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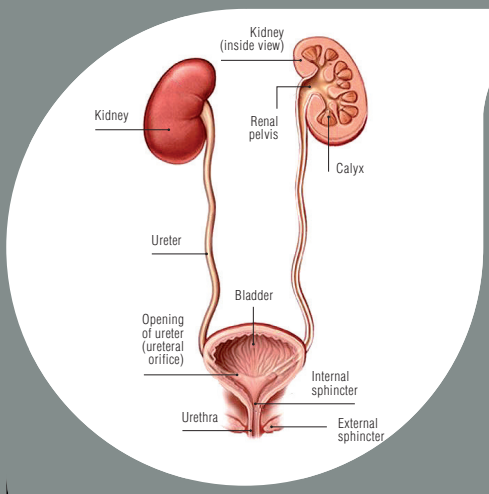
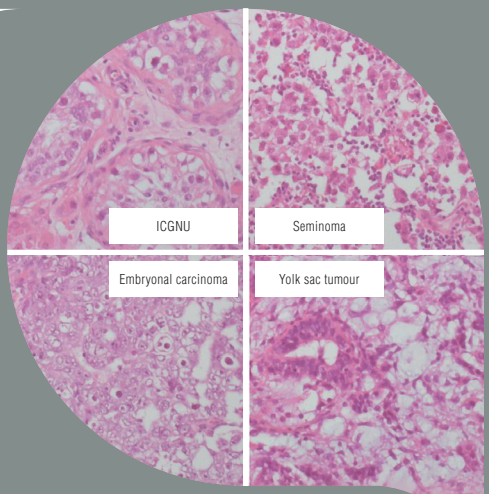
GENITOURINARY TRACT TUMOURS

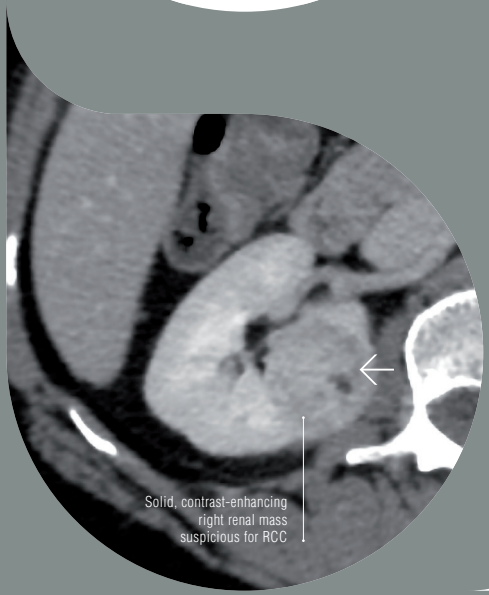
SECOND EDITION

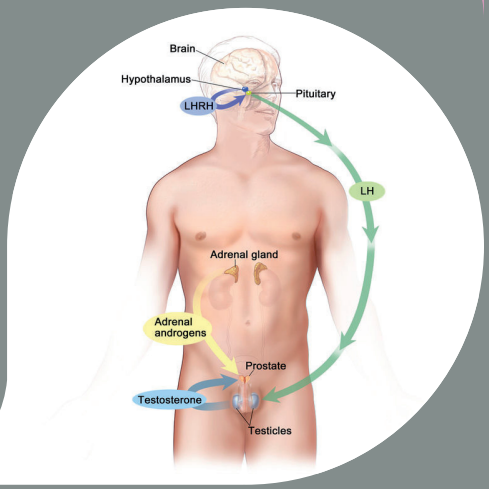
ESSENTIALS *for* CLINICIANS

edited by
Johann de Bono
Silke Gillessen
Niven Mehra
Yohann Loriot









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Genitourinary Tract Tumours Essentials for Clinicians

Second edition

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Essentials for Clinicians

Second edition

Edited by

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Contents

Preface

Treatment paradigms have rapidly changed in the field of urogenital oncology. This second edition of *Genitourinary Tract Tumours: Essentials for Clinicians* provides readers with an updated and comprehensive overview of urogenital malignancies, with a focus on bladder, prostate, renal and testicular cancer and also includes more uncommon cancers such as penile and adrenal tumours. We have strived to give our readers a complete and updated overview, including pathology, epidemiology, diagnosis and treatment encompassing surgical, radiotherapeutic and medical oncological modalities.

The book uses concise text paired with informative illustrations and includes a very useful appendices section with staging classifications. Each chapter includes take-home messages, revision questions and a further reading list for more detailed information on the topic. It is aimed at medical oncologists in training; however, the book is also informative for other physicians and practitioners wishing to receive continuing education in the field of urogenital oncology.

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Professor Johann de Bono is Regius Professor of Cancer Research and a Professor in Experimental Cancer Medicine at the Institute of Cancer Research (ICR), London and The Royal Marsden Hospital (RMH), London, UK. He is also Head of the Clinical Studies Division at the ICR and Director of the Drug Development Unit (DDU) at the Royal Marsden, leading the National Institute for Health Research (NIHR) Experimental Cancer Medicine Centre (ECMC) team and co-leading the NIHR Biomedical Research Centre.

The RMH DDU is one of the world's largest phase I clinical trials units for cancer, run jointly between the ICR and the RMH. Professor de Bono leads the Prostate Cancer Targeted Therapies team and has also led on multiple phase III trials that have changed the standard-of-care for prostate cancer patients, including trials of the ICR-discovered drugs abiraterone, cabazitaxel and enzalutamide. He has published more than 500 manuscripts, including multiple publications in *The New England Journal of Medicine* and *The Lancet*.

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Professor Silke Gillessen is a Medical Oncologist with focus on genitourinary cancer.

Since 2018, Professor Gillessen has been Genitourinary Cancer Systemic Therapy Research Chair at the University of Manchester and Honorary Consultant at The Christie NHS Foundation Trust, Manchester, UK, while continuing to work as a Consultant in the Department of Oncology/Haematology at the Cantonal Hospital St. Gallen, Switzerland.

Professor Gillessen was recently appointed Head of the Department of Medical Oncology, full professor at the Università della Svizzera Italiana (USI) and Director of the Istituto Oncologico della Svizzera Italiana (IOSI) in Lugano and Bellinzona, Switzerland.

Professor Gillessen completed her training in Basel and St. Gallen, Switzerland, and at the Dana-Farber Cancer Institute, Boston, MA, USA. After returning to Switzerland, she built up the medical oncology unit for genitourinary cancer in Cantonal Hospital, St. Gallen and served for two terms as president of the SAKK (Swiss Group for Clinical Cancer Research) GU group. She chaired the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Cancers Group and founded the Advanced Prostate Cancer Consensus Conference (APCCC).

Professor Gillessen has authored more than 150 publications.

Niven Mehra, MD, PhD

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Dr Niven Mehra is a Consultant in Medical Oncology at Radboud University, Nijmegen, Netherlands.

In 2002, he graduated in medicine from the University Medical Center Utrecht, Netherlands. After a PhD in translational research in 2006 (under Emile Voest), he trained in internal medicine from 2006 to 2011 and in medical oncology from 2011 to 2014.

In 2014 he focused on urogenital oncology during a clinical research fellowship at The Royal Marsden NHS Trust and the Institute of Cancer Research (under Johann de Bono), London, UK. His post-doctorate research was centred on biomarker discovery in liquid biopsies using next-generation sequencing techniques, and on the role of immune-suppressive cells driving treatment resistance in prostate cancer.

Since 2016 he has held a staff position as a clinician-scientist focusing on genitourinary cancer and immunotherapy. He is leading a translational research group on biomarker-driven personalised cancer therapy.

Niven Mehra is heading the Prostate Cancer Working Group of the Dutch Uro-Oncology Study (DUOS). He is a member of the European Society for Medical Oncology (ESMO) Educational Publications Working Group and author of peer-reviewed research papers in international journals, cancer textbooks and handbooks.

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Dr Yohann Loriot is a physician-scientist in Medical Oncology at the Gustave Roussy Institute, Université Paris-Saclay, Villejuif, France.

He trained in Paris, France, graduated in 2009 as a Medical Oncologist, and completed his PhD in 2014. From 2011-2012, he moved as a visiting scientist to the Vancouver Prostate Centre, Vancouver, Canada.

Dr Loriot's major clinical and translational research focus includes the study of mechanisms mediating progression to lethal disease in urothelial and prostate cancer and the use of this information to develop novel strategies and therapies. He has authored several peer-reviewed research papers in international journals, cancer textbooks and handbooks.

He is a member of the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO). He is the recipient of a number of grants and awards, including a UNICANCER-Fondation de France grant and an ASCO Young Investigator award 2013.

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Abbreviations

^{51}Cr-EDTA	Chromium-51 ethylenediamine tetraacetic acid
3D-CRT	Three-dimensional conformal radiotherapy
AA	Abiraterone acetate
AC	Adrenocortical carcinoma
AdC	Adenocarcinoma
ADC	Antibody-drug conjugate
AdjC	Adjuvant carboplatin
ADT	Androgen deprivation therapy
AE	Adverse event
AFP	Alpha-foetoprotein
aMVAC	Accelerated methotrexate/vinblastine/doxorubicin/cisplatin
APCCC	Advanced Prostate Cancer Consensus Conference
AR	Androgen receptor
AR-V7	Androgen receptor-splice variant 7
AS	Active surveillance
ASAP	Atypical small acinar proliferation
ASR	Age-standardised rate
AURKA	Aurora A kinase
BCF	Biochemical failure
BCG	Bacillus Calmette-Guérin
BEP	Bleomycin/etoposide/cisplatin
BHD	Birt-Hogg-Dubé
BT	Brachytherapy
ccRCC	Clear cell renal cell carcinoma
CDCT	Conventional dose chemotherapy
CDK	Cyclin-dependent kinase
ChT	Chemotherapy
CI	Confidence interval
CIS	Carcinoma *in situ*
CMR	Complete metabolic response
CNS	Central nervous system
CPS	Combined positive score
CR	Complete response
CRPC	Castration-resistant prostate cancer
CRT	Chemoradiotherapy
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DDR	DNA damage repair
DDRd	DNA damage repair defect
DLBCL	Diffuse large B-cell lymphoma
DRE	Digital rectal examination
DSNB	Dynamic sentinel lymph node biopsy
EBRT	External beam radiotherapy
ED	Erectile dysfunction
EGFR	Epidermal growth factor receptor
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EMT	Epithelial-to-mesenchymal transition
EORTC	European Organisation for Research and Treatment of Cancer
EP	Cisplatin/etoposide
ePLND	Extended pelvic lymph node dissection
ERSPC	European Randomized Study of Screening for Prostate Cancer
ESMO	European Society for Medical Oncology
EV	Enfortumab vedotin
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
GC	Gemcitabine/cisplatin
GCNIS	Germ cell neoplasia *in situ*
G-CSF	Granulocyte colony-stimulating factor
GCT	Germ cell tumour
GFR	Glomerular filtration rate
GIP	Cisplatin/ifosfamide/gemcitabine
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GnRH	Gonadotropin-releasing hormone
GTS	Growing teratoma syndrome
GWAS	Genome-wide association study
Gy	Gray
hCG	Human chorionic gonadotropin
HDAC	Histone deacetylase
HDACi	HDAC inhibitor
HDCT	High-dose chemotherapy
HD-MVAC	High-dose intensity MVAC
HDR	High-dose rate
HFX	Hypofractionation
HIFU	High-intensity focused ultrasound
HIF-α	Hypoxia-inducible factor alpha
HLRCC	Hereditary leiomyomatosis and renal cell carcinoma
HPRCC	Hereditary papillary renal cell carcinoma
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality of life
HSPC	Hormone-sensitive prostate cancer
IC	Immune cell
ICI	Immune checkpoint inhibitor
IFNα	Interferon alpha
IGCCCG	International Germ Cell Cancer Collaborative Group
IGCNU	Intratubular germ cell neoplasia, unclassified
IGF-1R	Insulin-like growth factor 1 receptor
IGRT	Image-guided radiotherapy
i.m.	Intramuscular
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IMRT	Intensity-modulated radiotherapy
IPFSG	International Prognostic Factors Study Group
ISUP	International Society of Urological Pathology
i.v.	Intravenous
KPS	Karnofsky performance score
LAG-3	Lymphocyte-activation gene 3
LDH	Lactate dehydrogenase
LDR	Low-dose rate
LMWH	Low-molecular-weight heparin
LN	Lymph node
LND	Lymph node dissection
LRN	Laparoscopic radical nephrectomy
LVI	Lymphovascular invasion
M0 CRPC	Non-metastatic castration-resistant prostate cancer
mAb	Monoclonal antibody
mCRPC	Metastatic castration-resistant prostate cancer
MDT	Multidisciplinary team
MEN 2	Multiple endocrine neoplasia type 2
MIBC	Muscle-invasive bladder cancer
MIBG	^{123}I metaiodobenzylguanidine
MiT	Microphthalmia transcription factor
MMAE	Monomethyl auristatin E
mOS	Median overall survival
mpMRI	Multi-parametric magnetic resonance imaging
mRCC	Metastatic renal cell carcinoma
MR	Magnetic resonance
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
mUBC	Metastatic urinary bladder cancer

