021 16:16
To: Andrew Anthony [redacted]
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
I can confirm they were sent yesterday morning first class.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
[redacted]

From: Andrew Anthony [redacted]
Sent: 13 January 2021 10:11

To: Kingsnorth, Patricia
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

I have not as yet received the records – can you let me know when they were sent. I have asked our reception staff to keep an eye out for them.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
Personal Information redacted by the USI
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M:
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia Personal Information redacted by the USI
Sent: 12 January 2021 15:37
To: Andrew Anthony Personal Information redacted by the USI
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
Apologies for the delay.

Please see letter attached from Dr Hughes and Questions he would like addressed. He has asked that he receives a response before **29 January 2021.**

We have sent the copies of notes for Mr O'Brien to review to your office via recorded delivery. As requested they have the used the same initial as previously sent from DLS. Apologies but I do not have the manpower to paginate the records at this time.
However, they are in order as filed. Please can I ask that the patient information sent is treated confidentially and that when you are concluded with them that they are either returned to the Trust for safe disposal or that the information is disposed of in the appropriate confidential waste by your office.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
Personal Information redacted by the USI

From: Andrew Anthony [redacted]
Sent: 07 January 2021 18:44
To: Kingsnorth, Patricia
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Thanks for your email. Can you please send the records to my office – address below?

I assume you will be forwarding notes for each of the patients whose care is being considered under the SAI processes.

If the notes are to be anonymised can you please ensure that we have an identification for each patient by letters or a number. The DLS have corresponded with me and provided brief summaries in relation to the various SAI's being investigated. Can you please relate the patient letter/name to the summary as that will assist in considering the records. Can I also suggest that the records are paginated and that the Trust keep a copy of the paginated records as that may assist in further communications.

Can you email me when the records are in the post in order that I can keep an eye out for them?

Kind regards,

Andrew

ANDREW ANTHONY
Partner
[redacted]
T: [redacted]
M
D

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia [redacted]
Sent: 06 January 2021 17:47
To: Andrew Anthony [redacted]
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
They will be sent via recorded delivery post.
Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
[redacted]

From: Andrew Anthony [redacted]
Sent: 06 January 2021 17:46
To: Kingsnorth, Patricia
Subject: RE: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Can you let me know how you propose to send them – hard or soft copies or both? I will then take instruction on where they should be sent.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
[redacted]
T:
M:
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Kingsnorth, Patricia [redacted]
Sent: 05 January 2021 17:26
To: Andrew Anthony [redacted]
Subject: RE: your Client [TS-Live.FID694915]

Dear Mr Anthony
I am arranging for copies of patient's notes to be made available to your client Mr Aidan O'Brien
Can you advised where I should send them please?

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
[redacted]

From: Andrew Anthony [redacted]
Sent: 23 December 2020 17:34
To: Kingsnorth, Patricia
Subject: FW: your Client [TS-Live.FID694915]

Dear Ms Kingsnorth,

Further to our previous correspondence please see the attached which I would be grateful if you would provide to Dr Hughes.

Kind regards,

Andrew

Andrew Anthony
Partner
Personal Information redacted by the USI
T: Personal Information redacted by the USI
M
D

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Andrew Anthony Personal Information redacted by the USI
Sent: 17 December 2020 10:42
To: Kingsnorth, Patricia <Patricia.King

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Dr Dermot Hughes
C/o Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital

Our Ref: AFA/AK/00003911.100

Your Ref:

Date: 22 January 2021

BY EMAIL

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Dear Dr Hughes

MR AIDAN O'BRIEN

I write further to my correspondence with you last week. As you will be aware Mr O'Brien suffered the loss of his mother-in-law on Monday 18 January 2021. That followed a bereavement of another close family member before Christmas. In those circumstances it was not possible or appropriate for me to endeavour to take instructions from Mr O'Brien last week.

In order for me to obtain instructions with a view to replying to your letter of 11 January 2021 (sent by email on the 12th) I will need additional information and time to obtain instructions.

The following request for documentation and/or information arises from the documentation you have provided entitled "Level 3 Serious Adverse Incident Review Urology Services".

Please provide the following:-

1. The Datix Forms referred to on the front page. I note there appear to be eight Datix Forms yet nine cases. Is there an additional Datix Form missing?

2. The Terms of Reference are said to be "proposed draft Terms of Reference". Can you please confirm the Terms of Reference are still in draft or have they been finalised? Clearly, we need to be working from a finalised Terms of Reference. If they have not been finalised when will that occur?

3. I note the Terms of Reference may be amended "pending engagement with all affected patients and families". Has that engagement now occurred if not when will it occur?

4. Has any consideration been given to engagement with Mr O'Brien in relation to the Terms of Reference and, in particular, to seek his views in relation to the system within which he was

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working? For example, I note the Consultant Urologist (from information publicly on the internet) on the Review Team, Mr Hugh Gilbert, appears to have worked only England. It is important he considers Mr O'Brien's practice in the context of the service he was working in at SHSCT. The Terms of Reference are open to interpretation. Can you please clarify your interpretation of the Terms of Reference and the extent to which the service within which Mr O'Brien was working is considered by you to be within the terms?

5. The review methodology is said to be "as per the Serious Adverse Incident Framework (2016)". Please provide a copy of that Framework. It is important that we are clear on the framework you are working to.

6. Please let me know how Mr O'Brien's confidentiality is to be preserved in this process (as referred to in the review methodology).

In relation to the document entitled "Questions for Mr O'Brien" please provide the following information and to ensure there is no misunderstanding and that we are working from the guidance/protocols, reviews and reports you refer to:-

(i) Please let me have a copy of the NICAN Guidance (2016) as referred to for Service User A. Please identify the particular paragraphs arising from that Guidance relevant to the issue identified in relation to Service User A.

(ii) Please let me have a copy of the Peer Review and Annual Report documents in relation to allocation of Nurse Specialists as referred to in relation to Service User A (this is repeated in relation to a number of other patients).

(iii) In relation to Service User B reference is made to the "NICAN Urological Clinical Guidance Pathway". Please clarify whether this is the same Guidance as the 2016 Guidance referred to above? If not, please provide a copy of this further Guidance. In any event, please identify the paragraphs it is said were not followed.

(iv) In relation to Service User B reference is made to "NICAN Regional Guidance" regarding androgen deprivation therapy." Please clarify whether this refers to the 2016 Guidance. If not, please provide a copy of any additional Guidance. In any event, please identify the specific paragraphs it is suggested were not adhered to.

(v) In relation to Service User D please provide a copy of the protocol referred to in relation to prescription of ADT. Please identify the paragraphs which it is suggested were not followed in relation to that protocol.

(vi) In relation to Service User G, you refer to the patient not being referred to the MDM in accordance with "guidance". Can you please identify what guidance this refers to and provide us with a copy of same identifying the paragraphs it is suggested were not followed?

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(vii) In relation to Service User H, can you please let me know whether you are referring to the 2016 Guidance? If not, please produce the Guidance you refer to. In any event, please identify the paragraphs it is suggested were not followed in relation to this patient.

I note the purpose of the review is to "consider the quality of treatment of the care provided by "Doctor 1 and understand if actual or potential harm occurred". As the review team are considering that Mr O'Brien should be allowed to address that issue, should he wish. Mr O'Brien had the opportunity of carrying out a preliminary review of the records, received by us in hard copy by post on the 14th of January, prior to his recent bereavement. From that review the following records have not been included, to enable Mr O'Brien to make observations on this crucial issue:-

1. Service User A: All information available on NIECR from 22 June 2020 until death in August 2020

2. Service User B: All information available on NIECR from 01 August 2020 to date

3. Service User C: All information available on NIECR from 12 August 2020 to date

4. Service User D: All information available on NIECR from 14 May 2020 until death in July 2020

5. Service User E: All information available on NIECR from 25 September 2019 to date

6. Service User F: All information available on NIECR from 02 October 2020 to date

7. Service User G: All information available on NIECR from 27 November 2020 to date

8. Service User H: All information available on NIECR from 25 February 2020 to date

9. Service User I: All information available on NIECR from 29 January 2020 to date

In your letter of 11 January 2021 you requested Mr O'Brien to provide comments in relation to nine separate cases by 29 January 2021. With respect, this is not a reasonable timescale. Your request for information needs to be set in the following context:-

1. Mr O'Brien was written to by the Trust on 11 July 2020 with a document entitled "Summary of Concerns". I replied on his behalf to the Trust on 16 July 2020 noting Mr O'Brien could not comment on concerns without the data upon which the document was based. Between then and 14h of January 2021 the only documentation which has been provided to Mr O'Brien by the Trust were partial copies of the records for Service Users A and B.

2. By 16 October 2020 the Review Team was appointed according to the document "Level 3 Serious Adverse Incident Review Urology Services".

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3. The Trust wrote, via its legal representatives, to me, on 25 October 2020. Within that correspondence they provided a "Summary table Serious Adverse Incidents (SAI) confirmed to date". The table included reference to altogether nine patients. As far as we can ascertain those patients are the same patients that you have written in relation to (although notably the matters you request to be addressed differ from the "elements of concern" identified within that correspondence). No underlying documents, such as records were provided with that correspondence.

4. On 29 October 2020 I requested information in relation to the SAI processes, including Terms of Reference, SAI notification forms and whether Mr O'Brien would be asked for any comments and when those would be expected. I also requested details of what information would be disclosed to him. I noted how Mr O'Brien was entitled to see all documentary evidence any concerns were based upon in order for him to be in a position to obtain advice and respond.

5. The first questions that have been put to Mr O'Brien by the Team were received on 12 January 2021. I appreciate there will have been a considerable amount of documentation for the team to consider, and that had to occur in the context of the pandemic.

6. Copies of records were delivered to my office on 14 January 2021 which had to be paginated and copied before being forwarded on to Mr O'Brien. He therefore received the records very recently, just prior to his recent bereavement.

From the above you will note I have been making efforts on behalf of Mr O'Brien to obtain details of the matters under consideration and copies of relevant documentation for a substantial period of time. Whilst I appreciate the desire to move on with the SAIs, that must be done in a fair manner cognisant to the rights of all parties (as the terms of reference stipulate). That will include a reasonable period of time for Mr O'Brien to provide any comments, following receipt of adequate information upon which he can seek advice.

For Mr O'Brien to understand the issues you request him to address we will need:-

1. Responses to the above requests for further information and documentation.

2. Adequate time for Mr O'Brien to consider the various records and obtain advice thereon. That is particularly challenging given the current pandemic. Instructions will have to be taken remotely in relation to several cases.

3. Even if the pandemic was not current, two weeks would be an inadequate timescale in which to consider voluminous records on several cases, consult, obtain instructions thereon, provide advice and draft and approve responses. This is an important matter for the patients, their families and also for my client, Mr O'Brien. Sufficient time should be allowed for Mr O'Brien to provide his comments.

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I can assure you that we will try to move matters on as quickly as possible. I am unable to obtain instructions at the current time due to recent bereavements of Mr O'Brien which is complicated ongoing close family illness as a result of the pandemic (including another close relative having been hospitalised).

I will get back to you as soon as I can when I have considered matters further to give you a realistic timescale within which to reply – however that will be dependent on you providing the information I have requested above. I would be grateful if you could respond as soon as possible.

Kind regards.

Yours sincerely

Personal Information redacted by USI

ANDREW ANTHONY

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Stinson, Emma M

From: Kingsnorth, Patricia
Sent: 28 January 2021 08:41
To: 'Andrew Anthony'
Subject: RE: Mr Aidan O'Brien Strictly Private and Confidential [TS-Live.FID694915]

Dear Mr Anthony
Apologies the email went into my junk box and I didn't see it until your follow up email.
I will forward the letter to Dr Hughes and will await his response.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
Personal Information redacted by the USI

Working together Excellence Openness & Honesty Compassion

From: Andrew Anthony Personal Information redacted by the USI
Sent: 22 January 2021 17:24
To: Kingsnorth, Patricia
Subject: Mr Aidan O'Brien Strictly Private and Confidential [TS-Live.FID694915]

Dear Ms Kingsnorth,

Please see the attached for Dr Hughes' attention. I have explained separately why it took a little time to get this letter to you due to Mr O'Brien's personal circumstances over the last week.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
Personal Information redacted by the USI
T: Personal Information redacted by the USI
M
D:
Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

In order to protect our staff, their families and our clients, our staff are now working remotely.

We are all still available by telephone and email and will ensure that you will continue to receive a prompt response.
A complete list of contacts is available on our **website.**

Thank you in anticipation of your understanding and cooperation.

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2015 – 2019
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Stinson, Emma M

From: Kingsnorth, Patricia
Sent: 04 February 2021 12:21
To: [redacted]
Subject: FW: Requested documents
Attachments: FINAL NICaN Urology Cancer Clinical Guidelines Mar16.pdf; MDT Prostate Cancer Guidance.pdf; Urology MDT Annual Report 2016_.pdf; Self Assessment Peer Review Report 2017 (2).pdf; 20161117_Procedure for the Reporting and Follow up of SAIs Version 1.1. Nov 2016.pdf

Dr Mr Anthony
I have forwarded your letter to Dr Hughes and he is considering his response which will follow in due course.
To expedite your request. Please see attached guidance as requested. The NIECR records will be sent via post today to your office.
I will advise that most of the information from NIECR is contained in the packs already sent. But we will resend all information from NIECR as requested.
Please let me know if you require any further information.

Kind regards
Patricia

Patricia Kingsnorth
Acting Acute Clinical Governance Coordinator
Governance Office
Room 53
The Rowans
Craigavon Area Hospital
[redacted]

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From: Andrew Anthony [redacted]
Sent: 27 January 2021 18:25
To: Kingsnorth, Patricia
Subject: FW: Mr Aidan O'Brien Strictly Private and Confidential [TS-Live.FID694915]

Dear Ms Kingsnorth,

I refer to the below attached – I do not appear to have received an acknowledgement. I would be grateful if you would confirm receipt and that the letter has been provided to Dr Hughes.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
Personal Information redacted by the USI
Personal Information redacted by the USI
T:
M
D:

Tughans / Marlborough House, 30 Victoria Street, Belfast BT1 3GG

From: Andrew Anthony Personal Information redacted by the USI
Sent: 22 January 2021 17:24
To: Kingsnorth, Patricia Personal Information redacted by the USI
Subject: Mr Aidan O'Brien Strictly Private and Confidential [TS-Live.FID694915]

Dear Ms Kingsnorth,

Please see the attached for Dr Hughes' attention. I have explained separately why it took a little time to get this letter to you due to Mr O'Brien's personal circumstances over the last week.

Kind regards,

Andrew

ANDREW ANTHONY
Partner
Personal Information redacted by the USI
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In order to protect our staff, their families and our clients, our staff are now working remotely.

We are all still available by telephone and email and will ensure that you will continue to receive a prompt response.
A complete list of contacts is available on our website.

Thank you in anticipation of your understanding and cooperation.

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NICaN Urology Cancer Clinical Guidelines

March 2016

Document Title	Guidelines for the Referral, Diagnosis, Treatment and Management of Urological Cancer
Document Date	March 2015 – version 1.1 January 2016 – version 1.2 March 2016 – version 1.3
Document Purpose	This guidance has been produced to support the diagnosis, treatment and management of urological cancer. Treatment decisions for individual patients require the weighing of a multiplicity of factors, which cannot all be accounted for in a CMG. The CMG provides a description of the range of treatment options available for a clinical scenario. To maximise the benefit of multi-professional working management strategies for the individual are best discussed with a multidisciplinary meeting (MDM).
Authors	Surgical: New NI guidelines have been developed by Ali Thwaini, Consultant Urologist, BHSCT, for Bladder, Prostate, Penile, Renal Cell, Testicular & Upper Urinary Tract Urothelial Cell Carcinomas Imaging: Yorkshire Cancer Network Imaging Guidelines (These guidelines have been adopted by the Network group as they reflect NI Practice) Pathology: Royal College of Pathologists Standards and Minimum Datasets for reporting Cancers (These guidelines have been adopted by the Network group as they reflect NI Practice) Systemic Anti-cancer Therapy Protocols: Reference to separate guidance developed on behalf of the NI Cancer Network and the HSCB Radiotherapy Protocols: These guidelines have been adopted by the Network group as they reflect NI Practice) Urological Nursing Sections: Kate O'Neill (SHSCT), Kerry Chambers (WHSCT), Patricia Thompson (SEHSCT), Hazel Kerr (SEHSCT) Follow up section: Transforming Cancer Follow Up Project team

Version 1	Original Draft
Version 1.1	Reformatted with inclusion of new Surgical guidelines, Imaging, Pathology, Clinical Nurse Specialist, Follow Up and Specialist Radiographer Sections
Version 1.2	Discussed at the Regional Urology Network Group Meeting on 29th January 2016
Version 1.3	Amendments following circulation January2016 Population base adjusted to reflect updated NISRA figures and NW urology population base NG12 Urology referral guidelines replace red flag guidelines Reference to guidance regarding 150 robotic prostatectomies requirement removed

Regional Agreements	Electronically agreed and issued 18th March 2016 (of note any change in commissioning arrangements will require inclusion)
Agreed:	
Review:	April 2017

Contents **Page No**

1.0 INTRODUCTION

Urological cancers include a range of tumours with different presentations including:

- Prostate cancer
- Bladder cancer
- Kidney cancer
- Testicular cancer
- Penile cancer

Prostate cancer is a form of cancer that develops in the prostate. Advanced prostate cancer can spread to other parts of the body. It accounts for 24% of all new cancers in UK males, and in 20-30% of cases, prostate cancer spreads to other locations in the body. In Northern Ireland, the average number of cases per year between 2009-2013 was 1,039 per year (figures provided by NI Cancer Registry).

Bladder cancer is any of several types of malignant growths of the urinary bladder and isthe 4th most common male tumour. The most common type of bladder cancer begins in cells lining the inside of the bladder and is called transitional cell carcinoma. Incidence of bladder cancer is higher in males than in females, with over 6,400 cases in 2009 in males compared to under 2,400 in females. In Northern Ireland, the average number of cases per year between 2009-2013 was 211 per year, with a breakdown of 150 males and 61 females (figures provided by NI Cancer Registry).

Kidney cancer is a form of cancer that develops in the kidneys. Kidney cancer is often asymptomatic until an advanced stage. In approximately one third of cases, the tumour is detected incidentally during imaging carried out for other reasons. The two most common types of kidney cancer, reflecting their location within the kidney, are renal cell carcinoma (RCC) and urothelial cell carcinoma (UCC) of the renal pelvis.

In Northern Ireland, the average number of cases per year between 2009-2013 was 288 per year, with a breakdown of 173 males and 115 females (figures provided by NI Cancer Registry).

Testicular cancer or cancer of the testicles is one of the less common cancers. It usually affects younger men between the ages of 15 and 49. Testicular cancer is relatively uncommon, accounting for just 1% of all cancers that occur in men. The most common type of testicular cancer is known as ‘germ cell testicular cancer’, which accounts for around 95% of all cases. In Northern Ireland, the average number of cases per year between 2009-2013 was 65 per year (figures provided by NI Cancer Registry).

Penile cancer is a rare type of cancer that occurs on the skin of the penis or within the penis. In the UK, around 550 men are diagnosed with cancer of the penis each year. It

most commonly affects men over 60 years of age. Over the last 30 years, the number of penile cancer cases has increased by more than 20%, possibly due to changes in sexual practices.

2.0 NETWORK CONFIGURATION OF THE UROLOGY CANCER SERVICES

Northern Ireland Cancer Network has three cancer MDTs which diagnose and treat patients with urological cancers. These are held at the following locations:

- Craigavon Area Hospital – Southern HSC Trust
- Belfast City Hospital – combined team for Belfast HSC Trust and South Eastern HSC Trust
- Altnagelvin Hospital – combined team for Western HSC Trust & Northern HSC Trust

The catchment populations of these MDTs are shown below:

Urology MDT	**Catchment**[1]
SHSCT	366,000
Combined for: BHSCT and SEHSCT	 366,000 341,085
Combined for: WHSCT and NHSCT	 297,000 467,000 *Of note the population base for urology is 480,000 representing the upper two thirds of both the NHSCT & WHSCT*
Total	**1,830,000**

Each MDT meets on a weekly basis. All MDTs have named surgeons who deal with urological cancers.

[1] *Source: NISRA, 2013 MYEs*

3.0 REFERRAL GUIDELINES FOR UROLOGY CANCER

Patients can be referred to their local hospital as 'red flags' (i.e. suspect cancer) by their GPs under the following NICE guidance:

This section is a direct lift from the NICE NG12 Suspect Cancer: Recognition and Referral (June 2015).

Prostate cancer

Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for prostate cancer if their prostate feels malignant on digital rectal examination. **[new 2015]**

Consider a prostate-specific antigen (PSA) test and digital rectal examination to assess for prostate cancer in men with:

- any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention **or**
- erectile dysfunction **or**
- visible haematuria. **[new 2015]**

Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for prostate cancer if their PSA levels are above the age-specific reference range. **[new 2015]**

Bladder cancer

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer if they are:

- aged 45 and over and have:
    - unexplained visible haematuria without urinary tract infection **or**
    - visible haematuria that persists or recurs after successful treatment of urinary tract infection, **or**
- aged 60 and over and have unexplained non-visible haematuria **and** either dysuria or a raised white cell count on a blood test. **[new 2015]**

Consider non-urgent referral for bladder cancer in people aged 60 and over with recurrent or persistent unexplained urinary tract infection. **[new 2015]**

Renal cancer

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for renal cancer if they are aged 45 and over and have:

- unexplained visible haematuria without urinary tract infection **or**
- visible haematuria that persists or recurs after successful treatment of urinary tract infection. **[new 2015]**

Testicular cancer

Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for testicular cancer in men if they have a non-painful enlargement or change in shape or texture of the testis. **[new 2015]**

Consider a direct access ultrasound scan for testicular cancer in men with unexplained or persistent testicular symptoms. **[new 2015]**

Penile cancer

Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for penile cancer in men if they have either:

- a penile mass **or** ulcerated lesion, where a sexually transmitted infection has been excluded as a cause, **or**
- a persistent penile lesion after treatment for a sexually transmitted infection has been completed. **[new 2015]**

Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for penile cancer in men with unexplained or persistent symptoms affecting the foreskin or glans. **[new 2015]**

3.1 Haematuria Referral Guideline – please see Appendix 1

4.0 UROLOGY CARE PATHWAYS

Cancer Care Pathways outline the steps and stages in the patient journey from referral to diagnostics, staging, treatment, follow up, rehabilitation and if applicable onto palliative care.

