- A delay > 45 d between diagnosis and resection of the tumour constitutes a risk for disease progression.
- Lymph node dissection associated with RNU is of therapeutic interest and allows for optimal staging of the disease.
- Lymphadenectomy in pN+ allows for reduction of the tumour mass to guide patients towards adjuvant treatments.
- Anatomic sites of lymphadenectomy have not yet been clearly defined.
- The number of lymph nodes to be removed depends on the tumour location.
- Lymphadenectomy appears to be unnecessary in cases of TaT1 UUT-UCCs.
- The safety of laparoscopic RNU has not yet achieved final proof. In early experience, there were reports of retroperitoneal metastatic dissemination and dissemination along the trocar pathway when large tumours were manipulated in a pneumoperitoneal environment.
- Recent data, however, show a tendency towards equivalent oncologic results between laparoscopic RNU and open surgery.
- In addition, the laparoscopic approach appears to be superior to open surgery only with regard to functional outcomes.
- When considering laparoscopic RNU the following precautions must be considered:
    - Entering the urinary tract should be avoided.
    - Direct contact of the instruments with the tumour should be avoided.
    - Laparoscopic RNU must take place in a closed system.
    - Morcellation of the tumour should be avoided, and an endobag is necessary to extract the tumour.
    - The kidney and ureter must be removed en bloc with the bladder cuff.
    - Invasive, large (T3/T4 and/or N+/M+), or multifocal tumours are contraindications for laparoscopic RNU, until proven otherwise.

Guidelines for radical management of UUT-UCC: radical nephroureterectomy

Indications for RNU for UUT-UCC	GR
Suspicion of infiltrating UUT-UCC on imaging	B
High-grade tumour (urinary cytology)	B
Multifocality (with two functional kidneys)	B
Techniques for RNU in UUT-UCC Open and laparoscopic access are equivalent in terms of efficacy	B
Bladder cuff removal is imperative	A
Several techniques for bladder cuff excision are acceptable except stripping	C
Lymphadenectomy is recommended in case of invasive UUT-UCC	C

Conservative surgery

- Conservative surgery for low-risk UUT-UCCs allows for preservation of the upper urinary renal unit while sparing the patient the morbidity associated with open radical surgery
- Conservative management of UUT-UCCs can be considered in imperative cases (renal insufficiency, solitary functional kidney) or in elective cases (i.e. when the contralateral kidney is functional) for low-grade, low-stage tumours.
- The choice of technique depends on technical constraints, the anatomic location of the tumour, and the experience of the surgeon.
    - Ureteroscopy: Endoscopic ablation can be considered in highly selected cases (96,97,98) and in these situations:
        - A flexible rather than a rigid ureteroscope, laser generator, and pliers (pluck) for biopsies are available.
        - The patient is informed of the need for closer, more stringent surveillance.
        - A complete resection is advocated.
    - Segmental resection:
        - It provides adequate pathologic specimens for definitive staging and grade analysis while also preserving the ipsilateral kidney.
        - Segmental resection is possible for the treatment of low- and high-risk tumours of the distal ureter .
        - It is necessary, however, to ensure that the area of tissue around the tumour is not invaded.
        - Segmental resection of the iliac and lumbar ureter is associated with a failure rate greater than that for the distal pelvic ureter.
        - Open resection of tumours of the renal pelvis or calices has almost disappeared.
        - Resection of pyelocaliceal tumours is technically difficult, and the recurrence rate is higher than for tumours of the ureter.
    - Percutaneous access:
        - It is considered for low-grade or non-invasive UUT-UCCs in the renal cavities.
        - This treatment option may be offered to patients with low-grade tumours in the lower caliceal system that are inaccessible or difficult to manage by ureteroscopy.
        - A theoretical risk of seeding exists in the puncture tract and in perforations that may occur during the procedure.
        - This approach, however, is being progressively abandoned due to enhanced materials and advances in distal-tip deflection of recent ureteroscopes.
    - Adjuvant topical agents:
        - BCG or mitomycin C in the urinary tract by percutaneous nephrostomy via a three-valve system open at 20 cm (after

complete eradication of the tumour), or even through a ureteric stent is technically feasible after conservative treatment of UUT-UCCs or for the treatment of CIS.

- The medium-term results are similar to those observed for the treatment of bladder tumours but have not been confirmed in long-term studies.

Guidelines for conservative management of UUT-UCC

Indications for conservative management of UUT-UCC	**GR**
Unifocal tumour	B
Small tumour	B
Low-grade tumour (cytology or biopsies)	B
No evidence of an infiltrative lesion on MDCTU	B
Understanding of close follow-up	B
Techniques used in conservative management of UUT-UCC	
Laser should be used in case of endoscopic treatment	C
Flexible ureteroscopy is preferable over rigid ureteroscopy	C
Open partial resection is an option for pelvic ureteral tumours	C
A percutaneous approach remains an option in small low-grade caliceal tumours unsuitable for ureteroscopic treatment	C

Advanced disease:

- There are no benefits of RNU in metastatic (M+) disease, although it can be considered a palliative option.
- Because UUT-UCCs are urothelial tumours, platinum-based chemotherapy is expected to produce similar results to those seen in bladder cancer.
- Limited evidence to support the used of neoadjuvant chemotherapy in RNU.
- Adjuvant chemotherapy (depending on patient fitness and renal function) achieves a recurrence-free rate of up to 50% but has minimal impact on survival.
- Adjuvant radiotherapy may improve local control of the disease.
- When given in combination with cisplatinum, it may result in a longer disease-free survival and longer overall survival.
- Radiation therapy appears to be scarcely relevant nowadays both as a unique therapy and associated with chemotherapy as a tumour adjuvant.

Follow-up

- Strict follow-up of UUT-UCC patients after surgical treatment is mandatory to detect metachronous bladder tumours.
- Bladder recurrence after treatment of a primary UUT-UCC varies considerably from 15% to 50%. Thus the bladder should be observed in all cases.
- A prior history of bladder cancer and upper tract tumour multifocality are the risk factors most often reported for bladder tumours following UUT-UCCs.
- The surveillance regimen is based on cystoscopy and urinary cytology for at least 5 yr.
- When conservative treatment is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of recurrence.

Guidelines for follow-up of UUT-UCC patients after initial treatment

After RNU, over at least 5 yr	**GR**
Noninvasive tumour Cystoscopy/urinary cytology at 3 mo and then yearly	C
MDCTU every year	C
Invasive tumour Cystoscopy/urinary cytology at 3 mo and then yearly	C
MDCTU every 6 mo over 2 yr and then yearly	C
After conservative management, over at least 5 yr	
Urinary cytology and MDCTU at 3 mo, 6 mo, and then yearly	C
Cystoscopy, ureteroscopy and cytology in situ at 3 mo, 6 mo, and then every 6 mo over 2 yr, and then yearly	C

10.0 UROLOGICAL NURSING

It is well-documented that the CNS plays an essential role within the cancer multidisciplinary team (MDT) in providing high-quality care from diagnosis throughout the patient journey (National Peer Review Programme, 2014). The National Institute for Clinical Excellence (NICE) (2002) called for major changes in improving outcomes for patients with Urological Cancers. In particular they recommended that the CNS should have specific knowledge and expertise and should be trained in advanced communication skills. More recently, NICE (2014) emphasised that the CNS can ensure that patients have information that is tailored to their individual needs, therefore enhancing shared decision making. The CNS is also in an excellent position to provide individualised care following treatment which promotes cancer survivorship (National Cancer Survivorship Initiative, 2011). A recent Macmillan census on specialist nurses workforce in Northern Ireland (2014) has highlighted that cancer care teams of the future will need to have more flexibility working with people who are living with cancer. This census emphasised that the role of the CNS must be optimised to support those living in the community with a diagnosis of cancer.

The combination of improved life expectancy, advancements in diagnostics and treatment, and increased use of PSA testing in primary Care have all contributed to a significant rise in Urological cancer diagnosis. In Northern Ireland the number of new cases of Urological cancers diagnosed annually has increased and the associated workload creating significant challenges for Urological cancer teams and further demands on Uro-Oncology Clinical Nurse Specialists (CNS).

10.1 Responsibilities of the Uro-oncology Specialist Nurses

All patients should be assigned a key worker (usually a CNS) at the time of diagnosis, and appropriate arrangements should be in place to facilitate easy access to the key worker during working hours and an appropriate source of advice in his/her absence, as per National Cancer Peer Review standards. All patients should be offered a holistic needs assessment (HNA) at diagnosis and subsequently if their disease status changes. Patients should be offered advice and support to address any immediate concerns – physical, mental, spiritual or financial – on completion of the HNA with onward referrals made as necessary.

The responsibilities of the uro-oncology CNS include, ensuring patients undergoing investigations for suspected cancers have adequate information and support. On diagnosis, the CNS has a supportive role and will help ensure that the patient and significant others are equipped to make informed decisions regarding their ongoing treatment and care. The CNS may have a role in the review of patients following treatment for urological cancer. The CNS also has a key role in equipping the patient to live with and beyond the urological cancer, as advocated by the National Cancer Survivorship Initiative (2011). National Cancer Survivorship Initiative (2011) has also recommended the use of Holistic Needs Assessment (HNA) by the CNS to assess patient's needs for physical, psychological, social, spiritual and financial support at key points of their journey. A structured pack has been provided for use by professionals to assist with this process (NCAT, 2010). This HNA approach and subsequent care planning is a process which would ensure that people's needs are met in a timely and appropriate way and that resources are targeted to those who need them most. As a result of the HNA patients should be appropriately referred or signposted to any required support services.

Where cystectomy is considered, the involvement of the Stoma Therapist and/or Urology Clinical Nurse Specialist soon after diagnosis is essential. Patients should be offered the opportunity to meet a patient who has had a cystectomy and urinary diversion to help the decision making process. Patients who may have problems with urinary incontinence should be given information about local continence services.

11.0 SUPPORTIVE AND PALLIATIVE CARE

Supportive care is available to people with cancer and their carers throughout the patient pathway, from pre-diagnosis onwards and is a term used to describe all services that may be required to support people with cancer and their carers(NICE,2004). It is identified by NICE (2004) that patients and carers may have a series of problems preceding diagnosis (when cancer is suspected) which may include physical and anxiety related symptoms which require appropriate management, and information should be available for patients at this stage if they require it. As recognised by NICE (2004) supportive care is the responsibility of all health and social care professionals involved in delivering care and effective communication within teams will enable a seamless transition from one service to another if and when required.

Patients with advanced urological cancer may benefit from supportive and palliative care. Palliative care is defined by the World Health Organization (WHO, 2014) as an approach that improves the quality of life of patients and their families, facing the problems associated with life threatening illness. Uncontrolled symptoms can adversely affect quality of life and a patient's ability to cope with their illness, therefore, early identification, thorough assessment and treatment of pain and other problems, physical, psychological and spiritual, is essential (WHO 2014). The overall goal of palliative care is to help manage the symptoms and difficulties that may arise with disease progression, through appropriate support and intervention.

Palliative Care is an integral part of the multidisciplinary team and patients may require palliative care at different stages of the patient pathway (NICE, 2004). Generalist palliative care is the level of care required by most people and is provided by non-palliative/ end of life care specialist's i.e. primary and secondary health care teams (Living Matters, Dying Matters, 2010). Specialist palliative care may be required for those patients with more demanding care needs, i.e. unresolved symptoms and complex psychosocial, end of life and bereavement issues (Living Matters, Dying Matters, 2010).Referral to Specialist Palliative Care may be made at any time in the course of the disease when the patient wishes and would benefit from it.

References:

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National Peer Review Programme (2014) Manual for Cancer Services- Urology Measures.

World Health Organisation (2014) http://www.who.int./cancer/palliative/definition/en/

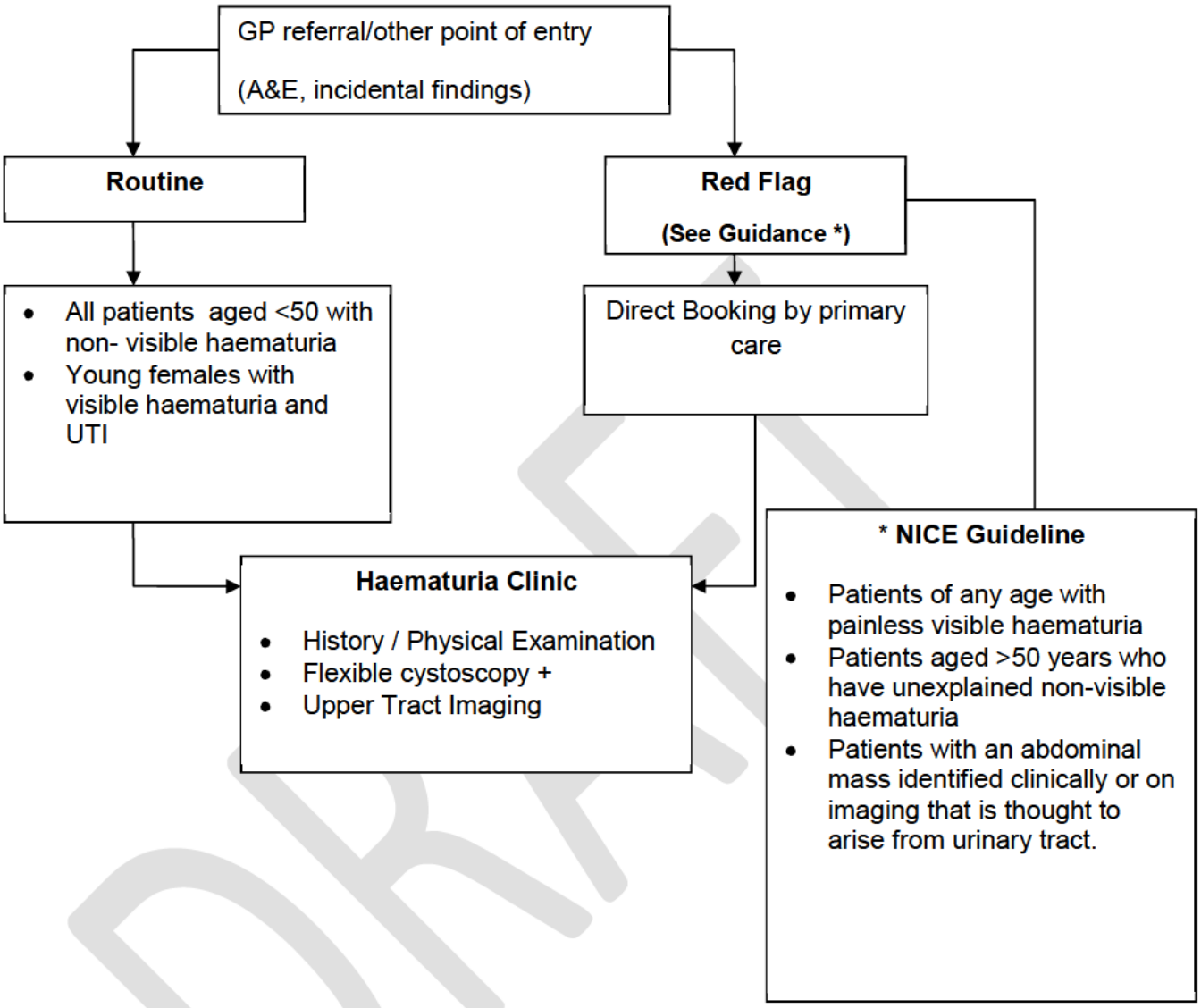
APPENDICES

1. **Haematuria Referral Guideline**

2. **Urology Care Pathways:**
   Prostate Pathway,
   Renal Tumour
   Testicular Cancer Pathway
   Transitional Cell Carcinoma
   Castration Resistant Prostate Cancer
   Penile Cancer Pathway

3. **Guidelines for nurse led follow up prostate cancer pathways**

Haematuria Referral Guideline



NOTE: Please Consider Nephrology referral as well as referral to haematuria clinic if the patient has any of the following:

- Diabetes
- Proteinuria
- Hypertension

Appendix 2; Urology Care Pathways

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

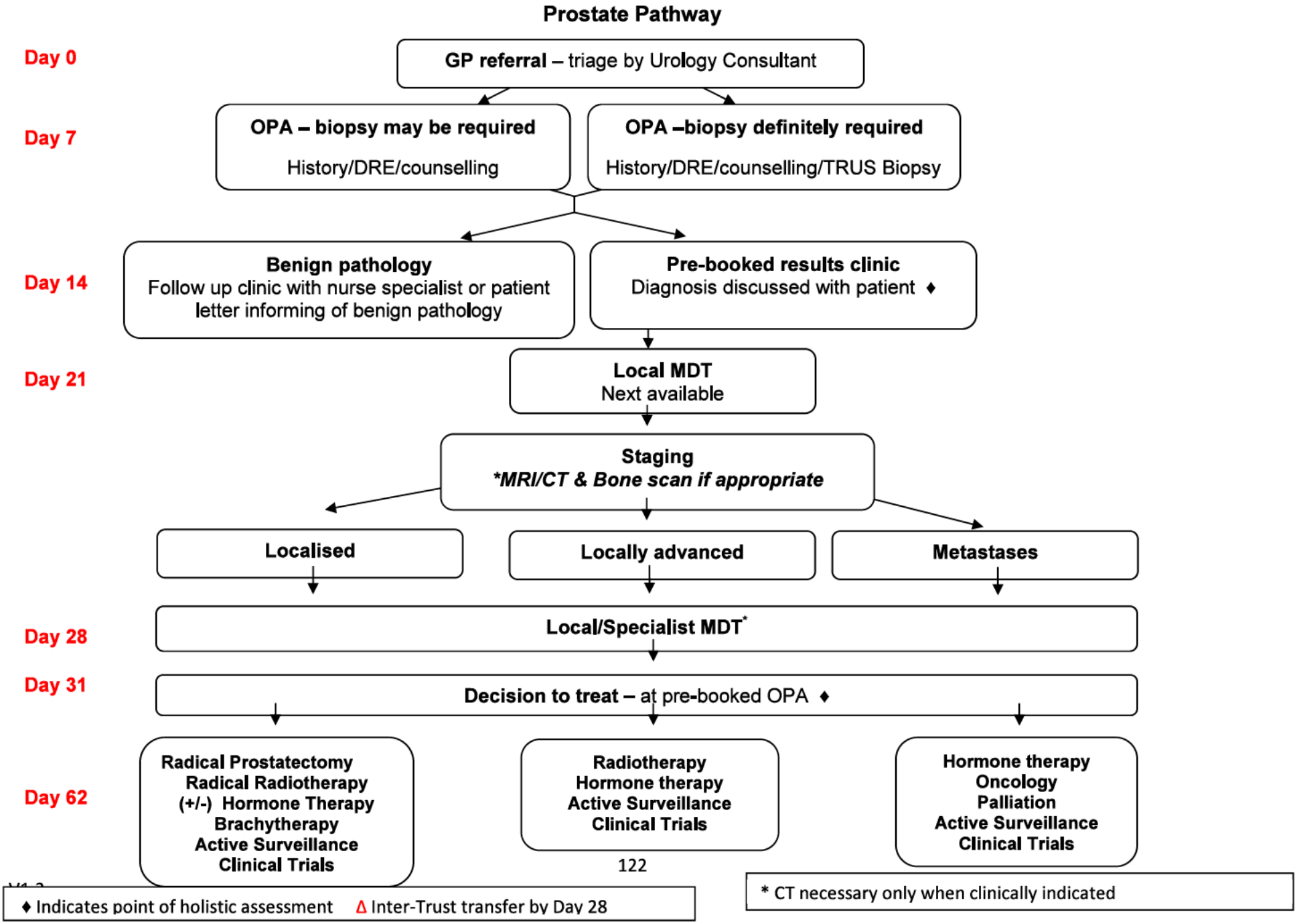
Timed effective care pathways are central to delivering quality and timely care to patients throughout their cancer journey and to the delivery of an equitable service. These pathways have been developed following with reference to available best practice guidance. They represent an 'ideal' pathway that can be adapted for local use. The timelines on the pathway are intended to facilitate the proactive management of patients within the access standards and it is to be noted that for some urological tumours, the patient will move much quicker through the pathway (e.g. testicular cancer).

The pathways are in draft form and amendments have been made following discussion at the workshop of the NICaN Regional Urology group held on Thursday 2nd October, 2008

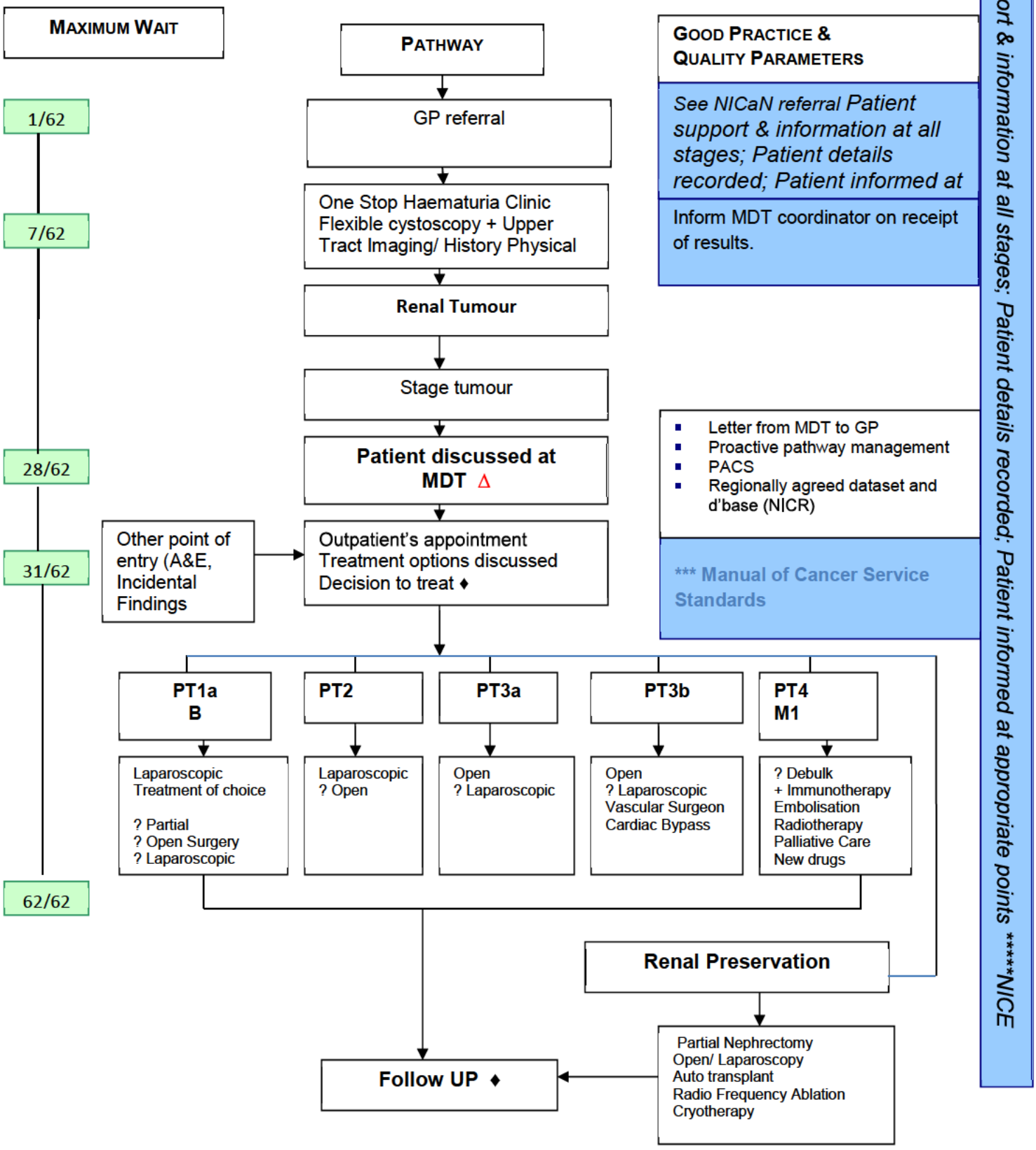
Document History

V1 Draft discussed at workshop 2/10/08
V2 Draft discussed 29/1/09 and amendments noted
Version 3 circulated for final comments 26/02/09
Pathways agreed at regional meeting 23/4/09