MVAC	Methotrexate/vinblastine/doxorubicin/cisplatin
NEPC	Neuroendocrine prostate cancer
NF1	Neurofibromatosis type 1
NMIBC	Non-muscle-invasive bladder cancer
NND	Number needed to diagnose
NNI	Number needed to invite
NPCA	UK National Prostate Cancer Audit
NSGCT	Non-seminomatous germ cell tumour
NSS	Nephron-sparing surgery
NTD	N-terminal domain
NYHA	New York Heart Association
ONJ	Osteonecrosis of the jaw
ORC	Open radical cystectomy
ORR	Overall response rate
OS	Overall survival
PADUA	Preoperative Aspects and Dimensions Used for Anatomical classification
PARP	Poly(ADP-ribose) polymerase
PC	Prostate cancer
PCWG	Prostate Cancer Working Group
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PH	Phaeochromocytoma
PIN	Prostatic intraepithelial neoplasia
PI-RADS	Prostate Imaging Reporting and Data System
PLCO	Prostate, Lung, Colorectal and Ovarian
PLND	Pelvic lymph node dissection
PN	Partial nephrectomy
PNET	Primitive neuroectodermal tumour
PSA	Prostate-specific antigen
PSA-TRICOM	Prostate-specific antigen-T cell costimulatory molecule
PSMA	Prostate-specific membrane antigen
PTa	Non-invasive papillary carcinoma
PTEN	Phosphatase and tensin homologue
PTis	Papillary carcinoma *in situ*
PUNLMP	Papillary urothelial neoplasm of low malignant potential
PVB	Cisplatin/vinblastine/bleomycin
RALP	Robotic-assisted laparoscopic prostatectomy
RARC	Robotic-assisted radical cystectomy
RC	Radical cystectomy
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RENAL	Radius, Exophytic/endophytic, Nearness, Anterior/posterior, Location
RFS	Recurrence-free survival
RLT	Radioligand therapy
RN	Radical nephrectomy
RP	Radical prostatectomy
RPCRC	Rotterdam Prostate Cancer Risk Calculator
RPLND	Retroperitoneal lymph node dissection
RSP	Risk stratification profile
RT	Radiotherapy
RTB	Renal tumour biopsy
SCC	Squamous cell carcinoma
SDH	Succinate dehydrogenase
SIOG	International Society of Geriatric Oncology
SNP	Single-nucleotide polymorphism
SoC	Standard-of-care
SRE	Skeletal-related event
SSIGN	Stage, Size, Grade and Necrosis
TCC	Transitional cell carcinoma
TCGA	The Cancer Genome Atlas
TEE	Thromboembolic event
TGCC	Testicular germ cell cancer
TIP	Cisplatin/ifosfamide/paclitaxel
TIM-3	T cell immunoglobulin and mucin domain 3
TKI	Tyrosine kinase inhibitor
TMT	Teratoma with malignant transformation
TNM	Tumour, node, metastasis
TRUS	Transrectal ultrasound
TURB	Transurethral resection of the bladder
TURBT	Transurethral resection of bladder tumour
UC	Urothelial carcinoma
UISS	UCLA-integrated staging system
UTT	Upper tract tumour
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VeIP	Vinblastine/ifosfamide/cisplatine
VHL	von Hippel-Lindau
VIP	Cisplatin/etoposide/ifosfamide
WHO	World Health Organization
WIT	Warm ischaemia time
ZoI	Zoledronic acid

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Yohann Loriot

A

What every oncologist should know

1 Anatomy of the genitourinary tract and histology of genitourinary tumours

Tumours of the kidney

>95% of kidney cancers have a characteristic morphology that can be classified as: clear cell, papillary and chromophobe renal cell carcinoma (RCC), and collecting duct carcinoma.

A small proportion of rare kidney cancer entities are defined on a molecular basis, e.g. the microphthalmia transcription factor (MiT) family translocation RCC and succinate dehydrogenase-deficient RCC.

A 2018 study from Carlo et al showed a high prevalence of cancer-associated germline mutations in advanced kidney cancers (especially in non-clear cell RCC: 11.7% RCC-associated gene mutations).

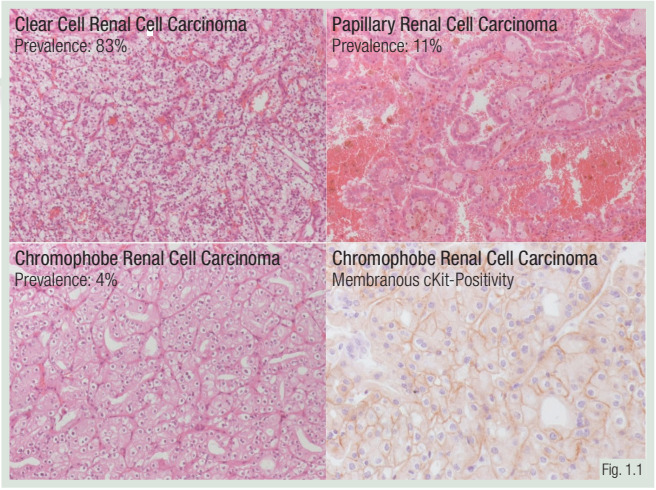


Fig. 1.1

Clinical and pathological classification of the primary tumour (pT)	
T1	Tumour 7 cm or less in greatest dimension, limited to the kidney
T2	Tumour more than 7 cm in greatest dimension, limited to the kidney
T3	Tumour extends into major veins or perinephric tissues
T4	Tumour invades beyond Gerota fascia

Fig. 1.2

Pathological tumour stage has a strong prognostic impact.

In the past, various grading systems (e.g. Thoenes or Fuhrmann) have been used for RCC staging. Today, the World Health Organization/International Society of Urological Pathology (WHO/ISUP) four-tiered system should be applied.

Tumour grade is defined mainly on the basis of nucleolar prominence.

'Benign' renal tumours

5%-7% of kidney tumours are benign. Oncocytoma is the most frequent benign kidney tumour. The tumour is well circumscribed, mahogany brown with a central scar.

Angiomyolipomas represent 1% of kidney tumours. They consist of varying proportions of mature fat, thick-walled blood vessels and smooth muscle.

Multilocular cystic renal neoplasm of low malignant potential is in principle a malignant tumour, but is entirely composed of cysts, with very few cancer cells. Metastases have not been reported.

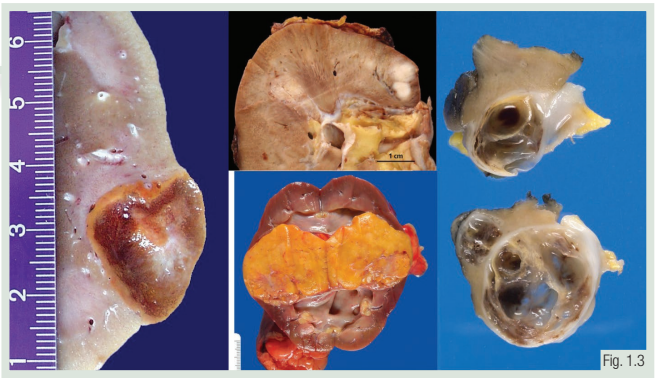


Fig. 1.3

Oncocytoma | Angiomyolipoma | Multilocular cystic renal cell carcinoma

REVISION QUESTIONS

1. What are the main subtypes of RCC?
2. What is the best predictor of prognosis in RCC?
3. Which carcinoma has the best prognosis?

Tumours of the urinary system

Urothelium is present in the kidney pelvis, ureters, urinary bladder and the urethra.

Urothelial neoplasms can occur in all of these organs but more than 90% are located in the urinary bladder.

The normal bladder wall consists of several tissue layers, the distinction of which is critical for bladder cancer staging.

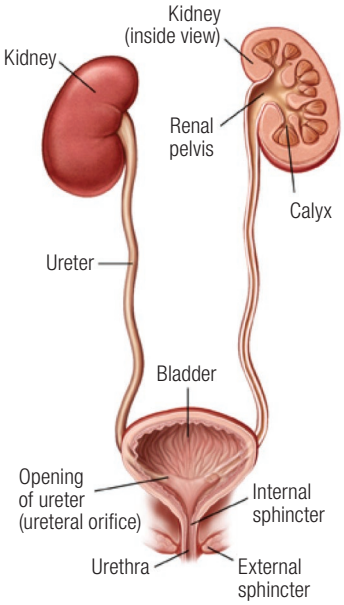


Fig. 1.4

Diagram showing the T stages of bladder cancer

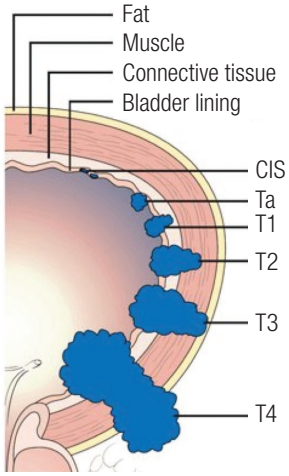


Fig. 1.5

CIS, carcinoma *in situ*.

The urothelium covers the inner surface of the bladder. The connective tissue layer between the urothelium and the muscular bladder wall is the lamina propria.

The staging system of urothelial neoplasms is unusual, as two non-invasive types of lesions exist: non-invasive papillary carcinoma (pTa) and carcinoma *in situ* (pTis).

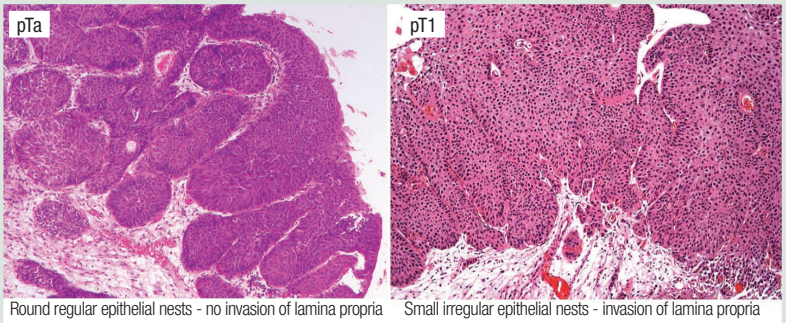
The invasive stages are pT1: invasion of lamina propria; pT2: invasion of muscular wall; pT3: invasion of perivesical fat and pT4: invasion of adjacent organs.

Staging of bladder neoplasms is critical for treatment decisions, but challenging for pathologists.

This is due to the nature of transurethral tumour resection, because it always leads to fragmentation and to substantial crush artefacts in the resected tissues.

The distinction between pTa and pT1 tumours can be very challenging and is subject to high interobserver variability.

pTa versus pT1: High interobserver variability



Round regular epithelial nests - no invasion of lamina propria

Small irregular epithelial nests - invasion of lamina propria

Author	N	pT1 downstaged to pTa
Abel 1988	28	25%
Witjes 1994	120	31%
Tosoni 2001	235	34%

Assessment of interobserver variability of staging pTa and pT1 tumours:
In these studies pT1 tumours were reviewed and the initial diagnosis was downstaged to pTa in 25%-34% of cases.

Fig. 1.6

REVISION QUESTIONS

1. What is the most common site for urothelial cancer?
2. What is the difference between stages pTa and pTis?
3. Which tumour stages are subject to particularly high interobserver variability?

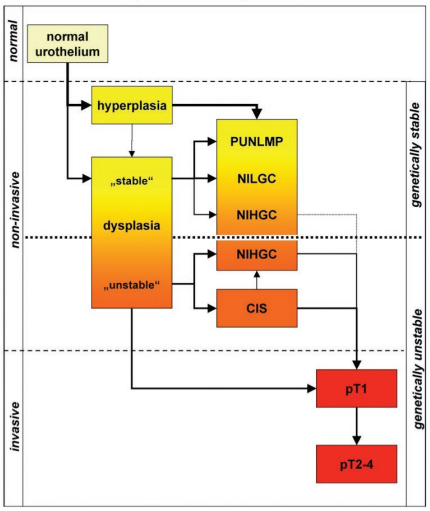
Tumours of the urinary system (continued)

Development and progression of urothelial neoplasia occurs through two quite different genetic pathways.

Non-invasive papillary cancers of low/intermediate grade (pTa, G1/2) develop from dysplasia/hyperplasia and almost never progress to invasive cancer.

Invasive carcinomas are mostly of high grade and are mainly derived from carcinoma *in situ* or high-grade non-invasive papillary carcinomas (pTa, G3).