Timed effective care pathways are central to delivering quality and timely care to patients throughout their cancer journey and to the delivery of an equitable service.

Please see **appendix 2** for the care pathways for:

- Prostate
- Renal Tumour
- Testicular Cancer Pathway
- Transitional Cell Carcinoma
- Castration Resistant Prostate Cancer
- Penile Cancer Pathway

5.0 REGIONAL GUIDELINES FOR THE IMAGING OF UROLOGICAL CANCERS

Document Title	**Guidelines for the Imaging of Urological Cancers**
Document Date	**March 2015 – Version 2**
Document Purpose	**This guidance has been produced to support the diagnosis, treatment and management of urological cancer** **Treatment decisions for individual patients require the weighing of a multiplicity of factors, which cannot all be accounted for in a CMG. The CMG provides a description of the range of treatment options available for a clinical scenario. To maximise the benefit of multi-professional working management strategies for the individual are best discussed with a multidisciplinary meeting (MDM).**
Authors	**Dr Arthur Grey – Consultant Radiologist** **Dr Stephen Vallelly – Consultant Radiologist** **Dr Eoin Napier – Consultant Radiologist**
Version Changes	**Version 1 – issued to Regional Group 7/4/11** **Version 1.1 – the updated Yorkshire Cancer Network Imaging Guidelines for the Investigation and Treatment of Urological Cancers were reviewed by the authors in September 2014 and they agreed to adopt the updated guidelines as they reflected NI Practice. The guidelines were circulated to the Urology Network Group for sign off on 17 April 2015. Copies of the Yorkshire Cancer Network Imaging Guidelines are available at http://www.ycn.nhs.uk/**

6.0 REGIONAL PATHOLOGY GUIDELINES FOR UROLOGICAL CANCERS

Document Title	**Regional Pathology Guidelines for Urological Cancers**
Document Date	**Version 2 29th January 2016**
Document Purpose	**The guidance has been produced to support the pathological diagnosis and staging of Urological Malignancies**
Author	**Dr G McClean**
Evidence	**Royal College of Pathologists Standards and Minimum Datasets for reporting Cancers;** **Dataset Adult Renal Parenchymal Cancer Histopathology Reports Nov 2006** https://www.rcpath.org/resourceLibrary/dataset-adult-renal-parenchymal-cancer-histopathology-reports.html **Dataset for penile and distal urethral cancer histopathology reports July 2015** https://www.rcpath.org/resourceLibrary/dataset-for-penile-and-distal-urethral-cancer-histopathology-reports.html **Dataset for histopathology reports for prostatic carcinoma (2nd edition) October 2009** https://www.rcpath.org/resourceLibrary/dataset-for-histopathology-reports-for-prostatic-carcinoma.html **Dataset for the histological reporting of testicular neoplasms May 2014** https://www.rcpath.org/resourceLibrary/dataset-for-the-histological-reporting-of-testicular-

	neoplasms.html **Dataset for tumours of the urinary collecting system** **(renal pelvis, ureter, urinary bladder and urethra) (2nd edition) April 2013** https://www.rcpath.org/resourceLibrary/dataset-for-tumours-of-the-urinary-collecting-system--renal-pelvis--ureter--urinary-bladder-and-urethra.html

Version changes

Version 1 – 23rd March 2015

Version 2 – 29th January 2016. Replacement of dataset for penile histopathology with dataset released July 2015. Update of website addresses for all datasets.

Statement:

Via Consultation with Pathologists at all Trusts it has been confirmed that all Pathologists in Northern Ireland are reporting to the standards laid down by the Royal College of Pathologists in the following College Publications and that there is no additionality of practice.

Dr Gareth McClean

7.0 REGIONAL SYSTEMIC ANTI-CANCER THERAPY PROTOCOLS FOR UROLOGICAL CANCERS

Document Title	**Systemic Anti-cancer Therapy Protocols**
Document Date	**2015**
Document Purpose	Please refer to separate NICaN guidance documents for the Systemic Anti-cancer Therapy Protocols for Bladder, Penile, Testicular Germ Cell tumours, Prostate and Renal Cell. These documents are available on the NICaN website **www.cancerni.net.**

8.0 REGIONAL RADIOTHERAPY PROTOCOLS FOR UROLOGICAL CANCER

Document Title	**Radiotherapy Protocols**
Document Date	**2015**
Document Purpose	Radiotherapy is delivered in the Northern Ireland Cancer Centre at the Belfast City Hospital with a second department due to open in Altnagelvin in 2016. The Cancer Centre is equipped with 10 Linear Accelerators and a full range of conventional and CT simulation equipment. The Radiotherapy Department employs approximately 90 radiographers. The department is accredited by ISO9000 and Charter mark standards. There is a modern treatment planning system with 10 planning terminals. A comprehensive radiology service is available within the Cancer Centre and in the main City Hospital. IMRT is routinely delivered for radically treating prostate cancer, radiotherapy may also be used palliatively for all urological cancers. Further details of treatment regimens and fractionations are contained within treatment protocols are located in the radiotherapy department. For further information please contact Joanne McCarthy Clinic Coordinator [redacted] or [redacted]

9.0 REGIONAL GUIDELILNES FOR THE SURGICAL TREATMENT AND MANAGEMENT OF UROLOGY CANCER

Document Title	**Guidelines for the Surgical Treatment and Management of Urological Cancer**
Document Date	March 2011 – Final Version January 2016 – Version updated and finalised
Document Purpose	This guidance has been produced to support the diagnosis, treatment and management of urological cancer Treatment decisions for individual patients require the weighing of a multiplicity of factors, which cannot all be accounted for in a CMG. The CMG provides a description of the range of treatment options available for a clinical scenario. To maximise the benefit of multi-professional working management strategies for the individual are best discussed with a multidisciplinary meeting (MDM)
Authors	Ali Thwaini, BHSCT
Version Changes	It was agreed at the Urology Network Meeting on 11th June 2014 to review the Surgical components of the EAU guidelines for urological cancers. Mr Ali Thwaini has developed new Urological surgical guidelines to reflect practice within NI. It was agreed at the Urology Network Meeting on 17th April 2015 that the EAU guidelines for Kidney would continue to be adopted by the Network group until the guideline has been reviewed by the relevant core members to highlight exceptions in practice in NI.

9.1 Bladder Cancer Surgical Guidelines (2014)

Bladder Cancer

Epidemiology:
Bladder cancer is the ninth most commonly diagnosed cancer worldwide, with more than 380,000 new cases each year and more than 150,000 deaths per year, and an estimated male-female ratio of 3.8:1. At any one time, 2.7 million people have a history of urinary bladder cancer. Recently, overall and stage-specific age-adjusted incidence rates of bladder cancer have been analysed in the U.S. (5 year survival and mortality rates between 1973 and 2009). Although the analysis of the Surveillance, Epidemiology and End Results (SEER) database implies some limitations it is worrying to note that in the last 30 years the mortality rate associated with bladder cancer has not changed substantially, highlighting gaps in diagnosis, monitoring and management of these patients (3). At the initial diagnosis of bladder cancer, 70% of cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) and approximately 30% as muscle-invasive bladder cancer (MIBC). Among patients treated with radical cystectomy because of MIBC, 57% had muscle invasion at presentation, while 43% were initially 8 MUSCLE-INVASIVE AND METASTATIC BLADDER CANCER - LIMITED UPDATE APRIL 2014 diagnosed with NMIBC that progressed despite organ-preserving treatment (4). Approximately one-third of patients diagnosed with MIBC have undetected metastases at the time of treatment for the primary tumour (5), while 25% of patients who undergo radical cystectomy present with lymph node involvement at the time of surgery.

Risk factors:
Tobacco smoking:

- is the most well-established risk factor for bladder cancer, causing 50-65% of male cases and 20-30% of female cases
- the incidence of bladder cancer is directly related to the duration of smoking and the number of cigarettes smoked per day
- the risk of bladder cancer is also higher in those who start smoking at a young age or who are exposed to environmental tobacco smoke during childhood
- the reduction of bladder cancer was about 40% within 1-4 years of quitting smoking and 60% after 25 years of cessation.

Occupational exposure:

- is the second most important risk factor for bladder cancer. Work-related cases have accounted for 20-25% of all bladder cancer cases in several series.
- substances involved in chemical exposure include benzene derivatives and aryl amines (2-naphthylamine, 4-ABP, 4,4'-methylenedianiline, and o-toluidine), and it is likely to occur in occupations in which dyes, rubbers, textiles, paints, leathers, and chemicals are used .

- risk of bladder cancer due to occupational exposure to carcinogenic aromatic amines is significantly greater after 10 years or more of exposure; the mean latency period usually exceeds 30 years.
- carcinogens can be inactivated by a metabolic acetylation pathway. The presence of an NAT2 slowacetylation genotype has been associated with a higher risk of bladder cancer (16), suggesting that patients who are slow acetylators may be more susceptible to bladder cancer than rapid acetylators. Other risk factors include phenacetin, which the International Agency for Research on Cancer (IARC) included in 1987 among proven human carcinogens. Some studies have suggested that the risk of bladder cancer due to phenacetin is dose-dependent; however, the data concerning its metabolite acetaminophen are controversial.

Radiotherapy: Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks of 2-4.

Dietary factors have been considered to be related to bladder cancer; however, the links remain controversial. Currently, there is limited evidence of a causal relationship between bladder cancer and dietary factors.

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean.

Chronic urinary tract infection: bladder cancer, particularly invasive squamous cell carcinoma, has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between bladder cancer and UTIs has been observed in several case-control studies, which have reported a two-fold increased risk of bladder cancer in patients with recurrent UTIs in some series.

Chemotherapy: The use of cyclophosphamide, an alkylating agent used to treat lymphoproliferative diseases and other nonneoplastic diseases, has been correlated with subsequent development of MIBC, with a latency period of 6-13 years. Acrolein is a metabolite of cyclophosphamide and is responsible for the increase in the incidence of bladder cancer. This effect occurs independently of the association of haemorrhagic cystitis with the same treatment and was counteracted with concomitant application of mercapto-ethanesulfonate (MESNA).

Synchronous and metachronous upper urinary tract tumours: In some cases, there is an association between upper tract urothelial carcinoma (UTUC) and bladder cancer.

- The incidence of UTUC after a diagnosis of NMIBC has been reported to be between 1.7% and 26%. Although synchronous UTUC and NMIBC are uncommon, 46% of UTUCs are invasive. In a retrospective review of 1,529 patients with primary non-muscle-invasive bladder carcinoma who underwent initial examination of the upper urinary tract with excretory urography, those with a tumour in the bladder trigone were almost six times more likely to develop a synchronous tumour in the upper urinary tract. Examination of the upper urinary tract alone in patients with a tumour in the trigone or with multiple bladder tumours was capable of diagnosing 41% or 69% of UTUCs, respectively.
- In multiple and high-risk tumours, there is an increased risk of tumour recurrence in the upper urinary tract.
- Carcinoma in situ (CIS) in the bladder is an important risk factor for subsequent upper urinary tract recurrence . It has been shown in various studies that tumour involvement of the distal ureter at RC is an independent risk factor for metachronous upper urinary tract (mUUT) recurrence, with an approximate 2.6-fold increase in the relative risk.
- The overall incidence of bladder cancer developing after treatment for UTUC has been reported in the literature as 15-50%.

Gender:

- women were more likely to be diagnosed with primary muscle-invasive disease than men (85% vs. 51%).
- women are more likely to be older than men when diagnosed, with a direct effect on their survival. In addition, delayed diagnosis is more likely in women after haematuria is observed, as the differential diagnosis in women includes diseases that are more prevalent than bladder cancer.
- Differences in the gender prevalence of bladder cancer may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, postmenopausal status was associated with an increase in bladder cancer risk, even after adjustment for smoking status.

Ethnic and socioeconomic status: There are limited data on this topic, but a study based on 13,234 cases diagnosed in the SEER database in the period 1979-2003 showed that the survival time from diagnosis was significantly lower among cancer cases in patients with low socioeconomic status (SES) compared with those with higher SES. Hazard ratios for all causes and cancer-specific mortality among blacks in comparison with whites for eight of the most common types of cancer combined lost statistical significance after adjustment for SES factors and treatments. However, blacks still had unfavourable prognoses in comparison with whites even after adjustment for SES and treatment for tumours such as breast, colorectal, and urinary bladder cancer (44).

Genetic factors: There is growing evidence that genetic susceptibility factors and family associations may influence the incidence of bladder cancer. The relationship between family history of cancer and risk of bladder cancer was examined in the Spanish Bladder Cancer Study. It was found that family history of cancer in first-degree relatives was associated with an increased risk of bladder cancer; the association being stronger among younger patients. Shared environmental exposure was recognised as a potentially confounding factor.

TNM classification of urinary bladder cancer (2009)

T - Primary Tumour
Tx Primary tumour cannot be assessed
T0 No evidence of primary tumour
Ta Non-invasive papillary carcinoma
Tis Carcinoma in situ: "flat tumour"
T1 Tumour invades subepithelial connective tissue
T2 Tumour invades muscle
T2a Tumour invades superficial muscle (inner half)
T2b Tumour invades deep muscle (outer half)
T3 Tumour invades perivesical tissue:
T3a Microscopically
T3b Macroscopically (extravesical mass)
T4 Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
T4b Tumour invades pelvic wall or abdominal wall
N - Regional Lymph Nodes
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph-node metastasis
N1 Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2 Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3 Metastasis in common iliac lymph node(s)
M - Distant Metastasis
M0 No distant metastasis
M1 Distant metastasis

World Health Organization grading for bladder cancer

1973 WHO grading
Urothelial papilloma
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated

2004 WHO grading
Flat lesions Hyperplasia (flat lesion without atypia or papillary aspects)
Reactive atypia (flat lesion with atypia)
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS is always high-grade
Papillary lesions
Urothelial papilloma (completely benign lesion)
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma

Non-muscle-invasive (Ta, T1 and CIS) Bladder Cancer

Diagnosis and Initial Treatment Steps

The following guidelines for urgent referral (within two weeks) have been published by the Department of Health:

- Macroscopic haematuria in adults.
- Microscopic haematuria in adults over 50 years.
- Swellings in the body of the testis.
- Palpable renal masses.
- Solid renal masses found on imaging.
- Elevated age-specific prostate specific antigen (PSA) in men with a 10 year life expectancy.
- A high PSA (>20ng/ml) in men with a clinically malignant prostate or bone pain.
- Any suspected penile cancer.

Papillary (Ta, T1) Tumours

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue.

The standard initial therapy for Ta and T1 papillary bladder tumours is complete macroscopic transurethral resection (TURB), including a part of the underlying muscle. TURB should be performed systematically in individual steps, which Non-muscle invasive (Ta, T1, CIS) Bladder Cancer 11 are described in the full version of the guidelines. Small tumours (< 1 cm) can be resected en bloc, including a part of the underlying muscle. Larger tumours should be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle and the edges of the resection area. The specimens from different fractions must be referred to the pathologist in separate containers.

A second TURB 2-6 weeks after initial resection is recommended in the following situations:

- After incomplete initial TURB, if there was no muscle in the specimen after initial resection (with exception of Ta low grade (G1) tumours);
- In all T1 tumours and in all high grade (G3) tumours (except primary CIS).

CIS

CIS is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies.

Biopsies are taken from suspect areas. In patients with positive urine cytology and no papillary tumour, multiple biopsies from normal looking mucosa including prostatic urethra (random

biopsies) are recommended. If equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy in these patients. Urine cytology is useful in the diagnosis and follow-up of CIS. CIS cannot be eradicated by TURB and further treatment is mandatory.

Guidelines for primary assessment of NMIBC	GR
Patient history should be taken and recorded regarding all important information with a possible association with bladder cancer, including risk factors and suspicious symptoms.	A
Renal and bladder US may be used during the initial work-up in patients with haematuria.	C
At the time of the initial diagnosis of bladder cancer, CT urography (or IVU) should be performed only in selected cases (e.g., tumours located in the trigone).	B
Cystoscopy is recommended in all patients with symptoms suggestive of bladder cancer. It cannot be replaced by cytology or by any other non-invasive test.	A

Guidelines for primary assessment of NMIBC	GR
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
Voided urine cytology is advocated to predict high grade tumour before TURB.	C
Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C

TURB	GR
TURB should be performed systematically in individual steps: • bimanual palpation under anaesthesia; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • bimanual palpation after resection; • protocol formulation; • formulation of order form for pathological evaluation.	C
Perform resection in one piece for small papillary tumours (< 1 cm), including part from the underlying bladder wall.	B
Perform resection in fractions (including muscle tissue) for tumours > 1 cm in diameter.	B
Biopsies should be taken from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder walls) are recommended only when cytology is positive or when exophytic tumour has a non-papillary appearance.	C
Biopsy of the prostatic urethra is recommended for cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
Biopsy of the prostatic urethra should be taken from abnormal areas and from the precollicular area (between 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, the cold-cup biopsy with forceps can be used.	C
If equipment is available, fluorescence-guided (PDD) biopsy should be performed instead of random biopsies when bladder CIS or high-grade tumour is suspected (e.g., positive cytology, recurrent tumour with previous history of a high-grade lesion)	B
The specimens from different biopsies and resection fractions must be referred	C

TURB	GR
to the pathologist in separate containers and labelled separately.	
TURB protocol must describe all steps of the procedure, as well as the extent and completeness of resection.	C
A second TURB is recommended in the following situations: • after incomplete initial TURB; • if there is no muscle in the specimen after initial resection, with exception of Ta G1 tumours and primary CIS; • in all T1 tumours; • in all G3 tumours, except primary CIS.	A
When done, a second TURB should be performed within 2-6 weeks after initial resection.	C

Classification and pathological report	GR
Depth of tumour invasion is classified according to the TNM system.	A
For histological classification, 1973 and 2004 WHO grading systems are used. Until the WHO 2004 is validated by more prospective trials and incorporated into prognostic models, both classifications should be used.	A
Whenever the terminology NMIBC is used in individual cases, the tumour stage and grade should be mentioned.	A
The pathological report should specify tumour location, tumour grade, depth of tumour invasion, presence of CIS, and whether the detrusor muscle is present in the specimen.	A
The pathological report should specify the presence of LVI or unusual histology	C

CIS = carcinoma in situ;
CT = computed tomography;
IVU = intravenous urography;
LVI = lymphovascular invasion;
PDD = photodynamic diagnosis;
US = ultrasound;
TURB = transurethral resection of the bladder

Prognostic Factors and Adjuvant Treatment

It is recommended to stratify patients according to prognostic factors into three risk groups that will facilitate treatment recommendations. Their definition, which takes into account the EORTC risk tables probabilities of recurrence and especially progression, can be found in Table 3. For individual prediction of the risk of tumour recurrence and progression at different intervals after TURB, application of EORTC risk tables and calculator (http://www.eortc.be/tools/bladdercalculator/) is strongly recommended.

Table 3: Treatment recommendations in Ta, T1 tumours and CIS according to risk stratification

Risk Category	**Definition**	**Treatment recommendation**
Low-risk Tumours	Primary, solitary, Ta, LG/ G1, < 3 cm, no CIS	One immediate instillation of Chemotherapy
Intermediate risk tumours	All cases between categories of low and high risk	One immediate instillation of Chemotherapy followed by further instillations, either chemotherapy for a maximum of 1 year or 1-year full dose BCG
High-risk Tumours	Any of the following: • T1 tumours; • HG/G3 tumours; • CIS; • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all these conditions must be presented)	Intravesical full dose BCG instillations for 1-3 years or cystectomy (in highest-risk tumours)
Subgroup of highest-risk tumours	T1G3 associated with concurrent bladder CIS, multiple and/or large T1G3 and/or recurrent T1G3, T1G3 with CIS in prostatic urethra, micropapillary variant of urothelial carcinoma, LVI	Radical cystectomy should be considered
	BCG failures	Radical cystectomy is recommended

CIS = carcinoma in situ; HG = high-grade; LG = low-grade; LVI = lymphovascular invasion

Since there is considerable risk for recurrence and/or progression of tumours after TURB, adjuvant intravesical therapy is recommended for all stages (Ta, T1, and CIS). Immediate postoperative

instillation of chemotherapy within 6 hours after TURB is recommended in tumours presumed to be at low or intermediate risk, except in cases of bladder perforation or severe bleeding. The choice of drug (mitomycin C, epirubicin, or doxorubicine) is optional. Intravesical chemotherapy reduces the risk of recurrence but not progression and is associated with minor side-effects. Intravesical immunotherapy with Bacillus Calmette-Guérin (BCG) (induction and maintenance) is superior to intravesical chemotherapy in reducing recurrences and in preventing or delaying progression to muscle-invasive bladder cancer. However, intravesical BCG is more toxic. The individual choice

of further intravesical adjuvant therapy depends on the patient's risk (Table 3). In patients at highest risk of progression (Table 3), radical cystectomy should be considered in patients with BCG failure since they are unlikely to respond to further BCG therapy; radical cystectomy is therefore the preferred option.