Appendix 2 of NICaN Urology Cancer Clinical Guidelines

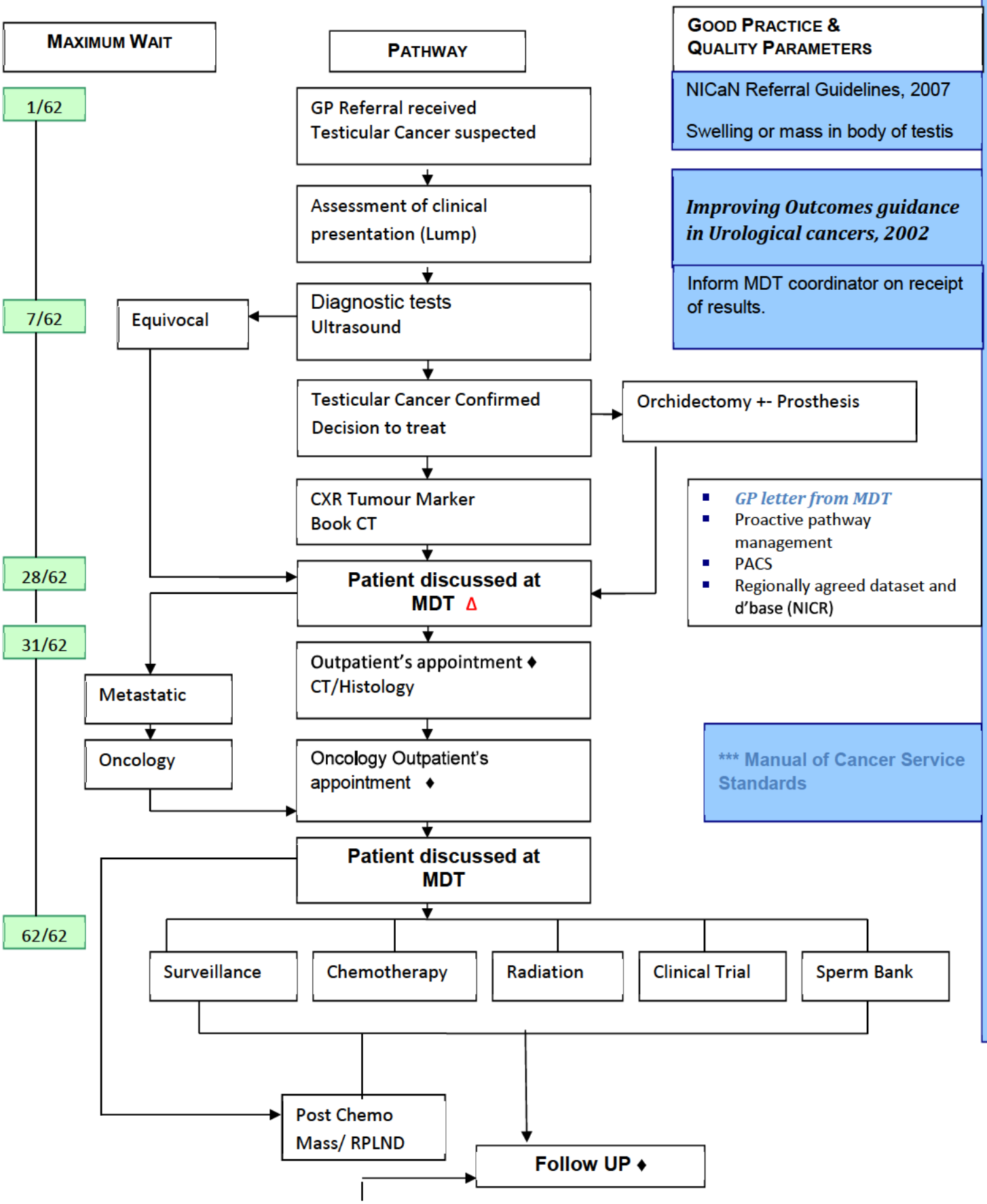


Renal Tumour



Appendix 2 of NICaN Urology Cancer Clinical Guidelines

Testicular Cancer Pathway

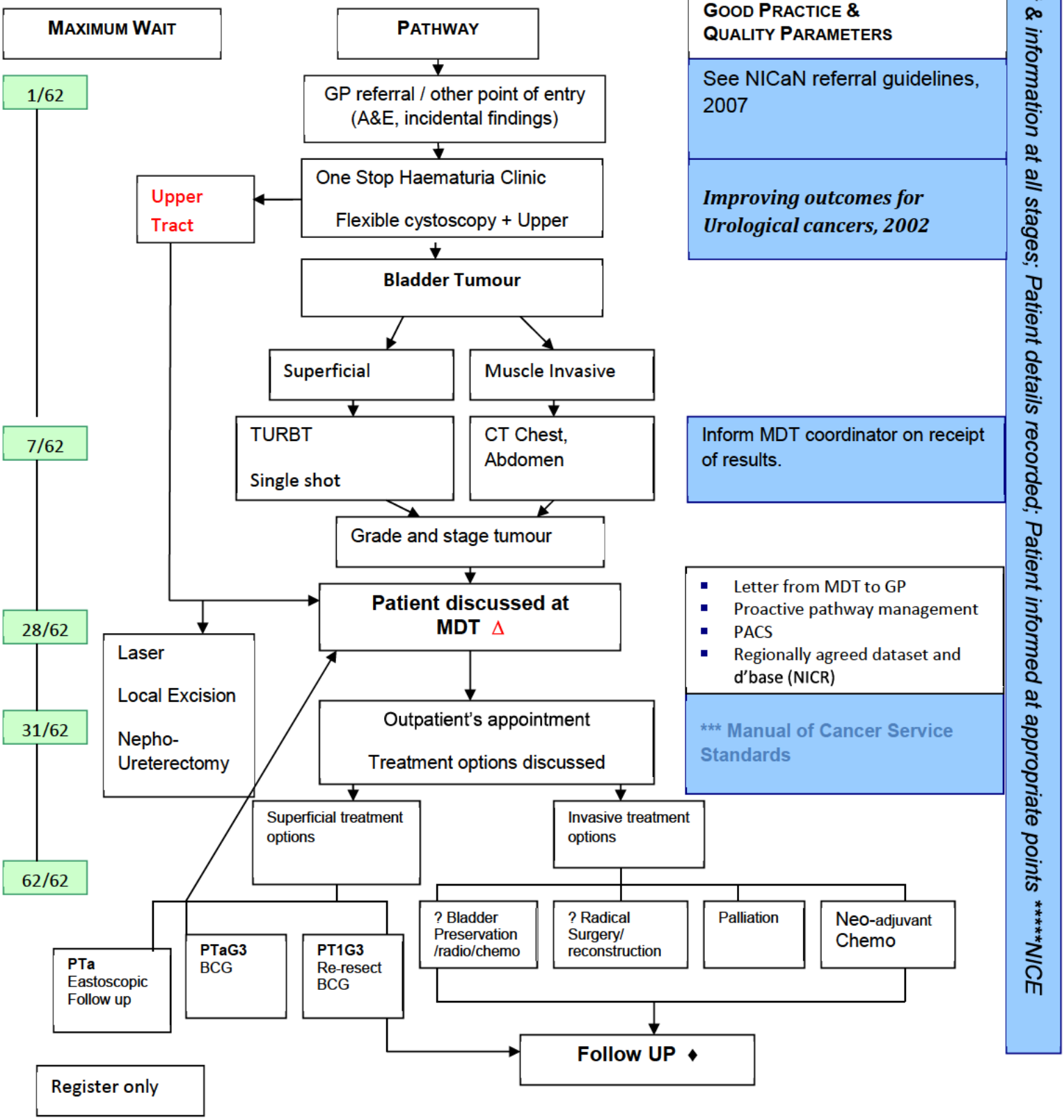


Patient support & information at all stages; Patient details recorded; Patient informed at appropriate points *****NICE

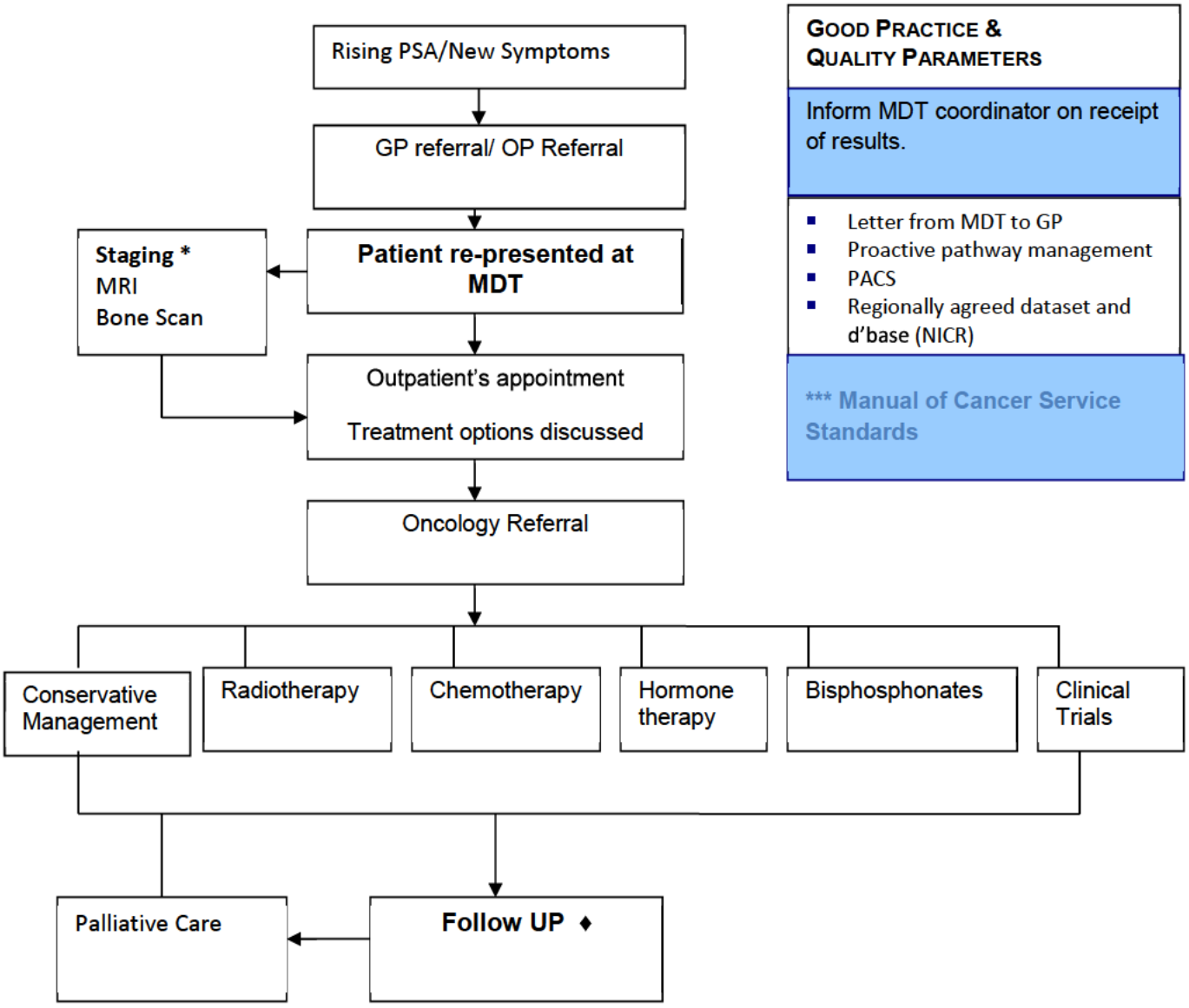
♦ Indicates point of holistic assessment Δ Inter-Trust transfer by Day 28

Appendix 2 of NICaN Urology Cancer Clinical Guidelines

♦ Indicates point of holistic assessment Δ Inter-Trust transfer by Day 28



Castration Resistant Prostate Cancer



GOOD PRACTICE & QUALITY PARAMETERS

Inform MDT coordinator on receipt of results.

- Letter from MDT to GP
- Proactive pathway management
- PACS
- Regionally agreed dataset and d'base (NICR)

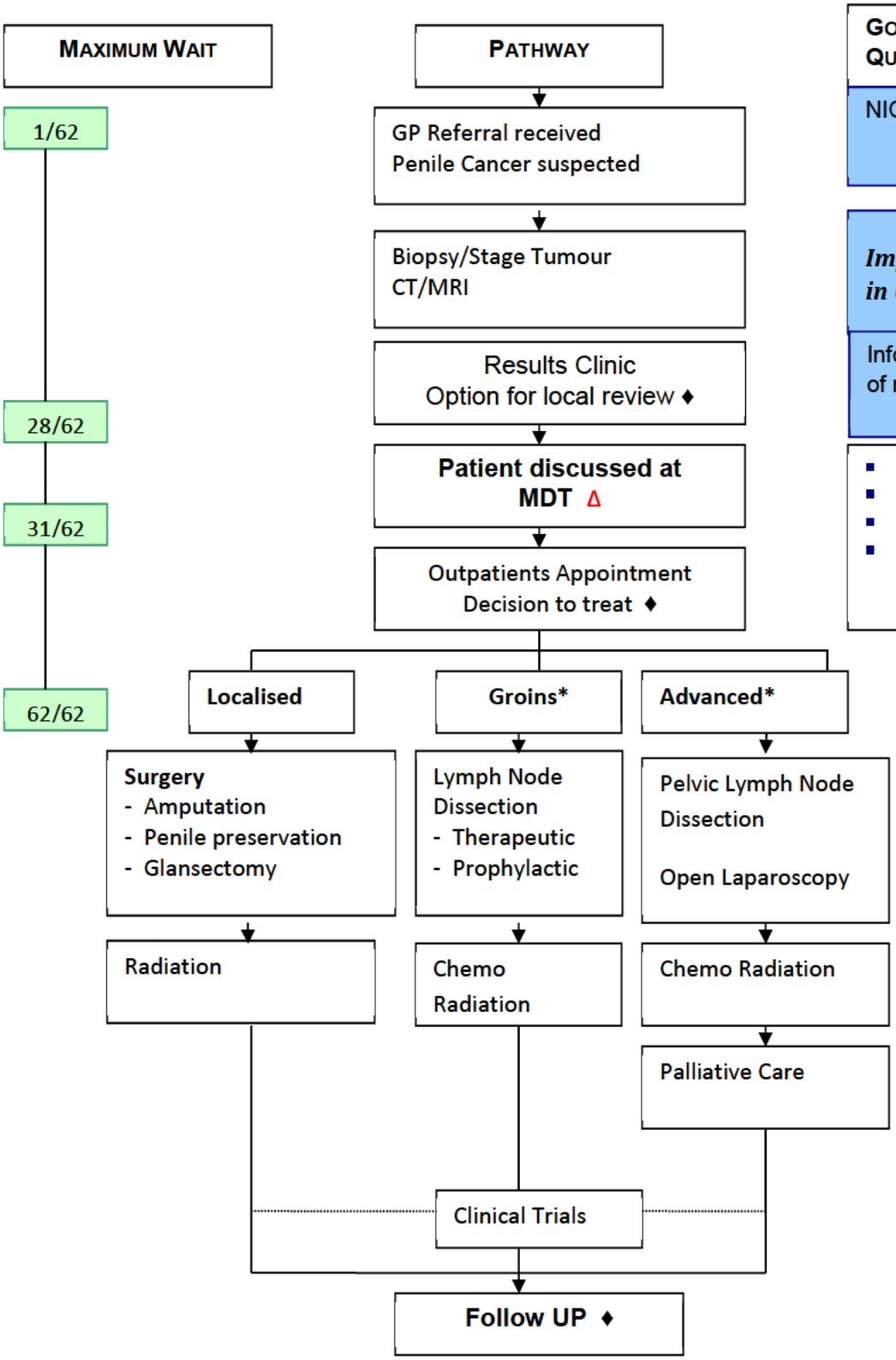
*** Manual of Cancer Service Standards

Patient support & information at all stages; Patient details recorded; Patient informed at appropriate points *****NICE*

* MRI/Bone Scan as clinically indicated

Appendix 2 of NICaN Urology Cancer Clinical Guidelines

Penile Cancer Pathway



GOOD PRACTICE & QUALITY PARAMETERS

NICaN Referral Guidelines, 2007

Improving Outcomes guidance in Urological cancers, 2002

Inform MDT coordinator on receipt of results.

- *GP letter from MDT*
- Proactive pathway management
- PACS
- Regionally agreed dataset and d'base (NICR)

*Patient support & information at all stages; Patient details recorded; Patient informed at appropriate points *****NICE*

V1.3 ♦ Indicates point of holistic assessment Δ Inter-Trust transfer by Day 28

References

- NICE (2002) Improving Outcomes in Urological Cancer
  http://www.nice.org.uk/guidance/index.jsp?action=byID&o=10889
- NICE (2008) Prostate Cancer: Diagnosis and Treatment
  http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11924
- British Association Of Urological Surgeons Guidelines
  http://www.baus.org.uk/
- European Association Of Urology
  http://www.europeanurology.com/

Policy Code / Reference No:

Trust Logo

Add Trust Name

Title:	**Guidelines for Nurse Led Assessment and Follow up of patients with stable Prostate Cancer**			
Author(s)	*Adapted from SET*			
Ownership:				
Approval by:	**NICaN Urology NSSG Group**		**Approval date:**	**29th November 2013**
Operational Date:			**Next Review:**	
Version No.	**3**	**Supercedes**	**N/A**	
Links to other policies	**Policy for consent to examination, Treatment and Care, European Association of Urologists (Feb, 2012) Guidelines on Prostate Cancer**			

1.0 INTRODUCTION / PURPOSE OF GUIDELINE

This document outlines the guiding principles for nurse led prostate cancer follow-up and should be closely followed. However these guidelines are only a foundation and it is recommended that nurses maintain their continuing education in this specialist area of care.

The aim of this guideline is to set a minimum standard for nurse led assessment and follow up of patients with prostate cancer which will:

- Enable the follow up of patients with prostate cancer who are on the watchful wait or hormone treatment pathway
- Promote the education of patients about their disease management and potential for self directed aftercare
- Monitor patient progress and enable detection of progression and refer to the appropriate Consultant Urologist
- Enable holistic assessment
- Identify late effects of treatment quickly, provide support and signpost to the appropriate service if necessary
- Inform patients about and refer them to specialists services that can help with their medical, practical, emotional and rehabilitation needs
- Support patients living with and beyond cancer
- Offer patients a choice of follow-up

1.1 Objectives

The objectives of this guideline are to improve and maintain standards of clinical practice and quality of care patients receive by:

- Providing evidence based guidance for establishing and maintaining a nurse led clinic for the assessment of patients with prostate cancer, promoting excellence in the care that is delivered
- Reducing variation in clinical practice and encouraging uniformity of practice
- Providing a framework from which individual practitioners can apply their own level of clinical expertise and competency
- To ensure that all patients entering the prostate cancer follow up service are on the appropriate risk stratified pathway (Appendix 5 & 6)
- Helping nurses and health care providers to make informed decisions, aiding the education process and reducing the risk of clinical negligence
- Identifying competencies for nursing care
- Aiding development of locally agreed guidelines
- Promoting audit

1.2 Background

The NHS is undergoing radical changes particularly in its approach to cancer. Traditional nursing roles are being challenged in a bid to meet the demands of the changing NHS climate. Prostate cancer follow up forms a substantial part of the urology outpatient workload. Nurse led clinics are becoming increasingly common, offering patients an alternative method of follow up either via more convenient clinics or the telephone. By developing these new roles and services, nurse are playing a key role in increasing patient choice, reducing waiting times, increasing accessibility to services and improving the quality of care

New standards have been developed within the Cancer Services Framework that are intended to ensure that patients experience the best possible quality of life after treatment by:

- providing new models of follow-up which focus on health and wellbeing
- improving access to psychological support

2.0 DEFINITIONS/SCOPE OF THE GUIDELINE

These guidelines should be used by suitably trained health care professionals who are providing nurse led follow up to patients with prostate cancer. Patients will enter nurse led follow up services on a clearly defined follow up pathway following discussion at MDM.

Recommended exclusion criteria

- Patients who do not wish to be followed up by a nurse
- Patients who require adjuvant treatment in the form of radiotherapy or chemotherapy
- Patients with dementia/short term memory loss (unless meeting patients with carer present)
- Patients who develop resistance to Hormone Therapy during follow up and require referral to oncologist
- Patients deemed unsuitable for review at a nurse led clinic by the consultant in charge

3.0 ROLES/RESPONSIBILITIES

Implementation of these guidelines is the responsibility of those involved in nurse led follow-up of prostate cancer patients.

Accountability is a key concern for all registered nurses today. Professional accountability is defined as being responsible for your actions and for the outcomes of these actions as part of the framework of clinical Governance, which aims to provide good quality, cost-effective evidence based care (Tilley & Watson 2004)

Nurses need to be aware of their limitations as well as their clinical competence. If there are any areas in which they do not feel clinically competent to undertake an activity they should decline the activity until the appropriate learning and practice activities have been achieved to demonstrate competency (NMC 2008)

Nurses are responsible for ensuring their own educational preparation and experience to safely perform the role. They should maintain documented evidence of completion of continuing education and of demonstrating clinical competence

Competencies required for assessing patients with prostate cancer can be found in (Appendix 2)

4.0 KEY GUIDELINE PRINCIPLES

4.1 Key Policy Statement

The purpose of the nurse led clinic is to enhance the quality of care and to promote the health and well being of patients who have been treated for prostate cancer. The clinic will also facilitate the provision of emotional support for patients and their families/carers requiring the opportunity to discuss treatment or care options
Nurse led clinics have been shown to improve the quality of care in the following ways:

- Provide continuity of care for patients and their family
- Provide information, education and support
- Be accessible to patients and their family
- Release consultant time to see more complex patients
- Apply the principles of transforming cancer follow up

A risk stratified model of aftercare in line with the National Cancer Survivorship Initiative will be utilised and patients will be stratified into different arms of the follow up pathway according to their staging and personal characteristics by the Consultant.

Risk stratified means that the clinical team and the person living with cancer make a decision about the best form of aftercare based on their knowledge of the disease, (what type of cancer and what is likely to happen next), the treatment (what the effects or consequences may be both in the short term and long term) and the person (whether they have other illnesses or conditions, and how much support that they feel they need).

This will include the ongoing follow up of patients who are clinically stable and are stratified into the relevant pathway

Watchful waiting	(Pathway 1)
Active surveillance	(Pathway 2)
Raised PSA – negative biopsy	(Pathway 3)
Post radical surgery	(Pathway 4)
Post brachytherapy	(Pathway 5)
Post radical radiotherapy	(Pathway 6)

4.2 Policy Principles

Patients with prostate cancer who are on the pathways outlined above will be risk stratified into a pathway as discussed below

- Self-Care with Support and Open Access

    - No routine outpatient attendances
    - Stable disease pattern
    - After treatment with curative intent
    - Holistic assessment completed and care plan agreed
    - Information and/or some form of educational intervention
    - Surveillance tests with results by post or phone co-ordinated by a provider
    - Ability to re access system with/without reference to GP

- Shared Care – where patients continue to have face to face or telephone contact with professionals as part of continuing follow up.

    - Planned follow up either as an outpatient or planned phone follow up
    - Clinical examination required
    - High clinical or individual risks identified (disease, treatment, person)
    - Multi professional input required
    - Patients with co-morbidities
    - Those who decline or are considered to be unable to self manage

4.3 Long-term follow-up

Definitive guidance on the long term follow-up for patients with prostate cancer is included within the pathways which are concordant with NICE and European Association of Urologists Clinical Management Guidelines on Prostate Cancer.

4.4 Telephone Review Protocol

A telephone review service enables the Clinical Nurse Specialist to follow up patients through an alternative route and thereby reduce unnecessary hospital appointments for patients who have stable disease and are not fit to travel.

This service will be offered to those patients referred to the nurse led clinic and a telephone assessment protocol will be utilised. See appendix 7

4.5 Holistic Needs Assessment (HNA)

The HNA is used to identify and address patient's needs and concerns. The HNA may build on action plans developed from previous assessments. The HNA should

be conducted during the follow-up appointment. The patient or carer is encouraged to complete the form and the assessor uses this as a guide to explore their needs and collaboratively develop an appropriate action or care plan

An agreed Holistic Needs Assessment (HNA) tool will be utilised within the aftercare pathways

4.6 Support Information and Education

The consultant or clinical nurse specialist should offer patients support information tailored to the individual. This should cover as a minimum:

- Disease Progression
- Fatigue
- Pain
- Urinary Symptoms
- Finances/benefits
- Nutrition/exercise
- Signposting
- Health and well being

4.7 Rapid Access Protocol

Prostate cancer follow-up is the responsibility of the MDT. All patients should be able to access the Consultant responsible for their care through the Urology CNS. Any patient that contacts the Urology CNS with worrying symptoms will be seen by a Consultant promptly. If necessary, their case should be discussed by the MDT.

4.8 Triage Protocol

Each patient will be able to contact the Urology CNS outside of scheduled follow up appointments The Urology CNS will triage the patient on their concerns/issues to the most appropriate member of the Urology team or refer on to other agencies accordingly. Outcomes may include:

- Face to face consultant appointment promptly
- Face to face Nurse led clinic (where appropriate)
- Advised to contact GP
- Advised to attend the emergency department
- Signpost to other support agencies e.g. Citizens Advice Bureau (CAB), AHP, Counselling

Only clinical issues will result in a clinical appointment.

5.0 IMPLEMENTATION OF POLICY

5.1 Dissemination

Urology Clinical Nurse Specialists

Urology Consultants

Oncologists

6.0 MONITORING

Monitoring of these guidelines is the responsibility of the Urology Nurse under the direction of the line manager.

7.0 EVIDENCE BASE / REFERENCES

Evidence:

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Service Framework for Cancer Prevention, Treatment and Care (2011)

Tilley, S. Watson, R. (2004) Accountability in Nursing and Midwifery. 2nd Edition. London: Blackwell Publishing.

8.0 CONSULTATION PROCESS

Cancer Services User Forum

NICaN Regional Urology Group

9.0 APPENDICES / ATTACHMENTS

See attached

10.0 EQUALITY STATEMENT

In line with duties under the equality legislation (Section 75 of the Northern Ireland Act 1998), Targeting Social Need Initiative, Disability discrimination and the Human Rights Act 1998, an initial screening exercise to ascertain if this policy should be subject to a full impact assessment has been carried out.
The outcome of the Equality screening for this policy is:

Major impact ☐

Minor impact ☐

No impact ☐

SIGNATORIES

(Policy – Guidance should be signed off by the author of the policy and the identified responsible director).

_____ **Date:**
Name
Title:

_____ **Date:**
Name
Title:

_____ **Date:**
Name
Title:

_____ **Date:**
Name
Title:

Appendix 1

Prostate Cancer Review Assessment Form

Name…….

Unit No……..

DOB……

Consultant…… GP……

Date:……. Time…….

Type of review: Telephone □ Clinic Contact □

Treatment Pathway: Hormone Treatment □Watchful Waiting □

Histology Gleason's Score …….. TNM ……

PSA

PSA Trigger.....

Date of PSA…….... Current PSA..... Previous PSA.....

PSA obtained from ECR……

Record what was discussed with patient

Changes in Urinary Symptoms

Storage	Yes / No
Voiding	Yes / No
Pain	Yes / No
Haematuria	Yes / No

If yes to any of the above, please comment and record advice given

General Symptoms

Hot Flushes	Yes/No
Tiredness	Yes/No
Weight gain	Yes/No
Breast Pain	Yes/No
Bone pain	Yes/No
Sexual Problems	Yes/No
Change in bowel pattern	Yes/No

Additional comments

Problems and concerns

Has patient had a Holistic Needs Assessment Yes/No

If yes, Date of HNA ……..