Model of bladder cancer development and progression based on genetic findings



CIS, carcinoma *in situ*; NIHGC, non-invasive high-grade carcinoma; NILGC, non-invasive low-grade carcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential. Fig. 1.7

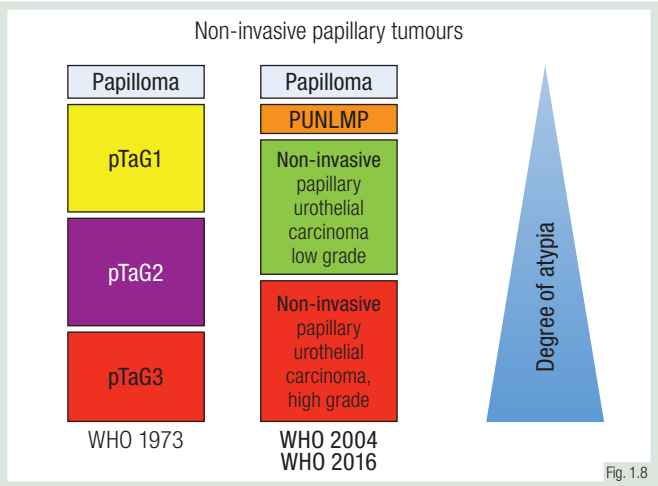


Fig. 1.8

PUNLMP, papillary urothelial neoplasm of low malignant potential; WHO, World Health Organization.

The classification of non-invasive papillary carcinomas is confusing because two 'non-congruent' systems are typically used, either alone or in parallel.

Most clinicians are familiar with the WHO 1973 grading system, which classifies non-invasive cancers as pTaG1, pTaG2 or pTaG3.

The WHO 2004 version (also adopted in the WHO 2016 version) also includes: papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade non-invasive papillary cancer and high-grade non-invasive bladder cancer.

The clinical term 'non-muscle invasive bladder cancer' is used for pTa and pT1 tumours.

pTa and pT1 tumours not only represent two different entities at the genetic level, but also have a completely different clinical course.

While pTa tumours rarely progress, pT1 tumours are early stages of highly malignant neoplasms.

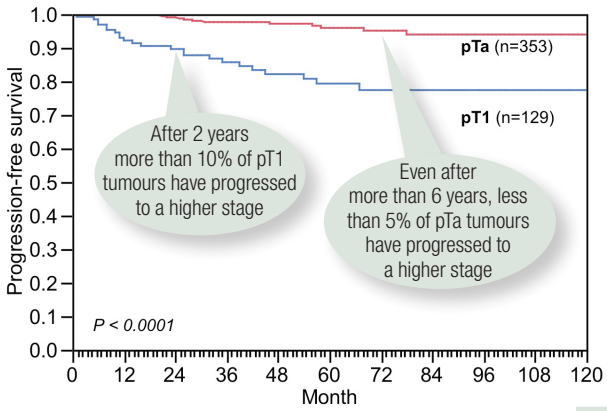


Fig. 1.9

REVISION QUESTIONS

1. What are the two main groups of urothelial neoplasms?
2. What is the difference between the WHO 1973 and WHO 2004/2016 classifications?
3. Why should the term 'superficial bladder cancer' be avoided?

Tumours of the prostate

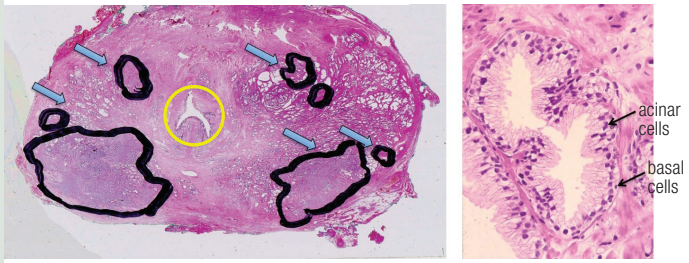
Prostate cancer (PC) is very common. A complete examination of the prostate will reveal cancer in 50% of men at the age of 50 and >75% at the age of 75 years.

Accordingly, precursor lesions are even more common in the prostate and many patients have more than one spatially separated PC.

Normal prostate epithelium is characterised by the presence of two cell layers: basal cells and acinar cells.

Prostate cancer is often multifocal
(Whole section through the prostate gland; blue arrow: prostate cancer, yellow circle: urethra)

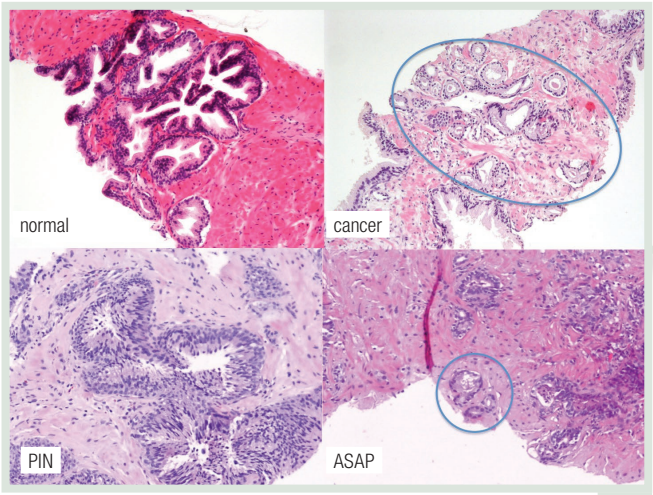
Normal prostate gland



Clinical and pathological classification of the primary tumour T

T1	Clinically unapparent tumour
T2	Tumour confined within the prostate
T3	Tumour extends through the prostatic capsule
T4	Tumour invades adjacent structures other than seminal vesicles

Fig. 1.10



ASAP, atypical small acinar proliferation; PIN, prostatic intraepithelial neoplasia.

Fig. 1.11

Prostate biopsy is the only tool for establishing a definitive diagnosis of PC.

Findings in prostate biopsies include: normal, prostatic intraepithelial neoplasia (PIN), atypical small acinar proliferation (ASAP) and carcinoma.

PIN is the precursor lesion of PC. ASAP is a diagnostic category that includes all changes that are suspicious for cancer but not unequivocally diagnostic.

PC is entirely composed of atypical cells, while basal cells are completely lost. Gleason grade is the strongest predictor of tumour aggressiveness.

In contrast with all other grading systems, the Gleason grade is based solely on tumour architecture and does not consider any cytological changes.

The Gleason score is defined as the sum of the two most common grade patterns. The traditional Gleason grading system only distinguishes 5 groups: ≤6, 3+4, 4+3, 8, 9-10, also termed ISUP grade groups 1-5. The use of tertiary grades or the percentage of Gleason 4/5 offers a finer assessment of cancer aggressiveness.

a) The original Gleason grading system diagram. b) and c) Impact of the Gleason pattern on patient prognosis (time to biochemical recurrence).

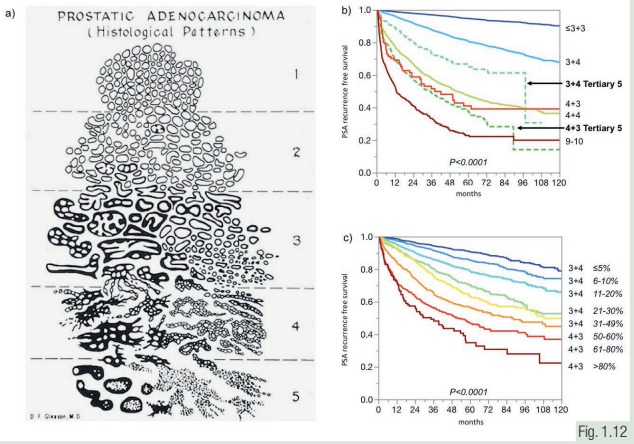


Fig. 1.12

PSA, prostate-specific antigen.

REVISION QUESTIONS

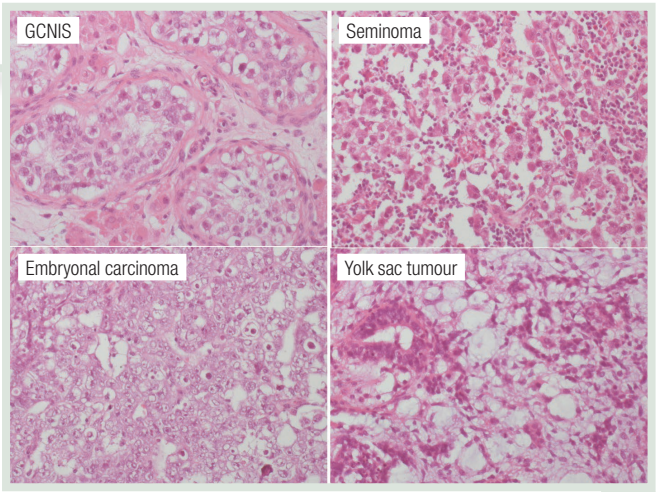
1. What is the precursor lesion of PC?
2. What is the meaning of 'ASAP' and when is this term used?
3. What is the characteristic of Gleason grading?

Tumours of the testis

More than 95% of all testicular neoplasias are germ cell tumours (GCTs). GCTs mostly occur at young age (peak frequency at the age of 30 years).

More than 90% of GCTs develop through germ cell neoplasia *in situ* (GCNIS), formerly called intratubular germ cell neoplasia, unclassified (IGCNU), which is commonly found in the vicinity of these cancers.

50% of GCNIS progress to invasive GCTs within 5 years, and at least 70% within 7 years.



GCNIS, germ cell neoplasia *in situ*.

Fig. 1.13

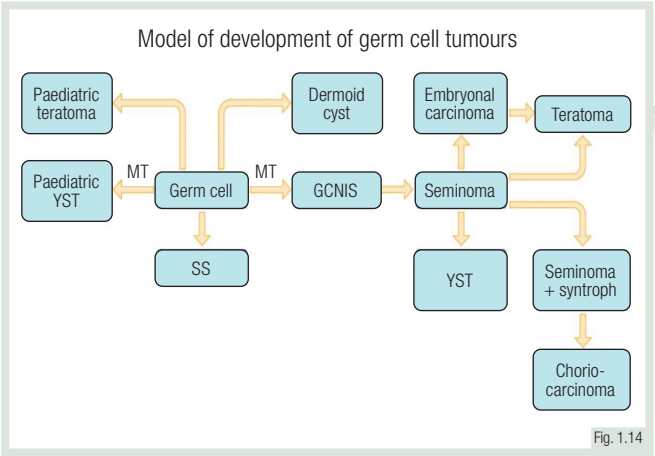


Fig. 1.14

GCNIS, germ cell neoplasia *in situ*; MT, malignant transformation; SS, spermatocytic seminoma; YST, yolk sac tumour.

Seminoma is the earliest development stage of invasive GCT.

About 50% of all testicular GCTs halt at that stage of development and are diagnosed as pure seminomas.

Teratoma in the adult is a 'differentiated type' of GCT having evolved from GCNIS and seminoma. Teratoma in adults is thus considered malignant.

Tumour stage (pT) is critical for subsequent therapy of testicular tumours.

Most pT2 stages are diagnosed because of vascular invasion.

Regional lymph nodes include the abdominal, para-aortic, preaortic, interaortocaval, precaval, paracaval, retrocaval and retroaortic lymph nodes.

Clinical and pathological classification of the primary tumour T	
T1	Tumour limited to testis and epididymis without vascular/ lymphatic invasion
T2	Tumour limited to testis and epididymis with vascular/ lymphatic invasion or tumour extending through tunica albuginea with involvement of tunica vaginalis
T3	Tumour invades spermatic cord
T4	Tumour invades scrotum

Fig. 1.15

REVISION QUESTIONS

1. What is the precursor lesion of most GCTs?
2. What is the typical age of diagnosis for GCT?
3. Why is a testicular teratoma in an adult considered malignant?