Recommendations for adjuvant therapy in Ta, T1 tumours and for therapy of CIS	GR
Smokers with confirmed NMIBC should be counselled to stop smoking.	B
The type of intravesical therapy should be based on risk groups.	A
One immediate chemotherapy instillation is recommended in tumours presumed to be at low or intermediate risk.	A
In patients with low-risk tumours, one immediate instillation of chemotherapy is recommended as the complete adjuvant treatment.	A
In patients with intermediate-risk Ta tumours, one immediate instillation of chemotherapy should be followed by 1-year full-dose BCG treatment, or by further instillation of chemotherapy for a maximum of 1 year.	A
In patients with high-risk tumours, full-dose intravesical BCG for 1-3 years is indicated.	A
In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillation of BCG can be offered.	C
In patients at highest risk of tumour progression (Table 3), immediate radical cystectomy should be considered.	C
In patients with BCG failure, radical cystectomy is indicated.	B
In patients with BCG failure ineligible for radical cystectomy, gemcitabine or MMC in combination with hyperthermia are options.	C

Intravesical chemotherapy	GR
One immediate instillation should be administered within 24 hours after TURB.	C

One immediate instillation of chemotherapy should be omitted in any case of overt or suspected intra- or extra-peritoneal perforation (after extensive TURB, or bleeding requiring bladder irrigation).	C
The optimal schedule of further intravesical chemotherapy instillation and its duration is not defined and should not exceed 1 year.	C
If intravesical chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug during instillation by reducing fluid intake.	B
The length of individual instillation should be 1-2 hours.	C

BCG intravesical immunotherapy	GR
Absolute contraindications of BCG intravesical instillation are: • during the first 2 weeks after TURB; • in patients with macroscopic haematuria; • after traumatic catheterization; • in patients with symptomatic urinary tract infection.	C
The management of side effects after BCG intravesical instillation should reflect their type and grade	C

BCG = bacillus Calmette-Guérin;
CIS = carcinoma in situ;
MMC = mitomycin C;
TUR = transurethral resection;
TURB =transurethral resection of the bladder

Follow-up for Non-Muscle Invasive Bladder Tumours

As a result of the risk of recurrence and progression, patients with Ta, T1 bladder tumours and with CIS need to be followed up. However, the frequency and duration of cystoscopy and imaging should reflect the individual patient's degree of risk.

When planning the follow-up schedule and methods, the following aspects should be considered:

- The prompt detection of muscle-invasive and HG/G3 nonmuscle-invasive recurrence is crucial because a delay in diagnosis and therapy can be life-threatening.

- Tumour recurrence in the low-risk group is nearly always low stage and LG/G1.

Small, non-invasive (Ta), LG/G1 papillary recurrence does not present an immediate danger to the patient, and early detection is not essential for successful therapy (LE: 2b).

Fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden.

- The first cystoscopy after TURB at 3 months is a very important prognostic indicator for recurrence and progression. The first cystoscopy should thus always be performed.

3 months after TURB in all patients with Ta, T1 tumours and CIS.

- In tumours at low risk, the risk of recurrence after 5 recurrence-free years is low.
- Discontinuation of cystoscopy or its replacement with less invasive methods can be considered.
- In tumours originally intermediate- or high-risk, recurrences after 10 years tumour-free are not unusual. Therefore, lifelong follow-up is recommended.
- The risk of upper urinary tract recurrence increases in patients with multiple and high-risk tumours.
- Positive urine test results have a positive impact on the quality of performed follow-up cystoscopy). It supports the adjunctive role of urine tests during follow-up.

The following recommendations are only based on retrospective experience.

Recommendations for follow-up	GR
The follow-up of Ta, T1 tumours and CIS is based on regular cystoscopy.	A
Patients with low-risk tumours should undergo cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years.	C
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly	C
Patients with intermediate-risk Ta tumours should have an in-between follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors.	C
Regular (yearly) upper tract imaging (CT-IVU or IVU) is recommended for high-risk tumours.	C
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is	B

Recommendations for follow-up	GR
positive	
During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or biopsies with PDD (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	B

CIS = carcinoma in situ;
CT-IVU = computed tomography intravenous urography;
IVU = intravenous urography;
PDD = photodynamic diagnosis;
R-biopsies = random biopsies.

Bladder Cancer – Muscle invasive and metastatic

DIAGNOSIS AND STAGING

Primary diagnosis

Symptoms: Painless haematuria is the most common presenting complaint. Others include urgency, dysuria, increased frequency, and in more advanced tumours, pelvic pain and symptoms related to urinary tract obstruction.

Physical examination: including rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after TURB, to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall. However, considering the discrepancy between bimanual examination and pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging), some caution is suggested with the interpretation of bimanual examination.

Endoscopic bladder imaging: Ultimately, the diagnosis of bladder cancer is made by cystoscopy and histological evaluation of resected tissue. In general, cystoscopy is initially performed in the office using flexible instruments. If a bladder tumour has been visualised unequivocally in earlier imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), diagnostic cystoscopy may be omitted and the patient can proceed directly to TURB for histological diagnosis. A careful description of the cystoscopic findings is necessary. This should include documentation of the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of mucosal abnormalities. Use of a bladder diagram is recommended. The use of photodynamic diagnosis could be considered, especially if a T1 high-grade tumour is present, to find associated CIS. The additional presence of CIS may lead to a modified treatment

plan. Photodynamic diagnosis is highly sensitive for the detection of CIS; with experience, the rate of false-positive results may be similar to that with regular white-light cystoscopy.

Urinary cytology and urinary markers: Examination of voided urine or bladder washings for exfoliated cancer cells has high sensitivity in high-grade tumours (LE: 3) and is a useful indicator in cases of high-grade malignancy or CIS. Positive urinary cytology may originate from a urothelial tumour located anywhere in the urinary tract. Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or intravesical instillations, but for experienced readers, specificity exceeds 90% (LE: 2b). However, negative cytology does not exclude tumour. Cytology should be performed on fresh urine with adequate fixation. Early morning urine is not suitable as cytolysis may often be present. There is no known urinary marker specific for the diagnosis of invasive bladder cancer.

Random bladder and prostatic urethral biopsy: Bladder tumours are often multifocal and can be accompanied by CIS or dysplasia. These lesions may present themselves as velvet-like, reddish areas, indistinguishable from inflammation, or may not be visible at all. The biopsies from normal-looking mucosa in patients with invasive bladder tumours, so-called random biopsies (R-biopsies) show a low yield. Fluorescence cystoscopy is performed using filtered blue light after intravesical instillation of a photosensitiser, such as 5-aminolevulinic acid (5-ALA), and more recently, hexaminolaevulinate (HAL), following approval by the European Medicines Agency. It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures in detecting malignant tumours, particularly CIS (9-12) (LE: 2a). However, false-positive results may be induced by inflammation, or recent TURB or intravesical instillation therapy. A recent multicentre, prospective, international trial showed that, in experienced hands, the rate of false-positive results is no higher than that seen for regular, white-light cystoscopy (7). Material obtained by random or directed biopsies must be sent for pathological assessment in separate containers. The involvement of the prostatic urethra and ducts in men with bladder tumours has been reported. The exact risk is not known, but it seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS, and in multiple tumours (LE: 3). Involvement of the prostatic urethra can be determined either at the time of primary TURB or by frozen section during the cystoprostatectomy procedure. A frozen section has a higher negative predictive value and is more accurate.

Second resection: In the case of high-grade non-muscle-infiltrative tumour, residual disease is observed in 33-53% of patients (18-24). In order to reduce the risk of understaging, a second TURB resection is often required to determine the future treatment strategy. In consultation with the patient, orthotopic neobladder should be considered in case reconstructive surgery does not expose the patient to excessive risk (as determined by comorbidity and age). Age greater than 80 years is often

considered to be the threshold after which neobladder reconstruction is not recommended, however, there is no exact age for strict contraindication. In most large series coming from experienced centres, the rate of orthotopic bladder substitution after cystectomy for bladder tumour is up to 80% for men and 50% for women. Nevertheless, no randomized controlled studies comparing conduit diversion with neobladder or continent cutaneous diversion have been performed. Diagnosis of urethral tumour before cystectomy or positive urethral frozen section leads to uretrectomy and therefore excludes neobladder reconstruction. If indicated, in males urethral frozen section has to be performed on the cysto-prostatectomy specimen just under the verumontanum and on the inferior limits of the bladder neck for females. When there are positive lymph nodes, orthotopic neobladder can nevertheless be considered in case of N1 involvement (metastasis in a single node in the true pelvis) but not for N2 or N3 tumours. Oncological results after orthotopic neobladder substitution or conduit diversion are similar in terms of local or distant metastasis recurrence, but secondary urethral tumours seem less common in patients with neobladder compared with those with conduits or continent cutaneous diversions.

Imaging for staging MIBC: The treatment and prognosis for MIBC is determined by tumour stage and grade. In clinical practice, CT and MRI are the imaging techniques used. The purpose of using imaging for staging MIBC is to determine prognosis and provide information to assist treatment selection. Tumour staging must be accurate to ensure the correct choice of treatment is made. Imaging parameters required for staging MIBC are:

- extent of local tumour invasion;
- tumour spread to lymph nodes;
- tumour spread to the upper urinary tract and other distant organs (e.g., liver, lungs, bones, peritoneum, pleura, and adrenal glands).

CT imaging for local staging of MIBC: The advantages of CT include high spatial resolution, shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to variable patient factors. Computed tomography is unable to differentiate between stages Ta and T3a tumours, but it is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension varies from 55% to 92% and increases with more advanced disease.

MRI for local staging of invasive bladder cancer: Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT, but poorer spatial

resolution. In studies performed before the availability of multidetector CT, MRI was reported as more accurate in local assessment. The accuracy of MRI for primary tumour staging varies from 73% to 96% (mean 85%). These values were 10-33% (mean 19%) higher than those obtained with CT. Dynamic contrast-enhanced (DCE) MRI may help to differentiate bladder tumour from surrounding tissues or post-biopsy reaction, because enhancement of the tumour occurs earlier than that of the normal bladder wall, due to neovascularisation. In 2006, a link was established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF), which may result in fatal or severely debilitating systemic fibrosis. Patients with impaired renal function are at risk of developing NSF and the non-ionic linear gadolinium-based contrast agents should be avoided (gadodiamide, gadopentetate dimeglumine and gadoversetamide). A stable macrocyclic contrast agent should be used (gadobutrol, gadoterate meglumine or gadoteridol). Alternatively, contrast-enhanced CT could be performed using iodinated contrast media (LE: 4).

TREATMENT

Recommendations for treatment failure of non-muscle-invasive bladder cancer

Recommendations	GR
In all T1 tumours at high risk of progression (i.e., high grade, multifocality, CIS, and tumour size, as outlined in the EAU guidelines for non-muscle-invasive bladder cancer [7]), immediate radical treatment is an option	**C**
In all T1 patients failing intravesical therapy, radical treatment should be offered.	**B**

CIS = carcinoma in situ

NEOADJUVANT CHEMOTHERAPY

Advantages and disadvantages:

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.

- Potential reflection of in vivo chemosensitivity.

- Tolerability of chemotherapy and patient compliance are expected to be better before rather than after cystectomy.
- Patients might respond to neoadjuvant therapy and reveal a favourable pathological status, determined mainly by achieving pT0, a negative lymph node status, and negative surgical margins.

- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy (8,9), although published studies on the negative effect of delayed cystectomy only entail series of chemonaive patients. There are no trials or large patient series indicating that delayed surgery, due to neoadjuvant chemotherapy, has a negative impact on survival.

Conclusions	**LE**
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (5-8% at 5 years).	1a
Neoadjuvant treatment of responders and especially patients who show complete response (pT0 N0) has a major impact on OS.	2
Currently, no tools are available to select patients who have a higher probability to benefit from neoadjuvant chemotherapy. In the future, genetic markers, in a personalised medicine setting, might facilitate the selection of patients for neoadjuvant chemotherapy and to differentiate responders from non-responders.	

Recommendations	**GR**
Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatin-based combination therapy.	A
Neoadjuvant chemotherapy is not recommended in patients who are ineligible for cisplatin-based combination chemotherapy.	A

RADICAL SURGERY AND URINARY DIVERSION

Radical cystectomy is the standard treatment for localised MIBC in most western countries. Recent interest in patients' quality of life (QoL) has increased the trend toward bladder preservation treatment modalities, such as radio- and/or chemotherapy. Performance status (PS) and age influence the choice of primary therapy, as well as the type of urinary diversion, with cystectomy being reserved for younger patients without concomitant disease and with a better PS. The value of assessing overall health before recommending and proceeding with surgery was emphasised in a multivariate analysis. The analysis found an association between comorbidity and adverse pathological and survival outcome following radical cystectomy. PS and comorbidity have a different impact on treatment outcome and must be evaluated independently. Controversy remains about age, radical cystectomy and the type of urinary diversion. Cystectomy is associated with the greatest risk reduction in disease-related and non-disease-related death in patients aged > 80 years. The largest, retrospective, single-institution study on cystectomy to date found that patients aged > 80 years had increased postoperative morbidity but

not increased mortality. Although some patients successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion. It is particularly important to evaluate the function and QoL of elderly patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation.

Each network should agree clear guidelines on treatment and follow up of bladder cancer which ensure that cystectomy is considered for patients with muscle-invasive or high-risk recurrent disease. Cystectomy is a complex operation which should be undertaken only by specialist surgeons working in cancer centres. Ideally, all radical cystectomies undertaken in each network should be carried out by a single team. Teams providing this form of surgery should carry out a cumulative total of at least 50 radical operations (cystectomies or radical prostatectomies) for bladder or prostate cancer per year.

Timing and delay of cystectomy:

Patients treated > 90 days after the primary diagnosis showed a significant increase in extravesical disease (81 vs 52%). Delay in cystectomy affects treatment outcome and the type of urinary diversion. In organ-confined urothelial cancer of the bladder, the average time from primary diagnosis to cystectomy was 12.2 months in patients who received a neobladder and 19.1 months in those who received an ileal conduit. This was even more noticeable with organ-confined invasive cancer; the average time to surgery was 3.1 months with a neobladder and 15.1 months with an ileal conduit (8). Similar results have been observed in a series of 247 patients: recurrence-free survival and OS were significantly better in patients treated before 90 days compared to others treated after 90 days.

LN removal at the time of cystectomy:

The extent of LND has not been established to date. Standard lymphadenectomy in bladder cancer patients involves removal of nodal tissue cranially up to the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa and external iliac nodes (10). Extended lymphadenectomy includes all lymph nodes in the region of the aortic bifurcation, and presacral and common iliac vessels medial to the crossing ureters. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the lymph node of Cloquet, as well as the area described for standard lymphadenectomy. A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery.

Morbidity and mortality from cystectomy:

The perioperative mortality was reported as 1.2-3% at 30 days and 2.3-5.7% at 90 days. In a large single-centre series, early complications (within 3 months of surgery) were seen in 58% of patients. Late morbidity is usually due to the type of urinary diversion. Early morbidity associated with radical cystectomy for NMIBC (at high risk for disease progression) is similar and no less than that associated with muscle-invasive tumours. In general, lower morbidity and (perioperative) mortality have been observed by surgeons and in hospitals with a higher caseload and therefore more experience.

Survival:

According to a multi-institutional database of 888 consecutive patients undergoing radical cystectomy for bladder cancer, the 5-year recurrence-free survival was 58% and the cancer-specific survival was 66%. Recent external validation of postoperative nomograms for bladder-cancer-specific mortality showed similar results, with 5-year OS of 45% and cancer-specific survival of 62%. Recurrence-free survival and OS in a large single-centre study of 1,054 patients was 68% and 66% at 5 years and 60% and 43%, at 10 years, respectively. The 5-year recurrence-free survival in node-positive patients who underwent cystectomy was considerably less at 34-43%. However, in patients with a low level of lymph node metastasis, the survival is better. In a surgery only study, the 5-year recurrence-free survival was 76% in patients with pT1 tumours, 74% for pT2, 52% for pT3, and 36% for pT4. Another study reported 10-year disease-specific survival and OS rates of 72.9% versus 49.1% for organ-confined disease (defined as pT < 3a), and 33.3% versus 22.8% for non-organconfined disease. A trend analysis according to the 5-year survival and mortality rates of bladder cancer in the United States, between 1973 and 2009 with a total of 148,315 bladder cancer patients, revealed an increased stage-specific 5-year survival rate for all stages, except for metastatic disease. However, no changes in mortality were recorded among localized and regional stage. In patients with visceral metastases an increase in mortality rates was observed, but differences were minor, and hardly of any clinical importance.

Recommendations:

Recommendations	**GR**
Radical cystectomy is recommended in T2-T4a, N0 M0, and high-risk non-MIBC (as outlined above).	A
Do not delay cystectomy for > 3 months because it increases the risk of progression and cancerspecific mortality.	B
Preoperative radiotherapy is not recommended in subsequent cystectomy with urinary diversion.	A
Lymph node dissection should be an integral part of cystectomy. Extended	B

Recommendations	GR
LND is recommended.	
The urethra can be preserved if margins are negative. If no bladder substitution is attached, the urethra must be checked regularly.	B
Laparoscopic cystectomy and robot-assisted laparoscopic cystectomy are both management options. However, current data have not sufficiently proven the advantages or disadvantages for oncological and functional outcomes.	C
Before cystectomy, the patient should be fully informed about the benefits and potential risks of all possible alternatives, and the final decision should be based on a balanced discussion between patient and surgeon.	B
Pre-operative bowel preparation is not mandatory. "Fast track" measurements may reduce the time of bowel recovery.	C
An orthotopic bladder substitute should be offered to male and female patients lacking any contraindications and who have no tumour in the urethra or at the level of urethral dissection.	B

NON-RESECTABLE TUMOURS

Recommendations	LE	GR
In patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is a palliative option and cannot be offered as curative treatment.		B
In patients with symptoms palliative cystectomy may be offered. Prior to any further interventions, surgery-related morbidity and quality of life should be fully discussed with the patient.	3	B

BLADDER-SPARING TREATMENTS FOR LOCALIZED DISEASE

Transurethral resection of bladder tumour (TURBT)

Recommendation	LE	GR
Transurethral resection of bladder tumour (TURB) alone is not a curative treatment option in most patients.	2a	B

External beam radiotherapy (EBRT)

Based on available trials, a Cochrane analysis has demonstrated that radical cystectomy has an overall survival benefit compared to radiotherapy. However, external radiotherapy is an alternative treatment in patients unfit for radical surgery. The target dose for curative radiotherapy for bladder cancer is 60-66 Gy, with a

subsequent boost using external radiotherapy or interstitial brachytherapy. The daily dose is usually 1.8-2 Gy and the course of radiotherapy should not extend beyond 6-7 weeks to minimize the repopulation of cancer cells. The use of modern standard radiotherapy techniques results in major, related, late morbidity of the urinary bladder or bowel in less than 5% of tumour-free patients. Overall, 5-year survival rates in patients with MIBC range between 30% and 60%, depending on whether they show a complete response (CR) following radiotherapy. Cancer-specific survival rates are between 20% and 50%.

Conclusions:

Conclusions	**LE**
External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation because of extensive local tumour growth.	3

Recommendation:

Recommendation	**GR**
Surgical intervention or multimodality treatment are the preferred curative therapeutic approaches because they are more effective than radiotherapy alone.	B

Chemotherapy

Chemotherapy alone rarely produces durable CRs. In general, a clinical CR rate of up to 56%, as reported in some series, must be weighed against a staging error of > 60%. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival, though it may be confounded by patient selection. For very selected patients, a bladder-conserving strategy with TURB and systemic cisplatin-based chemotherapy, preferably with MVAC, may allow long-term survival with intact bladder. However, this approach cannot be recommended for routine use.

Conclusion:

Conclusion	**LE**
With cisplatin-based chemotherapy as primary therapy for locally advanced	2b

tumours in highly selected patients, complete and partial local responses have been reported.	
Recommendation	**GR**
Chemotherapy alone is not recommended as primary therapy for localized bladder cancer.	A

Multimodality bladder-preserving treatment

Recent organ-preservation strategies combine TURB, chemotherapy and radiation (1,2). The rationale for performing TURB and radiation is to achieve local tumour control. Application of systemic chemotherapy, most commonly as methotrexate, cisplatin and vinblastine (MCV), aims at the eradication of micrometastasis. Many protocols use cisplatin and/or 5-FU and, recently, gemcitabine with radiation, because of their established role as radiosensitizers. Cisplatin-based chemotherapy in combination with radiotherapy, following TURB, results in a CR of 60-80%.

Conclusions:

Conclusions	**LE**
In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy.	3
Delay in surgical therapy can compromise survival rates.	2b

Recommendations	**GR**
Transurethral resection of bladder tumour alone cannot be offered as a standard curative treatment option in most patients.	B
Radiotherapy alone is less effective than surgery and is only recommended as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach.	B
Chemotherapy alone is not recommended as primary therapy for MIBC.	A
Surgical intervention or multimodality treatments are the preferred curative therapeutic approaches as they are more effective than radiotherapy alone.	B
Multimodality treatment could be offered as an alternative in selected, well-informed, well-selected and compliant patients, especially for whom cystectomy is not an option.	B

ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy after radical cystectomy for patients with pT3/4 and/or lymph node positive (N+) disease without clinically detectable metastases (M0) is under debate and still infrequently used.

The general benefits of adjuvant chemotherapy include:

- Chemotherapy is administered after accurate pathological staging, therefore treatment in patients at low risk for micrometastases is avoided.
- No delay in definitive surgical treatment.

The drawbacks of adjuvant chemotherapy are:

- Assessment of in vivo chemosensitivity of the tumour is not possible and overtreatment is an unavoidable problem.
- Delay or intolerability of chemotherapy, due to postoperative morbidity.

Conclusions:

Conclusion	**LE**
Neither randomised trials nor two meta-analyses have provided sufficient data to support the routine use of adjuvant chemotherapy.	1a
Recommendations	GR
Adjuvant chemotherapy should only be given within clinical trials, whenever possible.	A
Adjuvant cisplatin based combination chemotherapy may be offered to patients with pN+ disease if no neoadjuvant chemotherapy has been given.	C

METASTATIC DISEASE

Conclusions	LE
In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS > 1 and low haemoglobin (< 10 g/dL) 1b Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term disease-free survival reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based	2a

Conclusions	LE
chemotherapy in terms of complete response and survival.	
Non-platinum combination chemotherapy produces substantial responses in first- and second-line settings, but has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	2a
There is no defined standard chemotherapy for unfit patients with advanced or metastatic urothelial cancer.	2b
Vinflunine reaches the highest level of evidence ever reported for second-line use.	1b
Post-chemotherapy surgery after partial or complete response may contribute to long-term diseasefree survival.	3
Zoledronic acid and denosumab have been approved for all cancer types including urothelial cancer, because they reduce and delay skeletal related events in metastatic bone disease.	1b

Recommendations	GR
First-line treatment for fit patients: Use cisplatin-containing combination chemotherapy with GC, PCG, MVAC, preferably with G-CSF, or HD-MVAC with G-CSF.	A
Carboplatin and non-platinum combination chemotherapy is not recommended.	B
First-line treatment in patients ineligible (unfit) for cisplatin: Use carboplatin combination chemotherapy or single agents.	C
For cisplatin-ineligible (unfit) patients, with PS2 or impaired renal function, as well as those with 0 or 1 poor Bajorin prognostic factors and impaired renal function, treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin is indicated.	A
Second-line treatment: In patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered. Alternatively, treatment within a clinical trial setting may be offered.	A
Zoledronic acid or denosumab is recommended for treatment of bone metastases.	B

9.2 Prostate cancer

Epidemiology

Prostate cancer is the most common cancer in elderly males in Europe. It is a major health concern, especially in developed countries with their greater proportion of elderly men in the general population. The incidence is highest in Northern and Western Europe (> 200 per 100,000), while rates in Eastern and Southern Europe have showed a continuous increase. There is still a survival difference between men diagnosed in Eastern Europe and those in the rest of Europe. Overall, during the last decade, the 5-year relative survival percentages for prostate cancer steadily increased from 73.4% in 1999-2001 to 83.4% in 2005-2007.