Discuss resolution of any problems identified in previous HNA □

Are there any new concerns Yes/No

- Financial
- Psychological
- Information and Support

Please record any issues

Follow up

Nurse Led follow up 3 months yes/no 6months Yes/No

Referral to:

Urologist Yes/No
Oncologist Yes/No

Letter to GP □
Letter to Consultant □

Signature of CNS……

Appendix 2
Competencies for Nurse-led Follow-up

Competencies required assessing patients with stable prostate cancer include:

- Advanced nurse practitioner/clinical nurse specialist having been employed for a minimum of twelve months working with a urologist/oncologist in the follow up setting

- Demonstrate a full understanding of the network site specific group pathways for prostate cancer. As agreed by the local tumour network

- To be enrolled in or be undertaking, a programme of study in their specialist area of nursing practice which has been accredited for at least 20 CAT points at level 3 (DH2004) e.g. Health Assessment module

- Have advanced communication skills – to have enrolled in, or be undertaking a recognised course/module in communication skills (DH 2004)

- In order to run a clinic the individual must be a core member or extended member of the urology multidisciplinary team

- To be able to demonstrate knowledge of the disease trajectory in Prostate Cancer

- To be able to demonstrate knowledge of risk stratified pathways

- To have competent consultation and symptom analysis skills. To have worked under supervision for a minimum of six months and have been deemed competent by the consultant urologist/oncologist

- To be able to demonstrate knowledge of the tests and investigation required during follow up of prostate cancer patients

- To be competent at performing DRE (if appropriate)

- To be competent in the assessment of lower urinary tract symptoms (LUTS) and facilitate onward referral to LUTS clinic is required

- To be competent in bladder palpation

- To be competent in the assessment of bladder empting

- To demonstrate ability to advise on erectile dysfunction and know where and how to refer to appropriate service
- To be able to demonstrate knowledge of survivorship issues
- To be able to demonstrate knowledge of rehabilitation services
- Demonstrate knowledge of drugs and treatments used in prostate cancer including side effect

Appendix 3

Guideline for Nurse Led Assessment Protocol

Actions
Discuss • Nurse led clinic • History/treatment to date • Timeline for routine follow up such as PSA, DRE and Admission Profile
Physical Examination
Carry out physical assessment including: • Digital Rectal Examination (DRE) • International Prostate Symptom Score (IPSS) if required
Symptoms
Is the patient experiencing any symptoms . • Hot Flushes • Ask about pain – any new pain lasting more than a week (use locally agreed pain scale) • Weight loss/gain • Fatigue • Sexual dysfunction • Neurological symptoms – Numbness, tingling or odd sensations in limbs • Lower Urinary tract symptoms • Haematuria • Gynaecomastia • Change in bowel habit • Deterioration in renal function Is the patient experiencing any symptoms suggestive of local or metastatic disease • Abdominal /Pelvic /Skeletal pain • Weight loss • Anorexia • Nausea or vomiting

Ask about any other symptoms/concerns
Tests and investigations
• PSA at each visit if rising discuss with consultant • Admission Profile at each visit • FBP at first visit • Ultrasound renal tracts following discussion with Consultant
Holistic Assessment
Perform holistic assessment suggested tools: • Macmillan Concerns Checklist & Care-plan
Information
Nurse to check information has been provided and tailored to the individual patient. This will include information about: • Timeline for tests and investigations • Survivorship programme • Rapid Access to service • Contact numbers • What symptoms need to be reported • Consequences and side effects of the treatment • Holistic Assessment • Rehabilitation services
Rehabilitation
Discuss and offer referral to: • Community Health and Well-being Clinics • Signposting to other services
Documentation
Care plan Letter to patient Letter to GP & referring consultant with copy of assessment form,

To include:

- Date and time of nurse consultation
- Patients identifiable details
- Diagnosis
- Treatment,
- Assessment summary,
- Most recent PSA reading
- Date of next nurse appointment
- Potential or actual problems identified during the consultation.

Adapted from BAUN (British Association for Urological Nurses) - Guidelines for nurse-led assessment and follow up of men with stable prostate cancer (2008)

Appendix 4

Problem Management Plan

This plan will help to identify the appropriate actions when there is a change in the patients condition/needs during nurse led assessment and follow-up of patients with prostate cancer.

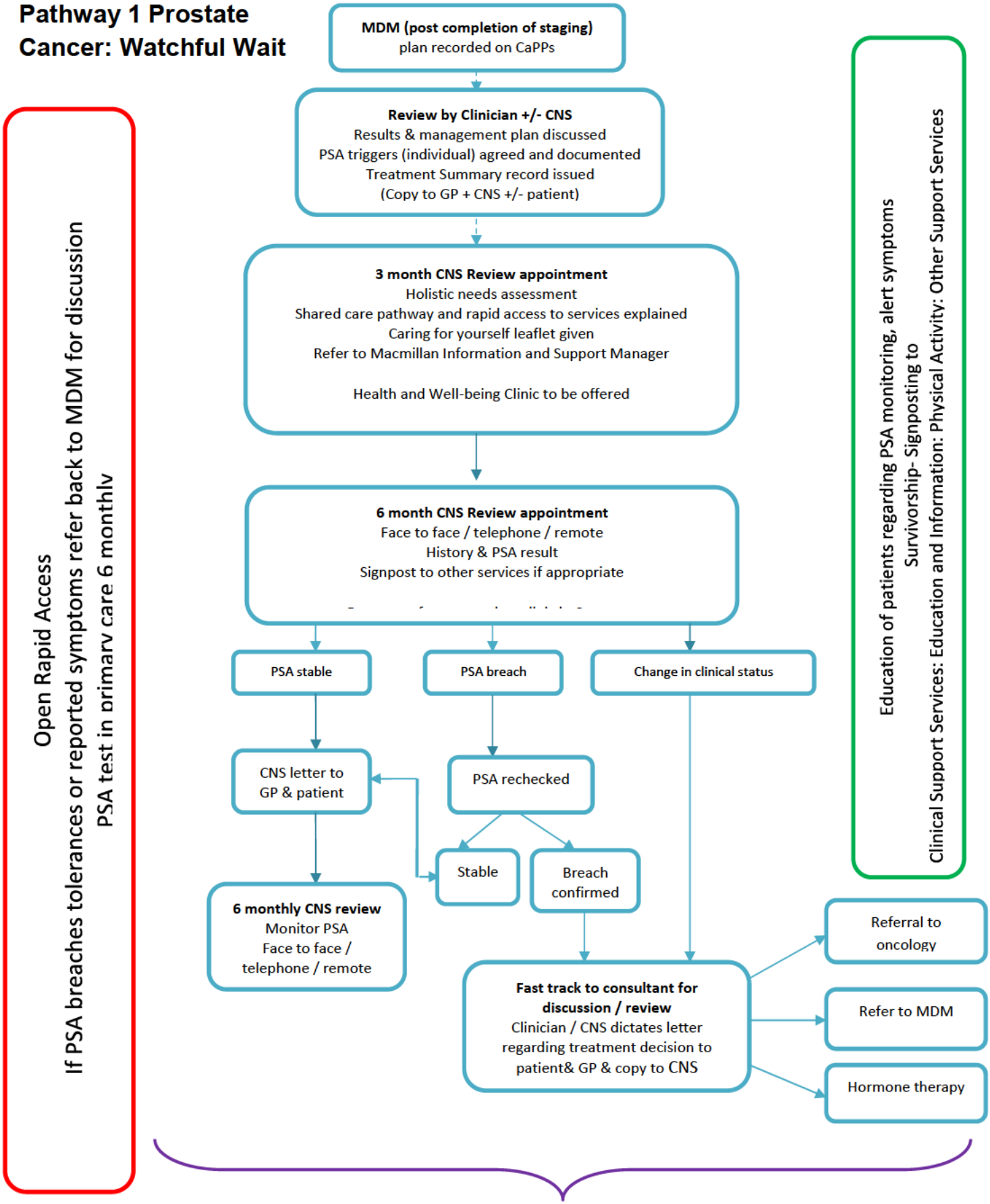
Problem	Management plan
Sudden Rise in PSA	Repeat PSA as determined by consultant
Lower urinary tract symptoms that are more bothersome to the patient	Refer to LUTS clinic Urinalysis to exclude UTI Refer or discuss with appropriate consultant
Haematuria	Exclude UTI Assess lower urinary tract symptoms Refer for investigations
Hot flushes	Give support and advice and discuss with consultant
Pain - new onset bone pain	Request investigations – bone profile, pain and neurological assessment(use locally agreed pain scale) Consider MSCC Appropriate referral to urologist/ oncologist for further management
Change in bowel habit	Assess asking about change in consistency regularity. Give advice or refer to specialist as appropriate
Weight loss	If unexplained weight loss refer to consultant. Refer to dietician if appropriate
Gynaecomastia	Discuss with consultant and if required refer to oncologist
Deterioration in renal function	Discuss and if appropriate refer back to urologist Assess for poor bladder emptying by post void residual scan Order USS of renal tracts if appropriate

Problem	Management plan
Weight gain, fatigue general malaise and anaemia	Give advice Consider referral for physical activity programme Check haemoglobin and if below normal levels discuss with consultant
Sexual Dysfunction	Assess for erectile dysfunction Give advice and consider referral to ED clinic if appropriate
Psychological needs	At time of the assessment any psychological concerns identified through use of NICaN Concerns Checklist will be discussed with the patient. Refer as appropriate to: Health and well being clinics Support groups Counselling Service Clinical psychologist
Financial concerns	Refer to CAB
Information needs	Discuss information needs Give written information if appropriate Consider onward referral if required Refer to Macmillan Information and Support Centre

Adapted from BAUN (British Association for Urological Nurses) - Guidelines for nurse-led assessment and follow up of men with stable prostate cancer (2008)

Appendix 3 of NICaN Urology Cancer Clinical Guidelines

Pathway 1 Prostate Cancer: Watchful Wait

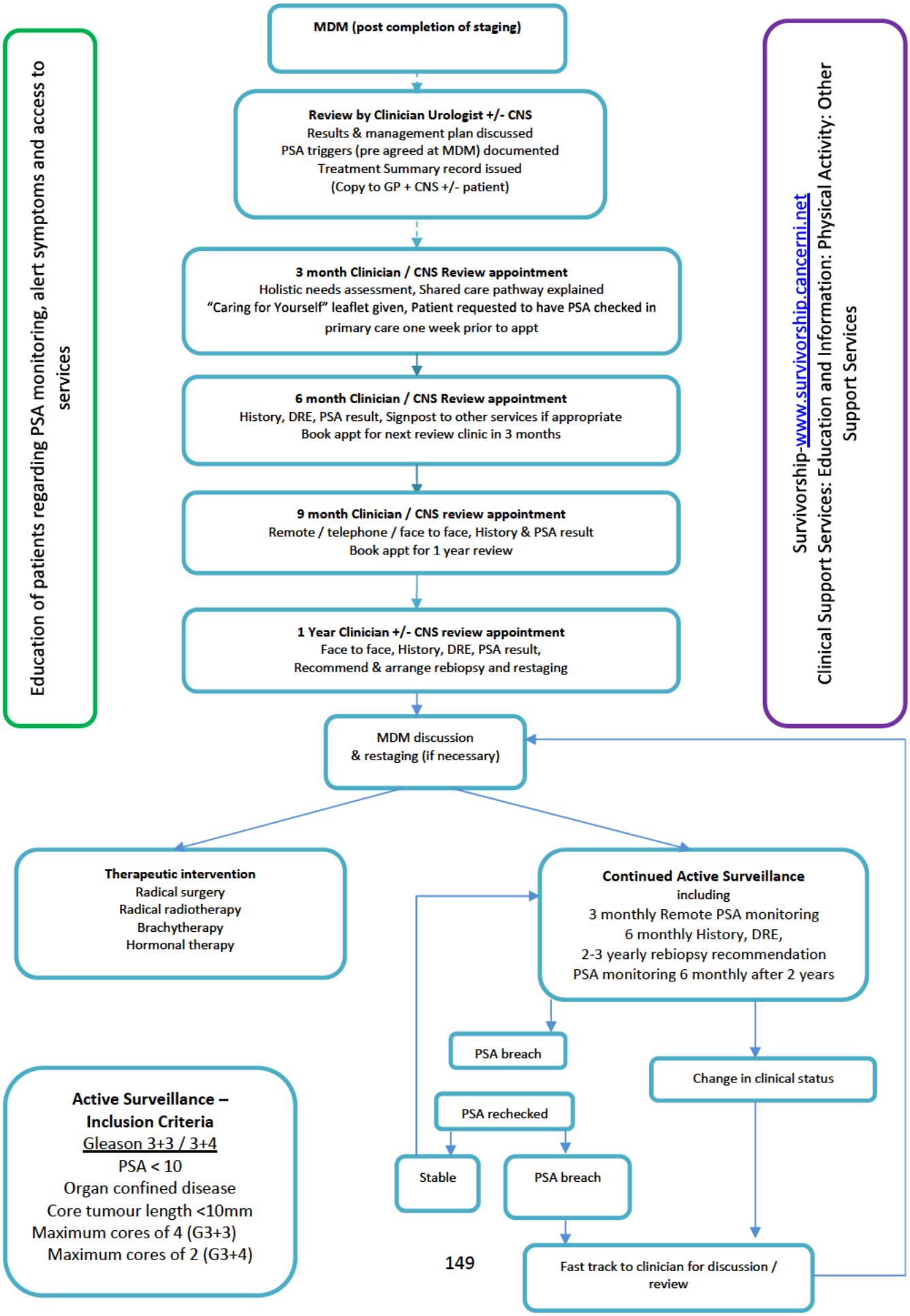


Watchful waiting – Adapted from NICE Guidance 2008

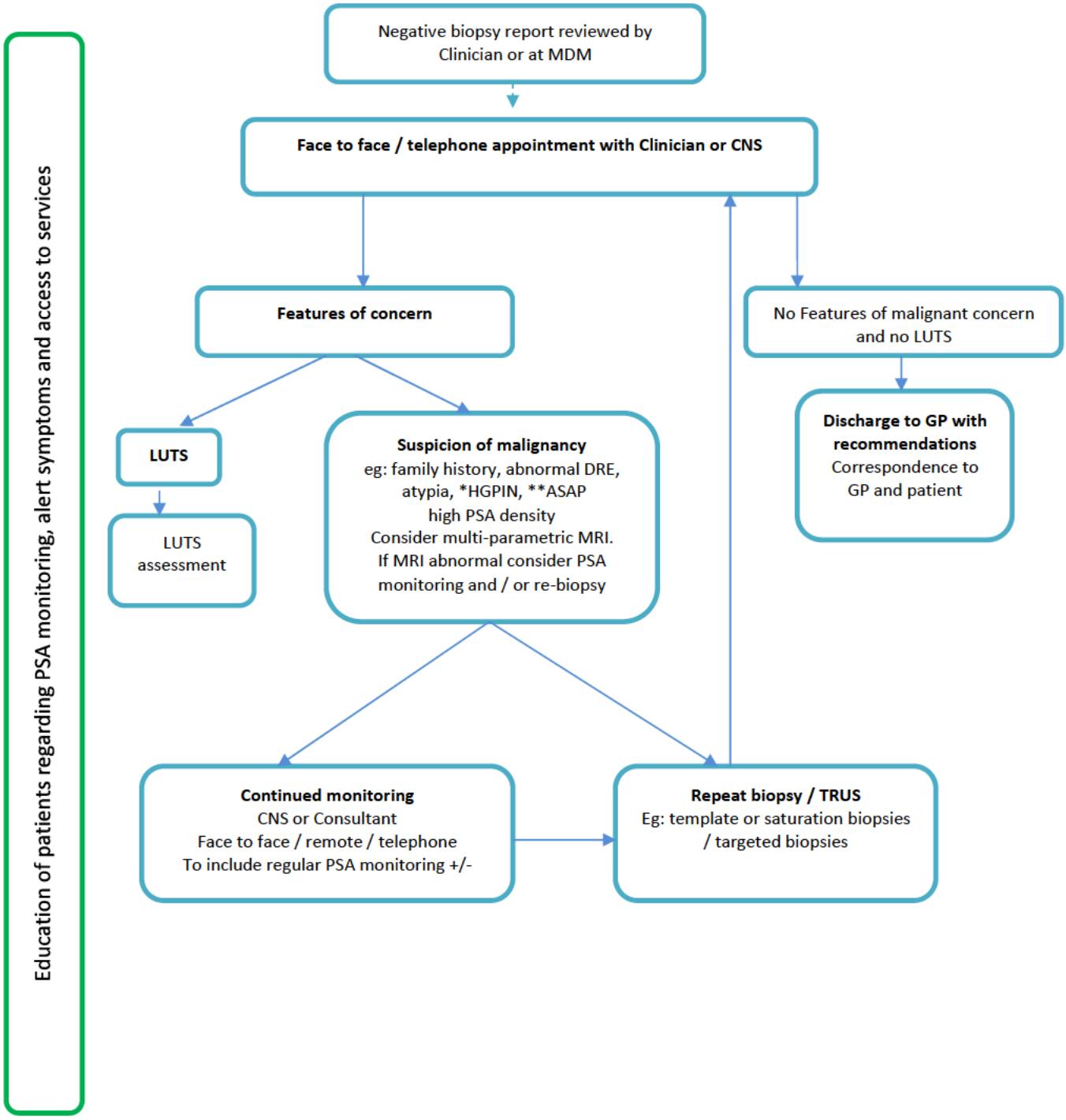
'Watchful Waiting is the form of continued review of Prostate Cancer patients for whom future therapeutic intervention with curative intent has been considered to be inappropriate'.

Appendix 3 of NICaN Urology Cancer Clinical Guidelines

Pathway 2 **Prostate Cancer: Active Surveillance**



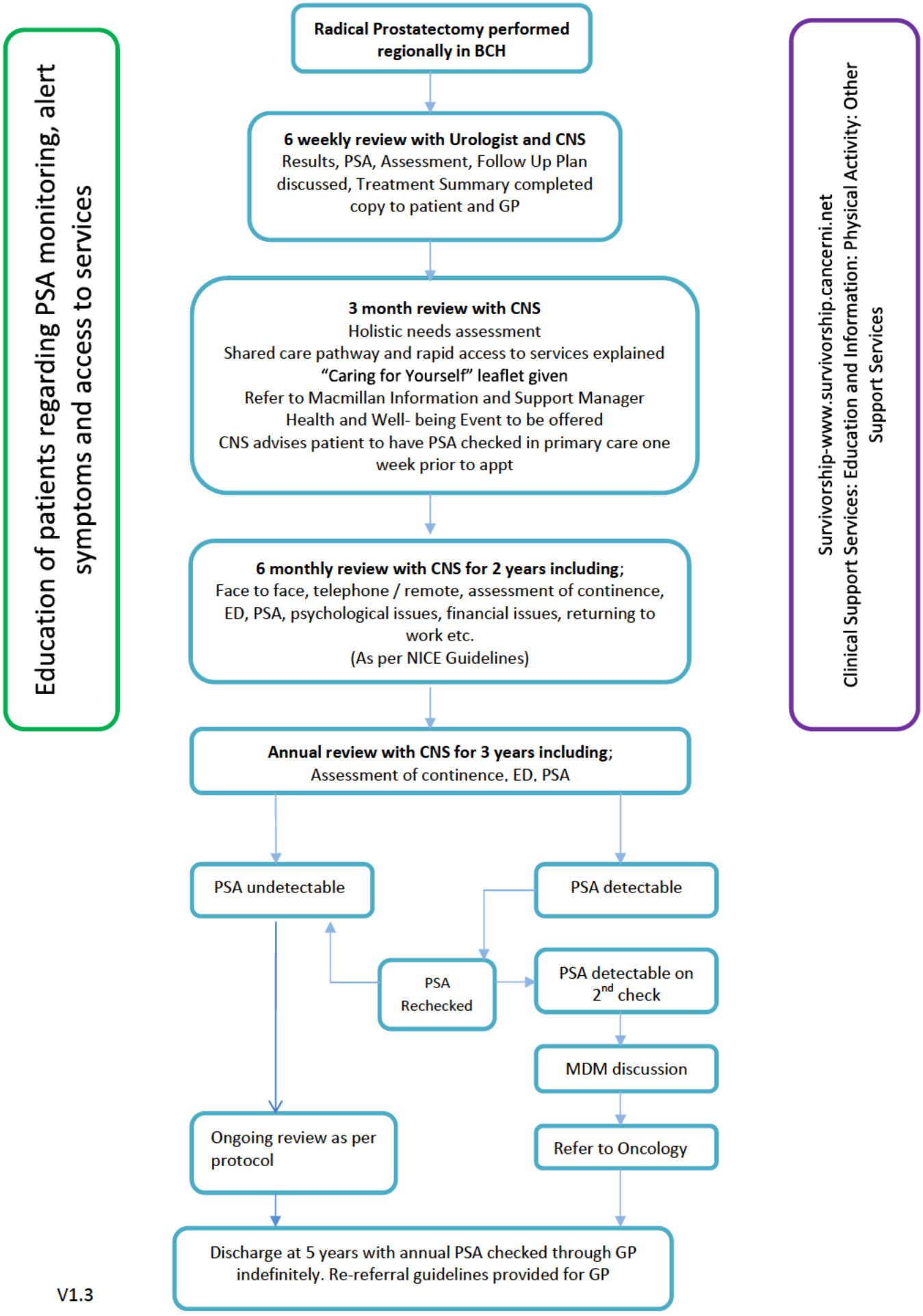
Pathway 3 Raised PSA & Negative Biopsy



*HGPIN – High grade prostatic intra-epithelial neoplasia
**ASAP – Atypical small acinar proliferation

Appendix 3 of NICaN Urology Cancer Clinical Guidelines

Pathway 4 **Prostate Cancer: Radical Surgery – Negative margins**



V1.3

Appendix 3 of NICaN Urology Cancer Clinical Guidelines

Pathway 5 Prostate Cancer: Permanent Prostate Brachytherapy (LDR)

Education of patients regarding PSA monitoring, alert symptoms and access to services

Permanent Prostate Brachytherapy Implant performed (Pt discharged)

Post implant AUR management if required

4week Post implant CT scan and QA/peer review (PSA, IPSS, Dosimetry to database)

3month - Radiographer telephone review (PSA to database)

6month - Consultant led clinical review (PSA, IPSS,IIEF,EPIC to database)

6monthly Consultant led clinical review.
GP check PSA every 3-6months
(PSA, IPSS,IIEF,EPIC to database)
Transfer to annual review at 3years if PSA <1ng/ml & falling

12monthly clinical review
GP check PSA every 6 months
(PSA, IPSS,IIEF, EPIC to database)
Discharge to GP care at 5 years if PSA <1ng/ml & falling

GP information letter re biochemical and clinical triggers and re-referral pathway

Sigmoidoscopy by experienced practitioner at year 5, 10, 15 If deemed fit for procedure

Rising PSA Year 0 – 3 could be benign PSA bounce.
PSA 3monthly with clinical review.
MRI/CT/IBS if:
1 PSA level>10ng/ml
2 Clinically indicated

Survivorship-www.survivorship.cancerni.net
Clinical Support Services: Education and Information: Physical Activity: Other Support Services

Selection criteria for Permanent Prostate Brachytherapy

Clinical inclusion criteria:
Organ confined prostate cancer T1 or T2
Estimated life expectancy >10yrs
Gleason 6 and PSA <15ng/ml
Gleason 7 and PSA <15ng/ml

Clinical exclusion criteria for brachytherapy:
Prostate volume >50ml (> 65ml prior to hormonal cytoreduction)
IPSS >9. (Would consider for implant is <15 & Qmax >12ml/sec)
Life expectancy <5years
Large or poorly healed TURP defect
Unacceptable operative risk
Relative contraindications for brachytherapy:
Large median lobe

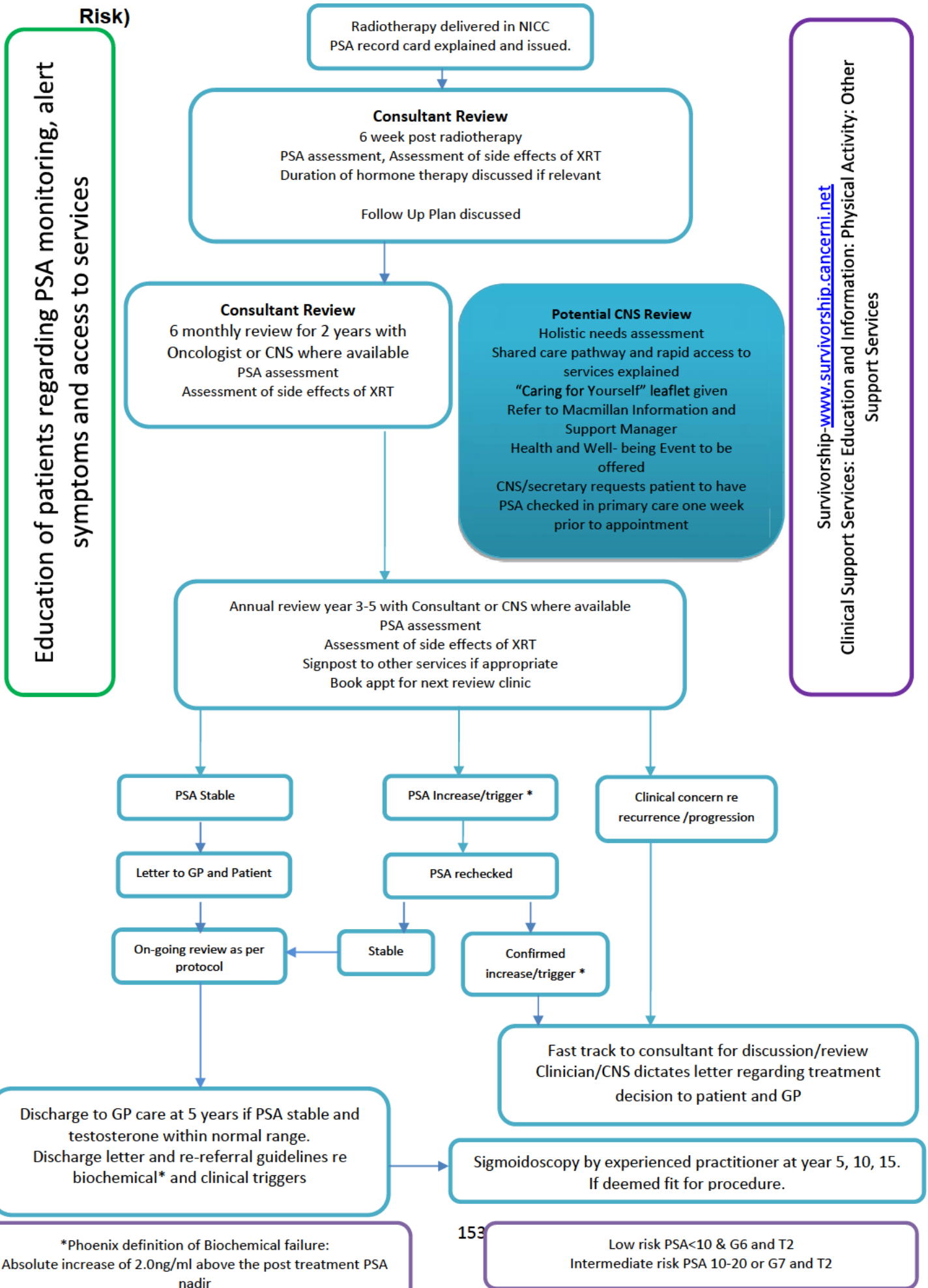
Selection criteria for combined Permanent Prostate Brachytherapy + EBRT

Selected men with:
High volume Gleason 7 or
Low volume Gleason >7 or
Early T3a disease
May be suitable for dose escalation with combination therapy and should be referred for discussion to central

Received from SHSCT on 05 May 2023. Annotated by the Urology Services Inquiry.