Summary: Anatomy of the genitourinary tract and histology of genitourinary tumours

- The most common kidney cancers are clear cell, papillary and chromophobe RCC
- Urothelium is present in the renal pelvis, ureters, urinary bladder and urethra, but >90% of urothelial neoplasms occur in the urinary bladder
- The staging system of urothelial neoplasms is unusual as two types of non-invasive lesions exist: pTa and pTis
- There is a high interobserver variability in staging pTa and pT1 tumours
- pTa and pT1 tumours represent two different entities at the genetic level and have a completely different clinical course
- PC is very common and will be found upon examination in >75% of men at the age of 75 years
- PC is graded according to Gleason grading, the strongest predictor of tumour aggressiveness. Since 2014, the ISUP grading system is also used
- More than 95% of all testicular neoplasias are GCTs
- GCTs mostly occur at young age
- GCTs include seminoma, embryonal carcinoma, yolk sac tumour, choriocarcinoma and teratoma

Further Reading

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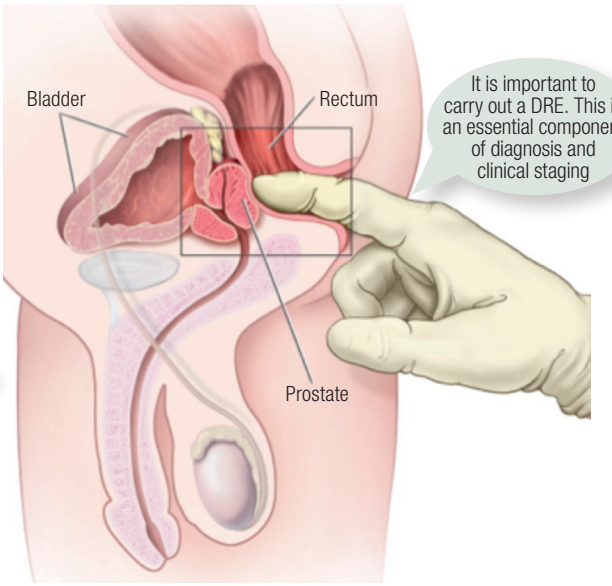
2 Staging and treatment of localised prostate cancer

Clinical staging

Clinical staging and risk stratification are determined after diagnosis by prostate biopsy. They use a combination of digital rectal examination (DRE), prostate-specific antigen (PSA) measurement, Gleason score with estimation of cores involved and percentage of involvement, supplemented by bone scanning and cross-sectional imaging. Multi-parametric magnetic resonance imaging (mpMRI) prior to biopsy is now an important component of this overall assessment.

DRE is important in clinical staging. It has inaccuracies, but helps to discriminate between T1/T2 and T3/T4 disease.

Transrectal ultrasound (TRUS)-guided biopsies are the most commonly used biopsy technique; however, the transperineal approach is increasingly being utilised particularly for anterior lesions. Both cognitive and fusion techniques are used to target specific lesions.



DRE, digital rectal examination. Fig. 2.1

Predicted probabilities are shown here for GS 7 and GS >8

Pathological outcome	GS 7 (95% CI)	GS >8 (95%CI)
Organ confined, pT2	8 (4-11)	4 (1-6)
ECE, pT3a	21 (15-27)	14 (9-20)
SVI, pT3b	54 (47-61)	56 (48-63)
Adjacent organ invasion, pT4	17 (11-21)	26 (18-32)
Positive lymph nodes	39 (32-45)	59 (51-65)
Positive surgical margins	54 (47-61)	78 (71-84)

CI, confidence interval; ECE, extracapsular extension; GS, Gleason score; SVI, seminal vesicle invasion. Fig. 2.2

In clinically localised disease, PSA levels >20 ng/mL and high Gleason grades are associated with microscopic metastatic pelvic nodal disease in a significant number of patients.

PSA is important in assessing tumour load, but is unreliable in isolation due to its production by benign glandular components and elevation after inflammation/instrumentation.

Bone scanning is usually negative in low-risk disease (PSA <10, Gleason score 6/7). If PSA >20 or >10 with high-grade disease (Gleason 8+), it will detect metastasis in 5%-15% of cases.

mpMRI is increasingly utilised prior to initial biopsy and in active surveillance (AS). It should be performed before biopsy; if carried out after biopsy it can be difficult to interpret accurately. MRI is helpful in diagnosis but its exclusive use without biopsy is controversial (Fig. 2.3 shows an apical lesion).

mpMRI includes three individual imaging sequences: diffusion-weighted with apparent diffusion coefficient, T2-weighted and dynamic intravenous contrast-enhanced imaging.

The PI-RADS (Prostate Imaging Reporting and Data System) score assigns a score from 1-5 to a lesion, with 1 most likely benign and 5 most likely malignant.

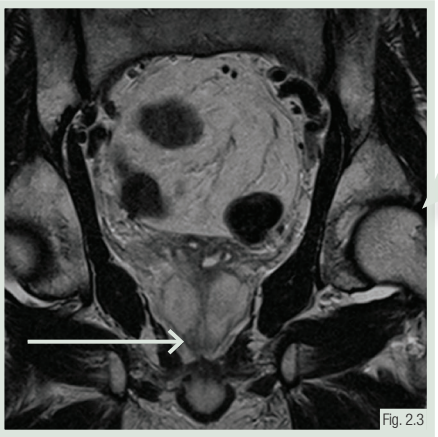


Fig. 2.3

CT, computed tomography; mpMRI, multi-parametric magnetic resonance imaging.

REVISION QUESTIONS

1. Is PSA alone sufficiently accurate for clinical staging?
2. What is the relevance of a PSA >20 ng/mL in a patient with clinically localised disease?
3. Is mpMRI alone diagnostic in clinically localised prostate cancer?

Treatment according to risk stratification

Management by AS, or intervention with surgery or radiotherapy (RT), is determined by risk stratification profile (RSP).

Published RSPs vary, but most rely on: absolute PSA levels, clinical stage, Gleason/ISUP (International Society of Urological Pathology) grade and the extent of disease in biopsy cores.

The first commonly used risk classifier, the 'D'Amico' classification, grades high risk as PSA ≥20 ng/mL, Gleason grade 8-10 and cT2c or greater. It is still used but other systems were published more recently. The ISUP grading system has now upgraded the Gleason system to improve its clinical relevance.

International Society of Urological Pathology 2014 grades	
Gleason score	**ISUP grade**
2-6	1
7 (3 + 4)	2
7 (4 + 3)	3
8 (4 + 4 or 3 + 5 or 5 + 3)	4
9-10	5

EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer			
Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA <10 ng/mL and GS <7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA >20 ng/mL or GS >7 (ISUP grade 4/5) or cT2b	Any PSA Any GS cT3-4 or cN+ Any ISUP grade
Localised			**Locally advanced**

EAU, European Association of Urology; GS, Gleason score; ISUP, International Society of Urological Pathology; PSA, prostate-specific antigen. Fig. 2.4

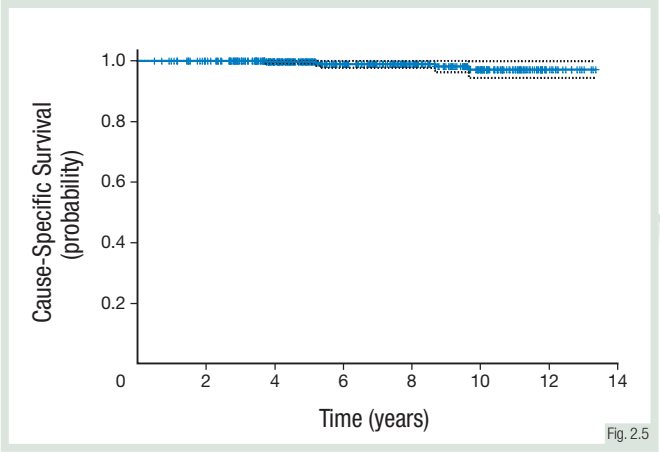


Fig. 2.5

AS is now the standard-of-care for most low-risk prostate cancer (PC). The UK National Prostate Cancer Audit (NPCA) 2017 reflects the decreasing international trend of radical intervention for low-risk disease (6% in 2017).

AS protocols involving serial monitoring of patients with low-volume (T1/T2) Gleason 6 disease are now routine. Five- and ten-year PC-related mortalities are low (99.7% and 97.2%, respectively).

AS involves regular PSA measurement, DRE and repeated MRI. Routine interval biopsy of the prostate is becoming less common in the era of mpMRI surveillance.

Long-term results confirm low disease progression rates but a significant number of men elect for active treatment within 5 years.

AS is a safe, viable option for low-risk PC. Results from a large cohort study showed 55% of men with low- or early intermediate-risk disease remained on surveillance at 15 years.

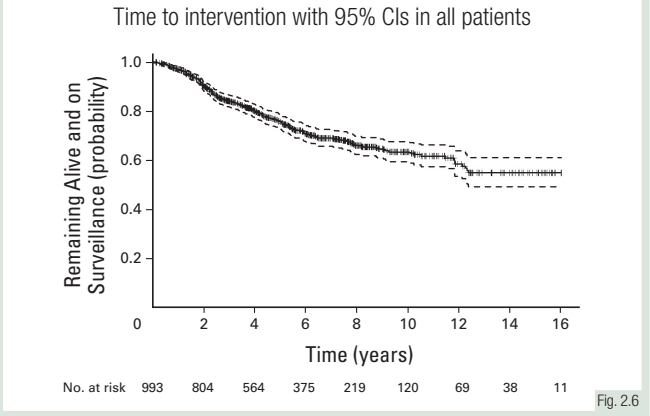


Fig. 2.6

CI, confidence interval.

REVISION QUESTIONS

1. Why is risk stratification important in clinically localised PC?
2. What are the determinants of high risk?
3. What is the current standard-of-care for low-risk PC?

Radical prostatectomy

Radical prostatectomy (RP) involves the removal of the prostate and seminal vesicles with re-anastomosis of the bladder back onto the urethra above the distal urethral sphincter.

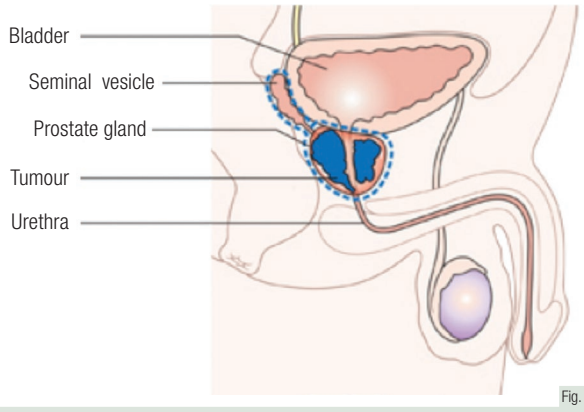


Fig. 2.7

Robotic-assisted laparoscopic prostatectomy (RALP) is now the most common surgical approach. With high-risk disease, a pelvic lymph node dissection (PLND) is usually carried out.

RALP is associated with reduced length of hospital stay and lower transfusion rates and postoperative pain, compared with open surgery. High-volume centres report improved outcomes.


Fig. 2.8

RALP involves one surgeon operating from a console with a surgical assistant at the operating table.

The system provides a high degree of accuracy with the ability to access and operate in confined spaces.

Preoperative high-risk cases usually have an extended PLND (ePLND), indicated when the risk of metastases is >5% (Briganti Nomogram). Areas of nodal tissue removed are shown in Fig. 2.9.

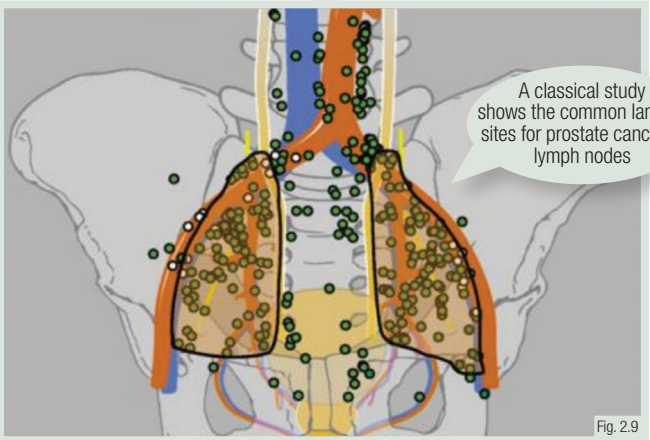


Fig. 2.9

Post-surgery complications include stress incontinence (approximately 10%) and erectile dysfunction (ED). Erectile nerve sparing is only worthwhile if there is no ED prior to surgery.

Nerve sparing can be performed in most low/intermediate-risk cases and some high-risk cases, with preservation of erectile function in up to 50%-70% of patients. When it is not possible, impotence is very likely. Recovery of erectile function can take up to 2 years.

Recent evidence from the large-scale RADICALS trial, confirmed by a meta-analysis with two other smaller trials (RAVES and TROG), has shown that delayed treatment following PSA failure is as effective as immediate RT in reducing rates of biochemical failure. Using this delayed treatment approach, 50% of men with high-risk features avoid additional treatment and the RT-related complications are reduced (Parker C et al, ESMO 2019).

REVISION QUESTIONS

1. What is removed during an RP and when is an ePLND undertaken?
2. What are the main complications of the procedure?
3. When is 'nerve sparing' possible and what are the long-term results?

Radiotherapy

RT includes external beam (EBRT) and brachytherapy (BT). BT involves temporary or permanent placement of radioactive sources within the prostate.

Low-dose rate (LDR) BT is given as monotherapy in low-risk and favourable intermediate-risk disease. Radioactive seeds (iodine-125 or palladium-123) are placed directly into the prostate under ultrasound guidance. High-dose rate (HDR) BT is usually combined with EBRT to allow for dose escalation in intermediate- and high-risk disease. The radioactive source is removed after treatment.