There are three well-established risk factors for PCa:

- increasing age;
- ethnic origin;
- heredity

Genetics:

- If one first-line relative has PCa, the risk is at least doubled. If two or more first-line relatives are affected, the risk increases by 5-11-fold.
- A small subpopulation of individuals with PCa (about 9%) have true hereditary PCa. This is defined as three or more affected relatives, or at least two relatives who have developed early onset disease, i.e. before age 55.
- Patients with hereditary PCa usually have an onset six to seven years earlier than spontaneous cases, but do not differ in other ways.

Geography:

- The frequency of autopsy-detected cancers is roughly the same in different parts of the world.
- This finding is in sharp contrast to the incidence of clinical PCa, which differs widely between different geographical areas, being high in the USA and northern Europe and low in South-East Asia.
- However, if Japanese men move from Japan to Hawaii, their risk of PCa increases. If they move to California their risk increases even more, approaching that of American men.

Metabolic syndrome and prostate cancer:

- Metabolic syndrome is weakly and non-significantly associated with the risk of PCa, but associations vary with geography.
- Among single components of the syndrome (body mass index, dysglycaemia or dyslipidaemia, high triglycerides, low HDL cholesterol) only hypertension and waist circumference >102 cm were associated with a significantly greater risk of PCa, increasing it by 15% (p = 0.035) and 56% (p = 0.007), respectively.

Chemoprevention in prostate cancer:

- Currently, there are no data to suggest that medical intervention would effectively reduce progression of PCa.
- Several 5-alpha-reductase inhibitors (5-ARIs) have been studied to assess their effect on reducing risk of developing PCa. Although it seems that 5-ARIs have a potential benefit in preventing or delaying the development of PCa (~25%, only of Gleason 6 cancer), this must be weighed against treatment-related sideeffects as well as the potential increased risk of high-grade PCa. None of the available 5-ARIs have been approved for this indication.

SCREENING FOR PROSTATE CANCER:

Prostate cancer screening is one of the most controversial topics in urological literature. The main summary of findings from literature published on PCa screening is the Cochrane review published in 2013. Its findings are as follows:

- Screening was associated with an increased diagnosis of PCa (RR: 1.3; 95% CI: 1.02-1.65).

- Screening was associated with more localized disease (RR: 1.79; 95% CI: 1.19-2.70) and less advanced PCa (T3-4, N1, M1) (RR: 0.80; 95% CI: 0.73-0.87).

- From the results of five RCTs, representing more than 341,000 randomized men, no PCa-specific survival benefit was observed (RR: 1.00; 95% CI: 0.86-1.17). This was the main objective of all the large trials.

- From the results of four available RCTs, no overall survival benefit was observed (RR: 1.00; 95% CI: 0.96-1.03).

ERSPC: at 11 years of median follow-up, there was a 21% reduction in PCa-specific mortality and a 29% reduction after adjustment for non-compliance. However, there is still no overall survival benefit.

Thus, an individualized risk-adapted strategy for early detection might be offered to a well-informed man with a least 10-15 years of individual life expectancy. Men who have less than a 15-year life expectancy are unlikely to benefit based on the PIVOT and the ERSPC trials. Screening is associated with minor and major harms such as overdiagnosis and overtreatment.

Recommendations:

Recommendations	LE	GR
An individualized risk-adapted strategy for early detection might be offered to a well-informed man with a good performance status and at least 10-15 years of life expectancy.	3	B
Early PSA testing in men at elevated risk of having PCa: • men over 50 years of age • men over 45 years of age and a family history of PCa • African-Americans • men with a PSA level of > 1 ng/mL at 40 years of age • men with a PSA level of > 2 ng/mL at 60 years of age	2b	A
A risk-adapted strategy might be considered (based on initial PSA level), which may be every 2 years for those initially at risk, or postponed up to 8 years in those not at risk. 3 C The age at which early diagnosis of PCa should be stopped is influenced by life expectancy and performance status; men who have < 15-year life expectancy are unlikely to benefit based on the PIVOT and the ERSPC trials.	3	A

DIAGNOSIS:

The following guidelines for urgent referral (within two weeks) have been published by the Department of Health:

- Macroscopic haematuria in adults.
- Microscopic haematuria in adults over 50 years.
- Swellings in the body of the testis.
- Palpable renal masses.
- Solid renal masses found on imaging.
- Elevated age-specific prostate specific antigen (PSA) in men with a 10 year life expectancy.
- A high PSA (>20ng/ml) in men with a clinically malignant prostate or bone pain.
- Any suspected penile cancer.

Digital rectal examination:

- Most prostate cancers are located in the peripheral zone of the prostate and may be detected by DRE when the volume is about 0.2 mL or larger.
- In about 18% of all patients, PCa is detected by a suspect DRE alone, irrespective of the PSA level.
- A suspect DRE in patients with a PSA level up to 2 ng/mL has a positive predictive value of 5-30%.
- An abnormal DRE is associated with an increased risk of a higher Gleason score and should therefore be considered an indication for prostate biopsy.

Prostate-specific antigen (PSA):

PSA is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate, which is organ- but not cancer specific. Thus, serum levels may be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. The level of PSA as an independent variable is a better predictor of cancer than suspicious findings on DRE or transrectal ultrasound (TRUS).

PSA and the risk of prostate cancer:

PSA level (ng/mL)	Risk of PCa (%)	Risk of Gleason > 7 PCa (%)
0.0-0.5	6.6	0.8
0.6-1.0	10.1	1.0
1.1-2.0	17.0	2.0
2.1-3.0	23.9	4.6
3.1-4.0	26.9	6.7

Practical modifications of serum PSA value that may improve the specificity of PSA in the early detection of PCa have been described. They include:

- PSA density;
- PSA velocity; defined as the absolute annual increase in serum PSA (ng/mL/year).
- PSA doubling time: the exponential increase in serum PSA over time, reflecting a relative change.
- age-specific reference ranges;
- The free/total PSA ratio: between 4 ng/mL and 10 ng/mL and a negative DRE, PCa was found on biopsy in 56% of men with f/t PSA < 0.10, but in only 8% of men with f/t PSA > 0.25.

PCA3: is an increasingly studied new biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The costly Progensa urine test for PCA3 is now commercially available. The amount of the prostate-specific non-coding mRNA marker PCA3 normalized against PSA mRNA (urine sediment) gives a PCA3 score. This is superior to total PSA and percent-free PSA in the detection of PCa in men with elevated PSA levels as it shows slight but significant increases in the area under the receiveroperator characteristics curve (AUC) for positive biopsies. The main current indication for the PCA3 urine test may be to determine whether a man needs a repeat biopsy after an initially negative biopsy outcome, but its cost-effectiveness remains to be shown.

Prostate biopsy:

- Indications: PSA level and/or a suspicious DRE.

- The first elevated PSA level should not prompt an immediate biopsy.

- The PSA level should be verified after a few weeks by the same assay under standardized conditions (i.e. no ejaculation, no manipulations such as catheterisation, cystoscopy or transurethral resection, and no urinary tract infections) in the same diagnostic laboratory, using the same methods.

- It is now considered the standard of care to perform prostate biopsies guided by ultrasound.

Types of prostatic biopsy:

- Transrectal approach is used for most prostate biopsies, with ultrasound-guided periprostatic block as state-of-the-art. The British Prostate Testing for Cancer and Treatment (PROTECT) Study recommended 10 core biopsies, with > 12 cores being not significantly more conclusive.

- Transperineal approach is another alternative used by some urologists, with less incidence of biopsy related sepsis, but requires sedation or general anaesthetic (GA). There are two types:
    - Template biopsy requiring 24-30 cores using the brachytherapy grid and is performed under GA, with higher tumour detection rate (38%), but with a higher incidence of acute urinary retention (AUR) (up to 10%).
    - Targeted biopsy, which requires less cores and is more tolerated and less incidence of AUR.

- Diagnostic transurethral resection of the prostate: is a poor tool for cancer detection.

- Transition zone sampling during baseline biopsies gives a very low detection rate and should therefore be confined to repeat biopsies.

- Indications for a repeat biopsy are:
  - rising and/or persistently elevated PSA;
  - suspicious DRE, 5-30% risk of cancer;
  - atypical small acinar proliferation (ASAP), 40% risk of cancer;
  - extensive (multiple biopsy sites) prostatic intra-epithelial neoplasia (PIN), 20-30% risk of cancer.
  - **Consider multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound 10–12 core biopsy to determine whether another biopsy is needed.**
  - **Do not offer another biopsy if the multiparametric MRI (using T2- and diffusion-weighted imaging) is negative, unless any of the risk factors above is present.**

- An isolated high-grade PIN as finding is no longer considered an indication for repeat biopsy.

- Antibiotics prior to biopsy: Oral or intravenous antibiotics are state-of-the-art treatment. Optimal dosing and treatment time vary. Quinolones are the drugs of choice, with ciprofloxacin being superior to ofloxacin, but increased resistance to quinolones associated with a rise in severe infectious complications after biopsy has been reported in the past few years.

- Percentage of complications per biopsy session, irrespective of the number of cores:

Complications	**Percentage of biopsies affected**
Haematospermia	37.4
Haematuria > 1 day	14.5
Rectal bleeding< 2 days	2.2
Prostatitis	1.0
Fever > 38.5°C (101.3°F)	0.8
Epididymitis	0.7
Rectal bleeding > 2 days ± requiring surgical intervention	0.7
Urinary retention	0.2
Other complications requiring hospitalisation	0.3

The role of imaging

- **TRUS:** Grey-scale TRUS is not adequately reliable at detecting areas of PCa. It is therefore used as a guide to direct systematic biopsies of the prostate gland.

- **Multiparametric MRI:**
  - has excellent sensitivity for detecting aggressive Gleason > 7 cancers
  - mMRI is particularly good at accurately detecting anterior tumours that are usually missed by systematic biopsy and therefore trigger a (targeted) repeat biopsy.
  - cost-effectiveness of mMRI as a triage test before the first biopsy has not been assessed.
  - Inter-reader variability is also a current concern, especially outside reference centres.

Recommendations for the diagnosis of prostate cancer:

Recommendations	LE	GR
Prostate cancer should be graded according to the ISUP 2005 modified Gleason grading system. 2a A The decision to biopsy should be based on PSA testing and DRE.	2b	A
For initial diagnosis, a core biopsy of 10-12 systematic transrectal or transperineal peripheral zone biopsies should be performed under ultrasound imaging guidance.	2a	B
Transrectal prostate needle biopsies should be taken under antibiotic protection.	1b	A
Local anaesthetic by periprostatic infiltration is recommended for prostate needle biopsies.	1a	A
Prostate core biopsies from different prostatic sites should be submitted separately for processing and pathology reporting.	3	A
Processing and reporting of prostatectomy specimens by pathology should follow the guidelines provided by the 2010 ISUP consensus meeting.	3	A

STAGING FOR PROSTATE CANCER

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
T1a	Tumour incidental histological finding in 5% or less of tissue resected
T1b	Tumour incidental histological finding in more than 5% of tissue resected

T1c Tumour identified by needle biopsy (e.g. because of elevated PSA level) T2 Tumour confined within the prostate T2a Tumour involves one half of one lobe or less T2b Tumour involves more than half of one lobe, but not both lobes T2c Tumour involves both lobes T3 Tumour extends through the prostatic 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: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional lymph nodes
NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Regional lymph node metastasis
M - Distant metastasis
MX Distant metastasis cannot be assessed M0 No distant metastasis M1 Distant metastasis M1a Non-regional lymph node(s) M1b Bone(s) M1c Other site(s)

- Provisional treatment intent should be determined (radical or non-radical) before decisions on imaging are made.

- Imaging should not be routinely offered to men who are not candidates for curative intent.

- Isotope bone scans should be offered when hormonal therapy is being deferred through watchful waiting to asymptomatic men who are at high risk of developing bone complications.

- Multiparametric MRI (or CT if MRI is contraindicated) should be offered for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management.

- Urological cancer MDTs should assign a risk category (below) to all newly diagnosed men with localised prostate cancer.

Risk stratification for men with localised prostate cancer

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

- CT of the pelvis should not be offered to men with low- or intermediate-risk localised prostate cancer (see table 1).
- Isotope bone scans should not be routinely offered to men with low-risk localised prostate cancer.
- Positron emission tomography imaging should not be offered for prostate cancer in routine clinical practice.

TREATMENT:

LOCALIZED PROSTATE CANCER (stage T1-T2c, Nx-N0, M0):

DEFERRED TREATMENT (ACTIVE SURVEILLANCE/ WATCHFUL WAITING):

Definitions:

Active surveillance is active monitoring, aiming at the proper timing of curative treatment; an active decision not to treat the patient immediately.

- The patient remains under close surveillance, and treatment is prompted by predefined thresholds indicative of the presence of a potentially life-threatening disease, while taking the patient's life-expectancy into consideration.

- The treatment options are intended to be *curative*.
- Aim is to reduce overtreatment in patients with clinically confined very low-risk PCa, without giving up the option of curative treatment.

Patients selected for active surveillance:

The various series have applied several eligibility criteria for enrolment in active surveillance programmes (D'Amico, Epstein, PRIAS, etc.):

- clinically confined PCa (T1-T2);
- Gleason score < 7 for most studies;
- PSA < 10-15 ng/mL;
- prostate cancer volume criteria on biopsies, e.g. number of positive biopsies, maximum cancer involvement of biopsy.

Protocol for active surveillance

There are several studies with variable protocols for the active surveillance patients. However, NICE recommends the following:

Timing	**Tests** [1]
At enrolment in active surveillance	Multiparametric MRI if not previously performed
Year 1 of active surveillance	Every 3–4 months: measure PSA[2] Throughout active surveillance: monitor PSA kinetics[3] Every 6–12 months: DRE[4] At 12 months: prostate rebiopsy
Years 2–4 of active surveillance	Every 3–6 months: measure PSA[2] Throughout active surveillance: monitor PSA kinetics[3]

	Every 6–12 months: DRE[4]
Year 5 and every year thereafter until active surveillance ends	Every 6 months: measure PSA[2] Throughout active surveillance: monitor PSA kinetics[3] Every 12 months: DRE[4]
[1] If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or rebiopsy. [2] May be carried out in primary care if there are agreed shared-care protocols and recall systems. [3] May include PSA doubling time and velocity. [4] Should be performed by a healthcare professional with expertise and confidence in performing DRE.	

Triggers for active treatment:

- A PSA doubling time (PSADT) with a cut-off value ranging between < 2 and < 4 years.
- Gleason score progression to > 7 during systematic follow-up biopsies, at intervals ranging from one to four years.
- Patients' requests for treatment are based mainly on anxiety.
- Radiological progression, supported with an updated biopsy.

Recommendations:

Recommendations - active surveillance	LE	GR
Active surveillance is an option in patients with the lowest risk of cancer progression: over 10 years of life-expectancy, cT1-2, PSA < 10 ng/mL, biopsy Gleason score < 6 (at least 10 scores), < 2 positive biopsies, minimal biopsy core involvement (< 50% cancer per biopsy).	2a	A
Follow-up should be based on DRE, PSA and repeated biopsies. The optimal timing for follow-up is still unclear.	2a	A
Patients with biopsy progressions should be recommended to undergo active treatment.	2a	A

Watchful waiting is the delayed application of palliative treatment options. The rationale behind watchful waiting is the observation that PCa often progresses slowly, and is predominantly diagnosed in older men in whom there is a high incidence of co-morbidity and related high competitive mortality. Watchful waiting can be considered as an option for treating patients with localized PCa and a limited life-expectancy, or for older patients with less aggressive cancers.

Recommendations:

Recommendations - watchful waiting	LE	GR
Watchful waiting may be offered to all patients not willing to accept the side-effects of active treatment, particularly patients with a short life-expectancy.	1b	A
When on watchful waiting, the decision to start any non-curative treatment should be based on symptoms and disease progression.	1a	B

RADICAL PROSTATECTOMY

- Radical prostatectomy can be offered to men with intermediate-risk localised prostate cancer.
- Radical prostatectomy can be offered to men with high-risk localised prostate cancer when there is a realistic prospect of long-term disease control.
- Patients for radical prostatectomy should be referred to urological cancer team that has a specialist interest in urological cancer and all team members must attend a majority of meetings. The team should carry out a cumulative total of at least 50 radical operations for prostate or bladder cancer per year.
- Commissioners of urology services should consider providing robotic surgery to treat localised prostate cancer.
- Commissioners should ensure that robotic systems for the surgical treatment of localised prostate cancer are cost effective by basing them in centres that are expected to perform at least 150 robot-assisted laparoscopic radical prostatectomies per year.

Low risk prostate cancer (cT1-T2a, Gleason score < 6 and PSA < 10 ng/mL):

- Patients should be informed about the results of two randomized trials comparing retropubic RP versus watchful waiting (WW) in localized PCa.
- In the SPCG-4 study, the survival benefit associated with RP was similar before and after 9 years of follow-up and was also observed in men with low-risk PCa, and was confined to men < 65 years of age.

- In the PIVOT trial, a preplanned subgroup analysis of men with low-risk tumours showed that RP did not significantly reduce all-cause mortality.
- The decision to offer RP in cases of incidental cancer should be based upon the estimated probability of clinical progression compared to the relative risk of therapy and potential benefit to survival.
- In stage T2a patients with a 10-year life expectancy, RP is one of the recommended standard treatments, as 35-55% of these patients will show disease progression after 5 years if not treated.
- Extended pelvic lymph node dissection (eLND) is not necessary in low-risk PCa because the risk for positive lymph nodes does not exceed 5%.

Intermediate-risk, localized prostate cancer (cT2b-T2c or Gleason score = 7 and/or PSA 10-20 ng/mL):

- Radical prostatectomy is one of the recommended standard treatments for patients with intermediate risk PCa and a life expectancy of > 10 years.
- The prognosis is excellent when the tumour is confined to the prostate, based on pathological examination
- Although active monitoring could be proposed for some selected patients with intermediate-risk localized tumours, however, when the tumour is palpable or visible on imaging and clinically confined to the prostate, disease progression can be expected in most long term survivors.
- An eLND should be performed in intermediate-risk PCa if the estimated risk for positive lymph nodes exceeds 5%.
- Limited LND should no longer be performed because this misses at least half of the nodes involved

High-risk localized and locally advanced prostate cancer (Gleason score 8-10 and/or PSA > 20 ng/mL):

- RP is a reasonable treatment option in selected patients.
- RP is offered after all treatments have been discussed at the multidisciplinary team, with the pros and cons of each therapy has been considered by the patients with regard to their own individual circumstances.
- If RP is performed, pelvic eLND must be performed, because the estimated risk for positive lymph nodes is 15-40%.
- The patient must be informed about the likelihood of a multimodal approach.
- Neoadjuvant androgen depriviation therapy before RP does not provide a significant DSF or OS advantage over prostatectomy alone.

Complications and functional outcome in RP and RALP:

Complication, mean %	Retropubic RP	RALP
Continence*	80-97	89-100
Potency *	51-81	26-63
Peri-operative death	0.1	0.04
Readmission	3.0	3.5
Reoperation	2.3	0.9
Vessel injury	0.04	0.08
Nerve injury	0.4	0.4
Ureteral injury	1.5	0.1
Bladder injury	0.05	0.07
Rectal injury	0.5	0.3
Bowel injury	0	0.09
Ileus	0.8	0.8
Deep vein thrombosis	1.0	0.3
Pulmonary embolism	0.5	0.3
Pneumonia	0.5	0.05
Myocardial infarction	0.2	0.2
Haematoma	1.6	0.7
Lymphocele	3.2	0.8
Anastomotic leakage	10.0	3.5
Fistula	0.07	0.03
Bladder neck/anastomotic stricture	2.2	0.9
Sepsis	0.2	0.1
Wound infection	2.8	0.7

RALP = robot-assisted laparoscopic prostatectomy
RP = radical prostatectomy
***** The major limitations of the included studies were the frequent retrospective study design and the use of different assessment tools preventing a proper comparison between techniques and series.

RADIOTHERAPY

Radical Radiotherapy:

- There have been no randomized studies comparing radical prostatectomy (RP) with either external-beam radiotherapy (EBRT) or brachytherapy for localized prostate cancer (PCa).