Appendix 3 of NICaN Urology Cancer Clinical Guidelines

Pathway 6: Prostate Cancer: Radiotherapy+/-Hormones (Low Intermediate Risk)



Multi-disciplinary Team (MDT) Guidance for Managing Prostate Cancer

September 2013

Produced by:

- **British Uro-oncology Group (BUG)**
- **British Association of Urological Surgeons (BAUS) Section of Oncology**

PLEASE NOTE: THIS GUIDANCE IS AN INTERIM PUBLICATION AND IS SCHEDULED FOR IMMEDIATE REVIEW IN 2014 WHEN IT WILL ADDRESS THE UPDATED NICE GUIDELINE AND THE OUTCOME OF OTHER RELEVANT TECHNOLOGY APPRAISALS

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The development and content of this guidance has not been influenced in any way by the supporting companies.

Abbreviations

3D-CRT: three-dimensional conformal radiotherapy

ADT: androgen deprivation therapy

ASAP: atypical small acinar proliferation

BF: biochemical failure

BPFS: Biochemical progression free survival

BPH: benign prostatic hyperplasia

CAB: combined androgen blockade

CHHiP: Conventional or Hypofractionated High Dose IMRT for Prostate Cancer

CI: confidence interval

CPA: cyproterone acetate

CPFS: clinical progression free survival

CT: computed tomography

DES: diethylstilbestrol

DFS: disease-free survival

DRE: digital rectal examination

EBRT: external beam radiation therapy

EPC: Early Prostate Cancer

ERSPC: European Randomised Study of Screening for Prostate Cancer

FFF: freedom from failure

FSH: follicle stimulating hormonE

GnRH: gonadotrophin-releasing hormone

HDR: high dose rate

HIFU: high-intensity focused ultrasound

HR: hazard ratio

HRPC: hormone-refractory prostate cancer

HT: Hormone therapy

IAD: intermittent androgen blockade

IGRT: image guided radiotherapy

IMRT: intensity modulated radiotherapy

ISUP: International Society of Urologic Pathology

IPSS: International Prostate Symptom Score

LDR: low dose rate

LH: luteinising hormone

LHRH: luteinising hormone releasing hormone

LTAD: long-term androgen deprivation

MDT: multi-disciplinary team

MRC: Medical Research Council

MRI: magnetic resonance imaging

MRS: magnetic resonance spectroscopy

NCCN: National Comprehensive Cancer Network

NICE: National Institute for Health and Clinical Excellence

ONJ: osteonecrosis of the jaw

OS: overall survival

OR: Odds ratio

PET: positron emission tomography

PFS: progression-free survival

PLCO: Prostate, Lung, Colorectal and Ovarian

ProtecT: Prostate Testing for Cancer and Treatment

PSA: prostate-specific antigen

PSADT: prostate-specific antigen doubling time

RANK: Receptor activator of nuclear factor kappa-B

RCT: randomised controlled trial

RECIST: Response Evaluation Criteria in Solid Tumors

SRE: skeletal-related events

STAD: short-term androgen deprivation

TRUS: transrectal ultrasound

TURP: transurethral resection of the prostate

CRPC: castration resistant prostate cancer

mCRPC : metastatic castration resistant prostate cancer

Integrated Care and the Multi-disciplinary Team (MDT)

- The concept of integrated care is becoming increasingly accepted as a way to overcome fragmentation of patient management and to provide a consistent treatment strategy across the MDT. It also creates an optimal structure that facilitates audit and peer review.
- Integration within the MDT is essential for patients with prostate cancer because the collaboration between MDT members (Table 1) is central to the treatment strategy, with ongoing support from the wider team to manage pain and the adverse effects of therapy. By being familiar with the complete spectrum of management strategies, the MDT can assist patients in making treatment decisions that are specific for their individual disease state, co-morbid conditions, age and lifestyle.

Table 1: The make-up of the MDT in the prostate cancer setting

• Urological surgeons	• Oncology and urology nurse specialists
• Clinical and medical oncologists	• Palliative care specialist
• MDT co-ordinator and secretarial support	• Histopathologists
• Radiologists	

- Moves to true integrated practice can add value in the following ways: [Integrated Care Network 2004]
  - Changing the identity or branding of a service to create more positive user responses and staff allegiances, enabling a clear break with the past.
  - Securing organisational efficiencies, for example, in the shape of shared support services, integrated management, innovative administrative processes and emerging hybrid roles.
  - Defining a focus for action that includes clearer processes of accountability and is less prone to distraction by wider organisational concerns.
  - Introducing more robust arrangements for team-working and leadership-working in challenging times.
  - Creating new opportunities for investment, for example, in IT systems, and opening access to new sources of funding.
- The algorithms presented in this guidance provide a single framework that is adapted for each major category of prostate cancer: localised, locally advanced and advanced (Figure 1).
- The treatment algorithms presented in this document (Figures 2–4) represent a management structure that goes beyond a simple co-ordinated system and will work most efficiently when the MDT is functioning as a single integrated unit.

Integrated care and clinical governance

- The effective functioning of the MDT and tailored care pathways for patients will support the (now routine) clinical governance procedures implemented throughout the NHS. Traditionally, clinical governance relates to a single organisation or service and this can raise challenges, with the recognition that patients require management across different organisations and services. Therefore, it is appropriate to apply the principles of clinical governance to individual patients or groups of patients.
- The focus should be on optimum patient satisfaction and care, rather than on performance of the NHS institution. The MDT and development of organised pathways ensures that the patient's journey is monitored and assessed as a single entity.

Approach within the MDT

Key questions for the MDT – Localised Prostate Cancer

- TNM stage?
- Gleason grade?
- Prostate-specific antigen (PSA)/PSA kinetics?
- Performance Status?
- Co-morbidity/life expectancy?
- Symptoms:
  - bowel
  - urine (IPSS score)
  - bone
- Sexual Function?
- Social Situation?
- Family History?
- Clinical Trials?

Diagnostic Tests

- Digital rectal exam (DRE)
- PSA
- Transrectal ultrasound
- (TRUS)/biopsy
- MRI/CT pelvic scan*
- Bone scan*

(*Not mandatory for low-risk patients)

Key points for discussion with the patient

- Prognosis with and without radical treatment?
- Treatment options?
- Treatment side-effects?
- Impact on quality of life?
- Importance of:
  - Sexual function?
  - Urinary function?
  - Bowel function?
  - Physical strength, energy?
  - Level of activity?
  - Accessibility to prescribed drugs?
  - Psychosocial impact on them and their family?
- Family history?
- Clinical trials?

Approach within the MDT

Key questions for the MDT – Locally Advanced Prostate Cancer

- TNM stage?
- Gleason grade?
- Prostate-specific antigen (PSA)/PSA kinetics?
- Performance Status?
- Co-morbidity/life expectancy?
- Symptoms:
  - bowel
  - urine (IPSS score)
  - bone
- Sexual Function?
- Social Situation?
- Family History?
- Clinical Trials?

Diagnostic Tests

- DRE
- PSA
- TRUS
- TRUS biopsy/Transperineal biopsy
- MRI/CT pelvic scan
- Bone scan
- Specialist imaging where indicated e.g. choline PET
- Consider lymph node sampling (if this will determine changes in management approach)

Key points for discussion with the patient

- Survival prognosis?
- Treatment options?
- Treatment side-effects?
- Impact on quality of life?
- Importance of:
  - Sexual function?
  - Urinary function?
  - Bowel function?
  - Physical strength, energy?
  - Level of activity?
  - Accessibility to prescribed drugs?
  - Psychosocial impact on them and their family?
- Family history?
- Clinical trials?

Approach within the MDT

Key questions for the MDT – Advanced Prostate Cancer

- TNM stage?
- Gleason grade?
- Prostate-specific antigen (PSA)/PSA kinetics?
- Performance Status?
- Co-morbidity/life expectancy?
- Symptoms:
  - bowel
  - urine (IPSS score)
  - bone
- Sexual Function?
- Social Situation?
- Family History?
- Clinical Trials?
- Palliative Care Referral?

Diagnostic Tests

- DRE
- PSA
- Limited? TRUS biopsy (to confirm histological diagnosis for future therapies – e.g. entry into clinical studies)
- Biochemistry screen
- Full blood count
- Bone scan
- Consider CT Chest / Abdomen; CT/MRI pelvis if it may influence management decisions and entry into future clinical trials

Key points for discussion with the patient

- Survival prognosis?
- Treatment options?
- Treatment side-effects?
- Impact on quality of life?
- Importance of:
  - Sexual function?
  - Urinary function?
  - Bowel function?
  - Physical strength, energy?
  - Level of activity?
  - Accessibility to prescribed drugs?
  - Psychosocial impact on them and their family?
- Family history?
- Clinical trials?

The MDT ***Meeting*** is an essential part of cancer management. However, there are often difficulties in identifying which patients to discuss and whether time allows for presentation of relapsed patients as well as new diagnoses, ensuring that their details and diagnoses are available, and keeping a record of decisions made at the meetings.

- MDTs have repeatedly been endorsed as the principal mechanism for ensuring that all relevant disciplines and professional groups contribute to, and participate in, decisions regarding the clinical management of patients [NICE 2002].
- MDT-working is positively related to a range of measures of effectiveness, including the quality of clinical care.
- It is important to emphasise the distinction between management and administration.
- A central concept of integrated care is to reinforce the role of the MDT (working as a single unit), but with enough clinical freedom to tailor management strategies to the needs of individual patients.
- Treatment strategies are influenced by the stage of disease and by an interaction between the risk of disease progression, survival and key patient characteristics, such as age, lifestyle and general health. The discussion of these factors is of crucial importance in determining the most appropriate way forward. For example, age and the presence of co-morbidities may be a restrictive factor when considering surgery.
- The case notes, pathology reports, test results and radiology for each patient must be available to be discussed at the meeting. The MDT must also ensure that the patient has the fullest possible role in determining treatment – the importance of this cannot be overstated. Patient preference should be discussed within the MDT. Although the majority of men with prostate cancer want to be involved in treatment decisions, an estimated one in five of all patients does not raise, or really understand, the potential issues and associated side-effects of treatments and alternatives that may be available to them [House of Commons Committee of Public Accounts 2006].
- The possibility of including a patient in a relevant clinical trial should be highlighted.

Approach to the Patient

The patient's expectations

The patient should have the right to discuss their treatment with appropriately trained members of the MDT

- After a diagnosis of prostate cancer, most men will want to have some involvement in the decisions concerning their care. The following aspects have been found to be important [Davison BJ, *et al* 2004]:
  - Honesty about the severity of the cancer and their prognosis
  - Discussion of the best treatment options
  - The clinician being up-to-date on ongoing and recent research
  - Disclosing all treatment options
  - How cancer may affect their daily functioning
- It is essential that the patient and healthcare professionals discuss the likelihood of adverse events associated with each treatment option and implications for their future lifestyle when determining management strategies.
- The patient and his partner, family and/or other carers should be fully informed about care and treatment options and therefore able to make appropriate decisions based upon the choices offered by their healthcare professionals. For example, the choice between radical treatment and active surveillance may be influenced by a patient's desire to retain sexual activity, physical energy and quality of life.
- Patients should be informed and advised regarding the available treatment options and the potential effects of these on their lifestyle and quality of life.

Discussing evidence with patients

There is a lack of evidence to guide how healthcare professionals can most effectively share clinical data with those patients facing treatment decisions. However, basing recommendations largely on relevant clinical studies and expert opinion, it is possible to achieve five communication objectives when framing and communicating clinical evidence.

1. Understand the patient's experience, expectations and preferences
2. Build partnerships with the patient and carer
3. Provide evidence and discuss uncertainties and side-effects
4. Present recommendations
5. Check for understanding and agreement

Assessment and Diagnosis

Screening

PSA screening remains a relatively contentious subject in the field of prostate cancer. Assessment of the value of a test, which is so widely disseminated in clinical practice, is a particular challenge. There is conflicting evidence regarding whether screening results in a reduction in mortality from the disease. As a consequence available evidence must be used to minimize the risk of harms and maximize the benefits for an individual man.

- Three ongoing large, randomised, controlled clinical trials are evaluating the value of PSA screening for prostate cancer: the European Randomised Study of Screening for Prostate Cancer (ERSPC) [Schroder FH, *et al* 2012], the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial in the US [Andriole GL, *et al* 2012] and the UK-based Prostate Testing for Cancer and Treatment (ProtecT) study [Rosario DJ, *et al* 2008]. The first reports from these trials have been published and have added further information to the PSA screening debate:
    - The PLCO study reported no mortality benefit with the combination of PSA screening and digital rectal examination (DRE) during a median follow-up of 13 years [Andriole GL, *et al* 2012]. However, this was not a trial of screening versus no screening, but rather of "systematic" versus "opportunistic" screening, and there were high rates of screening in the control group.
    - In contrast, the ERSPC trial found that PSA screening was associated with a 21% relative reduction in prostate cancer mortality at a median follow-up of 11 years, equivalent to the prevention of approximately 7 prostate cancer deaths per 10,000 men screened. This mortality benefit was associated with a high risk of overdiagnosis, with nearly 76% of men who underwent a biopsy following an elevated PSA value having no cancer detected on biopsy [Schroder FH, *et al* 2012].
    - ProtecT has demonstrated a benefit of repeat PSA testing in reducing the risk of high-grade prostate cancer in men with an initial PSA concentration of 3–20 ng/ml [Rosario DJ, *et al* 2008].
- Based on the results of these two large, randomised trials, the general consensus is that at present there is insufficient evidence for widespread mass screening for prostate cancer. However early detection (opportunistic screening) should be offered to the well-informed man Quality of life and cost-effectiveness analyses from the ERSPC and PLCO trials, along with mortality results from ProtecT are needed to help resolve the ongoing PSA screening debate.

Risk factors for prostate cancer

The risk factors for prostate cancer are generally well-documented, but are highlighted here for completeness of the Guidance.

- Age
    - Relatively rare in men under the age of 50 years.
    - Incidence increases in those over 60 years.
- Race
    - A higher incidence of the disease is seen in African-Caribbean, African-American and West African races. The UK PROCESS study demonstrated that black men in the UK have substantially greater risk of developing prostate cancer compared with white men [Ben-Shlomo Y, *et al* 2008]
    - Men of Chinese and Japanese origin have a lower incidence of disease [Delongchamps NB, *et al* 2006].

- Geography
  - The highest incidence of prostate cancer is currently seen in North America and Northern Europe.
- Family history
  - Men with a first-degree relative affected by prostate cancer have a relative risk of developing the disease themselves 2-fold greater than men with no relatives affected [Steinberg GD, *et al* 1990].
  - Those men with an affected second-degree relative have an increased relative risk of 1.7 of developing the disease.
  - Men with both a first- and second-degree relative affected have an increased relative risk of 8.8 of developing the disease.
  - A small subpopulation of individuals with prostate cancer (about 9%) has true hereditary prostate cancer. 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 [Hemminki K 2012].
  - There is also some evidence to show a link between an increased risk of prostate cancer where there is a family history of breast, ovarian, bladder or kidney cancer [Negri E, *et al* 2005].
  - The UK Familial Prostate Cancer Study is currently looking at the genetics of the disease with possible sites of interest lying on chromosomes 2, 5, Y and loss of heterozygosity at 10q and 16q.

Diagnostic tests

The main diagnostic tools for prostate cancer include digital rectal examination (DRE), serum prostate specific antigen (PSA), and transrectal ultrasound (TRUS). The definitive diagnosis depends on the histological verification of adenocarcinoma in prostate biopsy cores or operative specimens.

DRE

- The DRE remains valid as an initial method for assessing the prostate; however, DRE findings should not be regarded as a fail-safe test.

PSA

- PSA is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate.
- As an independent variable, PSA concentrations are a better predictor of cancer than suspicious findings on DRE or TRUS [Catalona WJ, *et al* 1994;Elgamal A-AA, *et al* 1996].
- PSA is organ specific but not cancer-specific. Therefore, serum concentrations of PSA can be elevated in the presence of benign prostatic hyperplasia (BPH), prostatitis and other non-malignant conditions. Furthermore, there is, as yet, no recommendation for the optimal PSA threshold value that most effectively avoids the detection of insignificant cancers that are unlikely to be life-threatening [Aus G, *et al* 2003; Aus G, *et al* 2004].
- While PSA concentrations generally increase with advancing disease stage, the ability of PSA levels to accurately predict pathological stage in any one individual is low [Hudson MA, *et al* 1989; Brawer MK & Lange PH 1989; Partic AW, *et al* 1990].

- Asymptomatic patients who request a PSA test should be counselled before the procedure for the following reasons [Dearnaley DP, *et al* 1999]:
  - Although the test may detect a cancer at a stage where curative treatment can be offered, PSA will fail to detect some early tumours.
  - A PSA test may detect early prostate cancer in an estimated 5% of men aged 50–65 years.
  - Treatment of early prostate cancer can put the patient at some risk of toxicity and may not necessarily improve life expectancy

Factors affecting PSA concentrations are summarised below.

Age and race

Table 2: Age-specific PSA (ng/ml) reference ranges, by race [DeAntoni EP, *et al* 1996]

Age (years)	White	Black	Latino	Asian
40–49	0–2.3	0–2.7	0–2.1	0–2.0
50–59	0–3.8	0–4.4	0–4.3	0–4.5
60–69	0–5.6	0–6.7	0–6.0	0–5.5
70–79	0–6.9	0–7.7	0–6.6	0–6.8

Biopsy/Transurethral Resection of the Prostate (TURP) can cause an increase in PSA for a variable time period (4–12 weeks) [Xu ZQ, *et al* 2002].

Prostatitis can cause an increase in PSA concentration, which can be reduced to within a normal range with antibiotic treatment [Tchetgen MB, *et al* 1997; Gamé X, *et al* 2003].

Prostate size – a benignly enlarged gland can influence PSA concentrations.

Infection – elevated PSA levels can be sometimes be seen with febrile urinary tract infections.

Free and complexed PSA should be understood. Catalona *et al*. conclude that percentage free PSA is most useful in men with a PSA concentration in the range 2–15 ng/ml (Table 3); the higher the percentage of free PSA the lower the probability of cancer [Catalona WJ, *et al* 1998].

Table 3: Probability of prostate cancer based on total and percentage free PSA [Catalona WJ, *et al* 1998].

	Probability of cancer (%)
Total PSA (ng/ml)	
0–2	~1
2–4	15
4–10	25
>10	>50
Free PSA (%)	
0–10	56
10–15	28
15–20	20
20–25	16
>25	8

PSA density i.e. $\frac{\text{PSA level (ng/ml)}}{\text{TRUS-determined prostate volume (ml)}}$

May be helpful in differentiating BPH from prostate cancer in patients who have a normal DRE with a PSA 4–10ng/ml. A PSA density >0.15 may suggest prostate cancer.

PSA velocity can be valuable in the follow-up of men with a normal PSA but prior negative biopsies. Velocity is measured by a change in PSA concentration in three consecutive measurements taken at 6-monthly intervals. A change in PSA concentration of >0.75 ng/ml per year is more likely to indicate prostate cancer than BPH. The usefulness of PSA velocity in those with a PSA concentration >10 ng/ml is unknown [Smith DS & Catalona WJ 1994].

Transrectal Ultrasound (TRUS)

- TRUS detects 50% more patients with prostate cancer than physical examination alone [Gustafsson O *et al* 1992; Mettlin C, *et al* 1996], but the ultrasonic appearance of prostate cancer is variable and only a very small number of cancers are detected if a DRE and PSA test are normal [Mettlin C, *et al* 1996; Jones WT & Resnick MI 1990; Ellis WJ, *et al* 1994]. Therefore, TRUS is mainly used to aid biopsy.

Biopsy and tumour grading

- 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 standardised conditions (i.e. no ejaculation and no manipulations).
- Prostate biopsies are traditionally guided by TRUS. The alternative is to use a transperineal approach with template biopsies.
- The National Institute for Health and Clinical Excellence (NICE) Prostate Cancer Guideline recommends that the serum PSA level alone should not automatically lead to a prostate biopsy [NICE 2008]. It states that to help men decide whether to have a prostate biopsy, healthcare professionals should discuss with them their PSA level, DRE findings (including an estimate of prostate size) and co-morbidities, together with their risk factors (including increasing age and black African and black Caribbean ethnicity) and any history of a previous negative prostate biopsy.
- NICE further highlights that men and their partners or carers should be given information, support and adequate time to decide whether or not they wish to undergo prostate biopsy [NICE 2008]. Men will need to comprehend the potential risks (such as potentially living with a diagnosis of prostate cancer that is deemed clinically insignificant) and the benefits of prostate biopsy.
- Where TRUS-guided biopsy is indicated, a minimum of 10 biopsies (as recommended by The British Prostate Testing for Cancer and Treatment Study) [Donovan J, *et al* 2003] should be obtained, according to the volume of the prostate. Biopsies should be performed under local anaesthetic and antibiotic cover [Eskicorapci SY, *et al* 2004].
- For each biopsy site, the number of biopsies positive for carcinoma and the International Society of Urologic Pathology (ISUP) 2005 Gleason score should be reported [Epstein JI, *et al* 2005]. The amount of cancer in each core should also be recorded either in terms of cancer core length (mm) or proportion of core involvement (%) as this correlates with tumour volume, extraprostatic extension, and prognosis after prostatectomy [Grossklaus DJ, *et al* 2002].
- The indications for a repeat biopsy if the first biopsy is negative include: rising and/or persistently elevated PSA; suspicious DRE; atypical small acinar proliferation (ASAP); extensive (multiple biopsy sites) prostatic intraepithelial neoplasia
- Magnetic Resonance Imaging (MRI) may be used to identify the possibility of an anterior located tumour and also allow targeted biopsies of any suspicious or abnormal area [Lemaitre L, *et al* 2009].
- A European study has reported that a prostate cancer detection rate for the first set of biopsies is 24% and for the second set of biopsies after a negative initial set as 13% [Djavan B, *et al* 2005].31
- Complications of transrectal biopsy include macrohaematuria and haematospermia. Severe infections were initially reported in <1% of cases, but this rate has increased in the last few years as a consequence of the evolution of antibiotic resistance strains with more post-biopsy hospitalisations for infectious complications while the rate of non-infectious complications has remained stable [Loeb S, *et al*. 2011].
- In some patients, prostate biopsy may be performed using a transperineal, template guided technique as the preferred approach. Possible reasons for this include: previous repeated negative TRUS biopsies; clinical or radiological suspicion of a large anterior tumour; more accurate characterization of tumour location and extent in order to guide management and assess eligibility for inclusion into focal therapy trials.
- In these patients, the prostate is divided into 20 anatomical zones and each zone is biopsied at 5mm intervals in a systematic manner using a template grid to guide the biopsy needle placement. Typically this results in between 40-70 biopsies depending on the size of the prostate gland.

- The biopsies are reported in a similar manner to TRUS-guided biopsies, with Gleason score, cancer core length (mm) and proportion of core involvement (%) recorded for each zone.
- This information can also be conveyed in a visual format by creating a 'map' of the prostate that illustrates the Gleason score and extent of tumour in each individual zone.

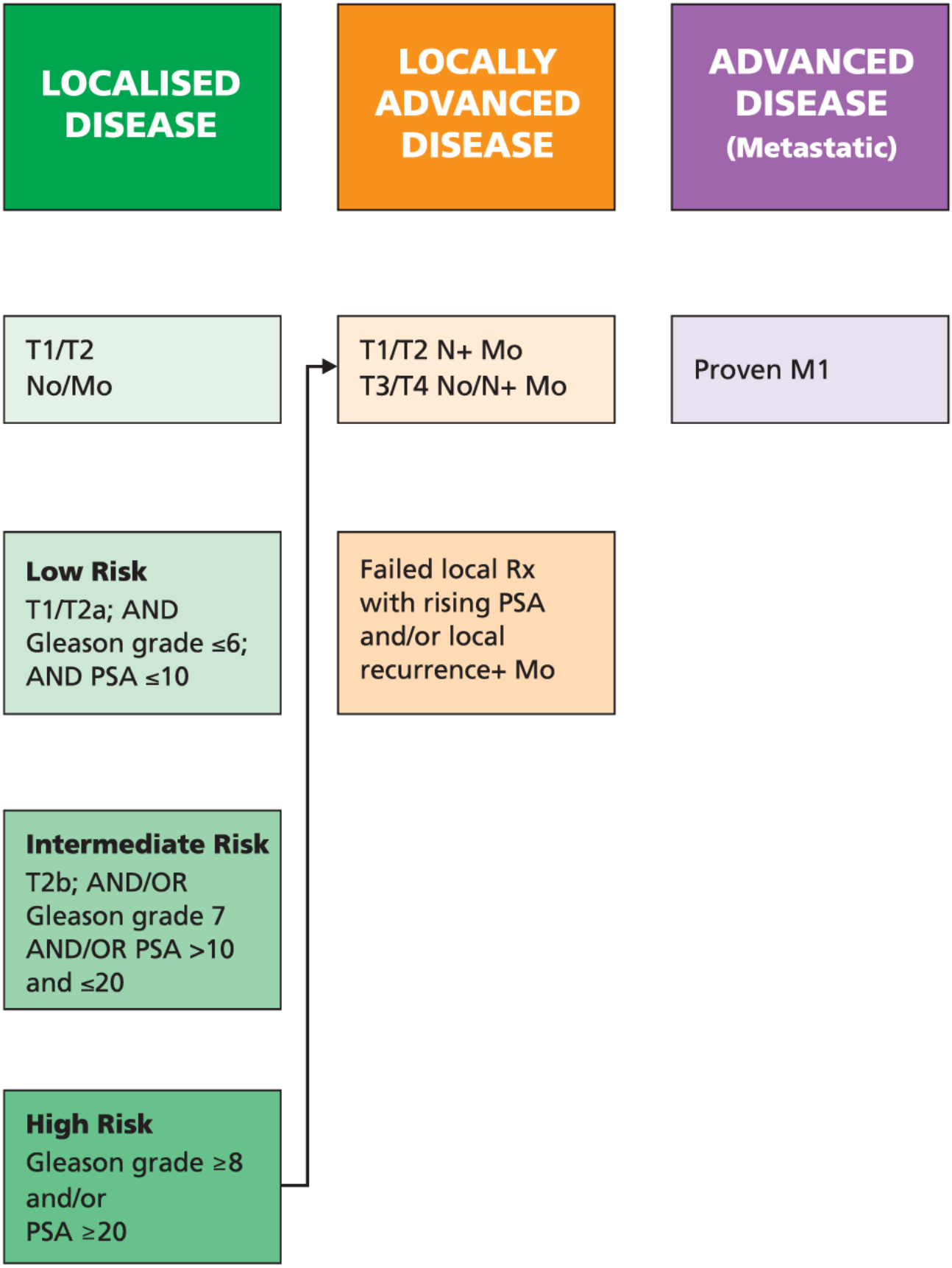
Magnetic Resonance Imaging (MRI)

- TNM staging, Gleason score, and PSA concentration facilitate estimation of the risk of extracapsular disease and lymph node metastases. Pelvic staging is required for those of high or intermediate risk (according to NCCN classification). MRI is the preferred option to stage pelvic lesions and where MRI is contraindicated, computed tomography (CT) should be used [NICE 2008].
- MRI is sensitive and specific in identifying extracapsular extension of prostate cancer in patients with high - or intermediate-risk disease [Allen DJ, *et al* 2004].
- NICE concludes [NICE 2008]:
    - MRI is now the most accurate and commonly-used imaging technique for tumour-staging men with prostate cancer. Many of the original publications on MRI technology are now considered to be outdated, and the accuracy reported for MRI is improving, typically with multiparametric, diffusion weighted scans
    - After transrectal prostate biopsy, intra-prostatic haematoma can affect image interpretation for at least 4-6 weeks.