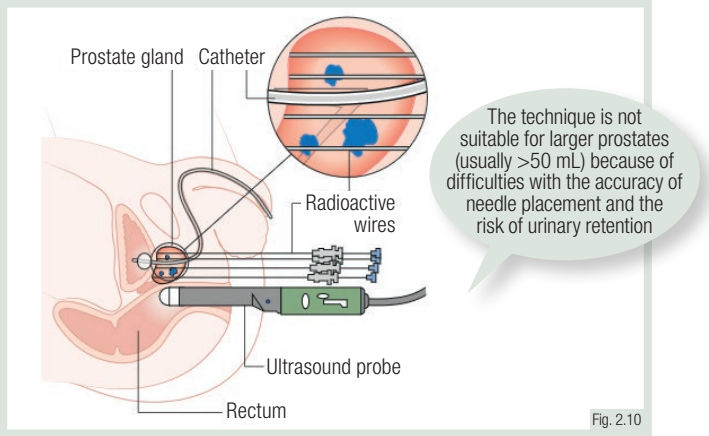


Fig. 2.10

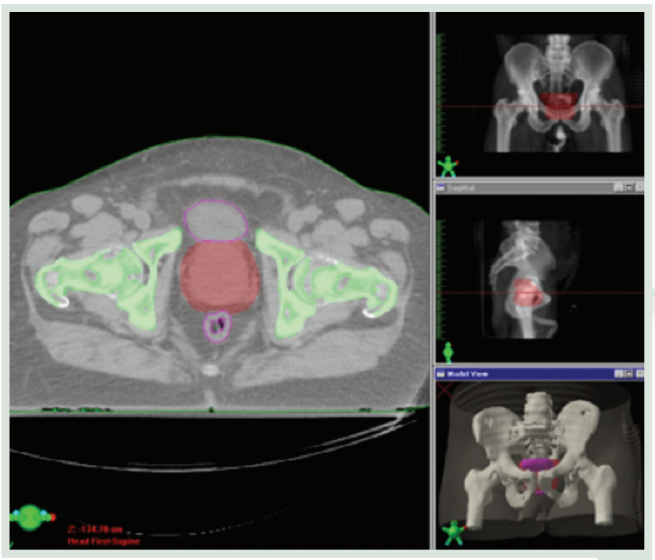


Fig. 2.11

EBRT is used to treat localised and locally advanced PC. The biological dose limit is determined by dose (measured in Gray [Gy]), number and interval between treatments (fractions). It may be combined with HDR BT.

EBRT uses targeting methods including conformal techniques (three-dimensional conformal RT [3D-CRT], intensity-modulated RT [IMRT] and image-guided RT [IGRT]). Fractionation varies between hyper- and hypofractionation (HFX). These improved techniques provide greater accuracy and precision with higher radiation doses while minimising exposure to surrounding healthy tissues.

Hyperfractionation uses 74-78 Gy for low-risk disease and 76-78 Gy for intermediate- and high-risk disease with 4-6 months of neo-adjuvant and 2-3 years of adjuvant androgen deprivation therapy (ADT) in high risk.

HFX uses a reduced number of fractions and higher radiation with a total biological dose that is equivalent to hyperfractionated methods. This is now used increasingly. Hyper- and hypofractionated regimens may be used with HDR boost techniques.

The CHHiP trial (Dearnaley et al, 2016) showed non-inferiority of HFX compared with conventional techniques with similar toxicity (60 Gy in 20 fractions over 4 weeks).

Short-term toxicity for treatment of this type includes urinary and gastrointestinal frequency. At 1 year, 50% of men become impotent and this is higher with concomitant ADT. The risk of rectal and bladder cancer increases slightly in the long term.

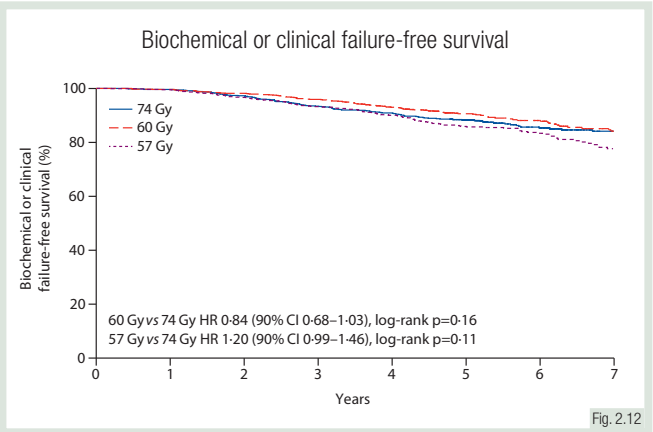


Fig. 2.12

CI, confidence interval; HR, hazard ratio.

REVISION QUESTIONS

1. What is the difference between seed implant and HDR BT?
2. How do conventional hyperfractionated EBRT schedules differ from hypofractionated schedules?
3. What are the short- and long-term toxicities of prostatic RT?

Radiotherapy and androgen deprivation

Intermediate-risk PC can be treated with combined IMRT and 3-6 months of ADT. IMRT with escalated dose (76-80 Gy) or IMRT and BT can also be used. Dual therapy with escalated dose IMRT (+/- pelvic nodes) and 2-3 years of ADT is commonly used for high-risk localised disease.

Classical studies (Bolla et al, 2009) have shown the RT/ADT combination improves survival significantly.

Two further large studies (SPCG-7 and MRC PR07/NCIC PR3) have confirmed that high-risk M0 cases are best treated with a combination of ADT and EBRT.

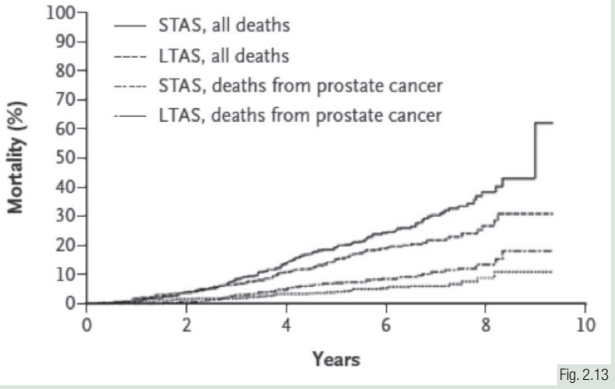


Fig. 2.13

LTAS, long-term androgen suppression; STAS, short-term androgen suppression.

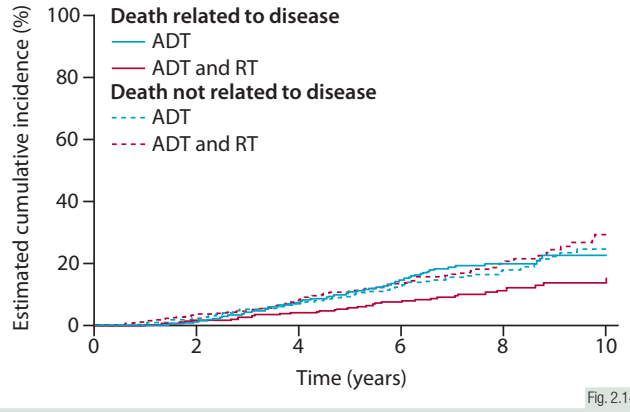


Fig. 2.14

ADT, androgen deprivation therapy; RT, radiotherapy.

The European Organisation for Research and Treatment of Cancer (EORTC) study by Bolla et al (2009) showed the benefit of long- vs short-term ADT in men with high-risk localised PC treated with EBRT and ADT.

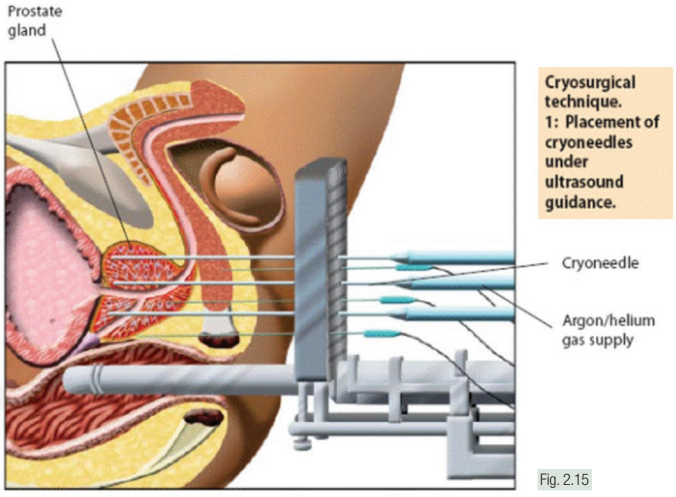
A trial testing the effect of EBRT and ADT in high-risk M0 PC also showed improved survival with combination treatment (Warde et al, 2011).

Post-RT failure is defined using the so-called 'phoenix' criteria: this is a rise of ≥2 ng/mL above the nadir PSA following treatment.

The date of failure is determined at the point the increase is called and is not backdated.

To further investigate biochemical failure (BCF) after radical treatment, positron emission tomography/computed tomography (PET/CT) imaging using choline or prostate-specific membrane antigen (PSMA)-PET scanning is increasingly used. Whole-body MRI is also advocated.

Salvage treatment following EBRT in non-metastatic patients can be considered and includes: salvage RP, BT, high-intensity focused ultrasound (HIFU) and cryotherapy. There is no level 1 evidence for their use and complication/failure rates are high. These treatment options should be discussed and applied only in specialised centres within a multidisciplinary team setting.



Cryosurgical technique. 1: Placement of cryoneedles under ultrasound guidance.

Fig. 2.15

REVISION QUESTIONS

1. What is the optimal duration of adjuvant ADT in high-risk disease?
2. Is radiation alone superior to combination EBRT and ADT?
3. How is biochemical failure defined after RT?

Summary: Staging and treatment of localised prostate cancer

- Clinically localised disease is potentially curable
- Clinical staging involves multi-modal testing and has inherent inaccuracies
- PSA levels are of value, but not in isolation
- mpMRI scanning is assuming greater importance in diagnosis and staging
- Bone scanning is of limited value when the PSA is <10 ng/mL and Gleason grade is ≤7
- AS is the standard-of-care for managing clinically low-risk disease
- Robotic-assisted RP is safe and effective. Stress incontinence and ED may occur postoperatively after surgery
- Post-RP RT improves biochemical recurrence but there is uncertainty about improvements in cancer-specific survival. Complications include irritative bladder/bowel symptoms and erectile failure (especially when combined with ADT)
- EBRT is effective in intermediate- and high-risk disease when combined with ADT. This is most effective when given as adjuvant treatment for at least 2 years. Irritative bowel/bladder symptoms and erectile failure are some of the side effects

Further Reading

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3A Treatment of metastatic castration-sensitive prostate cancer

Androgen deprivation and chemotherapy in metastatic prostate cancer

The basic standard treatment for metastatic castration-naïve prostate cancer (PC) is androgen deprivation therapy (ADT). The goal is to lower testosterone to a castrate level (<1.7 nmol/L).

ADT can be achieved by orchiectomy, gonadotropin-releasing hormone (GnRH) agonists or GnRH antagonists. Through constant stimulation of the receptor, GnRH agonists lead to a down-regulation.

GnRH agonists are associated with an initial testosterone flare (stimulation phase), hence an androgen receptor (AR) antagonist is added at treatment initiation. GnRH antagonists directly block the receptor and are not associated with an initial flare reaction.

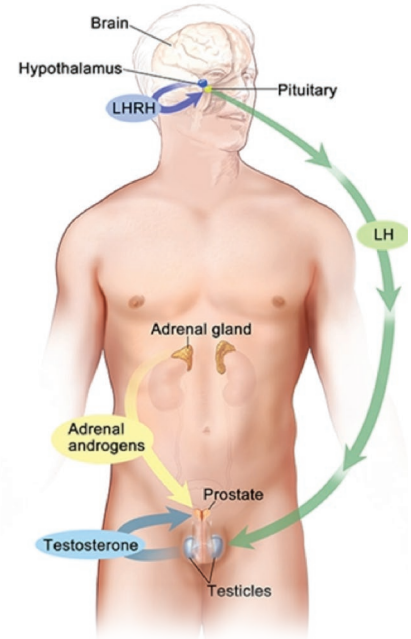


Fig. 3A.1

LH, luteinising hormone; LHRH, luteinising hormone-releasing hormone.