- The National Institutes of Health (NIH) consensus statement in 1988 stated that external irradiation offers the same long-term survival results as surgery.
- EBRT provides a QoL at least as good as that following surgery. A recent systematic review has provided a more sophisticated overview of outcomes from trials that meet the criteria for stratifying patients by risk group, standard outcome measures, numbers of patients, and minimum median follow-up period.
- Radiotherapy continues to be an important and valid alternative to surgery alone for curative therapy.
- Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard for EBRT.
- All centres that do not yet offer IMRT should plan to introduce it as a routine method for the definitive treatment of PCa.
- Radiotherapy can be offered to men with intermediate-risk localised prostate cancer.
- Radiotherapy can be offered to men with high-risk localised prostate cancer when there is a realistic prospect of long-term disease control.
- Radiotherapy should be offered for localised prostate cancer a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction.
- Men with intermediate- and high-risk localised prostate cancer should be offered a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone.
- Men with intermediate- and high-risk localised prostate cancer should be offered 6 months of androgen deprivation therapy before, during or after radical external beam radiotherapy.
- Androgen deprivation therapy can be continued for up to 3 years for men with high-risk localised prostate cancer and the benefits and risks of this option should be discussed with them.
- Incidence of late toxicity and outcome by Radiation Therapy Oncology Group (RTOG) grade (from EORTC trial 22863):

Toxicity	Grade 2 %	Grade 3 %	Grade 4 %	Any significant toxicity (> grade 2)%
Cystitis	4.7	0.5	0	5.3
Haematuria	4.7	0	0	4.7
Urinary stricture	4.7	1.3	1	7.1
Urinary incontinence	4.7	0.5	0	5.3
Overall GU toxicity	12.4	2.3	1†	15.9

Toxicity	Grade 2 %	Grade 3 %	Grade 4 %	Any significant toxicity (> grade 2)%
Proctitis	8.2	0	0	8.2
Chronic diarrhoea	3.7	0	0	3.7
Small bowel obstruction	0.2	0.2	0	0.5
Overall GI toxicity	9.5	0.2	0	9.8
Leg oedema	1.5	0	0	1.5
Overall toxicity*	19.0	2.7	1	22.8
Potency after 1 year	--	--	--	55
Secondary malignancy	--	--	--	0.16

- Men with signs or symptoms of radiation-induced enteropathy should be offered care from a team of professionals with expertise in radiation-induced enteropathy.
- The nature and treatment of radiation-induced enteropathy should be included in the training programmes for oncologists and gastroenterologists.
- Full investigations should be carried out, including flexible sigmoidoscopy, in men who have symptoms of radiation-induced enteropathy to exclude inflammatory bowel disease or malignancy of the large bowel and to ascertain the nature of the radiation injury.
- Caution should be used when performing anterior wall rectal biopsy after brachytherapy because of the risk of fistulation.

Immediate (adjuvant) post-operative external irradiation after RP:

There's currently conflicting evidence with biochemical free and overall survival advantages of adjuvant versus salvage radiotherapy in the following post RP patients:

- Patients classified as pT3 pN0.
- Positive margins (highest impact)
- Capsule rupture, and/or invasion of the seminal vesicles

- with a PSA level of < 0.1 ng/mL.

RADICALS trial outcome is awaited. However, currently two options can be offered in the framework of informed consent. These are:

- Immediate adjuvant radiotherapy to the surgical bed (79,81-83,86) after recovery of urinary function; or
- Clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL.
- Immediate post-operative radiotherapy after radical prostatectomy, even to men with margin-positive disease, other than in the context of a clinical trial.

Post radiotherapy biochemical failure:

- After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of > 80%) is any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir.
- In patients with BCF who are candidates for local salvage therapy, prostate multiparametric MRI can guide biopsy.
- Selected patients with localized PCa at primary treatment and histologically proven recurrence without evidence of metastatic disease should be treated with salvage RP (SRP).
- Due to the increased rate of treatment-related complications and side effects, SRP and salvage brachytherapy should only be performed in experienced centres.
- Permanent seed implantation, high-intensity focused ultrasound (HIFU) and cryosurgical ablation are treatment options in carefully selected patients without evidence of metastasis and with histologically proven local recurrence.

Experimental therapeutic options to treat clinically localized PCa:

- High frequency focused ultrasound (HIFU) has been shown to have a therapeutic effect in low-stage PCa, but prospective randomized comparison studies are not available to support its routine use.
- Cryotherapy for PCa compares unfavourably with external-beam radiation for the preservation of sexual function. Similarly this modality should be used in the context of clinical trials.
- Focal therapy of any sort is investigational, and the follow-up and retreatment criteria are unclear.

- In patients who are unfit for surgery or radiotherapy, cryotherapy can be an alternative treatment for PCa but cannot be recommended as a therapeutic alternative outside clinical trials.
- If HIFU is offered, the lack of long-term comparative outcome data (> 10 y) should be discussed with the patient.

LOCALLY ADVANCED PROSTATE CANCER (stage T3-T4, Nx-N0, M0):

DEFERRED TREATMENT

- Only indicated in selected patients with non-poorly differentiated T3 tumours and a life expectancy of less than 10 years.
- Significant risk factors associated with a worse outcome hence indications of active treatment are:
  - patients with a baseline PSA > 50 ng/mL.
  - in patients with a baseline PSA < 50 ng/mL, a PSADT of < 12 months carries the risk of PCa related death (approximately 7.5-fold).

RADICAL RADIOTHERAPY

- In patients with locally advanced PCa T3-4 N0 M0, concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external-beam irradiation for patients with WHO 0-2 performance status, is recommended, as it improves the overall survival.
- In a subset of patients with T2c-T3 N0-X and a Gleason score of 2-6, short-term androgen deprivation therapy ADT before and during radiotherapy can be recommended, as it may favourably influence the overall survival.

ADT monotherapy:

- ADT monotherapy can be offered to patients with locally advanced disease who are unwilling or unable to receive any form of associated local treatment.
- Immediate castration should be considered in the most aggressive situations (PSA > 50 ng/mL, PSADT < 12 months).
- Otherwise a wait-and-see policy with deferred treatment at clinical progression is a reasonable option.

RADICAL PROSTATECTOMY

- RP is optional in highly selected patients with cT3b-4 N0 or any cT N1 PCa in the context of a multimodality approach.
- When nodal involvement is detected after surgery:
  - Adjuvant ADT is recommended when > 2 nodes are involved;
  - Expectant management is optional when the patient has undergone eLND and < 2 nodes show microscopic involvement.

Focal therapeutic options:

High-intensity focused ultrasound and cryotherapy should not be offered to men with locally advanced prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions.

METASTATIC PCa (stage M1):

ANDROGEN DEPREVATION THERAPY (ADT):

- In patients with symptomatic metastatic prostate cancer, ADT is recommended to palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis).

- In patients who are asymptomatic from their metastatic disease:
  - Immediate ADT can be used to defer progression to a symptomatic stage and prevent serious disease progression-related complications.
  - An active clinical surveillance protocol is an acceptable option in clearly informed patients if survival is the main objective.

- Anti-androgens are initially used to reduce the risk of the 'flare-up' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist.

- It may be sufficient to give an anti-androgen for some weeks of concomitant use, starting treatment on the same day as an LHRH analogue is started, or for up to 7 days before the first LHRH analogue injection.

- Anti-androgens as monotherapy can be considered as an option in highly selected and motivated patients with a low PSA.

- Intermittent ADT:
  - When this method is used, it should reproduce what has been used in clinical trials; treatment is usually stopped when the PSA level is < 4 ng/mL (M1) and < 0.5-4 ng/mL (relapsing). Treatment is usually re-started when the PSA is > 4-10 (relapsing) and > 10-20 ng/mL (M1).
  - This can be used in patients with asymptomatic metastatic disease and are very motivated, with a major PSA response after the induction period.
  - Other cohort includes patients relapsing after radiotherapy; patients with a clear response after the induction period.

Contraindications of ADT

Therapy	**Contraindications**	**LE**	**GR**
Bilateral orchiectomy	Psychological reluctance to undergo surgical castration.	3	A
Oestrogens	Known cardiovascular disease.	2b	B
LHRH agonists monotherapy	Patients with metastatic disease at high risk for clinical 'flare-up' phenomenon.	2b	A
ADT, anti-androgen	Localized PCa as primary monotherapy (except in some high-risk localized situations in patients unwilling or unable to receive any form of local treatment).	1b	A

DEFERRED TREATMENT:

- Only indicated in asymptomatic patients with a strong wish to avoid treatment-related side-effects
- If a deferred treatment policy is chosen for a patient with advanced PCa, close follow-up must be possible.

RADICAL RADIOTHERAPY

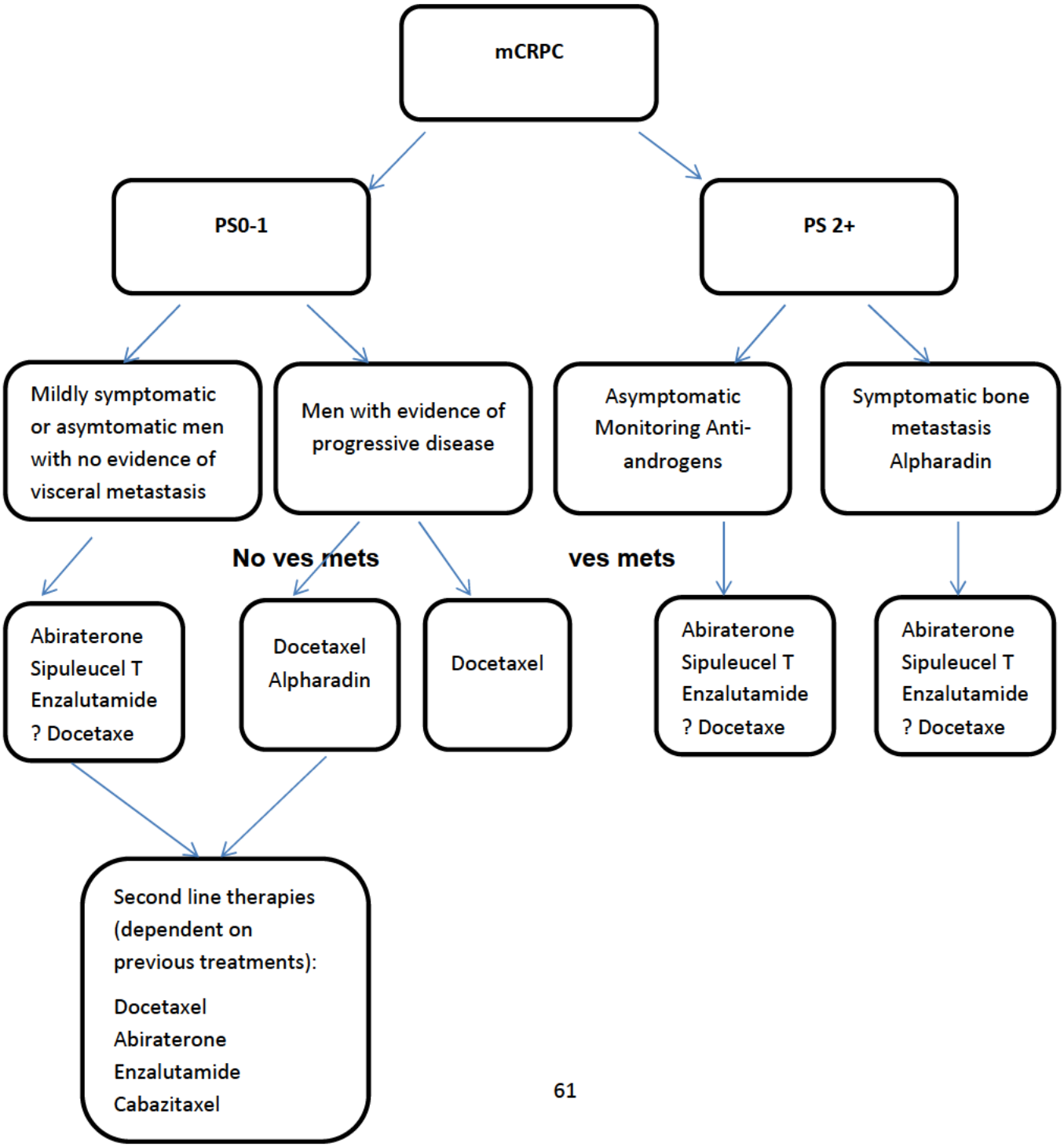
- In patients with very high-risk PCa c-pN1 M0, with no severe comorbidity, pelvic external irradiation and immediate long-term adjuvant hormonal treatment is recommended, as it may improve the overall survival, disease-specific failure rate, metastatic failure rate, and biochemical control.

CASTRATION-RESISTANT PCa (CRPC)

Defined as:

- Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either:
  - Biochemical progression: Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL. or
  - Radiological progression: The appearance of two or more bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in solid tumours).

Flowchart of the potential therapeutic options after PSA progression following initial hormonal therapy:



- Patients with mCRPC should be counselled, managed and treated by a multidisciplinary team.

FOLLOW UP

Guidelines for follow-up of prostate cancer patients with curative intent/watchful waiting:

- Men should be clearly advised with prostate cancer about potential longer-term adverse effects of treatment and when and how to report them.
- Men with prostate cancer who have chosen a watchful waiting regimen with no curative intent should normally be followed up in primary care in accordance with protocols agreed by the local urological cancer MDT and the relevant primary care organisation(s). Their PSA should be measured at least once a year.
- PSA levels for all men with prostate cancer who are having radical treatment should be checked at the earliest 6 weeks following treatment, at least every 6 months for the first 2 years and then at least once a year thereafter.
- DRE is not routinely offered to men with localised prostate cancer while the PSA remains at baseline levels [NICE].
- After radical prostatectomy, a serum PSA level of more than 0.2 ng/mL can be associated with residual or recurrent disease.
- After radiation therapy, a rising PSA level over 2 ng/mL above the nadir PSA, rather than a specific threshold value, is the most reliable sign of recurrent disease.
- Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence.
- Detection of local recurrence by imaging studies is only recommended if it will affect the treatment plan. In most cases, a biopsy is not necessary before second-line therapy.
- Routine bone scans and other imaging studies are not recommended in asymptomatic patients with no signs of biochemical relapse. If a patient has bone pain or other symptoms of disease progression, re-staging should be considered irrespective of the serum PSA level.
- In asymptomatic patients, a disease-specific history and a serum PSA measurement supplemented by DRE are the recommended tests for routine

follow-up. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually [EAU].

- After at least 2 years, follow-up can be performed outside hospital (for example, in primary care) by telephone or secure electronic communications to men with a stable PSA who have had no significant treatment complications, unless they are taking part in a clinical trial that requires formal clinic-based follow-up. Direct access to the urological cancer MDT should be offered and explained.

Guidelines for follow-up of prostate cancer patients on ADT:

- Patients should be evaluated at 3 and 6 months after the initiation of treatment.
- As a minimum, tests should include serum PSA measurement, DRE, serum testosterone, and careful evaluation of symptoms in order to assess the treatment response and side effects.
- In patients undergoing intermittent androgen deprivation, PSA and testosterone should be monitored at set intervals during the treatment pause (one or three months).
- Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given.
- In patients with stage M0 disease with a good treatment response, follow-up is scheduled every 6 months, and as a minimum should include a disease-specific history, DRE and serum PSA determination.
- In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3 to 6 months. As a minimum, this should include a disease-specific history, DRE and serum PSA determination, and is frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements. The testosterone level should be checked, especially during the first year.
- Patients (especially with M1b status) should be advised about the clinical signs that could suggest spinal cord compression.
- When disease progression occurs, or if the patient does not respond to the treatment given, follow-up needs to be individualized.
- In patients with suspected progression, the testosterone level must be checked. By definition, CRPC is based on the assumption that the patient has a testosterone level of at least < 50 ng/mL.
- Routine imaging of stable patients is not recommended.

9.3 PENILE CANCER

Penile carcinoma is mostly a squamous cell carcinoma (SCC) but other types of carcinoma exist as well. It usually originates from the epithelium of the inner prepuce or the glans. Also, penile SCC occurs in several histological subtypes. Penile SCC shares similar pathology with SCC of the oropharynx, the female genitalia (cervix, vagina and vulva) and the anus and it is therefore assumed that it also shares to some extent the natural history.

EPIDEMIOLOGY

- In Western countries, primary penile cancer is uncommon, with an incidence of less than 1.00 per 100,000 males in Europe and the United States.

- Incidence is also affected by race and ethnicity in North America, with the highest incidence of penile cancer found in white Hispanics (1.01 per 100,000), followed by a lower incidence in Alaskan, Native American Indians (0.77 per 100,000), blacks (0.62 per 100,000) and white non-Hispanics (0.51 per 100,000), respectively.

- In contrast, in some other parts of the world such as South America, South East Asia and parts of Africa the incidence of penile cancer is much higher and can represent 1-2% of malignant diseases in men.

- Penile cancer is common in regions with a high prevalence of human papilloma virus (HPV). The annual age-adjusted incidence is 0.7-3.0 per 100,000 men in India, 8.3 per 100,000 men in Brazil and even higher in Uganda, where it is the most commonly diagnosed cancer in men.

- There are no data linking penile cancer to HIV or AIDS.

- In European countries, the overall incidence has been stable from the 1980s until today. Recently, an increased incidence has been reported from Denmark and the UK.

- A longitudinal study from the UK has confirmed a 21% increase in incidence over the period 1979-2009.

- The incidence of penile cancer increases with age, with an age peak during the sixth decade of life. However, the disease does occur in younger men.

RISK FACTORS AND PREVENTION

Risk factors	Relevance
• Phimosis	OR 11-16 versus no phimosis
• chronic penile inflammation (balanoposthitis related to phimosis) • balanitis xerotica obliterans (lichen sclerosus)	Risk
• sporalene and UV-A phototherapy for various dermatologic conditions such as psoriasis	Incidence rate ratio 9.51 with > 250 treatments
• smoking	5-fold increased risk (95% CI: 2.0-10.1) versus nonsmokers
• HPV infection condylomata acuminata	22.4% in verrucous SCC and 36-66.3% in basaloid-warty
• Rural areas, low socio-economic status, unmarried	Risk
• multiple sexual partners early age of first intercourse	3-5-fold increased risk of penile cancer

- Neonatal circumcision reduces the incidence of penile cancer in countries and cultures where this is routinely practiced.
- The lowest incidence of penile cancer is reported from Israel amongst Jews (0.3/100,000/ year).
- Medical circumcision in adult life does not influence the incidence of penile cancer.
- The controversial discussion about any preventive value of neonatal circumcision must take into consideration that circumcision removes about 50% of the tissue that can develop penile cancer.
- The protective effect of neonatal circumcision against invasive penile cancer (OR 0.41) - which does apparently not apply to CIS (OR 1.0) - is much weaker when the analysis is restricted to men without a history of phimosis (OR 0.79, 95% CI 0.29-2).

TNM clinical and pathological classification of penile cancer (2009)

T - Primary Tumour
Tx Primary tumour cannot be assessed T0 No evidence of primary tumour Ta Non-invasive carcinoma Tis Carcinoma in situ T1 Tumour invades subepithelial connective tissue T1a Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2) T1b Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4) T2 Tumour invades corpus spongiosum and/or corpora cavernosa T3 Tumour invades urethra T4 Tumour invades adjacent structures
N - Regional Lymph Nodes
Nx Regional lymph nodes cannot be assessed N0 No palpable or clinically visible inguinal lymph-node N1 Palpable mobile unilateral inguinal lymph node N2 Palpable mobile multiple unilateral or bilateral inguinal lymph nodes N3 Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral
M - Distant Metastasis M0 No distant metastasis M1 Distant metastasis
Pathological classification The pT categories correspond to the clinical T categories. The pN categories are based upon biopsy or surgical excision.
pN - Regional Lymph Nodes
pNX Regional lymph nodes cannot be assessed pN0 No regional lymph node metastasis pN1 Intranodal metastasis in a single inguinal lymph node pN2 Metastasis in multiple or bilateral inguinal lymph nodes pN3 Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of any regional lymph node metastasis
pM - Distant Metastasis
pM0 No distant metastasis pM1 Distant metastasis
G - Histopathological Grading
GX Grade of differentiation cannot be assessed G1 Well differentiated G2 Moderately differentiated G3-4 Poorly differentiated/undifferentiated

Premalignant penile lesions (precursor lesions)

Lesions sporadically associated with SCC of the penis
• Cutaneous horn of the penis • Bowenoid papulosis of the penis • Lichen sclerosus (balanitis xerotica obliterans)
Premalignant lesions (up to one-third transform to invasive SCC)
• Intraepithelial neoplasia grade III • Giant condylomata (Buschke-Löwenstein) • Erythroplasia of Queyrat or Bowen's disease • Paget's disease (intradermal ADK)

Histological subtypes of penile carcinomas, their frequency and outcome

Subtype	**Frequency (% of cases)**	**Prognosis**
common SCC	48-65	depends on location, stage and grade
basaloid carcinoma	4-10	poor prognosis, frequently early inguinal nodal metastasis
warty carcinoma	7-10	good prognosis, metastasis rare
verrucous carcinoma	3-8	good prognosis, no metastasis
papillary carcinoma	5-15	good prognosis, metastasis rare
sarcomatoid carcinoma	1-3	very poor prognosis, early vascular metastasis
mixed carcinoma	9-10	heterogeneous group
pseudohyperplastic carcinoma	< 1	foreskin, related to lichen sclerosus, good prognosis, metastasis not reported
carcinoma cuniculatum	< 1	variant of verrucous carcinoma, good prognosis, metastasis not reported
pseudoglandular carcinoma	< 1	high grade carcinoma, early metastasis, poor prognosis
warty-basaloid carcinoma	9-14	poor prognosis, high metastatic potential (12) (higher than in warty, lower than in basaloid SCC)
adenosquamous carcinoma	< 1	central and peri-meatal glans, high grade carcinoma, high metastatic potential but low mortality
mucoepidermoid carcinoma	< 1	highly aggressive, poor prognosis
clear cell variant of penile carcinoma	1-2	exceedingly rare, associated with HPV, aggressive, early metastasis, poor prognosis, outcome lesion dependent, frequent lymphatic metastasis

DIAGNOSIS AND STAGING

The following guidelines for urgent referral (within two weeks) have been published by the Department of Health:

- Macroscopic haematuria in adults.
- Microscopic haematuria in adults over 50 years.
- Swellings in the body of the testis.
- Palpable renal masses.
- Solid renal masses found on imaging.
- Elevated age-specific prostate specific antigen (PSA) in men with a 10 year life expectancy.
- A high PSA (>20ng/ml) in men with a clinically malignant prostate or bone pain.
- Any suspected penile cancer:
  GPs should refer men with suspicious penile lesions such as growths, swelling at or near the glans, painless ulcers which do not appear to be due to infection, or other unexplained abnormalities such as plaques on the skin or foreskin of the penis, to a local urological cancer team.

Recommendations for the diagnosis and staging of penile cancer

Recommendations	**GR**
Primary tumour: • Physical examination, recording morphology, extent and invasion of penile structures. • MRI with artificial erection in selected cases with intended organ preserving surgery.	**C**
Inguinal lymph nodes: • Physical examination of groins, recording number, laterality and characteristics of inguinal nodes. • If nodes are not palpable, invasive lymph node staging in high-risk patients. • If nodes are palpable, a pelvic CT may be indicated, PET/CT is an option.	**C**
Distant metastases: • In N+ patients, abdomino-pelvic CT scan and chest X-ray are required for systemic staging. • PET/CT scan is an option. • In patients with systemic disease or with relevant symptoms, a bone scan may be indicated.	**C**

TREATMENT

Patients with penile cancer should be managed by specialist penile cancer teams working at the supra-network level. Such teams should serve up to four networks, with a combined population base of at least four million for penile cancer and expect to manage a minimum of 25 new patients each year. The team should include members of the specialist urological cancer team who work in the cancer centre within which it is based, and it should also have access to expertise in plastic surgery.