Bone scans

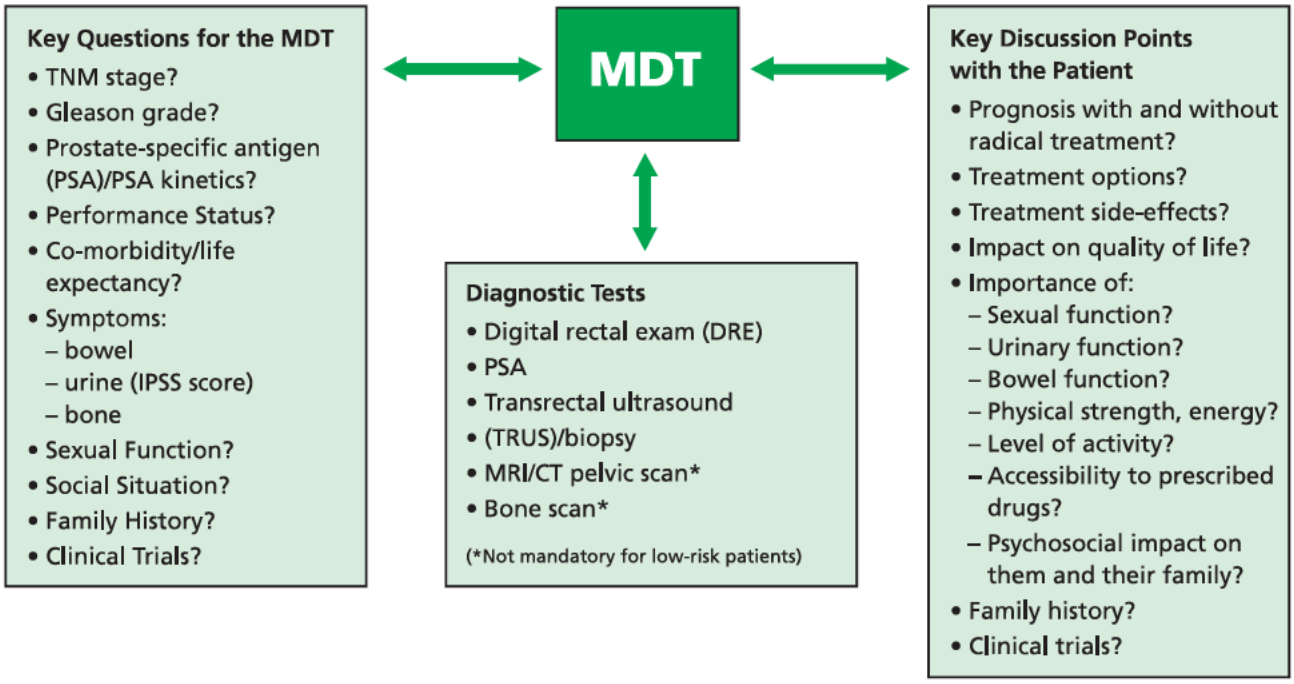
- Bone scans (particularly in patients with PSA concentration >20 ng/ml) are also important in the assessment process. A PSA concentration of <10 ng/ml is unlikely to indicate bone metastases at presentation. A PSA cut-off value of 10 ng/ml for men with Gleason grade ≤7 indicates a negative predictive value range of 91.5–100% [Gerber G & Chodak GW 1991].
- MRI can be an additional approach for distinguishing borderline metastases.

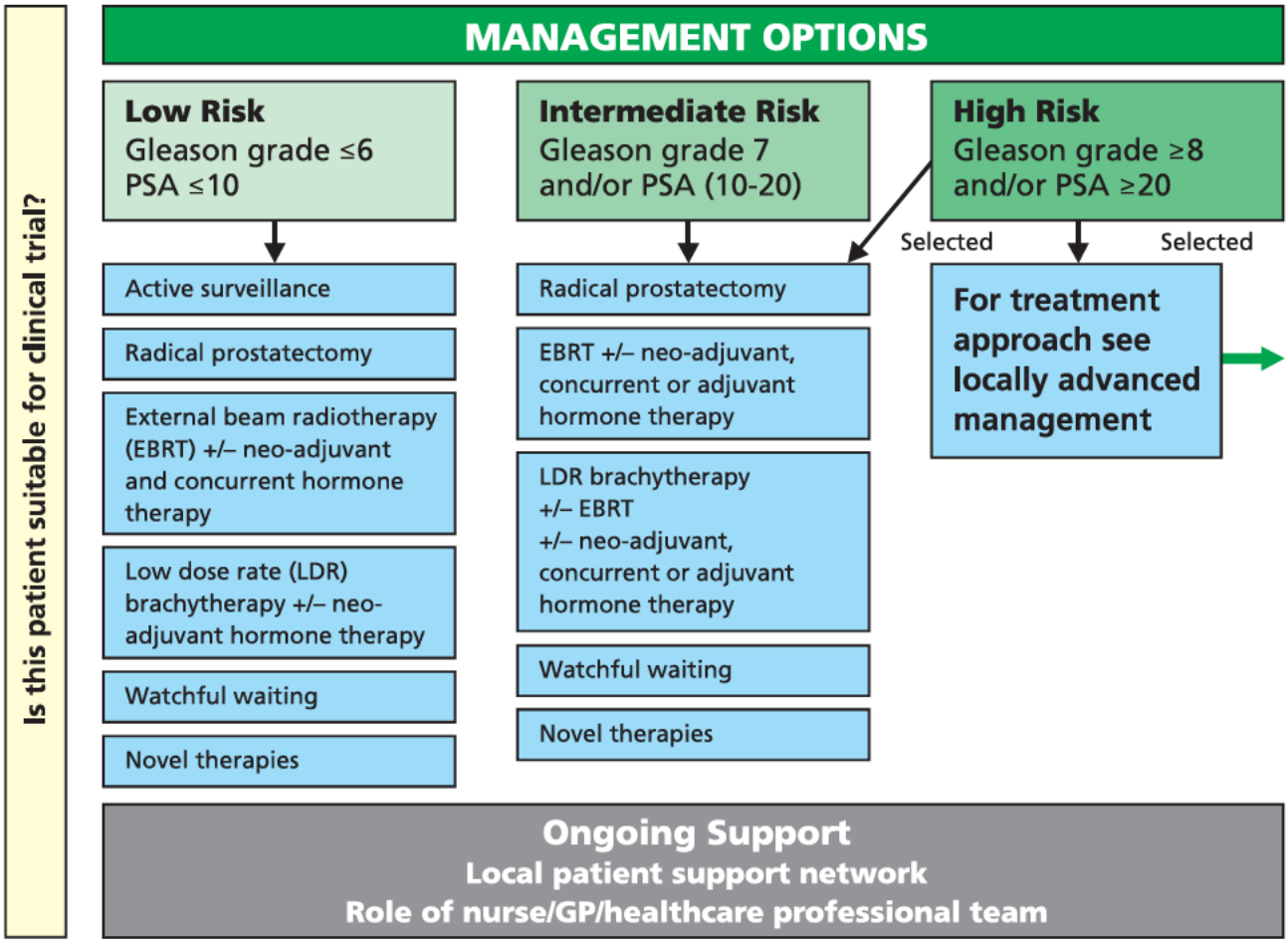
Figure 1: Summary of the definition of prostate cancer stages



Localised Disease: Management Options

Figure 2: Treatment algorithm for localised disease





The following guidance for managing localised prostate cancer focuses on low- and intermediate-risk categories, defined here as [D'Amico AV, *et al* 1998]:

- Low risk (T1/T2a; AND Gleason grade ≤6; AND PSA concentration ≤10 ng/ml)
- Intermediate risk (T2b; AND/OR Gleason grade 7 AND/OR PSA concentration: >10 and ≤20 ng/ml)

In the proposed management algorithms, high-risk localised disease falls more naturally into management of locally advanced disease.

Patient choice and the presence or absence of co-morbidities should be an essential component of management decisions in men with localised disease. Decisions concerning the choice of radical treatments need to be carefully balanced with the different options available and the impact of such treatments on a patient's co-morbidities.

In this section available evidence for the following management approaches is outlined:

- Active surveillance
- Watchful waiting
- Radical prostatectomy
- External Beam Radiation Therapy (EBRT)
- Low dose rate (LDR) brachytherapy
- Neoadjuvant/adjuvant hormone therapy
- Novel therapies

Active surveillance

Overview

- Active surveillance is an approach to the management of early prostate cancer in which the choice between curative treatment and observation is based on evidence of disease progression (PSA kinetics, repeat biopsy or MRI findings) during a period of close monitoring. The aim is to reduce the burden of treatment side-effects without compromising survival.
- Patients suitable for active surveillance are those with low-risk localised disease who are fit for radical treatment. Ongoing prospective studies of active surveillance have shown that 60–80% of such men will avoid the need for treatment, and that 99-100% prostate cancer-specific survival at 10 years is achievable [Selvadurai ED, *et al* 2013; van den Bergh RC, *et al* 2008].
- Active surveillance should be clearly distinguished from watchful waiting. Traditional watchful waiting involves relatively unstructured observation with late, palliative treatment for those who develop symptoms of progressive disease. In contrast, active surveillance involves close monitoring with early radical treatment in those with signs of disease progression.

Patient selection

- Low (or intermediate) risk, clinically localised prostate cancer
  - Clinical stage T1c/2a
  - Gleason grade ≤3+4
  - PSA concentration <15 ng/ml
  - Positive biopsies ≤50%
  - Age 50–80 years
  - Fit for radical treatment
- Active surveillance is particularly suitable for a subgroup of men with low-risk localised prostate cancer who have clinical stage T1c, a Gleason score of 3+3, a PSA density of <0.15 ng/ml per ml with <10 mm of any core involved [NICE 2008].

Side-effects

- Psychological uncertainty

Clinical evidence

- The case for active surveillance is based on the knowledge that PSA testing leads to significant overdiagnosis of prostate cancer. That is, approximately 50% of all cases detected as a result of PSA testing would never have been diagnosed in the absence of testing [Draisma G *et al* 2003]. It follows that treatment is 'unnecessary' in approximately half of all cases of PSA-detected prostate cancer.
- van den Bergh has reported the outcome of expectant management in 616 men who were diagnosed with prostate cancer between 1994 and 2007 at a mean age of 66.3 years in the ERSPC [van den Bergh RC, *et al* 2008]. All patients had low-risk disease with PSA <10 ng/ml, PSA density <0.2 ng/ml per ml, stage T1c/T2, Gleason score ≤3+3=6, and ≤2 positive biopsy cores. Median follow-up was 3.9 years. The 10-year prostate cancer-specific survival (21 patients at risk) was 100%, which sharply contrasted with 77% overall survival (OS), due to deaths from other causes.
- Selveduarai *et al*. reported the outcome of 471 men recruited to the Royal Marsden active surveillance study since 2002, at a median follow-up of 5.7 years [Selvadurai ED, *et al* 2013]. Median age was 66 years, and median initial PSA concentration 6.4 ng/ml. The 5-yr treatment-free probability was 70% (95% CI, 65–75%). There were two deaths from prostate cancer. Predictors of time to adverse histology were GS 7, PSAV >1 ng/ml per year, low ratio of free PSA to total PSA, and PPC >25%. There were two deaths from prostate cancer [Selvadurai ED, *et al* 2013].

Watchful waiting

Overview

- Watchful waiting is an approach to the management of localised prostate cancer that aims to avoid treatment, or delay it for as long as possible.
- Watchful waiting is particularly suitable for patients aged over 75 years or younger men with significant co-morbidities.
- Watchful waiting should be clearly distinguished from active surveillance. Conventional watchful waiting involves relatively unstructured observation with late, palliative treatment (usually hormone therapy) for those who develop symptoms of progressive disease. In contrast, active surveillance involves close monitoring with early, radical treatment in those with signs of progression.

Patient selection

- Asymptomatic clinically localised prostate cancer
  - Clinical stage T1–3 N0 M0
  - Gleason score ≤7
  - Any PSA concentration
  - Not suitable for radical treatment (usually by virtue of older age or co-morbidities)

Side-effects

- Uncertainty

Clinical evidence

- The NICE clinical guideline confirms a lack of evidence for watchful waiting and the Guideline Development Group reached a consensus that the recommendation from NICE would avoid unnecessary investigations [NICE 2008]:
  - Men with localised prostate cancer who have chosen a watchful waiting regimen and who have evidence of significant disease progression (rapidly rising PSA level or bone pain) should be reviewed by a member of the urological cancer MDT.

Radical Treatments

Radical Prostatectomy (RP)

Overview

- The procedure involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain a negative margin. This can be accompanied by bilateral pelvic lymph node dissection. There are now four approaches to performing a radical prostatectomy: retropubic, perineal, laparoscopic and robotic. Laparoscopic and robotic approaches have the potential advantage of reduced blood loss and shorter inpatient stays.
- Selley *et al*. reviewed a total of 17 studies (two randomised controlled trials [RCTs] and 15 observational studies involving a total of 5410 patients) to investigate the efficacy of radical prostatectomy for men with localised prostate cancer. Cancer-specific survival after 10 years of follow-up ranged from 86% to 91%, with clinical disease-free survival (DFS) ranging from 57% to 83% [Selley S, *et al* 1997].

Patient selection

- Anaesthetic fitness
- At least 10 years' life expectancy

Side-effects

- Based on the systematic review by Selley *et al*., the following side-effects should be considered [Selley S, *et al* 1997]:
  - Operative and post-operative mortality: 0.2–1.2%
  - Sexual dysfunction: 51–61%
  - Incontinence (mild stress): 4–21%
  - Incontinence (total): 0–7%

Clinical evidence

- Two randomised trials have compared radical prostatectomy with watchful waiting in localised prostate cancer [Bill-Axelson A, *et al* 2011].
    - After a follow-up of 15 years, the SPCG-4 trial showed that RP was associated with a reduction of all-cause mortality: RR=0.75 (0.61 to 0.92). According to a post hoc statistical sub-group analysis, the number to treat (NNT) to avert one death was 15 overall and 7 for men younger than 65 years of age. Radical prostatectomy was also associated with a reduction in prostate cancer-specific mortality: RR=0.62 (0.44 to 0.87).
- This OS and CSS benefit could not be reproduced in another prospective randomised study [Wilt TJ, *et al* 2012]. After a median follow-up of 10 years, the PIVOT trial showed that RP did not significantly reduce all cause mortality: HR=0.88 (0.71 to 1.08); p=0.22, nor did RP significantly reduce prostate cancer mortality: HR=0.63 (0.36 to 1.09); p=0.09. According to a preplanned sub-group analysis among men with low-risk prostate cancer (n=296), RP non-significantly increased all-cause mortality: HR=1.15 (0.80 to 1.66). For men with intermediate-risk tumours (n=249), RP significantly reduced all-cause mortality: HR=0.69 (0.49 to 0.98). Among men with high-risk tumours (n=157), RP non-significantly reduced all-cause mortality: HR=0.40 (0.16 to 1.00).Among men with PSA > 10, RP significantly reduced all cause mortality: HR=0.67 (0.48 to 0.94).
    - Faced with these figures, some patients would choose surgery, but should also be given the option of conservative management with active surveillance [Singer PA, *et al* 1991].

Neoadjuvant and adjuvant hormone therapy with radical prostatectomy

- A review and meta-analysis of the role of Neoadjuvant Hormone Therapy (NHT) and RP has shown that this approach did not improve OS or DFS, but did significantly reduce positive margin rates [relative risk (RR): 0.49; 95% confidence interval (CI): 0.42-0.56, P < 0.00001), organ confinement (RR: 1.63; 95% CI: 1.37-1.95, P < 0.0001) and lymph node invasion (RR: 0.49; 95% CI: 0.42-0.56, P < 0.02) [Shelley MD, *et al* 2009]. Therefore, evidence suggests that the down-staging achieved with neoadjuvant hormone therapy does not translate into improved DFS, and therefore cannot be recommended outside of clinical trials [Bonney WW, *et al* 1999; Paul R, *et al* 2004; Selli C & Milesi C. 2004; Witjes WPJ, *et al* 1997].
- Similarly, there is currently no evidence that adjuvant hormone therapy provides a survival advantage for patients with pathologically proven localised disease [Hachiya T, *et al* 2002; Prayer-Galetti T, *et al* 2000]. A recent Cochrane review and meta-analysis studied the role of adjuvant HT following RP: the pooled data for 5-year OS demonstrated an odds ratio (OR) of 1.50 and 95% CI: 0.79-2.84 [Shelley MD, *et al* 2009]. Although this finding was not statistically significant, there was a trend favouring adjuvant HT. There was no survival advantage at 10 years.

Adjuvant radiotherapy after radical prostatectomy

- Extracapsular invasion (pT3), Gleason score > 7, and positive surgical margins (R1) can be associated with a risk of local recurrence and the role of adjuvant treatments for this high risk group is considered in the section of locally advanced prostate cancer and radical prostatectomy.

External Beam Radiotherapy (EBRT)

Overview

- Selley *et al*. reviewed 21 observational studies and one RCT involving radiotherapy and found that survival and recurrence rates are associated with grade and stage of the disease. The 5-year DFS for those with T1–T2 stage disease averaged 70–80%. Local progression was observed in 10–20% of these patients, while distant metastases were observed in 20–40% [Selley S, *et al* 1997].
- Nilsson *et al*. performed a systematic overview of radiotherapy in prostate cancer. Data from 26 non-randomised trials of conventional EBRT showed a 10-year DFS of 100%, 69% and 57% for T1a, T1b and T2 stage disease, respectively [Nilsson S, *et al* 2004].
- Long-term follow-up after EBRT continues to demonstrate an improvement in cause-specific survival. Improved selection and technical developments in radiotherapy leading to increased doses have shown better results.

Three-dimensional conformal radiotherapy (3D-CRT)

- There is evidence that increased radiation dose is associated with increased cancer cell kill for men with localised prostate cancer. However, the traditional two-dimensional technique of treatment planning and delivery is limited by the normal tissue toxicity of the surrounding structures (bladder, rectum and bowel), such that the dose that can be safely delivered to the prostate by EBRT is of the order of 64Gy in 2Gy per day fractions. Several technological advances over the last 20 years have enhanced the precision of EBRT, and have resulted in improved outcomes.
- The three-dimensional conformal radiotherapy (3D-CRT) approach reduces the dose-limiting late side-effect of proctitis [Dearnaley DP, *et al* 1999] and has allowed for dose escalation to the whole prostate to up to78 Gy.

Intensity Modulated Radiotherapy (IMRT)

- IMRT is an advanced technique which has superseded 3D-CRT. IMRT can modify the shape and intensity of the multiple radiotherapy beams. It is very precise in targeting the treatment area, sparing surrounding tissue and allowing dose escalation above 80Gy. IMRT is currently recommended, particularly for the irradiation of pelvic lymph nodes.

Dose escalation

- Several randomised studies have shown that dose escalation with 3D conformal radiotherapy and more recently with IMRT has a significant impact on the 5-year biochemical relapse free survival. However, no trials to date have shown an improvement in long term overall survival
- Evidence of the benefits of dose escalation has been demonstrated for T1–T3 prostate cancer by Pollack *et al*. in a phase III randomised study undertaken at the MD Anderson Hospital [Pollack A, *et al* 2002].
    - A total of 305 men were randomised between 1993 and 1998 to compare the efficacy of 70 Gy versus 78 Gy with a median follow-up of 60 months. The primary endpoint was freedom from failure (FFF), including biochemical failure, which was defined as three rises in PSA level.
    - The FFF rates for the 70 Gy and 78 Gy arms at 6 years were 64% and 70%, respectively (p=0.03). Dose escalation to 78 Gy preferentially benefited those with a pre-treatment PSA concentration >10 ng/ml; the FFF rate was 62% for the 78 Gy arm versus 43% for those who received 70 Gy (p=0.01). For patients with a pre-treatment PSA concentration ≤10 ng/ml, no significant dose-response relationship was found, with an average 6-year FFF rate of about 75%.
    - Although no difference in OS occurred, the freedom from distant metastasis rate was higher for those with PSA levels >10 ng/ml who were treated to 78 Gy (98% versus 88% at 6 years, p=0.056).
- Dearnaley and colleagues have reported their findings from the MRC RT01 study [Dearnaley DP, *et al* 2007].
    - In this 3D-CRT trial, 843 men were randomised to a standard dose of 64 Gy compared with an escalated dose of 74 Gy, with all men also receiving neoadjuvant hormone therapy.
    - Patients receiving the conventional dose had 5-year biochemical PFS rates of 60% compared to 71% in the dose-escalated arm. Advantages were also seen in terms of clinical PFS and the decreased use of androgen suppression.
    - An update of this study with 10 years of follow up has not shown any further benefit in biochemical PFS of 54% (172 events) versus 42% (224 events), HR 0.688 (0.56-0.84) p<0.0001 in favour of the dose escalated group [Dearnaley DP, *et al* 2011]. However, no overall survival benefit was demonstrated, with both the 64Gy and 74Gy arms having an overall survival of 70% HR 0.99 (0.77-1.28) p=0.337. The number of men requiring long term hormone therapy was reduced in the dose escalated arm HR 0.77 (0.59-1.00) p=0.05.
- Recently the long-term follow-up of the pilot study, which provided the initial safety and feasibility information for the national MRC RT01 trial have been published [Creak A, *et al* 2013].
    - In this study, 126 patients were randomised to a standard dose of 64 Gy compared with an escalated dose of 74 Gy after neoadjuvant androgen suppression.
    - After a follow up of 13.7 years, 49 of 126 patients restarted AS, 34 developed metastases and 28 developed CRPC. Median OS was 14.4 years.
    - Although escalated dose results were favourable, no statistically significant differences were seen between the randomised groups; PSA control (hazard ratio (HR): 0.77 (95% confidence interval (CI): 0.47–1.26)), development of CRPC (HR: 0.81 (95% CI: 0.40–1.65)), PC-specific survival (HR: 0.59 (95% CI:0.23–1.49)) and OS (HR: 0.81 (95% CI: 0.47–1.40)).
- The Dutch randomised phase III trial comparing 68 Gy with 78 Gy also demonstrated a significant increase in the 5-year rate of freedom from clinical or biochemical failure in patients treated with a higher dose of radiotherapy [Peeters ST, *et al* 2006]

- The phase III trial of the French Federation of Cancer Centres compared 70 Gy with 80 Gy in men with localised prostate cancer, in 306 patients with a low risk of pelvic lymph node involvement [Beckendorf V, *et al* 2011]. At a median follow up of 61 months, they demonstrated improved 5-year biological outcomes in favour of dose-escalated radiotherapy group. Using the Phoenix definition, the 5-year biochemical relapse rate was 32% and 23.5%, respectively (p = .09).
- Although these and other studies have shown benefits from dose escalation this has been offset to a degree by a reported increase in late rectal toxicity.
- Prospective non-randomised studies conducted at the Memorial Sloan Kettering cancer centre have compared the outcomes of 1100 men who received doses in the range of 64–70 Gy and 76–86 Gy using IMRT [Zelefsky MJ, *et al* 2001].
    - The results were evaluated within prognostic risk groups (using clinical stage, Gleason grade and presenting PSA concentration). They demonstrated that increasing the dose delivered beyond 70.2 Gy in men with intermediate- and high-risk disease improved the 5-year actuarial PSA relapse-free survival rate from 50% to 70% and 21% to 47%, respectively, in these two risk categories.
- IMRT has the potential to reduce late rectal toxicity as shown in a further study that reports 3-year actuarial ≥grade 2 gastrointestinal toxicity at 4% [Zelefsky MJ, *et al* 2002].
- A further development under investigation involves a change in the traditional fractionation schedules. Hypofractionation may improve cancer control for the same level of radiation-related toxicity and be a more effective treatment for prostate cancer with a predicted low alpha/beta ratio. Phase II dose escalation studies using shortened schedules of hypofractionated IMRT regimens have indicated acceptable early toxicity [Amer AM, *et al* 2003].
- The CHHiP (Conventional or Hypofractionated High Dose IMRT for Prostate Cancer) study is currently recruiting patients in the UK to compare standard fractionation IMRT (74 Gy in 37 fractions) to two hypofractionated IMRT regimens (60 Gy in 20 fractions or 57 Gy in 19 fractions) in combination with neoadjuvant hormone therapy [South CP, *et al* 2008]. There is no overall survival data available from this trial as yet but preliminary safety results have shown that hypofractionated high-dose radiotherapy seems equally well tolerated as conventionally fractionated treatment at 2 years

Image Guided Radiotherapy (IGRT)

- The advantages of dose escalation using IMRT means that organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity to the bladder, rectum and bowel. Techniques should therefore combine IMRT with some form of IGRT (fiducial markers, imaging), in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still under investigation.