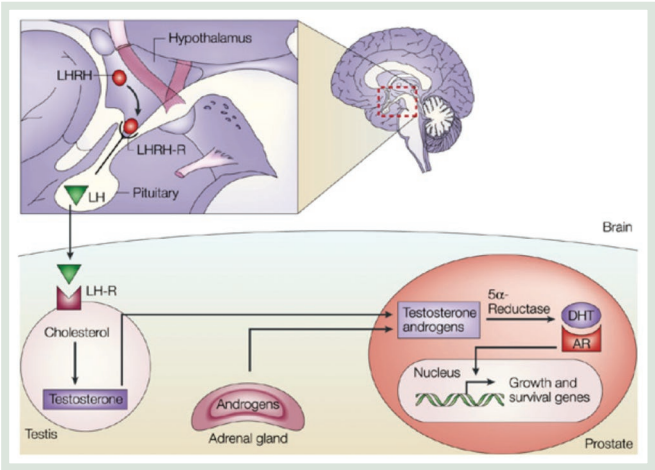


Fig. 3A.2

AR, androgen receptor; DHT, dihydrotestosterone; LH, luteinising hormone; LH-R, luteinising hormone receptor; LHRH, luteinising hormone-releasing hormone; LHRH-R, luteinising hormone-releasing hormone receptor.

AR antagonists block the binding of androgens to the AR. They are used at the start of GnRH agonist treatment to cover the testosterone flare phase.

Combined ADT: at progression on GnRH agonist/antagonist treatment alone, a first-generation AR antagonist (bicalutamide, nilutamide or flutamide) can be added or used upfront.

AR antagonist withdrawal: through mutations in the AR ligand binding domain, AR antagonists can become stimulants. After stopping AR antagonists, a typically short-lived prostate-specific antigen (PSA) decline can be observed in some patients.

Men starting ADT for advanced PC should be counselled about common side effects: hot flushes, erectile dysfunction, osteoporosis, weight gain, metabolic changes and increased cardiovascular risk.

In the majority of patients, initiation of ADT results in a decline in PSA level and testosterone concentration falls to castrate levels (<1.7 nmol/L).

Rising PSA on ADT generally suggests disease progression and, in the presence of castrate levels of testosterone, indicates castration-resistant PC (CRPC).

Side effects of androgen deprivation therapy
• Hot flushes
• Loss of libido and erectile dysfunction
• Weight gain
• Decreased muscle mass (sarcopenia)
• Accelerated bone mass loss, increased risk of fractures, osteoporosis
• Mood disturbances, cognitive function decline
• Altered metabolic profile (lipids, glucose)
• Increased cardiovascular risk

Fig. 3A.3

REVISION QUESTIONS

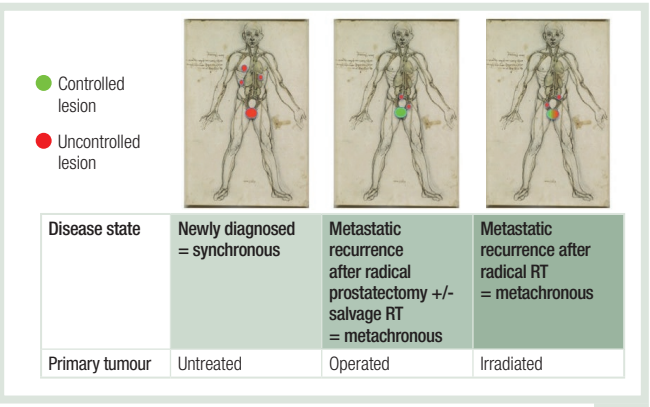
1. What is the standard treatment for metastatic PC?
2. How can the testosterone surge at the initiation of GnRH agonist treatment be controlled?
3. What are the most common side effects of ADT?

Newly diagnosed metastatic PC – Important definitions

For treatment selection in men with metastatic PC, some definitions are important.

De novo metastatic PC defines men diagnosed with synchronous metastatic disease without prior local treatment of the prostate.

Metachronous metastatic PC defines men diagnosed with metastatic PC after local treatment of the prostate (radiotherapy [RT] or prostatectomy).



RT, radiotherapy.

Fig. 3A.4

Important definitions		
Term	**Definition**	**Reference**
High-volume M1 disease	Visceral metastases and/or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis	CHAARTED Trial Sweeney NEJM 2015
High-risk M1 disease	At least 2/3 criteria: • Gleason score ≥8 • ≥3 Bone metastases • Visceral metastases	LATITUDE Trial Fizazi NEJM 2017
High-burden	= High-volume (see above)	STAMPEDE Trial Parker Lancet 2018
De-novo M1 disease	Newly diagnosed, no prior treatment for prostate cancer	

Fig. 3A.5

M1 Definition: Metastases outside of the pelvis including:
M1a: lymph node metastases outside of the pelvis
M1b: bone metastases
M1c: metastases outside of bone and lymph nodes

For treatment selection the number and volume of metastatic spread are prognostic, as well as Gleason score.

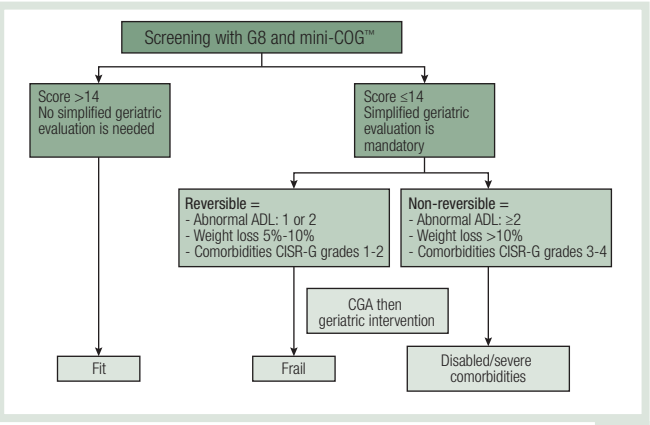
High-volume metastatic PC is defined as presence of visceral metastases and/or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis.

High-risk metastatic PC is defined as a combination of at least two out of three criteria: Gleason score ≥8 and/or ≥3 bone metastases and/or visceral metastases.

For treatment selection, assessment of the patient's health status is important.

The International Society of Geriatric Oncology (SIOG) has published recommendations on management of PC in elderly patients (>70 years old).

An initial evaluation of health status can be obtained by using the simple G8 screening tool and mini-COG assessments. Abnormal scores on the G8 tool should lead to a simplified geriatric assessment.



ADL, activities of daily living; CISR-G, cumulative illness score rating-geriatrics; CGA, comprehensive geriatric assessment.

Fig. 3A.6

REVISION QUESTIONS

1. What is the definition of synchronous metastatic PC?
2. What is the definition of high-volume metastatic PC?
3. How can the health status of an elderly patient with metastatic PC be assessed?

Newly diagnosed metastatic PC – Treatment options with ADT: docetaxel

Treatment decisions for newly diagnosed metastatic PC have become increasingly complex.

The definitions (outlined on the previous page) have limitations and should be interpreted carefully, especially if they are used for treatment selection.

Patients with newly diagnosed metastatic PC should be discussed at a multidisciplinary team (MDT) meeting to ensure a balanced treatment recommendation.

Treatment options for newly diagnosed* metastatic PC

	Fit and "high-volume" and/or "high-risk"	Unfit** and "high-volume" and/or "high-risk"	Fit and "low-volume" and/or "low-risk"	Unfit** and "low-volume" and/or "low-risk"
ADT	Standard	Standard	Standard – Consider focal therapy	Standard – Consider watchful waiting
ADT + Docetaxel	Yes, majority of patients (either of these options)	Generally no, but carefully consider investigating why patient is unfit and consider treatment intensification in selected patients	Carefully consider treatment intensification - patients may benefit from docetaxel or abiraterone***, enzalutamide*** or apalutamide***	Generally no
ADT + Abiraterone				
ADT + Enzalutamide				
ADT + Apalutamide				
Treatment of primary	Only if symptomatic	Only if symptomatic	Yes (RT)	Only if symptomatic

Fig. 3A.7

* Includes *de novo* and after local treatment M1
**Unfit patients: by geriatric assessment, no reversible causes, not directly tumour-related
*** Depending on approval in this situation

ADT, androgen deprivation therapy; PC, prostate cancer; RT, radiotherapy.

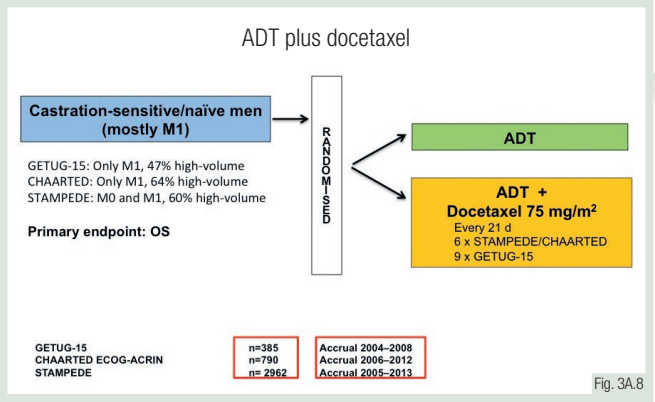


Fig. 3A.8

ADT, androgen deprivation therapy; OS, overall survival.

Three trials have evaluated the concept of a primary treatment intensification with docetaxel and have randomised men with newly diagnosed metastatic PC to ADT compared with ADT plus docetaxel.

The three trials differ with regards to accrual periods and inclusion criteria. Furthermore, the GETUG-15 trial used 9 cycles of docetaxel whereas the two other trials used 6 cycles.

The primary endpoint of overall survival (OS) was significantly improved in the two largest trials (CHAARTED and STAMPEDE) but not in the GETUG-15 trial.

In the subgroup of men with high-volume metastatic disease, OS was significantly improved by a median of 17 months.

In the subgroup of men with low-volume metastatic disease, no OS benefit has been demonstrated yet.

A meta-analysis of these three trials showed a clear improvement in median OS and failure-free survival for the addition of docetaxel to ADT in patients showing metastatic spread outside of the pelvis (=M1 patients).

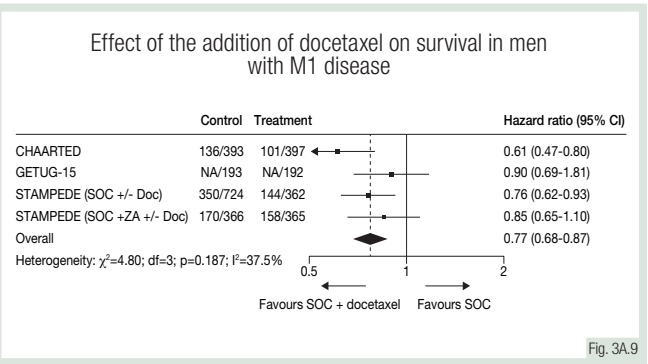


Fig. 3A.9

CI, confidence interval; Doc, docetaxel; SoC, standard of care; ZA, zoledronic acid.

REVISION QUESTIONS

1. Why should men with newly diagnosed metastatic PC be discussed by an MDT?
2. What is chemo-hormonal therapy?
3. What is the result of primary treatment intensification with docetaxel in addition to ADT?

Newly diagnosed metastatic PC – Treatment options with ADT: abiraterone acetate

Two large trials (STAMPEDE and LATITUDE) evaluated the concept of primary treatment intensification with abiraterone acetate (AA)/prednisone by randomising men with newly diagnosed metastatic PC to ADT or ADT plus AA.

The two trials differ with regards to inclusion criteria: importantly the LATITUDE trial only included men with high-risk metastatic PC.

The primary endpoint of OS was significantly improved in both trials.

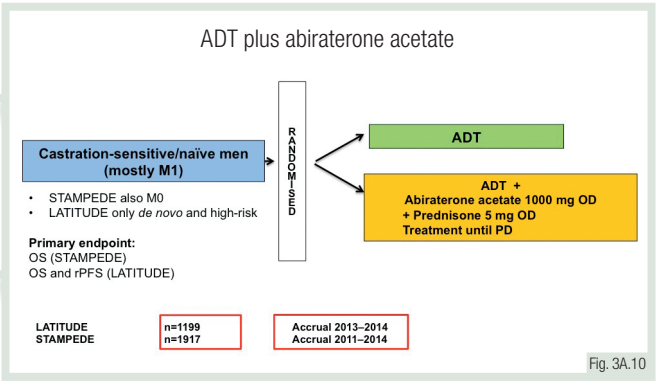


Fig. 3A.10

ADT, androgen deprivation therapy; OD, once daily; OS, overall survival; PD, progressive disease; rPFS, radiographic progression-free survival.