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

Local care is classed as:
(i) The diagnostic process only.
Local care should be carried out by local teams for their catchment.

It should also be carried out by specialist teams and supranetwork teams for the local catchment of their host locality.

Specialist care is classed as:
(i) Resection (except in cases needing penile reconstruction or lymph node resection).

All resections should be carried out in the host hospital of the team.

(ii) Radiotherapy and chemotherapy. The site(s) where this is carried out should be agreed in the
network guidelines.

Specialist care may be delivered by:

- A specialist urological team without a supranetwork interest in penile cancer provided this is agreed in the network guidelines and with the relevant supranetwork team. It should not be delivered by local urological teams.

- A supranetwork team for referring specialist teams provided this is agreed in the network guidelines.

- The supranetwork team for the local catchment of their host locality.

Supranetwork care is classed as:
Resection in cases needing penile reconstruction or lymph node resection.

All resections should be carried out in one of the hospitals named as part of the facilities of the host locality. All such operations should be carried out in the same hospital.

Supranetwork care should be delivered by the *supranetwork team only.* This is not subject to alteration by the network guidelines.

- The aims of the treatment of the primary penile cancer lesion are complete tumour removal with as much organ preservation as possible while radicality of the treatment should not be compromised.
- A local recurrence in itself has little influence on long-term survival so that organ preservation strategies are justified.
- There are no randomised controlled trials for any of the surgical management options of localised penile cancer, neither are there any observational studies comparing different surgical approaches or studies comparing surgical and non-surgical treatment modalities.
- The available studies all have one or more form of bias such as bias of selection, performance, detection, attrition, selective reporting or publication. Thus, the overall quality of the existing evidence must be regarded as low.
- Penile preservation appears to be superior in functional and cosmetic outcomes and should be offered as the primary treatment modality to men with localised penile cancer.
- Histological diagnosis with local staging must be obtained in all cases, especially if non-surgical treatment modalities are considered
- The treatment of the primary tumour and that of the regional nodes can be done as staged procedures.
- In both cases, it is essential to remove all malignant tissue with negative surgical margins.
- Patients must be counselled about all relevant treatment modalities.
- There are a variety of local treatment modalities for small and localized penile cancer including
    - excisional surgery,
    - external beam radiotherapy,
    - brachytherapy and laser ablation which are used to treat localized invasive disease.

Treatment of superficial non-invasive disease (CIS)

- For penile CIS, topical chemotherapy with imiquimod or 5-FU is an effective first-line treatment.
- Toxicity and adverse events of these topical treatments are relatively low but the efficacy is limited.
- Complete responses have been reported in up to 57% of cases of CIS.
- For the reason of a high rate of persistence and/or recurrence, close and long-term surveillance of such patients is required.
- If topical treatment fails it should not be repeated. Laser treatment can be used for CIS.
- Photodynamic control may be used in conjunction with CO2 laser treatment.
- Alternatively, total or partial glans resurfacing can be offered as a primary treatment modality for CIS and as a secondary treatment in case of treatment failure with topical chemotherapy or laser therapy.
- Glans resurfacing is a surgical technique which consists of complete abrasion of the glandular epithelium with covering by a split skin graft.
- With glans resurfacing for presumed non-invasive disease, up to 20% of patients are found to have superficial invasive disease.

Treatment of invasive disease confined to the glans (category Ta/T1a)

- Penis-preserving strategy is recommended.
- Prior to conservative treatment modalities, it is mandatory to obtain histopathological diagnosis by biopsy.
- All patients must be circumcised before considering conservative non-surgical treatment modalities.
- For tumours confined to the prepuce, radical circumcision alone may be curative, if negative surgical margins are confirmed by definitive histology.
- For all surgical treatment options, the intra-operative assessment of surgical margins by frozen section is recommended as tumour-positive margins lead to local recurrence.
- Total removal of the glans (glansectomy) and prepuce does have the lowest recurrence rate among the treatment modalities for small penile lesions (2%).
- Negative surgical margins are imperative when using penile-conserving treatments and a margin of 5 mm is considered oncologically safe.
- Treatment choice should depend on tumour size, histology including stage and grade, localization especially relative to the meatus, as well as patient preference as there are no documented differences in the long term local recurrence rates between surgery, laser and radiation therapy.

Summary of reported complications and oncological outcomes of local treatments

treatment	complications	local recurrence	nodal recurrence	cancer-specific deaths
Nd:YAG laser	none reported	10-48%	21%	2-9%
CO2-laser	bleeding, meatal stenosis(both < 1%)	14-23%	2-4%	none reported
Lasers (unspecified)	bleeding (8%), local infection 2%	11-26%	2%	2-3%
Moh's micrographic surgery	local infection 3%, meatal stenosis 6%	32%	8%	3-4%
Glans resurfacing	none reported	4-6%	not reported	not reported
Glansectomy	none reported	8%	9%	none reported
Partial penectomy	not reported	4-13%	14-19%	11-27%
Brachytherapy	meastal stenosis> 40%	10-30%	not reported	not reported
Radiotherapy	urethral stenosis 20-35%, glans necrosis10-20%	not reported	not reported	not reported

Recommendations for stage-dependent local treatment of penile carcinoma

Recommendations			
Primary tumour	Organ-preserving treatment is to be considered whenever possible	LE	GR
Tis	• Topical treatment with 5-fluorouracil or imiquimod for superficial lesions with or without photodynamic control. • Laser ablation with CO2 or Nd:YAG laser. • Glans resurfacing.	3	C
Ta, T1a (G1, G2)	• Wide local excision with circumcision CO2 or Nd:YAG laser surgery with circumcision.	3	C

Recommendations			
	• Laser ablation with CO2 or Nd:YAG laser. • Glans resurfacing. Glansectomy with reconstructive surgery, with or without skin grafting. • Radiotherapy by external beam or as brachytherapy for lesions < 4 cm.		
T1b (G3) and T2 confined to the glans	• Wide local excision plus reconstructive surgery, with or without skin grafting. • Laser ablation with circumcision. • Glansectomy with circumcision, with reconstruction. • Radiotherapy by external beam or brachytherapy for lesions < 4 cm in diameter.	3	C
T2 with invasion of the corpora cavernosa	• Partial amputation and reconstruction. • Radiotherapy by external beam or brachytherapy for lesions < 4 cm in diameter.	3	C
T3 with invasion of the urethra	• Partial penectomy or total penectomy with perineal urethrostomy.	3	C
T4 with invasion of other adjacent structures	• Neoadjuvant chemotherapy followed by surgery in responders. Alternative: palliative external beam radiation. • Local recurrence after conservative treatment Salvage surgery with penis-sparing treatment in small recurrences or partial amputation. • Large or high stage recurrence: partial or total amputation	3	C

Management of regional lymph nodes

- The development of lymphatic metastases in penile cancer follows some anatomic rules.
- The inguinal and the pelvic lymph nodes are the regional drainage system of the penis.
- The superficial and deep inguinal lymph nodes are thereby the first regional nodal group reached by lymphatic metastatic spread.
- Spread to the inguinal lymph nodes can be uni- or bilateral from any primary penile cancer.
- The second regional lymph node groups are the ipsilateral pelvic lymph nodes.

- Pelvic nodal disease does not seem to occur without ipsilateral inguinal lymph node metastasis and cross-over metastatic spread from one inguinal side to the other pelvic side has never been reported in penile cancer.
- Further metastatic lymph node spread from the pelvic nodes to paraaortic and paracaval nodes is outside the regional lymph node drainage system of the penis and is therefore classified as systemic metastatic disease.
- The management of regional lymph nodes is decisive for long-term patient survival.
- Cure can be achieved in metastatic disease confined to the regional lymph nodes.
- Lymphadenectomy is the treatment of choice for patients with inguinal lymph node metastases but multimodal treatment combining surgery and polychemotherapy is often indicated.
- Management of the regional lymph nodes should be stage-dependent. In clinically node-negative patients (cN0), there is a definite risk of micro-metastatic lymph node involvement in about 25% of cases which is related to local tumour stage and grade.
- In clinically positive lymph nodes (cN1/cN2), metastatic disease is highly likely and no time should be wasted on antibiotic treatment before surgical treatment.
- With enlarged fixed inguinal lymph nodes (cN3), multimodal treatment by chemotherapy and surgery is indicated. Capsular penetration and extranodal extension in lymph node metastasis even if present in only one node carries a high risk of progression and is classified as pN3 which also requires multimodal treatment.

Recommendations for treatment strategies for nodal metastases

Regional lymph nodes	**Management of regional lymph nodes is fundamental in the treatment of penile cancer**	**LE**	**GR**
No palpable inguinal nodes (cN0)	• Tis, Ta G1, T1G1: surveillance. • > T1G2: invasive lymph node staging by bilateral modified inguinal lymphadenectomy or DSNB.	2a	B
Palpable inguinal nodes (cN1/cN2)	Radical inguinal lymphadenectomy.		
Fixed inguinal lymph nodes (cN3)	• Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders. • Pelvic lymphadenectomy Ipsilateral pelvic lymphadenectomy is indicated if two or more inguinal nodes are involved on one side (pN2) and in extracapsular nodal metastasis (pN3).	2a	B

Regional lymph nodes	Management of regional lymph nodes is fundamental in the treatment of penile cancer	LE	GR
Adjuvant chemotherapy	• Indicated in pN2/pN3 patients after radical lymphadenectomy • Radiotherapy Radiotherapy is not indicated for the treatment of nodal disease in penile cancer.	2b	B

Chemotherapy

- Multimodal treatment can improve patient outcome in many tumour entities.
- The value of adjuvant chemotherapy after radical inguinal lymphadenectomy in node-positive penile cancer has a long-term disease-free survival (DFS) as opposed those without chemotherapy of (84% vs 39% respectively).
- There is limited evidence to support the use of neoadjuvant chemotherapy for patients with fixed, unresectable nodal disease, particularly with a triple combination including cisplatin and a taxane, whenever feasible.

Recommendations for chemotherapy in penile cancer patients

	LE	GR
Adjuvant chemotherapy (3-4 cycles of TPF) is an option for patients with pN2-3 tumours.	2b	C
Neoadjuvant chemotherapy (4 cycles of a cisplatin and taxane-based regimen) followed by radical surgery is recommended in patients with non-resectable or recurrent lymph node metastases.	2a	B
Chemotherapy for systemic disease is an option in patients with limited metastatic load.	3	C

FOLLOW UP

Recommendations for follow-up in penile cancer

	Interval of follow-up Years 1-2	Interval follow-up Years 3-5	Examinations examination and investigations	Minimum duration of follow-up	GR
Primary tumour: penile preserving treatment	3 months	6 months	Regular physician or self examination Repeat biopsy after topical or laser treatment for CIS.	5 years	C
Amputation	3 months	1 year	Regular physician or self examination	5 years	C
Recommendations for follow-up of the inguinal lymph nodes: Surveillance	3 months	6 months	Regular physician or selfexamination	5 years	C
pN0 at initial treatment	3 months	1 year	• Regular physician or self examination. • Ultrasound with FNAB optional.	5 years	C
pN+ at initial treatment	3 months	6 months	• Regular physician or selfexamination • Ultrasound with FNAC optional, • CT/MRI optional.	5 years	C

9.4 Renal Cell Carcinoma

Epidemiology:

- Renal cell carcinoma (RCC) represents 2-3% of all cancers.
- In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney cancer-related deaths in the European Union.
- In Europe, overall mortality rates for RCC increased up to the early 1990s, and stabilised or declined thereafter. Mortality has decreased since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend.
- Different RCC types have specific histopathological and genetic characteristics.
- There is a 1.5:1 male predominance, with peak incidence between 60 and 70 years.
- Having a first-degree relative with kidney cancer also increases the risk of RCC.
- Literature results are inconclusive regarding the association of specific dietary habits and occupational exposure to RCC.
- Moderate alcohol consumption appears to have a protective effect for unknown reasons.
- Effective prophylaxis includes avoidance of cigarette smoking and obesity.

Aetiology:

- Smoking:
  - The RR of RCC for ever-smokers is 1.38 times higher than that for non-smokers
  - A strong dose-response relationship between number of cigarettes smoked and increased risk of RCC has been established; Smokers with a history of ≥20 pack-years have an increased risk of RCC 1.35 times that of never-smokers

- Obesity:
  - Increasing body weight and body mass index (BMI) incrementally increases the risk of developing RCC
  - Being overweight (BMI 25–29.9 kg/m2) increases the risk of RCC by 1.35 times versus BMI

- Hypertension and antihypertensive therapy:
  - The presence of hypertension is estimated to increase the RR of RCC by 1.4–1.9 times compared with normotensive individuals
  - Systolic blood pressure ≥160 mmHg increases the RR of RCC by 2.5 times versus <120 mmHg.

- Diastolic blood pressure ≥100 mmHg increases the RR of RCC by 2.3 times versus <80 mmHg.
- Treatment with diuretics also increases the risk of RCC (OR 1.43), but this is only significant in women

- End-stage renal disease:
  - Patients undergoing dialysis for end-stage renal disease are estimated to have a 3.6 times higher RR of developing renal cancer than healthy individuals.

- Renal cancer syndromes:

Disease	**Renal and other tumours**	**Gene mutation**
Von Hippel–Lindau disease	Clear cell RCC: Clear cell renal cysts Retinal and central nervous system haemangioblastomas, phaeochromocytoma, pancreatic cyst and endocrine tumour, endolymphatic sac tumour, epididymal and broad ligament cystadenomas	VHL
Birt-Hogg-Dubé syndrome	Hybrid oncocytic RCC, chromophobe RCC, oncocytoma, clear cell RCC multiple and bilateral Cutaneous lesions (fibrofolliculoma +++, trichodiscoma, acrochordon), lung cysts, spontaneous pneumothorax, colonic polyps or cancer	Folliculin (FLCN)
Hereditary papillary RCC	Type 1 papillary RCC: multiple and bilateral	MET
Hereditary leiomyomatosis and RCC	Type 2 papillary RCC: solitary and aggressive Uterine leiomyoma and leiomyosarcoma, cutaneous leiomyoma and leiomyosarcoma	Fumarate hydratase
Tuberous sclerosis complex	Angiomyolipoma, clear cell RCC, cyst, oncocytoma: bilateral and multiple Facial angiofibroma, subungual fibroma, hypopigmentation and café au lait spots, cardiac rhabdomyoma, seizure, mental retardation, CNS tubers, lymphangioleiomyomatosis	TSC-1 TSC-2
Familial clear cell RCC	Clear cell RCC	Unknown

Diagnosis:

The following guidelines for urgent referral (within two weeks) have been published by the Department of Health:

- Macroscopic haematuria in adults.
- Microscopic haematuria in adults over 50 years.
- Swellings in the body of the testis.
- Palpable renal masses.
- Solid renal masses found on imaging.
- Elevated age-specific prostate specific antigen (PSA) in men with a 10 year life expectancy.
- A high PSA (>20ng/ml) in men with a clinically malignant prostate or bone pain.
- Any suspected penile cancer.
- Many renal masses remain asymptomatic until the late stages of the disease.
- More than 50% of renal cell carcinomas (RCCs) are detected incidentally when noninvasive imaging is used to investigate a variety of nonspecific symptoms and other abdominal diseases.
- The classic triad of flank pain, gross haematuria and palpable abdominal mass is now rare (<10%).
- Other clinical symptoms include new onset varicocele or bilateral lower extremity oedema; these symptoms should initiate radiological examinations.
- Renal Cell Carcinoma Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs.
- A few symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough.

Investigations:

- Radiological and other investigations of RCC Radiological investigations of RCC include CT imaging, before and after intravenous contrast to verify the diagnosis and provide information on:
    - function and morphology of the contralateral kidney
    - assess tumour extension
    - extrarenal spread
    - venous involvement
    - enlargement of lymph nodes and adrenals.
- Abdominal US and magnetic resonance (MR) imaging are supplements to CT.
- Contrast enhanced US can be helpful in specific cases (e.g., chronic renal failure with a relative contraindication for iodinated or gadolinium contrast media, complex cystic masses, and differential diagnosis of peripheral vascular disorders such as infarction and cortical necrosis).

- Magnetic resonance imaging can be used in patients with possible venous involvement, or allergy to intravenous contrast.
- Chest CT is the most accurate chest staging; a routine chest X-ray should be done as a minimum only.
- Indications of renal biopsy:
  - for histological diagnosis of radiologically indeterminate renal masses
  - to select patients with small renal masses for surveillance approaches
  - to obtain histology before ablative treatments
  - to select the most suitable form of targeted pharmacologic therapy in the setting of metastatic disease.
- Total renal function should always be evaluated.
- In patients with any sign of impaired renal function, a renal scan and total renal function evaluation should be undertaken to optimise the treatment decision.

Staging system:

The current UICC 2009 TNM (Tumour Node Metastasis) classification is recommended for the staging of RCC.

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney
T1a	Tumour ≤ 4 cm in greatest dimension, limited to the kidney
T1b	Tumour > 4 cm but ≤ 7 cm in greatest dimension
T2	Tumour > 7 cm in greatest dimension, limited to the kidney
T2a	Tumour > 7 cm in greatest dimension but ≤ 10 cm
T2b	Tumour > 10 cm limited to the kidney
T3	Tumour extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota's fascia
T3b	Tumour grossly extends into the vena cava below diaphragm
T3c	Tumour grossly extends into vena cava or its wall above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis

N1	Metastasis in a single regional lymph node
N2	Metastasis in more than one regional lymph node
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

Histopathological classification:

Fuhrman nuclear grade is the most commonly used grading system. The most aggressive pattern observed defines the Fuhrman grade. The most common histological subtypes of rCC are below:

Histological subtype	**Frequency (%)**
clear cell RCC	80-90%),
papillary RCC	10-15%),
chromophobe RCC	4-5%
collecting duct carcinoma	1%

- Generally, the RCC types have different clinical courses and responses to therapy.

Recommendations for diagnosis and staging of RCC:

Recommendations for the diagnosis and staging of RCC	GR
The Fuhrman grading system and classification of RCC subtype should be used	B
In a patient with one or more suspicious laboratory or physical findings, the possible presence of RCC should be suspected	B
Contrast-enhanced abdominal CT and MRI are recommended for the work-up of patients with RCC. These are the most appropriate imaging modalities for renal tumour staging prior to surgery	A
A chest CT is most sensitive for assessment of the lung, but at least a plain chest radiograph should be taken for clinical staging	A
In patients at risk for bone metastases (raised alkaline phosphatase level or bone pain), further evaluation with a bone scan is needed	A
Evaluation of renal function is recommended before treatment decision in any patient in whom renal impairment is suspected	B
Percutaneous biopsy is recommended in active surveillance strategies in order to stratify the follow-up according to tumour histology	B

Recommendations for the diagnosis and staging of RCC	GR
Percutaneous biopsy is always required before ablative therapy and systemic therapy without previous pathology	A
When biopsy is indicated, good-quality needle cores should be obtained with a coaxial technique in order to increase the safety of the procedure and maximize its diagnostic yield	B

Recommendations for "other renal tumours":

Recommendations for "Other renal tumours"	LE	GR
Except for angiomyolipomas, most of these less common renal tumours cannot be differentiated from RCC on the basis of radiology and should therefore be treated in the same way as RCC.	3	C
Bosniak cysts ≥ type III should be treated surgically. When possible, a nephron-sparing procedure should be performed in Bosniak type III.	3	C
In oncocytomas verified on biopsy, follow-up is an option.	3	C
In angiomyolipomas, treatment (surgery, thermal ablation, and selective arterial embolisation) can be considered in only very well selected cases. A nephron-sparing procedure is preferred	3	C
In advanced uncommon types of renal tumours, a standardised oncological treatment approach does not exist.	4	C

Bosniak classification of renal cysts:

Bosniak category	Features	Work-up
I	Simple benign cyst with a hairline-thin wall without septa, calcification, or solid components. Same density as water and does not enhance with contrast medium.	Benign
II	Benign cyst that may contain a few hairline-thin septa. Fine calcification may be present in the wall or septa. Uniformly high-attenuation lesions < 3 cm in size, with sharp margins without enhancement.	Benign
IIF	These may contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall. Minimal thickening of the septa or wall. The	Follow-up. Some are malignant.

Bosniak category	Features	Work-up
	cyst may contain calcification, which may be nodular and thick, with no contrast enhancement. No enhancing soft-tissue elements. This category also includes totally intrarenal, non-enhancing, high attenuation renal lesions > 3 cm. Generally well-marginated.	
III	These are indeterminate cystic masses with thickened irregular walls or septa with enhancement.	Surgery or active surveillance Over 50% are malignant
IV	Clearly malignant containing enhancing soft-tissue components.	Surgery. Most are malignant

Guidelines for primary treatment for RCC:

- Based on the available oncological and QoL outcomes, the current evidence suggests that localised renal cancers are best managed by nephron-sparing surgery (partial nephrectomy) rather than by radical nephrectomy, irrespective of the surgical approach.
- Radical nephrectomy with complete removal of the tumour-bearing kidney with perirenal fat and Gerota's fascia is currently recommended only for patients with localised RCC, who are not suitable for nephron-sparing surgery due to locally advanced tumour growth, when partial resection is technically not feasible due to an unfavourable localisation of the tumour or local growth.
- Complete resection of the primary RCC either by open or laparoscopic surgery offers a reasonable chance for cure.
- If pre-operative imaging is normal, routine adrenalectomy is not indicated.
- Lymphadenectomy should be restricted to staging because extended lymphadenectomy does not improve survival.
- In patients who have RCCs with tumour thrombus and no metastatic spread, prognosis is improved after nephrectomy and complete thrombectomy.
- Embolisation of the primary tumour is indicated in patients with gross haematuria or local symptoms (e.g. pain), in patients unfit for surgical intervention, and before surgical resection of large skeletal metastases. No benefit is associated with tumour embolisation before routine radical nephrectomy.