Patient selection

- EBRT can be unsuitable for patients with bilateral hip replacement, previous radiotherapy, severe proctitis or bowel morbidity (such as ulcerative colitis or Crohns' disease).

Side-effects

- Acute complications include cystitis, faecal frequency and urgency, proctitis and rectal bleeding.
- Late complications occurring 3 months or later after treatment include impotence, bleeding, proctitis and diarrhoea.

EBRT plus neoadjuvant hormone therapy

- Neoadjuvant hormone therapy with an LHRH agonist can reduce the prostate volume by up to 30–40% [Shearer RJ, *et al* 1992;Forman JD, *et al* 1995] This can allow smaller treatment fields and as a result the level of toxicity experienced.
- There are also reports of an additive or synergistic effect on tumour cell kill with combined therapy. Theories as to the mechanism of this include improved oxygenation by reducing tumour bulk and movement of hormone-responsive cells into a resting phase, which could reduce repopulation rate and enhance tumour cell death (increased apoptosis) [Hara I, *et al* 2002].
- The RTOG 86-10 trial randomised 471 men with T2–T4 prostate cancer to radiotherapy +/– 4 months of androgen deprivation therapy (ADT) before and during EBRT or to radiotherapy alone [Pilepich MV, *et al* 2001].
    - At median follow-up of 8.7 years, there was a trend to improved survival (8-year survival 53% versus 44%, p=0.1) for those treated by hormone therapy with radiotherapy, which was significant for the subgroup with Gleason grade 2–6 disease (70% versus 52%, p=0.015) [Pilepich MV, *et al* 2001]..
    - Ten-year OS estimates (43% versus 34%) and median survival times (8.7 versus 7.3 years) favoured combined therapy with hormones and radiation compared to radiation treatment alone; however, these differences did not reach statistical significance (p=0.12).
    - There was a statistically significant improvement in 10-year disease-specific mortality (23% versus 36%; p=0.01), distant metastases (35% versus 47%; p=0.006), DFS (11% versus 3%; p<0.0001) and biochemical failure (65% versus 80%; p<0.0001) with the addition of neoadjuvant hormone therapy, but no differences were observed in the risk of fatal cardiac events [Roach M 3rd, *et al* 2008].
- The TROG 96.01 trial has shown that in the intermediate-risk patient group a 6-month course of ADT has shown some benefit when compared with a 3-month course [Denham JW, *et al* 2008].
    - Relative to radiation alone, the HR of prostate cancer-specific mortality from randomisation was 0.95 (95%CI: 0.63–1.41; p=0.79) in the 3-month ADT treatment arm and 0.56 (95%CI: 0.36–0.88; p=0.01) in the 6-month arm.
- A separate 6-month study compared 3D-CRT plus ADT and 3D-CRT alone [D'Amico AV, *et al* 2004].
    - After a median follow-up of 4.52 years, patients receiving 3D-CRT + ADT demonstrated a significantly lower prostate cancer–specific mortality rate (p=0.02).
    - 5-year OS rates were estimated at 88% (95%CI: 80–95) in the 3D-CRT + ADT group versus 78% (95%CI: 68–88) in the 3D-CRT group (p=0.04).

EBRT plus adjuvant hormone therapy

- Refer to section "EBRT plus adjuvant hormonal therapy" on pp 40.

Low dose rate (LDR) brachytherapy

Overview

- In 2005, NICE reviewed the medical literature on LDR brachytherapy and concluded that, in the absence of randomised trials, the results of LDR brachytherapy are comparable to those achieved with surgery or EBRT in well-selected patients [NICE 2005].
- Suitable patients include those with localised disease (up to T2a) with a Gleason grade ≤6, and a PSA concentration ≤10 ng/ml. Patients with significant urinary symptoms or post-TURP may not be suitable.
- Brachytherapy is as effective as radical prostatectomy in patients with low-risk localised disease [Crook J, *et al* 2001; Grimm P, *et al* 2012].
- In intermediate-risk localised disease, the comparison is less clear, because many studies have added EBRT in combination [Merrick GS, *et al* 2001].
- Brachytherapy is a single-step day case procedure following a spinal or general anaesthetic.

Brachytherapy plus EBRT

- In a matched-pair analysis, the 5-year biochemical failure-free survival rate was 86% for patients treated with EBRT and LDR brachytherapy, and 72% for patients treated with EBRT alone (p=0.03). Both treatments were associated with comparable incidences of late genitourinary side-effects (18-19%). Late rectal toxicity decreased by 15% in patients treated with EBRT and brachytherapy (p=0.0003). [Singh AM, *et al* 2005].

Brachytherapy plus neoadjuvant hormone therapy

- The role of neoadjuvant hormone therapy with brachytherapy is controversial. It is used to reduce the prostate volume when it exceeds 50 ml, in order to facilitate brachytherapy. Volume reduction decreases the total isotope activity required, potentially improves implant dosimetry and decreases pubic arch interference. [Potters L, *et al* 2005].

Patient selection (exclusions)

- Prostate size >50 ml
- Recent TURP
- Significant urinary outflow obstruction
- Previous AP resection
- Previous high dose pelvic radiotherapy

Side-effects

- A review of 16 studies by Crook *et al*. showed acute adverse events as [Crook J, *et al* 2001]:
  - Irritant urinary symptoms: 46–54%
  - Acute urinary retention: 1–14%
  - Acute proctitis: 1–2%
  - Chronic adverse events (reinforced by Wills & Hailey, 1999 [Wills F & Hailey D. 1991]:
    - Incontinence: 5–6%
    - Haematuria: 1–2%
    - Strictures: 1–2%
    - Proctitis: 1–3%
    - Erectile dysfunction: 4–14% (or up to 38% in Wills & Hailey, 1999 [Wills F & Hailey D. 1991] and up to 50% at 5 years in Merrick *et al*., 2001 [Merrick GS, B, *et al* 2001]).

Clinical evidence

- Very few comparative studies to date have evaluated the results of treatment options for prostate cancer using the most sensitive measurement tools. PSA has been identified as the most sensitive tool for measuring treatment effectiveness. To date, comprehensive unbiased reviews of all the current literature are limited for prostate cancer. A large scale comprehensive review of the literature comparing risk stratified patients by treatment option and with long-term follow-up was carried out by Grimm *et al* 2012 [Grimm P, *et al* 2012]. The results of the studies were weighted, respecting the impact of larger studies on overall results. The review identified a lack of uniformity in reporting results amongst institutions and centres. A large number of studies had been conducted on the primary therapy of prostate cancer but very few randomised controlled trials had been conducted. The comparison of outcomes from individual studies involving surgery (radical prostatectomy or robotic radical prostatectomy), external beam radiation (EBRT) (conformal, intensity modulated radiotherapy, protons), brachytherapy, cryotherapy or high intensity focused ultrasound remains problematic due to the non-uniformity of reporting results and the use of varied disease outcome endpoints. Technical advances in these treatments have also made long-term comparisons difficult. This international group conducted a comprehensive literature review to identify all studies involving treatment of localised prostate cancer published during 2000-2010. Over 18,000 papers were identified and a further selection was made based on the following key criteria: minimum/median follow-up of 5 years; stratification into low-, intermediate- and high-risk groups; clinical and pathological staging; accepted standard definitions for prostate-specific antigen failure; minimum patient number of 100 in each risk group (50 for high-risk group). A statistical analysis of the study outcomes suggested that, in terms of biochemical-free progression, brachytherapy provided superior outcome in patients with low-risk disease. For intermediate-risk disease, the combination of EBRT and brachytherapy appears equivalent to brachytherapy alone. For high-risk patients, combination therapies involving EBRT and brachytherapy plus or minus androgen deprivation therapy appear superior to more localized treatments such as seed implant alone, surgery alone or EBRT.
- A significant correlation has been demonstrated between recurrence rates and the implanted dose [Stock RG, *et al* 1998]. It has been shown that men receiving a D90 of > 140 Gy had a significantly higher biochemical control rate (PSA < 1.0 ng/mL) at 4 years than those who received less than 140 Gy (92% vs. 68%).

- Kupelian *et al*. studied 2991 consecutive patients with T1/T2 tumours treated with radical prostatectomy, LDR brachytherapy, EBRT or a combination of EBRT and brachytherapy. Biochemical relapse-free survival was similar in all groups when EBRT <72 Gy was excluded [Kupelian PA, *et al* 2004].
- Potters *et al* studied 1,449 consecutive patients treated with permanent prostate brachytherapy between 1992 and 2000. The mean pre-treatment PSA of 10.1ng/ml and 55% presented with Gleason 6 prostate cancer and 28% Gleason 7 disease. 400 patients (27%) were treated with neoadjuvant hormones and 301 (20%) were treated with combination EBRT. At a median follow up of 82 months, the overall and disease specific survival at 12 years was 81% and 93%, respectively. The 12-year biochemical free recurrence rates varied between 77% and 81% depending on the method of reporting recurrence. They concluded from multivariate analyses that implant dosimetry remains an important predictor for biochemical recurrence and that the addition of adjuvant hormone therapy or external radiation had an insignificant effect. [Potters L, *et al* 2005].

Novel therapies

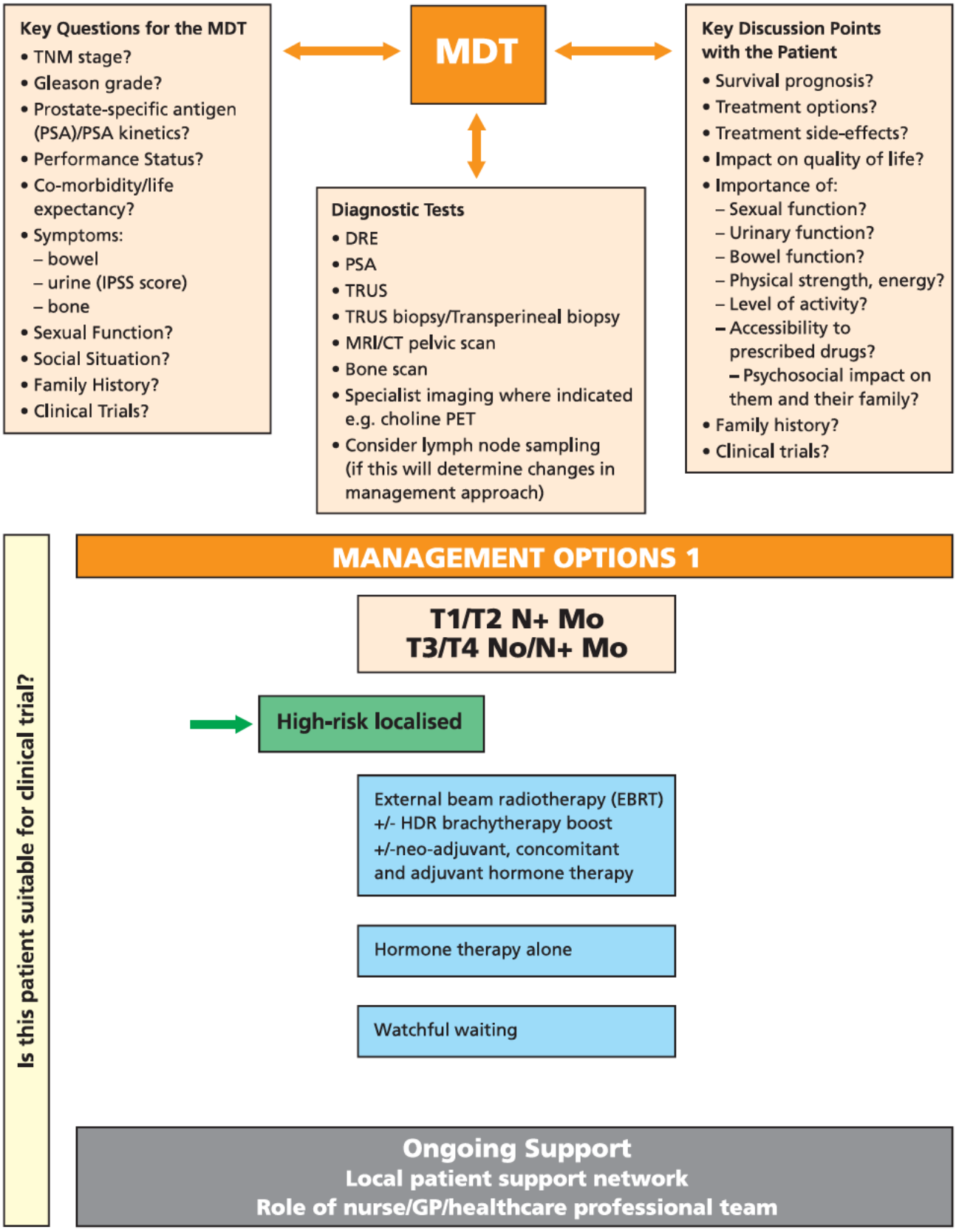
Cryotherapy/High-Intensity Focused Ultrasonography (HIFU)

The development of third-generation prostate cryotherapy has allowed the introduction of ultra-thin needles to deliver a minimally-invasive treatment for prostate cancer patients in the primary and salvage setting.

- Long *et al*. have performed a retrospective analysis of the multicentre, pooled, results of 975 patients treated with cryotherapy [Long JP, *et al* 2001]. The patients were stratified into three risk groups. Using PSA thresholds of 1.0 ng/mL and < 0.5 ng/mL and had a mean follow-up of 24 months. The 5-year actuarial biochemical disease free survival rates were:
  - 76% and 60%, respectively, for the low-risk group
  - 71% and 45%, respectively, for the intermediate-risk group
  - 61% and 36%, respectively, for the high-risk group
- Bahn *et al*. [Bahn DK, *et al* 2002], have reported the results of 7 year follow up on 590 patients treated with cryotherapy for clinically localised and locally advanced PCa. Using a PSA cut-off response level of < 0.5 ng/mL, the 7-year biochemical disease free survival for low-, medium- and high-risk groups was 61%, 68% and 61%, respectively.
- Longer-term follow-up series show biochemical DFS at 10 years of 80.56% for low-risk, 74.16% for moderate-risk and 45.54% for high-risk prostate cancer patients
- The toxicity from cryotherapy has reported erectile dysfunction in approximately 80% of patients and remains a consistent complication of the procedure, regardless of the generation of the system used. The complication rates described in third generation cryosurgery include tissue sloughing in about 3%, incontinence in 4.4%, pelvic pain in 1.4% and urinary retention in about 2% [De La Taille A, *et al* 2000]. Around 5% of all patients require transurethral resection of the prostate (TURP) for subvesical obstruction.
- This treatment has been approved by the American Urological Association and the European Association of Urology for treatment of patients with primary and radiation-failed prostate cancer
- In the NICE guidelines, the minimally-invasive treatments of cryosurgery and HIFU were considered to be experimental and for use only within the clinical trial setting [NICE 2008].
- Poissonnier reported on 227 patients with localised prostate cancer who were treated with HIFU at a single institution. The projected 5-year biochemical disease free survival rate was 66%, or 57% for patients with a pre-treatment PSA value of 4-10 ng/mL after a mean follow up of 27 months (range: 12-121) [Poissonnier L, *et al* 2007]
- Blana *et al*. have reported the results of 163 patients treated with HIFU for clinically organ confined prostate cancer. The actuarial disease free survival rate at 5 years was 66%, with salvage treatment initiated in 12% of patients [Blana A, *et al* 2008].
- In another study, 517 men with organ-confined or locally advanced PCa were treated with HIFU .Biochemical failure was defined as the PSA nadir + 2 ng/mL, After a median follow-up of 24 months, the biochemical disease free survival was 72% for the entire cohort. The biochemical disease free survival rates for low-, intermediate- and high-risk groups at 5 years was 84%, 64% and 45%, respectively (P < 0.0001) [Uchida T, *et al* 2009].
- Urinary retention appears to be one of the most common side effects of HIFU, with stress incontinence occurring in about 12% of patients. Subsequent TURP or bladder neck incision to treat subvesical obstruction can be used to treat these symptoms and is sometimes performed at the time of HIFU. Postoperative impotence has been reported in 55-70% of patients.

Locally Advanced Disease: Management Options

Figure 3: Treatment algorithm for locally advanced disease



The term 'locally advanced prostate' cancer can be used to encompass a spectrum of disease profiles that may include any of the following:

- Clinical stage T3, T4 or N1 cancers without evidence of distant metastases (M0)
- Clinical stages T1 and T2 ('localised') at diagnosis, where 'high-risk' features (PSA concentration ≥20 ng/ml or Gleason grade ≥8) indicate the likelihood of extraprostatic invasion or clinically undetectable metastatic disease.
- Pathological stage pT2 or pT3 disease with 'high-risk' features due to upstaging from additional pathological information after radical prostatectomy.

Men with locally advanced or high-risk prostate cancer generally have a significant risk of disease progression and cancer-related death if left untreated. These patients present two specific challenges. There is a need for local control and also a need to treat any microscopic metastases likely to be present but undetectable until disease progression. The optimal treatment approach will often therefore utilise multiple modalities. The exact combinations, timing and intensity of treatment continue to be strongly debated. Management decisions should be made after all treatments have been discussed by the MDT and the balance of benefits and side effects of each therapy modality have been considered by the patient with regard to their own individual circumstances.

Watchful waiting (deferred or immediate hormone therapy)

The waiting ('deferred treatment' or 'symptom-guided treatment') should be distinguished from active surveillance which involves close monitoring with early, radical treatment in those with signs of disease progression. Watchful waiting by contrast involves relatively unstructured observation with late, palliative treatment for those who develop symptoms of progressive disease.

Overview

- A pooled analysis of data from 2 RCTs involving 1036 men with locally advanced disease not suitable for curative treatment (T2–T4) suggested no survival benefit for immediate versus delayed hormone therapy at 1, 5 or 10 years [Wilt T, *et al* 2001].

Clinical evidence

- Adolfsson *et al*. prospectively followed 50 patients with locally advanced prostate cancer who were only treated upon patient request or when they became symptomatic. All patients were followed-up for more than 144 months, or had died before that point. OS and DFS at 5, 10 and 12 years was 68% and 90%, 34% and 74%, and 26% and 70%, respectively [Adolfsson J, *et al* 1999].
- Immediate versus deferred treatment for advanced prostate cancer was investigated by the MRC Prostate Working Party Investigators Group. An RCT of 943 men with asymptomatic metastases or locally advanced disease, not suitable for curative treatment, was undertaken, with randomisation to immediate or deferred hormone therapy [MRC Prostate Working Party Investigators Group 1997].
    - There was a significant advantage in the immediate treatment group in terms of distant progression. Mortality was only significantly changed by treating immediately in those with M0 disease (Table 5).
    - A modest but statistically significant increase in OS was seen in the immediate treatment group, but no significant difference in prostate cancer mortality or symptom-free survival was demonstrated.

- Due consideration must therefore be given to potential effects of long-term ADT versus the potential avoidance of such effects in patients if hormone therapy is deferred [Studer UE, *et al* 2008].

Table 5: Effect of immediate versus deferred hormonal treatment [MRC Prostate Working Party Investigators Group 1997]

		Immediate	Deferred
Distant progression		26%	45%
Mortality due to prostate cancer	M0 disease M1 disease	31.6% No significant difference	48.8% No significant difference

- A prospective randomised clinical phase III trial (EORTC 30981) by Studer UE *et al*, randomised 985 patients with T0-4 N0-2 M0 prostate cancer to immediate hormone or hormone treatment on the development of symptomatic disease progression [Studer UE, *et al* 2008]. After a median follow-up of 7.8 years, the overall survival hazard ratio was 1.25 (95% confidence interval [CI]: 1.05-1.48; non-inferiority $p > 0.1$) favouring immediate treatment. This appeared to be due to fewer deaths of non-prostatic cancer causes ($p = 0.06$). There was no difference in the time from randomisation to progression of hormone-refractory disease or prostate cancer-specific survival. The median time to the start of deferred treatment after study entry was 7 years. The conclusion suggested that immediate hormone therapy resulted in a modest but statistically significant increase in overall survival, but that there was no significant difference in prostate cancer mortality or symptom-free survival.
- The multicentre, International Early Prostate Cancer (EPC) study evaluated the efficacy and tolerability of adding the non-steroidal anti-androgen bicalutamide 150 mg once-daily to standard care (prostatectomy, radiotherapy or watchful waiting). 8,113 patients with localised or locally advanced non-metastatic prostate cancer were included [Iversen P, *et al* 2010].
  - Objective PFS and OS were defined as the primary endpoints. At a fourth analysis, the median follow-up was 9.7 years. Exploratory analyses were also conducted to determine the efficacy of bicalutamide in clinically relevant subgroups.
- A significant improvement in objective PFS in favour of bicalutamide 150 mg for all locally advanced disease patients was demonstrated. For those men with locally advanced disease who were managed by watchful waiting, there was a significant difference in PFS. The median time to progression was 6.6 years for those randomised to bicalutamide 150 mg compared to 3.7 years for those randomised to placebo. Patients in the watchful waiting subgroup showed a trend towards improved overall survival, this was statistically significant in sub-study 025 (carried out in Scandinavian in 1218 patients) HR=0.76 (0.59, 0.98) p=0.031 but did not reach significance in sub-study 24 (carried out in Europe, South Africa, Australia, Israel, and Mexico in 3603 patients) HR=1.03 (0.77, 1.37) p=0.844 [Iversen P, *et al* 2010].

Hormone therapy versus radiotherapy and hormone therapy

- A study by Widmark *et al* has shown that the addition of radiotherapy to hormone therapy for men with locally advanced or high-risk prostate cancer halves the 10-year prostate cancer-specific mortality and substantially decreases overall mortality [Widmark A, *et al* 2009].
    - This phase III study comparing endocrine therapy with and without local radiotherapy randomised 875 patients with locally advanced prostate cancer (T3; 78%; PSA concentration <70 ng/ml; N0; M0) to hormone therapy alone (3 months of total androgen blockade followed by continuous endocrine therapy using flutamide), or to the same hormone treatment combined with radiotherapy.
    - After a median follow-up of 7.6 years, 79 men in the hormone therapy group and 37 men in the hormone therapy plus radiotherapy group had died of prostate cancer. The cumulative incidence at 10 years for prostate cancer-specific mortality was 23.9% in the hormone alone group and 11.9% in the hormone therapy plus radiotherapy group (difference 12.0%; 95%CI: 4.9–19.1).
    - The 10-year cumulative incidence for overall mortality was 39.4% in the hormone therapy group and 29.6% in the hormone therapy plus radiotherapy group (difference 9.8%; 95%CI: 0.8–18.8).
    - The 10-year cumulative incidence for PSA recurrence was substantially higher in men in the hormone therapy group (74.7% versus 25.9%; HR 0.16; 95%CI: 0.12–0.20; p<0.0001).
    - After 5 years, urinary, rectal, and sexual problems were slightly more frequent in the hormone plus radiotherapy group.
- The National Cancer Institute of Canada (NCIC)/UK Medical Research Council (MRC)/Southwest Oncology Group (SWOG) intergroup PR3/PR07 study included 1,205 patients with stage T3-4 (n = 1057) or stage T2 with additional high risk features i.e. PSA > 40 ng/mL, or PSA > 20 ng in addition to Gleason Score > 8 and N0-X M0 prostate cancer [Warde, P, *et al* 2011]. These patients were randomly assigned to lifelong hormone therapy (bilateral orchidectomy or LHRH agonist), with or without radiotherapy (65-70 Gy to the prostate, with or without 45 Gy to the pelvic lymph nodes). The addition of radiotherapy to lifelong hormone treatment at a median follow up of 6 years demonstrated a reduced the risk of death from any cause by 23% (P = 0.03) and the risk of death due to prostate cancer by 46% (P = 0.0001) [Warde, P, *et al* 2011].

Side-effects of Hormone Therapy

- LHRH agonists: side-effects include erectile dysfunction and loss of libido, reduction in bone mineral density, hot flushes and sweating, and weight gain and metabolic effects.
- Bicalutamide (anti-androgens): side-effects include gynaecomastia and breast tenderness.
    - Mild to moderate gynaecomastia and breast pain are the most common adverse events described [McLeod DG, *et al* 2006].

External beam radiotherapy (EBRT) +/– neoadjuvant, concomitant and adjuvant hormone therapy

Radiotherapy Alone

- In locally advanced disease, EBRT alone has been shown to have a poorer outcome than in localised prostate cancer. Consequently, combination therapy with radiotherapy and hormone therapy is accepted as standard practice.
- Although it has been widely used, there are still many uncertainties associated with radical radiotherapy with regard to the optimum dose and field size (particularly to what extent the treatment volume should try to include pelvic lymph nodes). The advent of 3D Conformal radiotherapy (3D-CRT) and Intensity Modulated Radiotherapy (IMRT) in combination with Image Guided Radiotherapy (IGRT) has allowed the radiation field to be more precisely targeted to the tumour volume, thereby potentially reducing the side-effects of treatment and possibly allowing dose escalation that enhances its local efficacy.

Three-dimensional conformal radiotherapy (3D-CRT)

- There is evidence that increased radiation dose is associated with increased cancer cell kill for men with localised prostate cancer. However, the traditional two-dimensional technique of treatment planning and delivery is limited by the normal tissue toxicity of the surrounding structures (bladder, rectum and bowel), such that the dose that can be safely delivered to the prostate by EBRT is of the order of 64 Gy in 2 Gy per day fractions. Several technological advances over the last 20 years have enhanced the precision of EBRT, and have resulted in improved outcomes.
- The 3D-CRT approach reduces the dose-limiting late side-effect of proctitis [Dearnaley DP, *et al* 1999] and has allowed for dose escalation to the whole prostate to up to78 Gy.

Intensity Modulated Radiotherapy (IMRT)

- IMRT is an advanced technique which has superseded 3D-CRT. IMRT can modify the shape and intensity of the multiple radiotherapy beams. It is very precise in targeting the treatment area, sparing surrounding tissue and allowing dose escalation above 80 Gy. IMRT is currently recommended, particularly for the irradiation of pelvic lymph nodes.

Dose escalation

- Evidence suggests that patients treated with radiotherapy to the prostate have a significantly better outcome, because the dose to the gland is increased. The benefit is greatest in those patients with high-risk features.
- Debate remains over the best way of increasing the dose without significantly increasing normal tissue toxicity. 3D-CRT, IMRT and High Dose Rate (HDR) brachytherapy boost are methods currently under evaluation.
- Several randomised studies have shown that dose escalation with 3D-CRT and more recently with IMRT has a significant impact on the 5-year biochemical relapse free survival. However no trials to date have shown an improvement in long term overall survival.