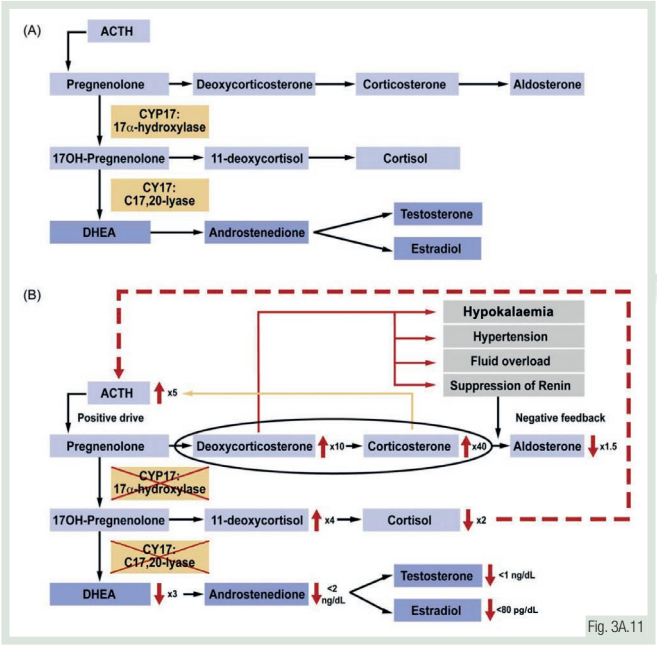


Fig. 3A.11

ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone.

AA is an inhibitor of the 17α-hydroxylase and 17,20-lyase. AA is administered with 1-2 x 5 mg prednisone/prednisolone to counteract side effects.

The main side effects of AA relate to a secondary mineralocorticoid excess (hypertension, fluid retention, hypokalaemia). Furthermore, elevated liver function tests and cardiac dysfunction have been reported.

Importantly, in both trials AA was given with only 5 mg prednisolone once daily (unlike the 2 x 5 mg in the CRPC setting). The lower steroid dose may lead to higher rates of hypertension, fluid retention and hypokalaemia.

Both the LATITUDE and STAMPEDE trials have shown a significant improvement in OS for early AA plus ADT in the overall trial population and in M1 patients.

Early AA also significantly improved failure-free survival and time to first symptomatic skeletal event.

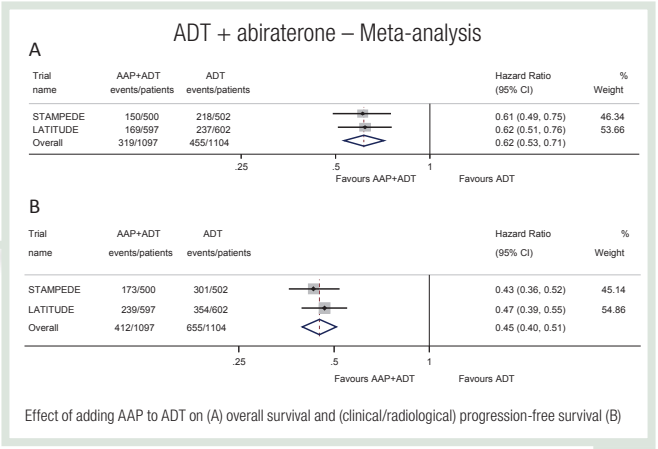


Fig. 3A.12

AAP, abiraterone acetate plus prednisone/prednisolone; ADT, androgen deprivation therapy; CI, confidence interval.

REVISION QUESTIONS

1. What is the concept of primary treatment intensification with AA in addition to ADT?
2. What are the main side effects of AA?
3. What are the main results of the LATITUDE and STAMPEDE trials?

Newly diagnosed metastatic PC – Treatment options with ADT: enzalutamide, RT of the primary tumour

Three large trials (ARCHES, TITAN, ENZAMET) have evaluated the concept of primary treatment intensification with novel AR receptor antagonists (ARCHES and ENZAMET with enzalutamide, TITAN with apalutamide).

Importantly, the control arm in the ENZAMET trial included ADT plus a first-generation AR antagonist and about 45% of included patients received concurrent docetaxel.

All three trials showed a significant benefit for their chosen primary endpoint. The combination with additional docetaxel in ENZAMET has not yet shown an additional survival benefit.

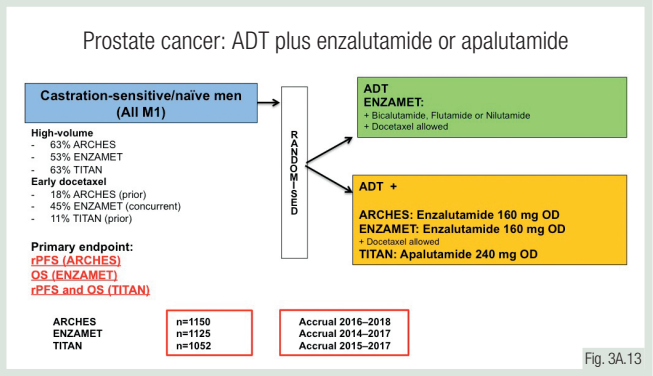


Fig. 3A.13

ADT, androgen deprivation therapy; OD, once daily; OS, overall survival; rPFS, radiographic progression-free survival.

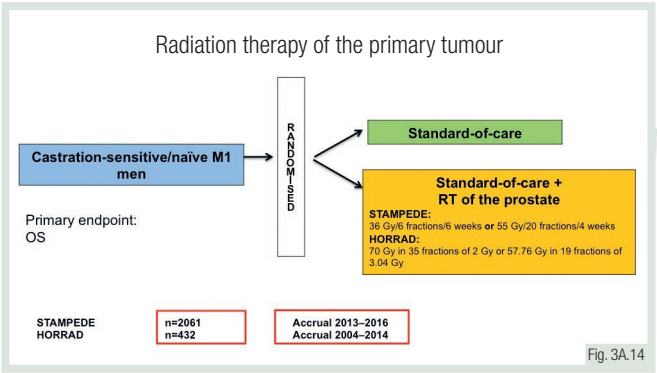


Fig. 3A.14

OS, overall survival; RT, radiotherapy.

The STAMPEDE and HORRAD trials evaluated the concept of local RT to the primary tumour in men with newly diagnosed metastatic PC.

The two trials differed with regards to inclusion criteria, sample size and RT schedules applied.

Neither trial met its primary endpoint of OS.

In the large subgroup of patients with low-burden (= low-volume) metastatic disease in the STAMPEDE trial, a significant OS benefit was seen at 3 years with an absolute risk reduction of 8%.

In the HORRAD trial, a similar trend was seen in the subgroup of men with <5 bone metastases.

In men with newly diagnosed low-volume metastatic PC, treatment of the primary tumour with RT should be discussed by an MDT.

Radiotherapy therapy of the primary tumour			
STAMPEDE			
	OS at 3 years	HR (95% CI)	NNT
Total population (N=2061)	65% vs 62%	0.92 (0.80–1.06)	NA
Low-burden (N=817)	81% vs 73%	0.68 (0.52–0.90)	13
High-burden (N=1117)	53% vs 54%	1.07 (0.90–1.28)	NA
HORRAD			
Total population (N=432)	Median OS 45m vs 43m	0.90 (0.70–1.14)	
<5 metastases ≥5 metastases		0.68 (0.42–1.10) 1.06 (0.8–1.39)	

Fig. 3A.15

CI, confidence interval; HR, hazard ratio; NA, not applicable; NNT, number needed to treat; OS, overall survival.

REVISION QUESTIONS

1. What is the concept of primary treatment intensification with enzalutamide/apalutamide in addition to ADT?
2. What is the concept of radiation treatment of the primary tumour in the metastatic situation?
3. What were the main results of the HORRAD and STAMPEDE trials with regards to RT of the primary tumour?

Summary: Treatment of metastatic castration-sensitive prostate cancer

- ADT is the basis of standard treatment for metastatic PC
- ADT can be achieved by orchiectomy, GnRH agonists or GnRH antagonists
- For treatment selection, the definitions of high-volume and high-risk metastatic PC are important
- In men with metastatic PC aged >70 years, a health status assessment is recommended
- In the last 5 years several large trials have reported an OS benefit for upfront treatment intensification by adding docetaxel, AA/prednisone, enzalutamide or apalutamide to ADT, compared with ADT alone
- In men with newly diagnosed castration-sensitive PC, RT to the primary tumour can be considered in case of low-volume metastatic disease
- Men with newly diagnosed castration-sensitive PC should be discussed at MDT meetings to evaluate the different treatment options

Further Reading

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3B Treatment of castration-resistant prostate cancer

Development of castration resistance

In the majority of prostate cancer (PC) patients, initiation of androgen deprivation therapy (ADT) results in a decline in prostate-specific antigen (PSA) and testosterone concentration falls to castrate levels (<1.7 nmol/L).

Rising PSA on ADT generally indicates disease progression and, in the presence of castrate levels of testosterone, is defined as castration-resistant PC (CRPC).

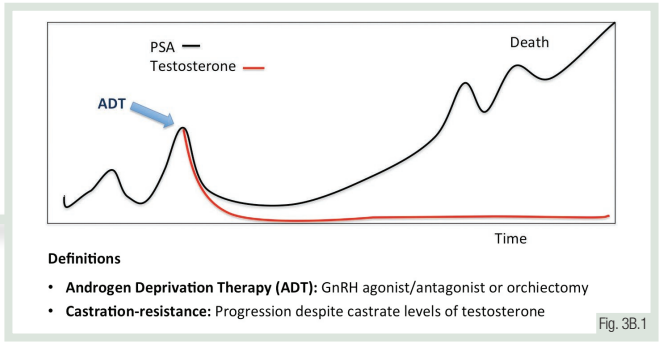


Fig. 3B.1

GnRH, gonadotropin-releasing hormone; PSA, prostate-specific antigen.

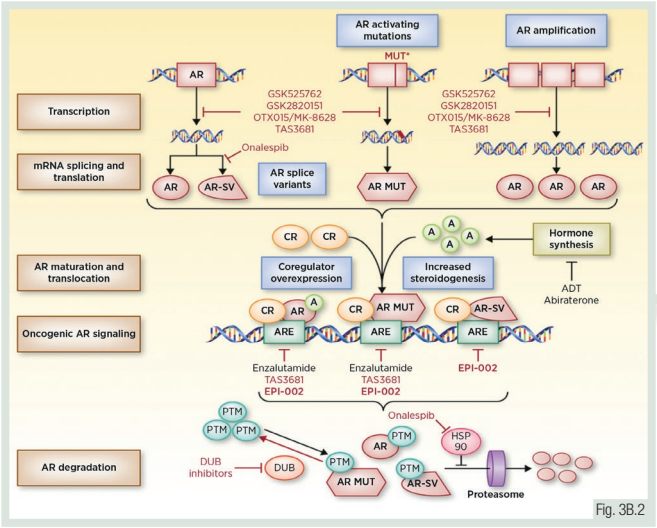


Fig. 3B.2

A, androgen; ADT, androgen deprivation therapy; AR, androgen receptor; ARE, androgen response element; AR MUT, AR activating mutation; AR-SV, AR splice variant; CR, coregulator; DUB, deubiquitinating enzyme; mRNA, messenger RNA; PTM, post-translational modification.

In most men developing CRPC, ongoing androgen receptor (AR) signalling is a major driver of cancer activity.

Biological mechanisms of castration resistance include: increased expression of AR coregulators, AR amplification, AR-activating mutations and increased steroidogenesis; otherwise due to cross-talk through alternative pathways activation.

Many active treatments developed for metastatic CRPC (mCRPC) target the AR pathway, either directly (abiraterone acetate [AA] or enzalutamide) or indirectly (taxanes) by blocking AR nuclear translocation and transcriptional activity.

Non-metastatic castration-resistant prostate cancer (M0 CRPC)

If on staging examinations (computed tomography [CT] of chest-abdomen-pelvis) and bone scintigraphy, no evidence of metastatic sites can be detected in the presence of a rising PSA on ADT, the situation is called M0 CRPC.

PROSPER, SPARTAN, and ARAMIS trials randomised M0 CRPC patients with a PSA of ≥2 and a doubling time ≤10 months to either enzalutamide, apalutamide or darolutamide (all next-generation AR antagonists) vs placebo.

All three trials showed a significant improvement in median metastasis-free survival for enzalutamide, apalutamide and darolutamide compared with placebo.

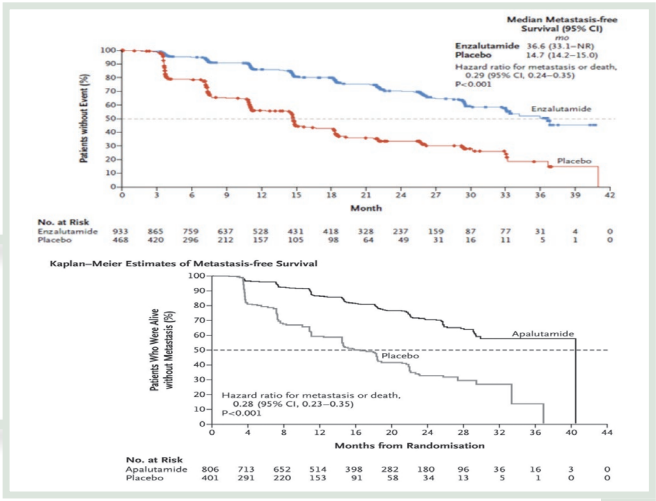


Fig. 3B.3

CI, confidence interval; NR, not reached.