Nephron sparing surgery (NSS):

- Absolute indications for partial nephrectomy are
  - anatomical or functional solitary kidney or
  - bilateral RCC.
- Relative indications are
  - a functioning opposite kidney affected by a condition that might impair renal function and
  - hereditary forms of RCC with a high risk of developing a tumour in the contralateral kidney.
- Elective indications also localised unilateral RCC with a healthy contralateral kidney, which is the recommended approach, when technically feasible, since recurrence-free and long-term survival rates are similar to those for radical nephrectomy.
- Even in selected patients with a tumour diameter of up to 7 cm, nephron-sparing surgery has achieved results equivalent to those of a radical approach.
- If the tumour is completely resected, the thickness of the surgical margin (> 1 mm) does not correlate with the likelihood of local recurrence.
- If RCCs of larger size are treated with nephron-sparing surgery, follow-up should be intensified, as there is an increased risk of intrarenal recurrences.
- These procedures should only be delivered under the care of members of the specialist urology team and this is not subject to change by the network's own guidelines (National Cancer Action Team- Manual of Cancer Services 2011).

Laparoscopic radical and partial nephrectomy:

- Laparoscopic radical and partial nephrectomy Laparoscopic radical nephrectomy has a lower morbidity compared with open surgery.
- It has become an established surgical procedure for RCC.
- Whether done retro- or transperitoneally, the laparoscopic approach must duplicate established, open surgical, oncological principles.
- Long-term outcome data indicate equivalent cancer-free survival rates versus open radical nephrectomy.
- Thus, laparoscopic radical nephrectomy is now considered the standard of care for patients with T1 and T2 RCCs, who are not treatable by nephron-sparing surgery.
- Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial resection is indicated. Laparoscopic and robot assisted nephron-sparing surgery has become available treatment options in experienced hands.
- Laparoscopic partial resection has a risk for longer intraoperative ischaemia time than open partial nephrectomy and therefore carries a higher risk for reduced long-term renal function.
- The oncological outcome seems comparable in available series.

- Robotic-assisted partial nephrectomy requires further evaluation and more mature data before any conclusive technical recommendations can be made.
- Conclusion: Radical nephrectomy, preferably laparoscopic, is recommended for patients with localised RCC, who are not suitable for nephron-sparing surgery. Nephron-sparing surgery is the standard of care despite the surgical approach.

Minimally invasive alternative treatment:

- Minimally invasive techniques, such as ablation with percutaneous radio-frequency, crytherapy, microwave, and high-intensity focused US (HIFU), are suggested alternatives to surgery.
- Microwave therapy should only be used within the context of research.
- Potential advantages of these techniques include reduced morbidity, outpatient therapy, and the ability to treat high-risk patients not fit for conventional surgery.
- These experimental treatments might be recommended for selected patients with small, incidentally found, renal cortical lesions, elderly patients, patients with a genetic predisposition to multiple tumours, patients with a solitary kidney, or patients with bilateral tumours.
- The oncological efficacy remains to be determined for both cryotherapy and RFA, which are the most often used minimally invasive techniques.
- Current data suggest that cryoablation, when performed laparoscopically, results in fewer re-treatments and improved local tumour control compared with RFA.
- Current evidence on the safety and efficacy of percutaneous radiofrequency ablation (RFA) for renal cancer in the short and medium term appears adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit, and provided that patients are followed up in the long term.
- For both treatments, tumour recurrence rates are higher compared with nephron-sparing surgery.
- Further research is needed to determine the oncological success rate and complications associated with these procedures.
- NICE encourages collection and publication of data on the long-term outcomes of these procedures.

Adjuvant therapy:

- Adjuvant tumour vaccination may improve the duration of the progression-free survival (PFS), which is especially important in patients at high risk of metastases, e.g. T3 RCC. Cytokine therapy does not improve survival after nephrectomy.
- Although there is no current data supporting adjuvant therapy with targeting agents, three worldwide phase III randomised trials are ongoing.

- Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery.

Surgical treatment for metastatic RCC (mRCC):

- Nephrectomy of the primary tumour is curative only if surgery can excise all tumour deposits.
- For most patients with mRCC, nephrectomy is palliative.
- In a meta-analysis of two randomised studies, comparing nephrectomy + immunotherapy versus immunotherapy alone, increased long term survival was found in patients who underwent prior nephrectomy.
- For targeting agents, there is no current knowledge whether cytoreductive surgery is advocated before or after successful medical therapy. The CARMENA and SURTIME trials comparing cytoreductive nephrectomy with neoadjuvent/adjuvant (respectively) targeted therapy versus control arms of nephrectomy alone are awaited.
- However, in the absence of available evidence data, cytoreductive nephrectomy is recommended when possible.
- Complete removal of metastases contributes to improved clinical prognosis.
- Metastasectomy should be carried out in patients with resectable disease and a good PS.
- It should also be considered in patients with residual and respectable metastatic lesions, who have previously responded to systemic therapy.

Radiotherapy for metastasis:
For selected patients with non-resectable brain or osseous lesions, radiotherapy can induce significant symptom relief.

Systemic chemotherapy for mRCC:
Chemotherapy as monotherapy should not be considered effective in patients with mRCC.

Immunotherapy for mRCC:

- Interferon-alpha monotherapy is no longer recommended as first-line therapy for mRCC.
- Interferon alpha monotherapy still has a role only in selected cases (good performance status, clear cell type, lung metastases only).
- Interleukin-2 has more side effects than INF-α.
- High-dose IL-2 is associated with durable complete responses in a limited number of patients.

- Interleukin-2 can be considered as monotherapy in selected patients with a good prognosis profile.
- A combination of bevacizumab and IFN-α is more effective than IFNα in treatment-naïve, low-risk and intermediate-risk tumours.
- Vaccination therapy with tumour antigen 5T4 showed no survival benefit over the first-line standard of care.

Recommendations:

Recommendations for immunotherapy	**GR**
Monotherapy with IFN-α or high-dose bolus IL-2 can only be recommended as a first-line treatment for mRCC in selected patients with clear cell histology and good prognostic factors.	A
Bevacizumab + IFN-α is recommended as first-line therapy in low-risk and intermediate-risk patients.	B
Cytokine combinations, with or without additional chemotherapy, do not improve the overall survival in comparison with monotherapy.	A

Drugs targeting VEGF or mammalian target of rapamycin (mTOR):

- Recent advances in molecular biology have led to the development of several novel agents for the treatment of mRCC.
- In sporadic clear cell RCC, HIF accumulation due to von Hippel-Lindau (VHL) inactivation results in overexpression of VEGF and PDGF, both of which promote neoangiogenesis and contributes to the development and progression of RCC.
- At present, several targeting drugs have been approved both in the USA and in Europe for the treatment of mRCC:
- Their general inability to produce durable CRs necessitates chronic treatment in most patients
- The benefits must therefore be weighed against the overall burden of treatment, including acute and chronic toxicity, time and cost.

Recommendations:

Recommendations	**GR**
Sunitinib is recommended as first-line therapy in favorable-risk and intermediate-risk patients.	A
Bevacizumab + IFN-α is recommended as first-line therapy in favourable-risk and intermediate-risk patients.	A
Sorafenib is recommended as a second-line treatment for mRCC after	A

Recommendations	GR
cytokine failure.	
Pazopanib is recommended as first-line or after cytokine failure in favourable-risk and intermediaterisk patients.	A
Temsirolimus is recommended as first-line treatment in poor-risk patients.	A
Everolimus is recommended as second-line treatment after failure of tyrosine kinase inhibitors.	A
Axitinib is recommended as second-line treatment after failure of cytokines or tyrosine kinase inhibitors.	A

EAU recommendations for first and second line systemic therapy in mRCC:

Treatment	Risk or prior treatment	Recommended agent
First-line	Low- or intermediate-risk mRCC	Sunitinib Bevacizumab + IFN-a Pazopanib
	High-risk mRCC	Temsirolimus
Second-line	Prior cytokine therapy	Sorafenib Pazopanib
	Prior VEGFR therapy Prior mTOR inhibitor therapy	Everolimus Clinical trials

Surveillance following surgery for RCC:

- The aim of surveillance is to detect either local recurrence or metastatic disease while the patient is still surgically curable.
- There is no evidence for whether early versus later diagnosis of recurrence improves survival.
- Depending on the availability of new effective treatments, more strict follow-up schedules may be required, particularly as there is a higher local recurrence rate after cryotherapy and RFA.
- At present there is no evidence-based standard for the follow-up of patients with RCC as well as the optimal duration of follow-up.
- It is therefore a need for a surveillance algorithm that monitors patients after treatment for RCC that recognises not only the patient's risk profile but also treatment efficacy.

Algorithm for surveillance following treatment for RCC taking into account patient risk profile and treatment efficacy

Risk profile	**Treatment**	**Surveillance**						
		6 months	1 year	2 years	3 years	4 years	5 years	After 5 years
Low	RN/PN only	US	CT	US	CT	US	CT	Discharge
Inter-mediate	RN/PN/cryo/ RFA	CT	US	CT	US	CT	CT	CT alternate 2 years
High	RN/PN/cryo/ RFA	CT	CT	CT	CT	CT	CT	CT alternate years

Recommendations:

Recommendations	LE	GR
Surveillance after treatment for RCC should be based on a patient's risk factors and the type of treatment delivered.		C
For low-risk disease, CT/MRI can be used infrequently.	4	C
In the intermediate-risk group, intensified follow-up should be performed, including CT/MRI scans at regular intervals in accordance with a risk-stratified nomogram.	4	C
In high-risk patients, the follow-up examinations should include routine CT/MRI scans.	4	C
There is an increased risk of intrarenal recurrences in larger-size (> 7 cm) tumours treated with nephron-sparing surgery, or when there is a positive margin. Follow-up should be intensified in these patients		C

9.5 Testicular Cancer

Background:

- Testicular cancer represents between 1% and 1.5% of male neoplasms and 5% of urological tumours in general, with 3-10 new cases occurring per 100,000 males/per year.
- Data from the Surveillance Epidemiology and End Results (SEER) Program during the years 1973 to 1998 show a continuing increased risk among Caucasian men in the USA only for seminoma.
- Only 1-2% of cases are bilateral at diagnosis.
- There is a clear predominance (90-95%) of germ cell tumours
- Peak incidence is in the third decade of life for non-seminoma, and in the fourth decade for pure seminoma.
- Familial clustering has been observed, particularly among siblings
- Epidemiological risk factors for the development of testicular tumours are:
    - history of cryptorchidism or undescended testis (testicular dysgenesis syndrome)
    - Klinefelter's syndrome
    - familial history of testicular tumours among first-grade relatives (father/brothers)
    - the presence of a contralateral tumour or TIN
    - infertility.

PATHOLOGICAL CLASSIFICATION

The recommended pathological classification (modified from the 2004 version of the World Health Organization [WHO] guidance) is shown below:

- **Germ cell tumours**
    - Intratubular germ cell neoplasia, unclassified type (IGCNU)
    - Seminoma (including cases with syncytiotrophoblastic cells)
    - Spermatocytic seminoma (mention if there is sarcomatous component)
    - Embryonal carcinoma
    - Yolk sac tumour
    - Choriocarcinoma
    - Teratoma (mature, immature, with malignant component)
    - Tumours with more than one histological type (specify percentage of individual components)
- S**ex cord/gonadal stromal tumours**
    - Leydig cell tumour
    - Malignant Leydig cell tumour

  - Sertoli cell tumour - lipid-rich variant - sclerosing - large cell calcifying
  - Malignant Sertoli cell tumour
  - Granulosa cell tumour - adult type - juvenile type
  - Thecoma/fibroma group of tumours
  - Other sex cord/gonadal stromal tumours
    - incompletely differentiated
    - mixed
  - Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma)
- **Miscellaneous non-specific stromal tumours**
  - Ovarian epithelial tumours
  - Tumours of the collecting ducts and rete testis
  - Tumours (benign and malignant) of non-specific stroma.

DIAGNOSIS:

The following guidelines for urgent referral (within two weeks) have been published by the Department of Health:

- Macroscopic haematuria in adults.
- Microscopic haematuria in adults over 50 years.
- Swellings in the body of the testis.
- Palpable renal masses.
- Solid renal masses found on imaging.
- Elevated age-specific prostate specific antigen (PSA) in men with a 10 year life expectancy.
- A high PSA (>20ng/ml) in men with a clinically malignant prostate or bone pain.
- Any suspected penile cancer.

- **Clinical examination.**
- **Testicular imaging:**
  - US serves to confirm the presence of a testicular mass and to explore the contralateral testis.
  - Its sensitivity in detecting a testicular tumour is almost 100%, and it has an important role in determining whether a mass is intra- or extratesticular
  - Ultrasound of the testis has to be performed in young men without a palpable testicular mass who have retroperitoneal or visceral masses or elevated serum human chorionic gonadotrophin (hCG) or AFP or in men consulting for fertility problems
  - Ultrasound may be recommended in the follow-up of patients at risk, when other risk factors than microlithiasis are present (e.g. size < 12 ml or

atrophy, inhomogeneous parenchyma). Solely, the presence of microlithiasis is not an indication for a regular scrotal US
    - MRI of the scrotum offers a sensitivity of 100% and a specificity of 95-100%, but its high cost does not justify its use for diagnosis.
- **Serum tumour markers at diagnosis**
    - AFP (produced by yolk sac cells)
    - hCG (expression of trophoblasts)
    - LDH (lactate dehydrogenase).
- **Inguinal exploration and orchidectomy**
- **Organ-sparing surgery:** indicated in:
    - In synchronous bilateral testicular tumours
    - metachronous contralateral tumours
    - in a tumour in a solitary testis with normal pre-operative testosterone levels
    - organ preserving surgery can be performed when the tumour volume is less than 30% of the testicular volume and surgical rules are respected
    - the rate of associated TIN is high (at least up to 82%)
    - all patients must be treated with adjuvant radiotherapy (16-20 Gy) at some point.

STAGING

Serum tumour markers:

- The mean serum half-life of AFP and hCG is 5-7 days and 2-3 days, respectively.
- Tumour markers have to be re-evaluated after orchidectomy to determine half-life kinetics.
- Marker decline in patients with clinical stage I disease should be assessed until normalisation has occurred.
- Markers before start of chemotherapy are important to classify the patient according to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification.
- The persistence of elevated serum tumour markers after orchidectomy might indicate the presence of metastatic disease (macro- or microscopically), while the normalisation of marker levels after orchidectomy does not rule out the presence of tumour metastases.
- During chemotherapy, the markers should decline; persistence has an adverse prognostic value

Radiological staging:

- Abdominopelvic CT offers a sensitivity of 70-80% in determining the state of the retroperitoneal nodes.
- Magnetic resonance imaging (MRI) produces similar results to CT in the detection of retroperitoneal nodal enlargement.
- MRI can be helpful when abdominopelvic CT or US are inconclusive, when CT is contraindicated because of allergy to contrast media, or when the physician or the patient are concerned about radiation dose.
- There is no evidence to support the use of the fluorodeoxyglucose (FDG)-PET in the staging of testis cancer.
- It is recommended in the follow-up of patients with seminoma with any residual mass at least 6 weeks after chemotherapy in order to decide on watchful waiting or active treatment.
- The use of FDGPET is not recommended in the re-staging of patients with non-seminomatous tumours after chemotherapy.

Recommended tests for staging at diagnosis

Test	**Recommendation**	**GR**
Serum tumour markers	AFP hCG LDH	A
Abdominopelvic CT	All patients	A
Chest CT	All patients	A
Testis US (bilateral)	All patients	A
Bone scan	In case of symptoms	
Brain scan (CT/MRI)	In case of symptoms and patients with metastatic disease with multiple lung metastases and high beta-hCG values	

Further investigations

Fertility investigations: Total testosterone LH FSH Semen analysis	B
Sperm banking should be offered	A

TNM classification for testicular cancer (UICC, 2009):

pT Primary tumour

pTX Primary tumour cannot be assessed

pT0 No evidence of primary tumour (e.g. histological scar in testis)

pTis Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)

pT1 Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade tunica albuginea but not tunica vaginalis

pT2 Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis

pT3 Tumour invades spermatic cord with or without vascular/lymphatic invasion

pT4 Tumour invades scrotum with or without vascular/lymphatic invasion

N Regional lymph nodes clinical

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension

N2 Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension

N3 Metastasis with a lymph node mass more than 5 cm in greatest dimension

pN Pathological

pNX Regional lymph nodes cannot be assessed

pN0 No regional lymph node metastasis

pN1 Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension

pN2 Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumour

pN3 Metastasis with a lymph node mass more than 5 cm in greatest dimension

M Distant metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

M1a Non-regional lymph node(s) or lung

M1b Other sites

S Serum tumour markers

Sx Serum marker studies not available or not performed

S0 Serum marker study levels within normal limits

	LDH (U/l)		hCG (mIU/mL)		AFP (ng/mL)
S1	< 1.5 x N	and	< 5,000	and	< 1,000
S2	1.5-10 x N	or	5,000-50,000	or	1,000-10,000
S3	> 10 x N	or	> 50,000	or	> 10,000

Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group (IGCCCG):

Good-prognosis group Non-seminoma (56% of cases) 5-year PFS 89% 5-year survival 92%	All of the following criteria: • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
Seminoma (90% of cases) 5-year PFS 82% 5-year survival 86%	All of the following criteria: • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate prognosis group Non-seminoma (28% of cases) 5-year PFS 67% 5-year survival 72%	• Testis/retroperitoneal primary • AFP 1,000 - 10,000 ng/mL or • No non-pulmonary visceral metastases • hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN
Seminoma (10% of cases) 5 years PFS 75% 5-year survival 80%	All of the following criteria: • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor prognosis group Non-seminoma (16% of cases) 5-year PFS 41% 5-year survival 48%	Any of the following criteria: • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
Seminoma	No patients classified as poor prognosis

Prognostic factors for occult metastatic disease in testicular cancer

	For seminoma	For non-seminoma
Pathological (for stage I)		
Histopathological type invasion of the primary tumour	• Tumour size (> 4 cm) • Invasion of the rete testis	• vascular/lymphatic • Proliferation rate > 70% • Percentage of embryonal carcinoma > 50%
Clinical (for metastatic disease)		
• Primary location • Elevation of tumour marker levels • Presence of non-pulmonary visceral metastasis		

TREATMENT: STAGE I GERM CELL TUMOURS

Supranetwork Testicular Team

- The minimum catchment population for the specialist treatment of testicular cancer is two million.
- Supranetwork teams for testicular cancer deliver supranetwork care for their referring catchment.
- The minimum catchment population of two million means that currently no cancer network in England should host more than one such team on the basis of their own network population and some networks will not be able to host a team, needing to refer such patients to a team in a neighbouring network.
- In order that supranetwork teams for testicular cancer experience the full range of practice for the disease, they are required to deliver all of the care including local care to at least part of their network, usually the local catchment of their host locality. For testicular teams to add their full potential value to patient care, some surgical procedures and their immediate post-op care are required to be restricted to certain named hospitals.

Stage I seminoma

- After modern staging procedures, about 15-20% of stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchidectomy alone.

Surveillance

- The actuarial relapse rate is in the order of 15-20% at 5 years, and most of the relapses are first detected in infra-diaphragmatic lymph nodes.
- In patients with low risk the recurrence under surveillance is as low as 6%.
- Chemotherapy, according to the IGCCCG classification, is a possible treatment for seminoma relapse under surveillance.
- The overall cancer-specific survival rate reported under surveillance performed by experienced centres is 97-100% for seminoma stage I.
- The main drawback of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes, for at least 5 years after orchidectomy.
- There is a small but clinically significant risk of relapse more than 5 years after orchidectomy for stage I seminoma, which supports the need for long term surveillance.

Adjuvant chemotherapy

- Compared with adjuvant radiotherapy, studies did not show a significant difference with regard to recurrence rate, time to recurrence and survival after a median follow-up of 4 years.
- Adjuvant carboplatin therapy using a dosage of one course AUC 7 is an alternative to radiotherapy or surveillance in stage I seminoma.

Adjuvant radiotherapy

- Seminoma cells are extremely radiosensitive.
- Adjuvant radiotherapy to a para-aortic (PA) field or to a hockeystick field (para-aortic and ipsilateral iliac nodes), with moderate doses (total 20-24 Gy), will reduce the relapse rate to 1-3%.
- After modern radiotherapy, nearly all relapses will first occur outside the irradiated field (supradiaphragmatic lymph nodes or in the lungs).
- Adjuvant irradiation of supradiaphragmatic lymph nodes is not indicated in seminoma stage I. With regard to the irradiation dose, the MRC recently finished a large randomised trial of 20 Gy versus 30 Gy PA radiation in stage I seminoma that showed equivalence for both doses in terms of recurrence rates.
- The rate of severe radiation-induced long-term toxicity is < 2%. Moderate chronic gastrointestinal (GI) side-effects are seen in ~5% of patients, and moderate acute GI toxicity in ~60%.

Retroperitoneal lymph node dissection (RPLND)

- Post RPLND incidence of retroperitoneal relapses is high (9.5%).
- This policy should not be recommended in stage I seminoma.

Risk-adapted treatment

- Using tumour size > 4 cm and rete testis invasion, patients with seminoma stage I may be subdivided into a low-and high-risk group of occult metastatic disease.
- Patients with and without both risk factors have a risk of occult disease of 32% and 12%, respectively.
- These risk factors were introduced by an analysis of retrospective trials (29). A prospective trial based on these risk factors (no risk factors: surveillance; both risk factors: two courses of carboplatin AUC 7) showed the feasibility of a risk-adapted approach.
- Early data with limited follow-up indicate that patients without either risk factor have a 6.0% risk of relapse at 5 years.
- Patients in the high risk group treated with carboplatin experienced a 1.4% relapse rate at mean follow-up of 34 months.
- However, given the fact that cure is achieved in ~100% in patients with stage I seminoma whatever therapy used (adjuvant radiotherapy, adjuvant chemotherapy, or surveillance) and that the relapse rate in large surveillance series not using risk factors is ~15-20%, indicates a risk of over-treatment. Therefore, the therapeutic decision should be shared with an informed patient.