- Evidence of the benefits of dose escalation has been demonstrated for T1–T3 prostate cancer by Pollack *et al*. in a phase III randomised study undertaken at the MD Anderson Hospital [Pollack A, *et al* 2002].
    - A total of 305 men were randomised between 1993 and 1998 to compare the efficacy of 70 Gy versus 78 Gy with a median follow-up of 60 months. The primary endpoint was freedom from failure (FFF), including biochemical failure, which was defined as three rises in PSA level.
    - The FFF rates for the 70 Gy and 78 Gy arms at 6 years were 64% and 70%, respectively (p=0.03). Dose escalation to 78 Gy preferentially benefited those with a pre-treatment PSA concentration >10 ng/ml; the FFF rate was 62% for the 78 Gy arm versus 43% for those who received 70 Gy (p=0.01). For patients with a pre-treatment PSA concentration ≤10 ng/ml, no significant dose-response relationship was found, with an average 6-year FFF rate of about 75%.
    - Although no difference in OS occurred, the freedom from distant metastasis rate was higher for those with PSA levels >10 ng/ml who were treated to 78 Gy (98% versus 88% at 6 years, p=0.056).
- Dearnaley and colleagues have reported their findings from the MRC RT01 study [Dearnaley DP, *et al* 2007].
    - In this 3D-CRT trial, 843 men were randomised to a standard dose of 64 Gy compared with an escalated dose of 74 Gy, with all men also receiving neoadjuvant hormone therapy.
    - Patients receiving the conventional dose had 5-year biochemical PFS rates of 60% compared to 71% in the dose-escalated arm. Advantages were also seen in terms of clinical PFS and the decreased use of androgen suppression.
    - An update of this study with 10 years of follow up has not shown an a further benefit in biochemical PFS of 54% (172 events) versus 42% (224 events) , HR 0.688 (0.56-0.84) p<0.0001 in favour of the dose escalated group. However, no overall survival benefit was demonstrated, with both the 64 Gy and 74 Gy arms having an overall survival of 70% HR 0.99 (0.77-1.28) p=0.337. The number of men requiring long term hormone therapy was reduced in the dose escalated arm HR 0.77 (0.59-1.00) p=0.05 [Dearnaley DP, *et al* 2011].
- Recently the long-term follow-up of the pilot study, which provided the initial safety and feasibility information for the national MRC RT01 trial have been published [Creak A, *et al* 2013].
    - In this study, 126 patients were randomised to a standard dose of 64 Gy compared with an escalated dose of 74 Gy after neoadjuvant androgen suppression.
    - After a follow up of 13.7 years, 49 of 126 patients restarted AS, 34 developed metastases and 28 developed CRPC. Median OS was 14.4 years.
- Although escalated dose results were favourable, no statistically significant differences were seen between the randomised groups; PSA control (hazard ratio (HR): 0.77 (95% confidence interval (CI): 0.47–1.26)), development of CRPC (HR: 0.81 (95% CI: 0.40–1.65)), PC-specific survival (HR: 0.59 (95% CI:0.23–1.49)) and OS (HR: 0.81 (95% CI: 0.47–1.40))
- The Dutch randomised phase III trial comparing 68 Gy with 78 Gy also demonstrated a significant increase in the 5-year rate of freedom from clinical or biochemical failure in patients treated with a higher dose of radiotherapy [Peeters ST, *et al* 2006].

- The phase III trial of the French Federation of Cancer Centres compared 70 Gy with 80 Gy in men with localised prostate cancer, in 306 patients with a low risk of pelvic lymph node involvement [Beckendorf V, *et al* 2011]. At a median follow up of 61 months, they demonstrated improved 5-year biological outcomes in favour of dose-escalated radiotherapy group. Using the Phoenix definition, the 5-year biochemical relapse rate was 32% and 23.5%, respectively (p = .09).
- Although these and other studies have shown benefits from dose escalation this has been offset to a degree by a reported increase in late rectal toxicity.
- Prospective non-randomised studies conducted at the Memorial Sloan Kettering cancer centre have compared the outcomes of 1100 men who received doses in the range of 64–70 Gy and 76–86 Gy using IMRT [Zelefsky MJ, *et al* 2001].
    - The results were evaluated within prognostic risk groups (using clinical stage, Gleason grade and presenting PSA concentration). They demonstrated that increasing the dose delivered beyond 70.2 Gy in men with intermediate- and high-risk disease improved the 5-year actuarial PSA relapse-free survival rate from 50% to 70% and 21% to 47%, respectively, in these two risk categories.
- IMRT has the potential to reduce late rectal toxicity as shown in a further study that reports 3-year actuarial ≥grade 2 gastrointestinal toxicity at 4% [Zelefsky MJ, *et al* 2002].
- A further development under investigation involves a change in the traditional fractionation schedules. Hypofractionation may improve cancer control for the same level of radiation-related toxicity and be a more effective treatment for prostate cancer with a predicted low alpha/beta ratio. Phase II dose escalation studies using shortened schedules of hypofractionated IMRT regimens have indicated acceptable early toxicity [Zelefsky MJ, *et al* 2001].
- The CHHiP (Conventional or Hypofractionated High Dose IMRT for Prostate Cancer) study is currently recruiting patients in the UK to compare standard fractionation IMRT (74 Gy in 37 fractions) to two hypofractionated IMRT regimens (60 Gy in 20 fractions or 57 Gy in 19 fractions) in combination with neoadjuvant hormone therapy [Zelefsky MJ, *et al* 2002]. There is no overall survival data available from this trial as yet but preliminary safety results have shown that hypofractionated high-dose radiotherapy seems equally well tolerated as conventionally fractionated treatment at 2 years
- Debate remains over the best way of increasing the dose without significantly increasing normal tissue toxicity. 3D-CRT, IMRT and HDR brachytherapy boost are methods currently under evaluation.

Image Guided Radiotherapy (IGRT)

The advantages of dose escalation using IMRT means that organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity to the bladder, rectum and bowel. Techniques should therefore combine IMRT with some form of IGRT (fiducial markers, imaging), in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still under investigation.

Radiotherapy target volume/lymph nodes

- In high-risk patients the consensus is that the seminal vesicles should be included. There remains some debate for the benefit for prophylactic whole-pelvic irradiation, since randomised trials have failed to show conclusive advantages.
- The RTOG 9413 trial was designed to determine whether there was an advantage in terms of PFS with androgen deprivation therapy, whole pelvic radiotherapy followed by a prostate boost compared with androgen deprivation therapy and prostate-only radiotherapy. The trial also investigated the timing of hormone therapy with a further randomisation. One group received neoadjuvant hormone therapy followed by concurrent total androgen suppression and radiotherapy while the other group was treated with radiotherapy followed by adjuvant hormone therapy. Patients with non-metastatic disease but an estimated risk of lymph node involvement of >15% were randomised between the 4 arms [Lawton CA, *et al* 2007].
    - The difference in OS for the 4 arms was statistically significant (p=0.027).
    - However, no statistically significant differences were found in PFS or OS between neoadjuvant versus adjuvant hormone therapy and whole pelvis radiotherapy compared with prostate-only radiotherapy. A trend towards a difference was found in PFS (p=0.065) in favour of the whole pelvic radiotherapy + neoadjuvant hormone arm compared with the prostate-only radiotherapy + neoadjuvant hormones and whole pelvic radiotherapy + adjuvant hormone treatment arms.
    - These results have demonstrated that when neoadjuvant hormone therapy is used in conjunction with radiotherapy, whole pelvic treatment yields a better PFS than prostate-only radiotherapy. It also showed an improved OS when whole pelvic radiotherapy was combined with neoadjuvant rather than short-term adjuvant hormone therapy.

Patient selection

- EBRT can be unsuitable for patients with bilateral hip replacement, previous radiotherapy, severe proctitis or bowel morbidity.

Side-effects

- Acute complications include cystitis, faecal frequency and urgency, proctitis and rectal bleeding.
- Late complications occurring 3 months or later after treatment include impotence, bleeding, proctitis and diarrhoea.

HDR brachytherapy boost

- HDR brachytherapy using an iridium-92 temporary implant is a safe, reproducible and effective way of boosting conventional EBRT. There is published evidence for this approach demonstrating improved biochemical control and cause-specific survival without a significant increase in toxicity.
- Currently, HDR brachytherapy is mainly used as a boost treatment in combination with EBRT
- In a single randomised trial of EBRT vs. EBRT plus HDR brachytherapy boost, 220 patients with organ confined prostate cancer were randomised to EBRT alone with a dose of 55 Gy in 20 fractions, or EBRT with a dose of 35.75 Gy in 13 fractions, followed by HDR brachytherapy with a dose of 17 Gy in two fractions over 24 hours. In comparison with EBRT alone, the combination of EBRT and HDR brachytherapy showed a significant improvement in the biochemical relapse free survival (P = 0.03). There were no differences in the rates of late toxicity. Patients randomly assigned to EBRT plus brachytherapy had a significantly better QoL as measured by their Functional Assessment of Cancer Therapy-Prostate (FACT-P) score at 12 weeks. However, a very high, uncommon rate of early recurrences was observed in the EBRT arm alone, even after 2 years, possibly due to the uncommon fractionation used [Hoskin PJ, *et al* 2007].

- A further single centre study evaluated the 10-year outcomes for 472 intermediate- and high-risk prostate cancer patients treated with pelvic EBRT to a dose of 46 Gy in 23 fractions and a HDR brachytherapy boost. The HDR dose fractionation was divided into two dose levels. The prostate biologically equivalent dose (BED) low-dose-level group received <268 Gy, and the high-dose group received >268 Gy. Phoenix biochemical failure (BF) definition was used.At a median follow up of 8.2 years , the 10-year biochemical failure rate 43.1% vs. 18.9%, ($p < 0.001$), the clinical failure rate of 23.4% vs. 7.7%, ($p < 0.001$), and the distant metastasis of 12.4% vs. 5.7%, ($p = 0.028$) were all significantly better for the high-dose level group. Grade 3 genitourinary complications were 2% and 3%, respectively, and grade 3 gastrointestinal complication was <0.5%.This prospective trial using P-EBRT with HDR boost and hypofractionated dose escalation demonstrates a strong dose-response relationship for intermediate- and high-risk prostate cancer patients [Martinez AA, *et al* 2011].

EBRT plus neoadjuvant hormone therapy

- Neoadjuvant hormone therapy reduces prostate volume by 30–40% [Shearer RJ, *et al* 1992; Forman JD, *et al* 1995]. This can reduce the size of the treatment field and as a result the potential level of toxicity experienced.
- There are also reports of an additive or synergistic effect on tumour cell kill with combined therapy. Theories as to the mechanism of this include improved oxygenation by reducing tumour bulk and movement of hormone-responsive cells into a resting phase, which could reduce repopulation rate and enhance tumour cell death (increased apoptosis) [Hara I, *et al* 2002].
- The RTOG 86-10 trial randomised 471 men with T2–T4 prostate cancer to radiotherapy +/– 4 months of ADT (goserelin 3.6 mg depot once-monthly plus flutamide 250 mg tid) before and during EBRT or to radiotherapy alone. The median follow-up was 6.7 years for all patients and 8.6 years for surviving patients [Pilepich MV, *et al* 2001].
    - At median follow-up of 8.7 years for surviving patients, there was a trend to improved survival (8-year survival 53% versus 44%, p=0.1) for those treated by hormone therapy with radiotherapy, which was significant for the subgroup with Gleason grade 2–6 disease (70% versus 52%, p=0.015) [Pilepich MV, *et al* 2001].
    - Ten-year OS estimates (43% versus 34%) and median survival times (8.7 versus 7.3 years) favoured combined therapy with hormones and radiation compared to radiation treatment alone; however, these differences did not reach statistical significance (p=0.12) [Roach M, *et al* 2008].
    - There was a statistically significant improvement in 10-year disease-specific mortality (23% versus 36%; p=0.01), distant metastases (35% versus 47%; p=0.006), DFS (11% versus 3%; p<0.0001) and biochemical failure (65% versus 80%; p<0.0001) with the addition of neoadjuvant hormone therapy, but no differences were observed in the risk of fatal cardiac events [Roach M, *et al* 2008].

EBRT plus adjuvant hormonal therapy

- Long-term application of adjuvant androgen suppression should be seriously considered in prostate cancer patients with an unfavourable prognosis.
- A combination of radiotherapy and hormone therapy is superior to radiotherapy alone in patients with locally advanced disease. The combination is associated with better survival and increased time to progression.
- Optimal duration of adjuvant therapy is uncertain (6 months to indefinite) and the results of further studies are awaited.

Clinical evidence

- Adjuvant androgen suppression immediately after radical radiotherapy has been shown to significantly increase OS, PFS, and significantly reduce local progression, distant metastases and biochemical progression in several large randomised studies.
- Bolla *et al*. (EORTC 22863) randomised 415 patients with locally advanced prostate cancer (T1–4, Nx, M0) to receive either radiotherapy with immediate goserelin 3.6 mg therapy (every 4 weeks for 3 years) plus cyproterone acetate (CPA) during the first month of treatment for disease flare (n=207) or radiotherapy alone (n=208) [Bolla M, *et al* 2010].
    - After a mean follow-up of 9.1 years the 10-year clinical DFS was 22·7% (95% CI 16·3-29·7) in the radiotherapy-alone group and 47·7% (39·0-56·0) in the combined modality therapy group (HR= 0·42, 95% CI 0·33-0·55, p<0·0001). The 10-year OS was 39·8% (95% CI 31·9-47·5) in patients receiving radiotherapy alone and 58·1% (49·2-66·0) in those allocated combined treatment (HR 0·60, 95% CI 0·45-0·80, p=0·0004), and 10-year prostate-cancer mortality was 30·4% (95% CI 23·2-37·5) and 10·3% (5·1-15·4), respectively (HR 0·38, 95% CI 0·24-0·60, p<0·0001). No significant difference in cardiovascular mortality was noted between treatment groups.
- In the EORTC 22961 study, men with locally advanced prostate cancer who had all previously completed EBRT and 6 months of adjuvant ADT were randomised to receive either no further treatment (short-term ADT), or 2.5 years of further treatment with a LHRH agonist (long-term ADT) [Bolla M, *et al* 2009].
    - The 5-year overall mortality rates were 19.0% for short-term ADT versus 15.2% for long-term ADT (HR 1.42; p=0.65 for non-inferiority).
    - The 5-year prostate cancer-specific mortality rates were 4.7% for short-term ADT versus 3.2% for long-term ADT (HR 1.71; 95%CI: 1.14–2.57; p=0.002).
    - This study showed inferior survival for men treated with RT and 6 months of ADT compared with RT plus 3 years of ADT in the treatment of locally advanced prostate cancer.
- Pilepich *et al*. (RTOG 85-31) randomised 977 patients with locally advanced non-metastatic prostate cancer to receive either pelvic radiation plus goserelin 3.6 mg depot (started during the last week of radiotherapy, to be continued indefinitely every month or until relapse; n=488) or radiotherapy alone (n=489) [Pilepich MV, *et al* 2005].
    - A total of 945 patients remained appropriate for analysis: 477 in the adjuvant arm and 468 in the control arm. Thirty-two patients were retrospectively classified as ineligible. the most common reason was a T2 primary tumour with negative lymph nodes
    - Median follow-up was 7.6 years for all patients and 11 years for surviving patients.
    - The data clearly identified that the use of goserelin in combination with radiotherapy in this group of high-risk patients resulted in significant improvements in all endpoints.
    - Goserelin adjuvant therapy significantly (p<0.002) reduced the risk of dying by approximately 25%. The absolute 10-year survival rate compared with radiotherapy alone was 49% versus 39%. The improvement in survival appeared preferentially in patients with a Gleason grade of 7–10.
    - Goserelin treatment also resulted in a significant improvement in local control, freedom from distant metastasis, DFS and biochemical DFS.

- Horwitz *et al*. (RTOG 92-02) investigated the use of long-term androgen suppression following neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced prostate cancer (T2c to T4 with no extra pelvic lymph node involvement and PSA <150 ng/ml) [Horwitz EM, *et al* 2008].
    - A total of 1554 patients were treated with goserelin and flutamide for 2 months prior to and 2 months during radiotherapy, and then randomised to 24 months of goserelin long-term (LTAD) or no further treatment short-term hormone therapy (STAD).
    - At 10 years, the LTAD and radiotherapy group showed significant improvement over the STAD + radiotherapy group for all endpoints except OS: DFS (13.2% versus 22.5%; p<0.0001), disease-specific survival (83.9% versus 88.7%; p=0.0042), local progression (22.2% versus 12.3%; p<0.0001), distant metastasis (22.8% versus 14.8%; p<0.0001), biochemical failure (68.1% versus 51.9%; p≤0.0001) and OS (51.6% versus 53.9%, p=0.36).
    - One subgroup analysed consisted of all cancers with a Gleason score of 8–10 cancers. An OS difference was observed (31.9% versus 45.1%; p= 0.0061), as well as in all other endpoints.
- As previously described, in the EPC study, exploratory analyses were conducted to determine the efficacy of bicalutamide in clinically relevant subgroups with a median follow-up of 9.7 years at the third analysis. The primary endpoints were objective PFS and OS [McLeod DG, *et al* 2006].
- Patients who derived benefit from bicalutamide in terms of PFS were those with locally advanced disease, with OS significantly favouring bicalutamide in patients with locally advanced disease undergoing radiotherapy (HR = 0.70 (CI 0.51 to 0.97), p=0.03). The overall tolerability of bicalutamide was consistent with previous analyses, with breast pain (73.7%) and gynaecomastia (68.8%) the most frequently reported adverse events in patients randomized to bicalutamide.

Radical Prostatectomy

There is debate about the role of radical prostatectomy for men with locally advanced or high risk prostate cancer. Surgical treatment of this stage has traditionally been discouraged because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse

Radical prostatectomy may be considered for selected cases with low volume tumour provided that the tumour is not fixed to the pelvic side wall, or that there is no invasion of the urethral sphincter. Management decisions should be made after all treatments have been discussed by the multidisciplinary team and after the balance of benefits and side effects of each therapy modality have been considered by the patients with regard to their own individual circumstances. It is essential that patients are counselled regarding the high risks of needing additional adjuvant and salvage therapies and understand that the surgery may be part of a multimodality approach.

It is recommended that lymph node dissection should be performed in all high-risk cases.

Clinical evidence

- The Mayo clinic have reported 15-year outcomes for 5662 men with locally advanced prostate cancer treated with radical prostatectomy [Ward JF, *et al* 2005].
    - Freedom from local or systemic disease at 5, 10, and 15 years after radical prostatectomy were reported as 85%, 73% and 67%; the respective cancer-specific survival rates were 95%, 90% and 79%. Significantly many men who did not receive neoadjuvant therapy (27%) were clinically over-staged (pT2) and most men with pT3 disease (78%) received adjuvant therapy. The mean time to adjuvant therapy after radical prostatectomy was 4.0 years. Pathological grade (> or =7), positive surgical margins, and nondiploid chromatin were all independently associated with a significant risk for clinical disease recurrence, while preoperative PSA level had little effect on outcome.
    - The authors also noted that many patients with clinically T3 prostate cancer are overstaged (pT2) (27% in this series who did not have neoadjuvant hormone therapy)
- In a further single institution series the 10-year outcomes of radical prostatectomy in 200 men with unilateral clinical T3a disease who had not received neoadjuvant hormone therapy, have been reported by Hsu [Hsu CY, *et al* 2007]. Clinical over-staging was again noted in 23.5% of cases who had a pathological stage of pT2. 56% of patients received adjuvant or salvage therapy. The overall survival at 5 and 10 years was 95.9% and 77.0%, respectively, and cancer specific survival was 98.7% and 91.6%. Biochemical progression free survival (BPFS) at 5 and 10 years was 59.5% and 51.1%, respectively, and clinical progression free survival (CPFS) was 95.9% and 85.4%. Margin status was a significant independent predictor in BPFS; cancer volume was a significant independent predictor in CPFS.

Radical Prostatectomy and Neoadjuvant/Adjuvant Hormone Therapy

- A review and meta-analysis of the role of NHT and prostatectomy has shown that NHT before prostatectomy did not improve OS or disease-free survival (DFS), but did significantly reduce positive margin rates [relative risk (RR): 0.49; 95% confidence interval (CI): 0.42-0.56, P < 0.00001), organ confinement (RR: 1.63; 95% CI: 1.37-1.95, P < 0.0001) and lymph node invasion (RR: 0.49; 95% CI: 0.42-0.56, P < 0.02) [Shelley MD, *et al* 2009]. Therefore, evidence suggests that the down-staging achieved with neoadjuvant hormone therapy does not translate into improved DFS, and therefore cannot be recommended outside of clinical trials [Bonney WW, *et al* 1999; Paul R, *et al* 2004; Selli C & Milesi C. 2004; Witjes WPJ, *et al* 1997].

- Similarly, there is currently no evidence that adjuvant hormone therapy provides a survival advantage for patients with pathologically proven localised disease [Hachiya T, *et al* 2002; Prayer-Galetti T, *et al* 2000]. A recent Cochrane review and metaanalysis studied the role of adjuvant HT following RP: the pooled data for 5-year OS demonstrated an odds ratio (OR) of 1.50 and 95% CI: 0.79-2.84 [Shelley MD, *et al* 2009]. Although this finding was not statistically significant, there was a trend favouring adjuvant HT. There was no survival advantage at 10 years. The pooled data for DFS gave an overall OR of 3.73 and 95% CI: 2.3-6.03. The overall effect estimate was highly significant (P < 0.00001) in favour of the HT arm.
- The ECOG 7887 trial compared adjuvant ADT after radical prostatectomy and deferred hormonal therapy in patients with nodal metastases [Messing EM, *et al* 2006]. A total of 98 patients with locally advanced prostate cancer (T1–T2, N+ disease) who had undergone pelvic lymphadenectomy were included in the study. These patients were randomised to receive adjuvant hormone ablation or followed until disease progression and then given hormone therapy [Messing EM, *et al* 2006].
    - At 11.9 years' median follow-up, adjuvant ADT increased survival by 2.6 years compared with surgery alone, in node-positive patients. Median survival in the adjuvant ADT and deferred treatment groups was 13.9 and 11.3 years, respectively. 64% of patients treated with adjuvant ADT were still alive at this time, compared with 45% of patients who received radical prostatectomy alone.
    - In this setting, adjuvant ADT reduced the risk of dying by approximately 46% compared with RP alone (HR 0.54; 95%CI: 0.99–0.30; p=0.04).

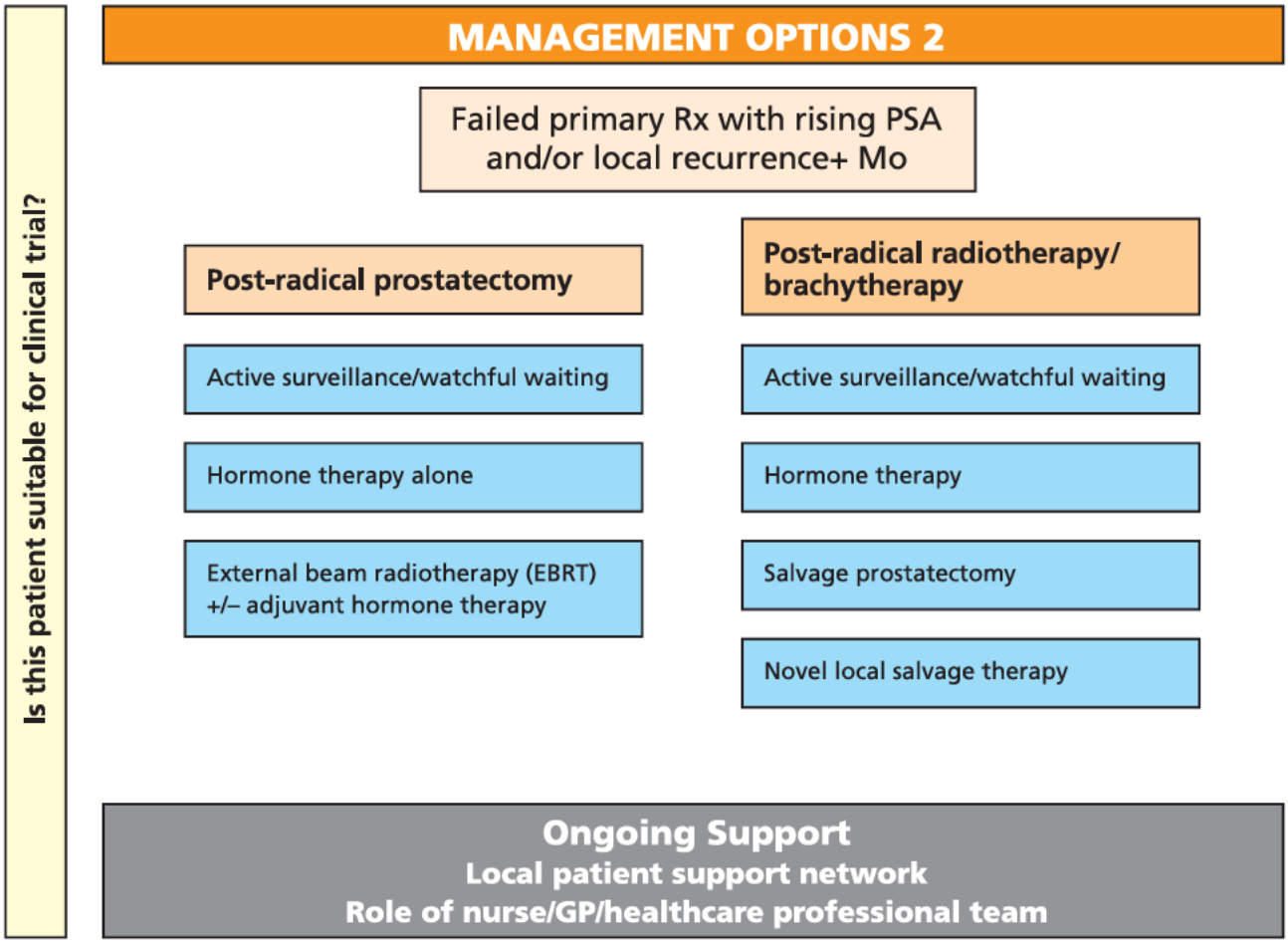
Radical Prostatectomy and Adjuvant Radiotherapy

- Extracapsular invasion (pT3), Gleason score > 7, and positive surgical margins (R1) can be associated with a risk of local recurrence [Hanks GE. E 1988]. Adjuvant radiotherapy has been assessed in three prospective randomised studies
- The EORTC 22911 study was designed to investigate benefit for immediate postoperative radiotherapy (60 Gy) in a target sample size of 1005 patients with pT3 disease or positive surgical margins as opposed to salvage radiotherapy offered for biochemical or clinical relapse [Bolla M, *et al* 2012].
    - After a median follow up of 10 years, overall survival did not differ significantly between the treatment arms. For patients younger than 70, the study concluded that adjuvant RT significantly improved the 10-year biological PFS: 60.6% vs. 41.1%. A previous reported difference in the clinical progression rates for the entire cohort that favoured adjuvant RT after 5 years of follow up was not sustained at 10 years, although locoregional control was improved after immediate irradiation (hazard ratio, HR = 0.45, P < 0.0001).
    - In terms of toxicity, adjuvant RT was well tolerated with no reported Grade 4 toxicity. The grade 3 genitourinary toxicity rate was 5.3%, in comparison with 2.5% in the observation group after 10 years.
- SWOG 8794 reported the results of 425 men with pT3 disease who were randomised to adjuvant radiotherapy to the prostate bed (60–64 Gy) or observation and subsequent salvage therapy [Swanson GP, *et al* 2008]. At a median follow up of more than 12 years, this study demonstrated a significant improvement in metastasis-free survival, with a 10-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, P = 0.016) and a 10-year OS of 74% vs. 66% (median: 1.9 years prolongation; P = 0.023)

- The ARO trial 96-02 randomly assigned men with pT3 N0 tumours and an undetectable post operative PSA to immediate post operative radiotherapy (114 men) or a 'wait and see' policy (154 men). After a median follow-up period of 54 months, the radiotherapy group demonstrated a significant improvement in biochemical PFS of 72% vs. 54%, respectively (P = 0.0015). Further follow up is needed to assess metastases-free survival and overall survival. The rate of grade 3 to 4 late adverse effects was 0.3% [Wiegel T, *et al* 2009].
- The Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) study is investigating the timing of radiotherapy (immediate versus early salvage) and hormone duration and will be important in guiding future decision making.