Guidelines for the treatment of seminoma stage I

Guidelines	**GR**
Surveillance is the recommended management option (if facilities available and patient compliant).	A
Carboplatin-based chemotherapy (one course at AUC 7) is recommended.	B
Adjuvant treatment is not recommended for patients at very low risk.	A
Radiotherapy is not recommended as adjuvant treatment.	A

NSGCT stage I

- Up to 30% of NSGCT patients with clinical stage I (CS1) disease have subclinical metastases and will relapse if surveillance alone is applied after orchidectomy

Surveillance

- The largest reports of the surveillance strategy indicate a cumulative relapse rate of ~30%, with 80% of relapses occurring during the first 12 months of follow-up, 12% during the second year and 6% during the third year, decreasing to 1% during the fourth and fifth years, and occasionally even later.

- About 35% of relapsing patients have normal levels of serum tumour markers at relapse.
- About 60% of relapses are in the retroperitoneum. Despite very close follow-up, 11% of relapsing patients presented with large-volume recurrent disease.
- Based on the overall cancer-specific survival data, surveillance within an experienced surveillance programme may be offered to patients with non-risk stratified clinical stage I non-seminoma as long as they are compliant and informed about the expected recurrence rate as well as the salvage treatment.

Primary chemotherapy

- Two courses of chemotherapy with cisplatin, etoposide and bleomycin (PEB) as primary treatment for high-risk patients (having ~50% risk of relapse) are recommended , with a relapse rate of only 2.7% was reported, with very little long-term toxicity.
- Adjuvant chemotherapy do not seem to adversely affect fertility or sexual activity.
- Long term (> 20 years) side effects of adjuvant chemotherapy in this setting are currently unknown.
- It is important to be aware of slow-growing retroperitoneal teratomas after primary chemotherapy.

Risk-adapted treatment

- It is based on the risk factor vascular invasion.
- Risk-adapted treatment is an equally effective alternative treatment of choice in CS1 NSGCT.
- If applied, patients with vascular invasion are recommended to undergo adjuvant chemotherapy with two cycles of PEB, and patients without vascular invasion are recommended to undergo surveillance.
- The Swedish-Norwegian Testicular Cancer Project (SWENOTECA) recently showed that in a large population-based study with a risk-adapted approach within a management programme and a median follow-up of 4.7 years, the relapse rate was 3.2% for patients with vascular invasion treated with only one adjuvant PEB.
- Taken together, ~300 patients with high-risk CS I have been adjuvantly treated with 1 x PEB with a follow-up of > 5 yrs. As long as 1 x PEB has not been proven superior or at least equivalent to 2 courses PEB, this adjuvant treatment cannot be recommended outside of a clinical trial or a prospective registry.

Retroperitoneal lymph node dissection

- If performed, ~30% of patients are found to have retroperitoneal lymph node metastases, which corresponds to pathological stage II (PS2).
- 10% of the PS1 patients relapse at distant sites.
- The main predictor of relapse in CS1 NSGCT is histopathological evidence of vascular invasion by tumour cells in, or near, the primary tumour in the testis.
- For CS1, patients without vascular invasion have only a 15-20% risk of relapse on surveillance, compared with a 50% relapse rate in patients with vascular invasion.
- The risk of relapse for PS1 patients is < 10% for those without vascular invasion and ~30% for those with vascular invasion.
- If two (or more) courses of cisplatin-based chemotherapy are given adjuvant to RPLND in PS2 cases, the relapse rate is reduced to < 2%, including teratoma relapse).
- The risk of retroperitoneal relapse after a properly performed nerve-sparing RPLND is very low (< 2%), as is the risk of ejaculatory disturbance or other significant side-effects.
- If there is a rare indication to perform a staging RPLND, a laparoscopic or robot-assisted RPLND is feasible in expert hands. This minimal-invasive approach cannot be recommended as a standard approach outside of a specialised laparoscopic centre.
- In a randomised comparison of RPLND with one course of PEB chemotherapy, adjuvant chemotherapy significantly increased the 2-year recurrence-free survival to 99.41% (confidence interval [CI] 95.87%, 99.92%) as opposed to surgery, which had a 2-year recurrence-free survival of 92.37% (CI 87.21%, 95.50%).
- Therefore, one course of adjuvant PEB is superior to RPLND with regard to recurrence rates in patients unstratified for risk factors . In the SWENOTECA data mentioned in section 7.3.3 it was also found that one adjuvant PEB reduced the number of recurrences to 3.2% in the high-risk and to 1.4% in the low-risk patients.

CS1S with (persistently) elevated serum tumour markers

- If the marker level increases after orchidectomy, the patient has residual disease. If RPLND is erformed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum (165). An
- US examination of the contralateral testicle must be performed, if this was not done initially.
- The treatment of true CS1S patients is still controversial. They may be treated with three courses of primary PEB chemotherapy and with follow-up as for CS1B patients after primary chemotherapy, or by RPLND. The presence of vascular invasion may strengthen the indication for primary chemotherapy as most CS1S with vascular invasion will need chemotherapy sooner or later anyway.

Guidelines for the treatment of NSGCT stage I

NSGCT stage 1	**GR**
CS1 risk-adapted treatments based on vascular invasion or surveillance without using risk factors are recommended treatment options.	A
Risk-adapted treatments for CS1 based on vascular invasion	
CS1A (pT1, no vascular invasion): low risk	
If the patient is willing and able to comply with a surveillance policy, long-term (at least 5 years) close follow-up should be recommended.	A
In low-risk patients not willing (or suitable) to undergo surveillance, adjuvant chemotherapy or nerve-sparing RPLND are treatment options. If RPLND reveals PN+ (nodal involvement) disease, chemotherapy with two courses of PEB should be considered.	A
CS1B (pT2-pT4): high risk	
Primary chemotherapy with two courses of PEB should be recommended (one course of PEB within a clinical trial or registry).	A
Surveillance or nerve-sparing RPLND in high-risk patients remains an option for those not willing to undergo adjuvant chemotherapy. If pathological stage II is revealed at RPLND, further chemotherapy should be considered.	A

TREATMENT: METASTATIC GERM CELL TUMOURS

The treatment of metastatic germ cell tumours depends on:

- the histology of the primary tumour;
- prognostic groups as defined by the IGCCCG.

Low-volume metastatic disease (stage IIA/B)
Seminoma:

- The standard treatment for stage IIA/B seminoma has been radiotherapy.
- The radiation dose delivered in stage IIA and IIB is approximately 30 Gy and 36 Gy, respectively.
- The standard radiation field compared with stage I will be extended from the PA region to the ipsilateral iliac field (the hockey-stick field).
- Overall survival is almost 100%. Conversely, dose reduction to 27 Gy has been associated with 11% of relapses.

Non-seminoma

- Initial chemotherapy is recommended in all advanced cases of NSGCT (except for stage II NSGCT disease without elevated tumour markers, which alternatively can be managed by primary RPLND or surveillance to clarify stage).
- If surveillance is chosen, one follow-up after 6 weeks is indicated to document whether the lesion is growing, remaining stable or shrinking.
    - A shrinking lesion is likely to be of non-malignant origin and should be observed further.
    - A stable or growing lesion indicates either teratoma or an undifferentiated malignant tumour.
    - If the lesion is growing without a corresponding increase in the tumour markers AFP or beta-hCG, RPLND should be performed by an experienced surgeon because of suspected teratoma.
    - Patients with a growing lesion and a concomitant increase in the tumour markers AFP or beta-hCG should not undergo surgery; they require chemotherapy with PEB according to the treatment algorithm for patients with metastatic disease and IGCCCG recommendations.
- An alternative to the surveillance strategy in marker-negative II A/B non-seminoma with suspicion of an undifferentiated malignant tumour is a (CT-guided) biopsy, if technically possible.
- There is insufficient published data on PET scans in this situation.
- Patients not willing to undergo primary chemotherapy have the option of primary nerve-sparing RPLND with adjuvant chemotherapy (two cycles of PEB) in case of metastatic disease.
- Primary chemotherapy and primary RPLND are comparable options in terms of outcome but side-effects and toxicity are different, allowing for involvement of the patient in selecting the treatment of choice. The cure rate with either approach will be close to 98%.

Advanced metastatic disease

- The primary treatment of choice for advanced disease is three or four cycles of PEB combination chemotherapy, depending on the IGCCCG risk classification. This regimen has proven superiority to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease.
- Good prognosis group (IGCCCG Classification):
    - standard treatment consists of three cycles of PEB
    - in very selected cases where bleomycin is contraindicated, four cycles of EP.
- Intermediate prognosis group (5-year survival rate of ~80%):
    - four cycles of PEB as standard treatment.
- Poor prognosis group (5-year progression-free survival is 45-50%):
    - standard treatment consists of four cycles of PEB, or etoposide and ifosfamide (PEI) with similar effect but more toxicity.

- poor-prognosis patients should be transferred to a reference centre because a better outcome was reported for intermediate and poor prognosis patients who had been treated within a clinical trial in a high volume centre.
- There are no general recommendations for treatment modifications for patients with a poor general condition (Karnofsky < 50%) or extended liver infiltration (> 50%).
- Patients with extended pulmonary infiltration are at risk for acute respiratory distress syndrome: adapting the doses of the PEB regimen in the first cycle of chemotherapy (only 3 days of EP without bleomycin) was suggested to reduce the risk of early death in this setting.

Residual tumour resection

- A residual mass of seminoma should not be primarily resected, irrespective of the size, but controlled by imaging investigations and tumour markers.
- FDG-PET has a high negative predictive value in patients with residual masses after treatment of seminoma but false positive results can be a problem and scans should not be performed < 2 months after chemotherapy.
- In patients with residuals of > 3 cm, FDG-PET should be performed in order to gain more information on the viability of these residuals.
- In patients with residuals of < 3 cm, the use of FDG-PET is optional.
- On progression, salvage therapy is indicated (chemotherapy, salvage surgery, radiotherapy) .
- In patients with concurrent hCG elevation, progressing seminoma after first-line chemotherapy should be treated by salvage chemotherapy (or radiotherapy if only small volume recurrence is present).
- Progressing patients without hCG progression should undergo histological verification (e. g. by biopsy or open surgery) before salvage chemotherapy is given. In the case of non-seminoma and complete remission after chemotherapy (no tumour visible), residual tumour resection is not indicated.
- The long-term relapse rate in this patient group is 6-9%, however, one third of the late relapsing patients will not survive.
- In the case of any visible residual mass and marker normalisation, surgical resection is indicated. In patients with lesions < 1 cm, there still is an increased risk of residual cancer or teratoma although the role of surgery in this setting is debated.
- In persistent larger volume retroperitoneal disease, all areas of primary metastatic sites must be completely resected within 4-6 weeks of completion of chemotherapy.
- If technically feasible, a nerve-sparing procedure should be performed.

- Overall, following PEB induction chemotherapy, only 10% of residual masses contain viable cancer, 50% contain mature teratoma, and 40% contain necrotic-fibrotic tissue.
- As yet, no imaging investigations, including PET or a prognosis model, are able to predict histological differentiation of the non-seminomatous residual tumour. Thus, residual tumour resection is mandatory in all patients with residual disease > 1 cm.
- The extent of surgery should be based on the risk of relapse of an individual patient and quality of life issues. If possible, all the masses should be resected, because a complete resection, in the setting of viable malignant cells, is more critical than recourse to post-operative chemotherapy.
- There is growing evidence that “template” resections in selected patients yield equivalent long-term results compared to bilateral systematic resections in all patients.
- Mere resection of the residual tumour (so called “lumpectomy”) should not be performed.
- The histology may diverge in different organ sites. Resection of contralateral pulmonary lesions is not mandatory in case pathologic examination of the lesions from the first lung shows complete necrosis.

Consolidation chemotherapy after secondary surgery

- After resection of necrosis or mature/immature teratoma, no further treatment is required.
- In the case of incomplete resection of other germ cell tumour pathologies, two adjuvant cycles of conventionally dosed cisplatin-based chemotherapy may be given in certain subgroups (e.g. ‘poor prognosis’ patients).
- After complete resection of ‘vital’ tumour < 10% of the total volume, especially in patients with an initially good prognosis group according to IGCCCG, the relapse rate is very low and adjuvant chemotherapy is not beneficial for preventing further relapse.
- The prognosis will definitely deteriorate if vital malignant neoplasm is found in resection specimens after second- and third-line chemotherapy. In this latter situation, post-operative chemotherapy is not indicated and is unable to improve the prognosis.

Systemic salvage treatment for relapse or refractory disease

- Cisplatin-based combination salvage chemotherapy will result in long-term remissions for about 50% of the patients who relapse after first-line chemotherapy (255). The.

- Regimens of choice are four cycles of PEI/VIP (etoposide, ifosfamide, cisplatin), four cycles of TIP (paclitaxel, ifosfamide, cisplatin) or four cycles of VeIP (vinblastine, ifosfamide, cisplatin)
- Due to the lack of evidence, it is therefore of the utmost importance that these rare patients are treated within clinical trials and at experienced centres.

Treatment of brain metastases

- Brain metastases occur in the frame of a systemic relapse and rarely as an isolated relapse.
- The longterm survival of patients presenting with brain metastases at initial diagnosis is poor (30-40%)
- 5-year survival-rate for brain metastasis as a recurrent disease is even poorer (2-5%)
- Chemotherapy is the initial treatment in this case, and some data support the use of consolidation radiotherapy, even in the case of a total response after chemotherapy.
- Surgery can be considered in the case of a persistent solitary metastasis, depending on the systemic state, the histology of the primary tumour and the location of the metastasis.

FOLLOW-UP AFTER CURATIVE THERAPY

Recommended follow-up schedule in a surveillance policy: stage I non-seminoma

Procedure	**Year**	**Year**	**Year**	**Year**
	1	**2**	**3-5**	**6-10**
Physical examination	4 times	4 times	Once/year	Once/year
Tumour markers	4 times	4 times	Once/year	Once/year
Plain radiography chest	Twice	Twice		
Abdominopelvic CT	Twice (at 3 and 12 months)			

Recommended follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy: stage I non-seminoma

Procedure	**Year**	**Year**	**Year**	**Year**

	1	2	3-5	6-10
Physical examination	4 times	4 times	Once/year	Once/year
Tumour markers	4 times	4 times	Once/year	Once/year
Plain radiography chest	Twice	Twice		
Abdominopelvic CT	Once	Once		

Recommended follow-up schedule for post-orchidectomy surveillance, radiotherapy or chemotherapy: stage I seminoma

Procedure	**Year**	**Year**	**Year**	**Year**
	1	**2**	**3-5**	**6-10**
Physical examination	4 times	4 times	Once/year	Once/year
Tumour markers	4 times	4 times	Once/year	Once/year
Plain radiography chest	Twice	Twice		
Abdominopelvic CT	Once	Once		

Recommended minimum follow-up schedule in advanced NSGCT and seminoma

Procedure	**Year**	**Year**	**Year**	**Year**
	1	**2**	**3-5**	**Thereafter**
Physical examination	4 times	4 times	Twice/year	Once/year
Tumour markers	4 times	4 times	Twice/year	Once/year
Plain radiography chest	Twice	Twice	Twice/year	Once/year
Abdominopelvic CT	Twice	Twice	As indicated	As indicated
Chest CT	As indicated	As indicated	As indicated	As indicated
Brain CT	As indicated	As indicated	As indicated	As indicated

9.6 Upper Urinary Tract Urothelial Cell Carcinomas

Epidemiology:

- Upper urinary tract urothelial cell carcinomas (UUT-UCCs) are uncommon and account for only 5-10% of urothelial carcinomas
- The estimated annual incidence of UUT-UCCs in Western countries is about one or two new cases per 100,000 inhabitants.
- Pyelocaliceal tumours are about twice as common as ureteral tumours.
- In 8-13% of cases, concurrent bladder cancer is present.
- Recurrence of disease in the bladder occurs in 30-51% of UUT-UCC patients
- Recurrences in the contralateral upper tract are observed in 2-6%.
- 60% of UUT-UCCs are invasive at diagnosis.
- Upper urinary tract urothelial cell carcinomas have a peak incidence in people in their 70s and 80s, and UUT-UCC is three times more prevalent in men than in women.
- There are familial/hereditary cases of UUT-UCCs linked to hereditary nonpolyposis colorectal carcinoma (HNPCC)

Risk factors:

- Tobacco and occupational exposure remain the principal exogenous risk factors for developing these tumours. Exposure to tobacco increases the relative risk of developing a UUT-UCC from 2.5 to 7
- UUT-UCC “amino tumours” are related to occupational exposure to certain aromatic amines. These aromatic hydrocarbons are used in many industries (e.g., dyes, textiles, rubber, chemicals, petrochemicals, and coal). They are responsible for the carcinogenicity of certain chemicals, including benzidine and β-naphthalene. The estimated risk (odds ratio) of developing UCC after exposure to aromatic amines is 8.3.
- Upper urinary tract tumours resulting from phenacetin consumption almost disappeared after the product was banned in the 1970s.
- Although the incidence of Balkan endemic nephropathy is also on the decline, roles have been proposed for aristolochic acid and the consumption of Chinese herbs in the physiopathology and induction, respectively, of this nephropathy.
- One polymorphism specific to UUT-UCC has been reported so far. A variant allele, SULT1A1*2, which reduces sulfotransferase activity, enhances the risk of developing UUT-UCC.
- Epidermoid carcinoma of the UUT is associated with chronic inflammatory and infectious disease arising from stones in the UUT.

TNM classification of UUT-UCC (2009)

T - Primary Tumour
Tx Primary tumour cannot be assessed

T0 No evidence of primary tumour Ta Non-invasive papillary carcinoma Tis Carcinoma in situ T1 Tumour invades subepithelial connective tissue T2 Tumour invades muscle T3 (Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat T4 Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional Lymph Nodes
Nx Regional lymph nodes cannot be assessed N0 No regional lymph-node metastasis N1 Metastasis in a single lymph node 2 cm or less in the greatest dimension N2 Metastasis in a single lymph node more than 2 cm but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension N3 Metastasis in a lymph node more than 5 cm in greatest dimension
M - Distant Metastasis M0 No distant metastasis M1 Distant metastasis

World Health Organization grading for bladder cancer

1973 WHO grading
Urothelial papilloma
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated

Diagnosis:

The following guidelines for urgent referral (within two weeks) have been published by the Department of Health:

- Macroscopic haematuria in adults.
- Microscopic haematuria in adults over 50 years.
- Swellings in the body of the testis.
- Palpable renal masses.
- Solid renal masses found on imaging.
- Elevated age-specific prostate specific antigen (PSA) in men with a 10 year life expectancy.
- A high PSA (>20ng/ml) in men with a clinically malignant prostate or bone pain.
- Any suspected penile cancer.

Imaging:

CT Urogram (CTU)

- CTU is the gold standard for exploration of the upper urinary tract and has replaced intravenous excretory urography.
- It must be conducted under optimal conditions, particularly with acquisition of an excretory phase.
- The detection rate of UUT-UCC is satisfactory for this type of imaging: 96% sensitivity and 99% specificity for polypoid lesions between 5 and 10 mm.
- Sensitivity drops to 89% for polypoid lesions < 5 mm and 40% for polypoid lesions < 3 mm.

Magnetic resonance imaging (MRI):

- MRI urography is indicated in patients who cannot be subjected to a CTU.
- The detection rate of MRI is 75% after contrast injection for tumours < 2 cm.
- MRI urography with contrast injection, however, remains contraindicated in selected patients with severe renal impairment (< 30 ml/min creatinine clearance) due to the risk of nephrogenic systemic fibrosis.
- Magnetic resonance urography without contrast is less helpful compared with CTU in diagnosing UUT-UCCs.

Cystoscopy and urinary cytology

- Positive urine cytology is highly suggestive of UUT-UCC when bladder cystoscopy is normal and if CIS of the bladder or prostatic urethra has been excluded.
- Cytology is less sensitive for UUT-UCC than for bladder tumours, even for high-grade lesions, and it should ideally be performed in situ (i.e. in the renal cavities).
- A positive cytology may be valuable in staging because it has been associated with muscle-invasive and nonorgan-confined disease.

Diagnostic ureteroscopy

- Ureteroscopy is a better approach to diagnose UUT-UCCs.
- Flexible ureteroscopy is especially useful when there is diagnostic uncertainty, when conservative treatment is being considered, or in patients with a solitary kidney.
- The possible advantages of ureteroscopy should be discussed in the preoperative assessment of any UUT-UCC patient. Combining ureteroscopic biopsy grade, ipsilateral hydronephrosis, and urinary cytology may help decision making on radical nephroureterectomy (RNU) versus endoscopic treatment.

Guidelines for the diagnosis of UUT-UCC

Recommendations	GR
Urinary cytology	A
Cystoscopy to rule out a concomitant bladder tumour	A
CTU	A

Prognostic factors:

- Upper urinary tract urothelial cell carcinomas that invade the muscle wall usually have a very poor prognosis.
- The 5-yr specific survival is < 50% for pT2/pT3 and < 10% for pT4.
- Tumour stage and grade: the primary recognised prognostic factors.
- Age: poor prognosis with advanced age at diagnosis.
- Gender: no relation.
- Tumour location: no relation.
- Lymphovascular invasion: is present in approximately 20% of UUT-UCCs and an independent predictor of survival.
- Extensive tumour necrosis: is an independent predictor of clinical outcomes in patients who undergo RNU.
- The tumour architecture (e.g., papillary vs. sessile) of UUT-UCCs appears to be associated with prognosis after RNU. A sessile growth pattern is associated with worse outcomes (LE: 3) (8,63,69).
- The presence of concomitant CIS in patients with organ-confined UUT-UCC is associated with a higher risk of recurrent disease and cancer-specific .

Treatment

Localised disease:

- Radical nephroureterectomy (RNU)with excision of the bladder cuff is the gold standard treatment for UUT-UCCs, regardless of the location of the tumour in the upper urinary tract
- The RNU procedure must comply with oncologic principles, which consist of preventing tumour seeding by avoiding entry into the urinary tract during tumour resection.
- Resection of the distal ureter and its orifice is performed because it is a part of the urinary tract with considerable risk of recurrence.
- After removal of the proximal part, it is almost impossible to image or approach it by endoscopy during follow-up.
- Plucking/endoscopic resection of the distal ureter (apart from ureteral stripping) are non-inferior to excision of the bladder cuff.