Locally Advanced Disease: Recurrence after Primary Treatment

Figure 3a: Treatment algorithm for locally advanced disease (cont.)



Rising PSA levels

- The PSA concentration at which to define treatment failure after prostatectomy varies in the literature. An international consensus states that recurrent cancer may be defined by two consecutive PSA values of > 0.2 ng/mL [Heidenreich A, *et al*. EAU guidelines 2013].

Definitions of recurrence

- The Phoenix definition of relapse after radiotherapy is PSA nadir plus 2 ng/ml [Roach M, *et al* 2006].
- Patients whose PSA never falls to an undetectable level in the post-operative period are generally considered to have systemic disease. However, some may have local disease amenable to salvage radiotherapy, and so need to be carefully assessed to determine the best management plan.
- A PSA concentration that rises rapidly in the post-operative setting may be indicative of metastatic disease, while a PSA that remains undetectable over a long period then gradually rises may be more likely to indicate local recurrence.

- Pound *et al*. carried out a retrospective review of 1997 men undergoing radical prostatectomy by a single surgeon for clinically localised disease with no neoadjuvant or adjuvant treatment [Pound CR, *et al* 1999]. A PSA ≥0.2 ng/ml was deemed evidence of recurrence.
    - At 15 years, 15% had PSA elevation and 34% of these had developed metastases.
    - The median time from PSA elevation to metastatic disease was 8 years.
    - After development of metastases, the median actuarial time to death was 5 years. In the survival analysis, time to biochemical progression, Gleason grade and PSA doubling time were predictive of the probability and time to the development of metastatic disease.
- After completion of radiotherapy and hormonal treatment, testosterone recovery usually occurs. This may cause some PSA elevation that is related to normal prostate tissue recovery and not disease recurrence.
- The definition of disease recurrence in the setting of combined therapy remains a matter of debate and consensus is awaited.
- Benign PSA rises (PSA bounce) occur in approximately 12% of patients following EBRT and 30% following LDR brachytherapy in the absence of neoadjuvant hormonal treatment (starting between 18 months and 2 years after treatment).

Local recurrence after radical prostatectomy

Overview

- Overall, approximately 40% of patients who have a radical prostatectomy have biochemical evidence of recurrence at some point.
- Determining whether relapse is local or distant is important in determining optimal treatment. However, post-prostatectomy imaging is often unhelpful. Other factors that may aid this distinction include:
  - Timing and pattern of PSA relapse (rapid rise post-operatively favours distant spread)
  - Involvement of seminal vesicles or lymph nodes
  - Margin status at surgery
  - Gleason grade
- Radical salvage treatment is usually via radiotherapy to the prostate bed +/– hormone therapy. The optimal time of treatment, i.e. immediate adjuvant or early salvage EBRT, is currently uncertain. The timing and duration of hormone therapy is also unclear.
- The RADICALS study is investigating the timing of radiotherapy (immediate versus early salvage) and hormone duration [Parker C, *et al* 2007].

Clinical evidence

- Extracapsular invasion (pT3), Gleason score > 7, and positive surgical margins (R1) can be associated with a risk of local recurrence [Hanks GE. 1988]. Adjuvant radiotherapy has been assessed in three prospective randomised studies.

Adjuvant radiotherapy

- The EORTC 22911 study was designed to investigate benefit for immediate postoperative radiotherapy (60Gy) in a target sample size of 1005 patients with pT3 disease or positive surgical margins as opposed to salvage radiotherapy offered for biochemical or clinical relapse [Bolla M, *et al* 2012].

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- Further results are awaited from a recently completed randomised controlled phase III study from the RTOG-96-01 in 771 men comparing salvage radiotherapy and placebo vs. a combination of salvage radiotherapy and bicalutamide 150 mg daily in the postoperative setting [Heney N *et al*, 2010]. At a median follow-up of 7.1 years, actuarial OS at 7 years was 91% for the RT and bicalutamide group and 86% for RT alone. Too few primary end-point events have occurred to allow a statistical comparison between groups. Freedom from PSA progression at 7 years was 57% for the combined modality group and 40% for RT alone (P < 0.0001) and for the 134 men with Gleason Score 8-10 was 56% and 26% (P < 0.0008). The 7-yr cumulative incidence of metastatic prostate cancer was less in the RT and bicalutamide arm, 7% vs. 13% in the RT alone arm (p<0.041). Late grade 3-4 toxicities were similar in both arms.

- The Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) study is investigating the timing of radiotherapy to a dose of 66Gy in 33 fractions (immediate versus early salvage) and hormone duration and will be important in guiding future decision making.

Salvage hormone therapy

- Systemic failure following radical prostatectomy is predicted with > 80% accuracy by a PSA relapse < 1 year, a PSADT of 4-6 months, Gleason score 8-10, and stage pT3b, pTx pN1. In this situation early hormone therapy may help delay progression in selected patients.
- A retrospective study including 1,352 patients with postoperative PSA recurrence showed no significant difference overall in the time to clinical metastases with early hormone therapy (after PSA recurrence, but before clinical metastases) vs. delayed hormone therapy (at the time of clinical metastases). However, for high risk patients (Gleason score > 7 and/or a PSA doubling time < 12 months) it was found that early hormone therapy delayed the time to clinical metastases although had no overall impact on prostate cancer specific mortality [Moul JW, *et al* 2004].

Recurrence after radical radiotherapy

Overview

- After radiotherapy, local failure is documented by a positive prostatic biopsy and negative imaging studies for systemic disease such as CT or MRI and bone scan.
- It must however be noted that most imaging studies are not sensitive enough to identify the anatomic location of relapsing PCa at PSA levels < 0.5-1.0 ng/mL. Prostatic biopsy after RT is only considered necessary if local procedures with curative intent, such as a salvage radical prostatectomy, are indicated in an individual patient.
- The therapeutic options for recurrence following radiotherapy include:
  - Salvage radical prostatectomy: associated with 5-year biochemical DFS rates of 55–69%, but the technique is associated with a significant incidence of complications, such as rectal injury, anastamotic stricture and urinary incontinence. In general, salvage radical prostatectomy should be considered only after multidisciplinary team and patient discussion with regards to potential benefits and toxicities. It should be limited to men with low comorbidity, a life expectancy of at least 10 years, an organ-confined prostate cancer with a Gleason score < 7, and preoperative PSA < 10 ng/mL.
  - Salvage cryotherapy: 5-year biochemical PFS ranges from 40% to 73%. The complications of salvage cryotherapy are erectile dysfunction, pelvic, rectal or perineal pain, recto-urethral fistula, bladder outlet obstruction and urethral stricture.
  - Salvage HIFU is currently under investigation.
  - Hormone therapy can be given in combination with local treatments or as monotherapy.

Clinical evidence

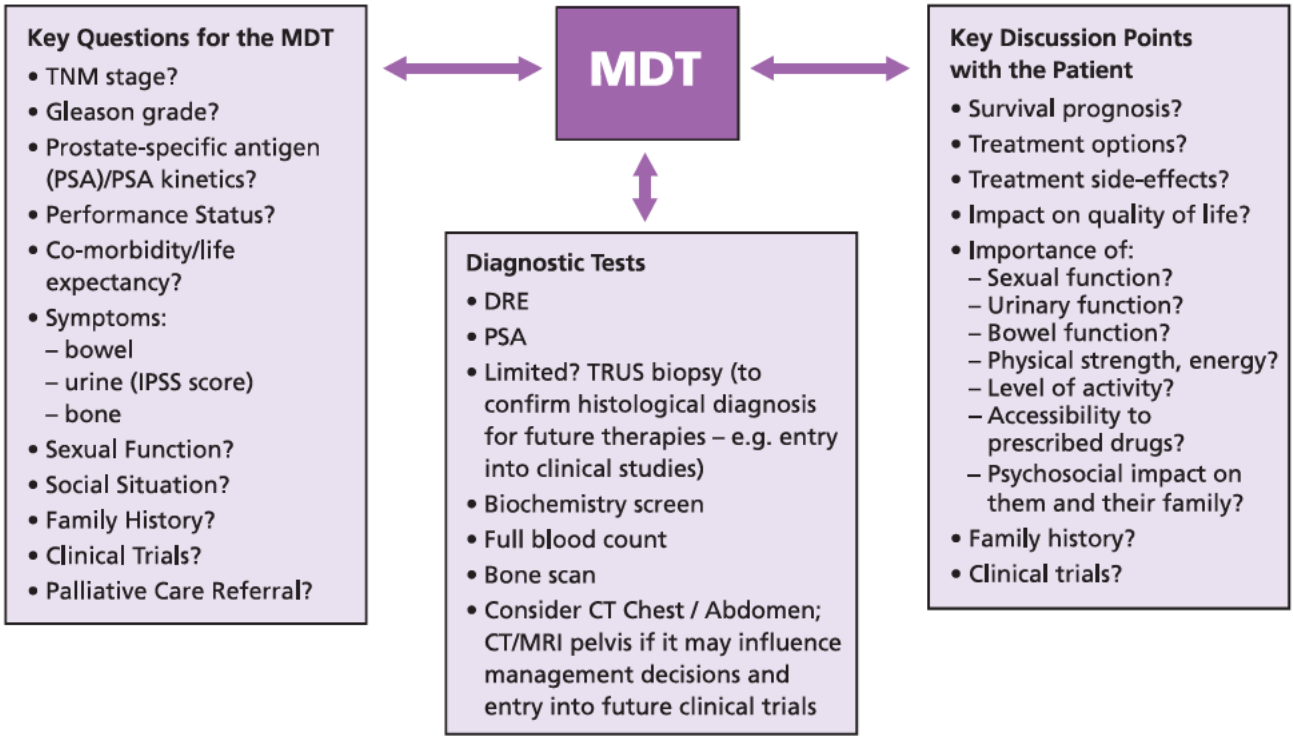
- In a recent systematic review of the literature, Chade *et al*. showed that salvage radical prostatectomy allowed 5-year and 10-year biochemical recurrence-free survival estimates ranging from 47% to 82% and from 28% to 53%, respectively. The 10-year cancer-specific and OS rates ranged from 70% to 83% and from 54 to 89%, respectively. The PSA value before salvage radical prostatectomy and prostate biopsy Gleason score were the strongest predictors of the presence of organ-confined disease, progression, and cancer specific survival [Chade DC, *et al* 2011]
- The four studies of salvage cryotherapy reviewed used varying definitions of recurrence. The 5-year biochemical PFS ranged from 40% when failure was defined as PSA 2 above nadir, to 62% and 73% when failure was defined as PSA greater than 2 and greater than 4, respectively.
    - The complications of salvage cryotherapy are erectile dysfunction, pelvic, rectal or perineal pain, rectourethral fistula, bladder outlet obstruction and urethral stricture.
- In a multicentre study reporting the current outcome of salvage cryotherapy in 279 patients, the 5-year biochemical -free survival estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15 of the 46 patients (32.6%) who underwent prostate biopsy following the procedure. The urinary incontinence rate was 4.4%. The rectal fistulae rate was 1.2%, and 3.2% of patients had to undergo transurethral resection of the prostate (TURP) for removal of sloughed tissue [Pisters LL, *et al* 2008].
- In 71 patients with localised disease following EBRT who were treated with salvage HIFU, 80% demonstrated negative biopsies and 61% had a nadir PSA concentration <0.5 ng/ml [Gelet A, *et al* 2004].
    - At a mean follow-up of 14.8 months, 44% of the patients had no evidence of disease progression.
    - Adverse events included recto-urethral fistula in 6%, grade 3 incontinence in 7%, and bladder neck stenosis in 17% of patients.

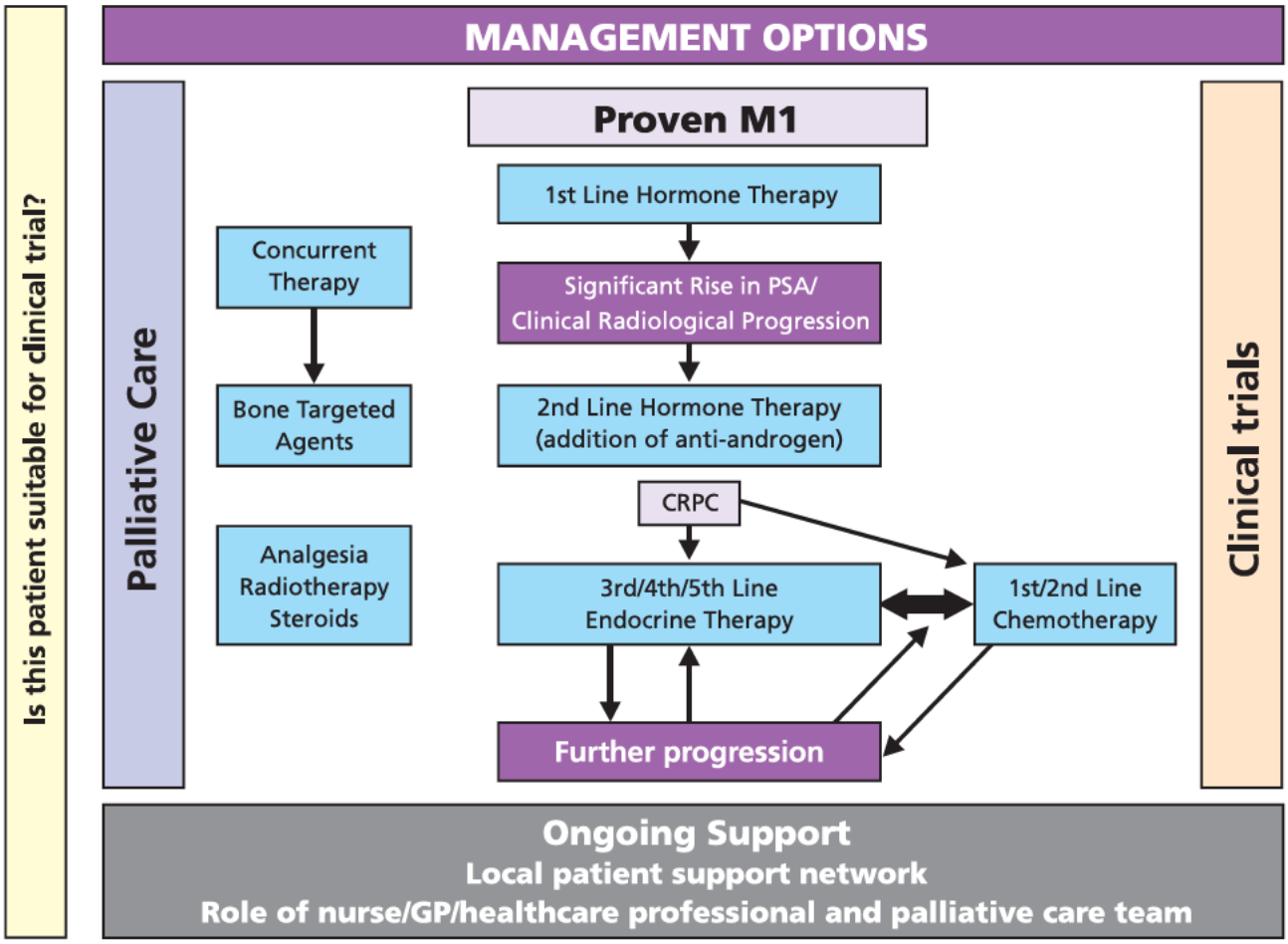
Salvage hormone therapy

- Patients with a PSA relapse who are not eligible for salvage therapy or who have high risk of systemic disease may be treated with immediate or delayed hormone therapy. Intermittent androgen deprivation for PSA elevation after radiotherapy may improve quality of life and theoretically delay hormone resistance. Overall survival rates of intermittent versus continuous androgen deprivation have been assessed in a noninferiority randomised trial.1386 patients with a PSA level greater than 3 ng/ml more than 1 year after primary or salvage radiotherapy for localised prostate cancer were randomised. Intermittent treatment was provided in 8-month cycles, with non-treatment periods determined according to the PSA level [Crook JM, *et al* 2012].
- At a median follow-up of 6.9 years, OS was 8.8 years in the intermittent-therapy group versus 9.1 years in the continuous-therapy group (hazard ratio for death, 1.02; 95% confidence interval, 0.86 to 1.21). The estimated 7-year cumulative rates of disease-related death were 18% and 15% in the two groups, respectively (P=0.24). Intermittent androgen deprivation was shown to be noninferior to continuous therapy in this setting with respect to OS. In the intermittent-therapy group, testosterone recovery to the trial-entry threshold occurred in 79%. Intermittent therapy provided potential benefits with respect to physical function, fatigue, urinary problems, hot flashes, libido, and erectile function.

Advanced (Metastatic) Prostate Cancer Management Options

Figure 4: Treatment algorithm for advanced (metastatic) disease





Based on MRC evidence, the majority of patients with advanced (metastatic) disease should be treated. Deferred treatment is acceptable only in highly selected, informed patients.

First line hormone therapy

Overview

- Androgen deprivation therapy (ADT) is standard first-line treatment for the management of patients with advanced disease. ADT can involve orchidectomy, LHRH agonists, and gonadotrophin-releasing hormone (GnRH) antagonists and anti-androgens
- Orchidectomy remains the gold-standard ADT against which all other treatments are compared because of its rapid effects on total testosterone concentrations [Tombal B.2007].
- The standard castrate level is <50 ng/dL. It was defined more than 40 years ago and current, more accurate methods of testosterone measurement have shown the mean value after surgical castration is 15 ng/dL(1.7 nmol/L) [Oefelein MG, *et al* 2000]. This has led to a revisiting of the current definition of castration, with many authors suggesting a more appropriate level is < 20 ng/dL
- Long-acting luteinising hormone-releasing hormone (LHRH) agonists have been used in advanced prostate cancer for more than 15 years. They are synthetic analogues of LHRH, generally delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. After the first injection, they stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH release leading to a testosterone and potential clinic flare phenomenon, which begins 2-3 days after administration and lasts for about 1 week. The effects of the testosterone flare can be blocked by the co administration of an antiandrogen before and up to 2 weeks after the initial injection. Survival is generally considered equivalent with LHRH agonists and orchidectomy [Vogelzang NJ, *et al* 1995; Kaisary AV, *et al* 1995]. Although a meta-analysis has indicated that 2-year survival may be worse with medical treatment than with orchidectomy [Seidenfeld J, *et al* 2000].
- Patients, however, generally prefer medical treatment and in terms of usage, drug treatment represents the standard of care for advanced prostate cancer [Shahinian VB, *et al* 2005; Shahinian VB, *et al* 2006; Cassileth BR, *et al* 1992].
- In contrast to LHRH agonists, GnRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The effect is a rapid decrease in LH, FSH and testosterone levels without any testosterone flare. Now licensed on the evidence of phase III clinical trial data, degarelix demonstrates reduced testosterone concentrations to below castrate levels in 3 days (90% decrease in median testosterone compared with leuprolide group experiencing a 65% increase in median testosterone levels; p<0.001) [Klotz L, *et al* 2010].
    - Degarelix shows long term suppression of testosterone for up to 364 days. 97.2% of patients on degarelix maintained medical castrate levels (<50 ng/dl from day 28 to Day 364 (95% /CIS) compared to 96.4% with leuprolide.
    - PSA levels were lowered by 64% after 2 weeks, 85% after 1 month and 95% after 3 months and remained suppressed throughout the 1-year treatment.
    - An extended follow-up has been recently published (median 27.5 months), suggesting that degarelix might result in better progression-free survival compared to monthly leuprorelin [Crawford ED, *et al* 2011].
    - Ongoing research suggests that degarelix may reduce the risk of further cardiovascular events in men who have suffered an event prior to commencing hormone therapy [Smith MR, *et al* 2011].
    - Degarelix can cause local skin reactions after delivery of the initial injection but this isles common with subsequent treatments.

Immediate versus deferred hormonal treatment

- All symptomatic advanced prostate cancer patients should have immediate treatment with ADT.
- Immediate versus deferred treatment for advanced prostate cancer was investigated by the MRC Prostate Working Party Investigators Group. An RCT of 943 men with asymptomatic metastases or locally advanced disease, not suitable for curative treatment, was undertaken, with randomisation to immediate or deferred hormone therapy [MRC Prostate Working Party Investigators Group 1997].
    - There was a significant advantage in the immediate treatment group in terms of distant progression. Mortality was only significantly changed by treating immediately in those with M0 disease (Table 6).
    - A modest but statistically significant increase in OS was seen in the immediate treatment group, but not significant difference in prostate cancer mortality or symptom-free survival was demonstrated.
    - Due consideration must therefore be given to potential effects of long-term ADT versus the potential avoidance of such effects in patients if hormone therapy is deferred [Studer UE, *et al* 2008].

Table 6: Effect of immediate versus deferred hormonal treatment [MRC Prostate Working Party Investigators Group 1997].

		Immediate	Deferred
Distant progression		26%	45%
Mortality due to prostate cancer	M0 disease M1 disease	31.6% No significant difference	48.8% No significant difference

Combined androgen blockade (CAB)

- There is debate over the use of combined androgen blockade (CAB). In 2000, the Prostate Cancer Trialists' Collaborative Group published a meta-analysis of the available trials of CAB versus monotherapy. The analysis included 27 trials, which incorporated 8275 men, representing 98% of men ever randomised in trials of CAB versus monotherapy [Prostate Cancer Trialists' Collaborative Group 2000; Klotz L 2001].
    - The 5-year survival for all patients receiving CAB was 25.4%, compared with 23.6% for patients receiving monotherapy.
    - In subgroup analyses, patients treated with cypretone acetate (CPA) seemed to fare slightly worse than those treated with flutamide or nilutamide, mostly secondary to non-prostate cancer-related deaths.

- If the CPA studies were excluded, the results were as follows [Prostate Cancer Trialists' Collaborative Group 2000]:
    - CAB with flutamide alone was associated with an 8% reduction in the risk of death (95%CI: 0.86–0.98; p=0.02), which translates to a small but significant improvement in 5-year survival over castration alone.
    - CAB with flutamide plus nilutamide was associated with an 8% reduction in the risk of death (95%CI: 1.00–1.27; p=0.005), which translates to a small but significant improvement in 5-year survival of 2.9% over castration alone.
    - Conversely, CAB with CPA is associated with an increased risk of death of 13% (95%CI: 1.00–1.27; p=0.04), which translates to a small but significant reduction in 5-year survival of 2.8% over castration alone.
- It can be concluded that the choice of anti-androgen used for CAB has an impact on outcome, and that CAB with a non-steroidal anti-androgen may offer a small but significant survival benefit.

Intermittent versus Continuous Androgen Blockade

- The use of intermittent androgen blockade (IAD) has the advantage of potentially reducing the toxicities of therapy and improving quality of life in the periods of no treatment and also a potential theoretical advantage of delaying the emergence of the androgen-independent clone.
- A systematic review has concluded that intermittent IAD was feasible and accepted by patients [Abrahamsson PA 2010]. Results from ongoing randomised controlled trials are awaited although many studies had mixed advanced and locally advanced patients and used different criteria for starting and stopping ADT and the duration of therapy time.
- A study of 766 patients conducted by the South European Uroncological (SEUG) Group included 30% with advanced disease. After a median follow-up of 51 months, there was no difference in either time to progression (HR: 0.81; p = 0.11) or overall survival (HR: 0.99). No overall quality of life benefit was demonstrated but there was a clear benefit for improved sexual function in the IAD group, with 28% sexually active vs. 10% in the continuous group at 15 months after randomization, respectively [Calais da Silva FE, *et al* 2009].
- The FinnProstate Study VII, randomized 554 patients (50% with advanced disease) to intermittent versus continuous ADT. After a median follow-up of 65 months, no significant difference was observed in the median PFS (34.5 months in the IAD group vs. 30.2 months in the continuous group, p = 0.29) in either the total study population or in the N+ or M1 subgroup populations. The median OS was 45 months in both groups.
- Results are awaited from the SWOG trial 9346, which is the largest study to randomize patients with advanced prostate cancer (1134 men out of 3040) to intermittent and continuous ADT [Hussain M, *et al* 2012]. The presented abstract indicated that IAD was not 'non inferior' compared to continuous ADT (median OS 5.1 years for IAD compared to 5.8 years for the continuous treatment arm).
- Published results of this and other ongoing studies are awaited to determine the further benefits and safety of IAD in men with advanced disease.