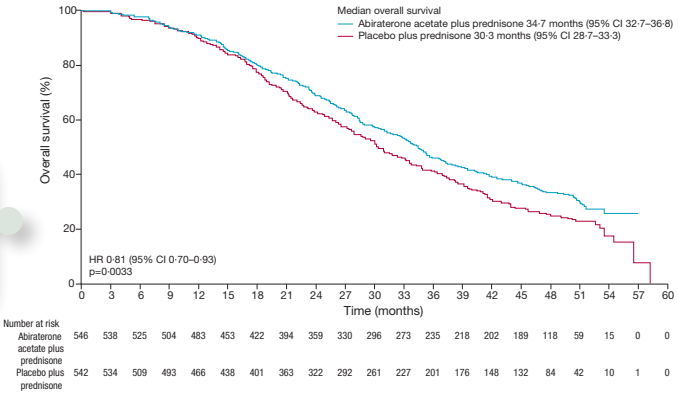
REVISION QUESTIONS

1. What are the most common side effects of ADT?
2. What are the biological mechanisms of castration resistance?
3. What was the primary endpoint of the three large trials in M0 CRPC with enzalutamide, apalutamide and darolutamide, and what were the results?

Treatment options for metastatic CRPC

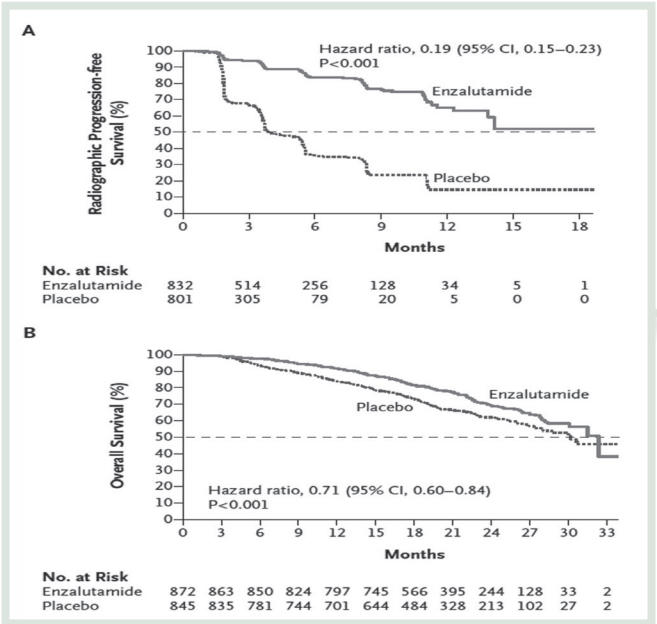
The COU-AA-302 trial randomised men with asymptomatic/minimally symptomatic chemotherapy (ChT)-naïve mCRPC to AA plus prednisone, vs placebo plus prednisone.

The COU-AA-302 trial found that AA plus prednisone significantly improved radiographic progression-free survival (PFS) and median overall survival (mOS) vs prednisone alone.



CI, confidence interval; HR, hazard ratio.

Fig. 3B.4



CI, confidence interval.

Fig. 3B.5

The PREVAIL trial randomised men with asymptomatic/minimally symptomatic ChT-naïve mCRPC to enzalutamide vs placebo.

In this trial, enzalutamide significantly prolonged PFS and mOS vs placebo.

The most common side effects of enzalutamide are fatigue, hypertension and hot flushes, and, in <1% of patients, seizures.

Docetaxel was tested in the TAX 327 phase III trial in two schedules (3-weekly, weekly) compared with mitoxantrone.

Docetaxel was the first agent to significantly prolong mOS in CRPC patients. The docetaxel weekly schedule was not superior to mitoxantrone.

Characteristic side effects of docetaxel are haematological toxicity, neurotoxicity, alopecia, nail changes and fluid retention.

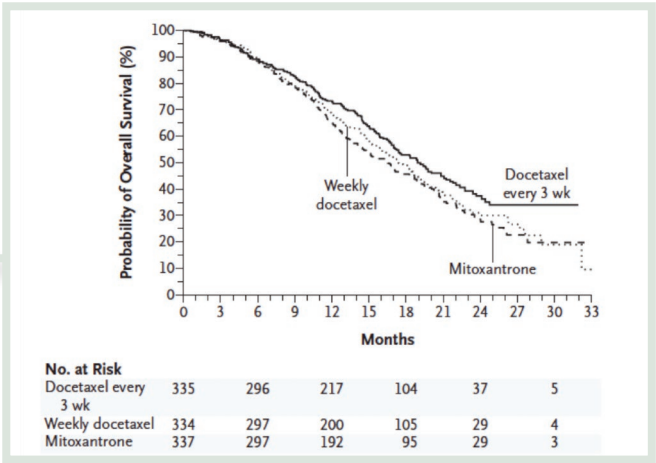


Fig. 3B.6

REVISION QUESTIONS

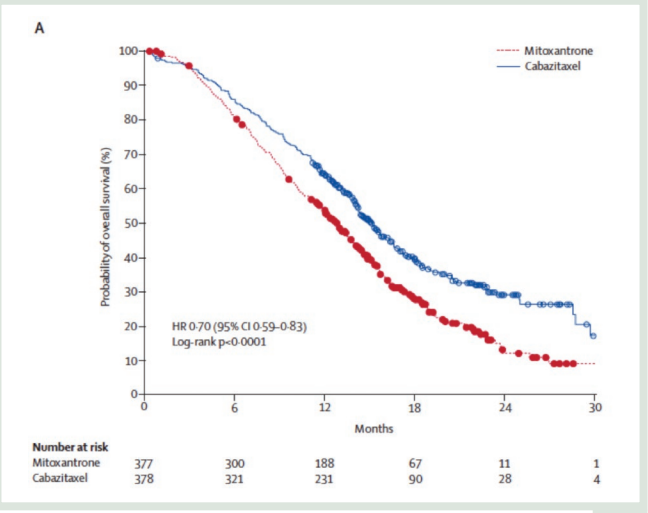
1. Name one of the co-primary endpoints of the COU-AA-302 trial.
2. What are the most common side effects of enzalutamide?
3. What are the typical side effects of docetaxel?

Treatment options for metastatic CRPC (continued)

Cabazitaxel is a taxane ChT selected for development due to its activity in preclinical docetaxel-resistant models.

The TROPIC phase III trial, in patients who progressed under or after docetaxel, found that use of cabazitaxel vs mitoxantrone led to a significant improvement in mOS. The PROSELICA trial compared cabazitaxel 25 mg/m^2 with 20 mg/m^2 and found no difference in OS for the lower dose.

Cabazitaxel, especially at the lower dose (20 mg/m^2), has a good safety profile with the main side effect being haematological toxicity. Compared with docetaxel, neurotoxicity and alopecia/nail changes are lower.



CI, confidence interval; HR, hazard ratio.

Fig. 3B.7

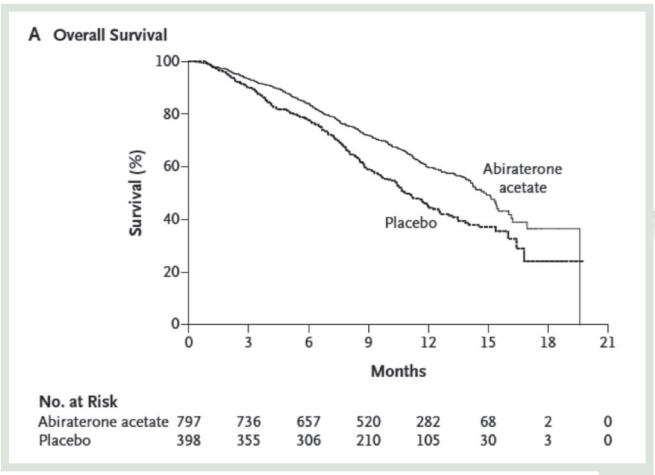


Fig. 3B.8

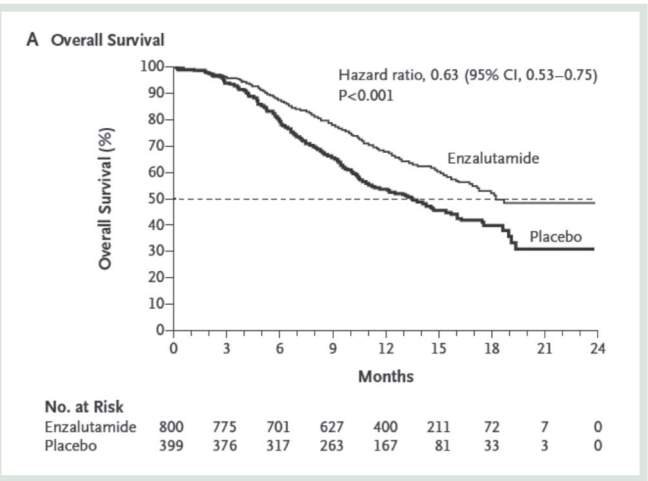
The COU-AA-301 study compared AA plus prednisone/prednisolone with placebo plus prednisone/prednisolone in docetaxel-pretreated CRPC patients and reported significantly prolonged mOS (15.8 vs 11.2 months, respectively).

AA also significantly improved secondary endpoints: radiographic PFS (5.6 vs 3.6 months) and time to PSA progression (8.5 vs 6.6 months, respectively).

In the AFFIRM trial, enzalutamide compared with placebo significantly prolonged mOS in docetaxel-pretreated CRPC patients.

Enzalutamide also significantly improved secondary endpoints: radiographic PFS (8.3 vs 2.9 months) and time to PSA progression (8.3 vs 3 months).

Hypertension was more common in enzalutamide-treated patients; 0.6% of patients had a seizure on enzalutamide (none on placebo).



CI, confidence interval.

Fig. 3B.9

REVISION QUESTIONS

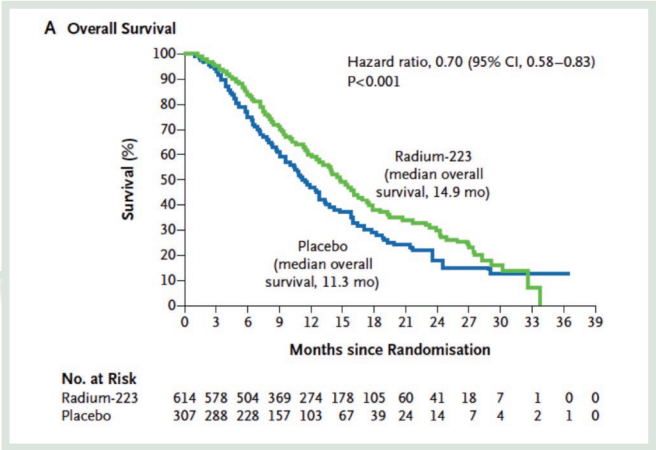
1. In which patient population was cabazitaxel tested?
2. What was the treatment in the control arm of the COU-AA-301 and AFFIRM studies?
3. What are the most common side effects of enzalutamide compared with AA/prednisone?

Radium-223 and osteoprotective therapy in CRPC treatment

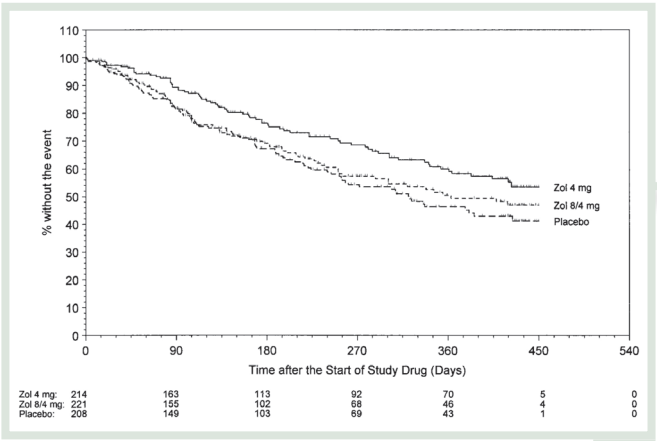
Radium-223 is a radiopharmaceutical (alpha-emitter) and a bone-seeking calcium mimetic. It was tested in patients who were unfit for (or refused) docetaxel ChT, or were post-docetaxel and had no visceral disease or lymph nodes >3 cm in short axis.

In the ALSYMPCA trial, radium-223 was compared with placebo, and significantly prolonged mOS in both ChT-naïve and post-docetaxel patients. Radium-223 is mainly associated with haematological toxicity (low rates of grade 3 or 4) and diarrhoea.

Due to an increased risk of fractures, radium-223 should not be combined with AA. Patients receiving radium-223 should also be treated with bone-health agents, such as denosumab or zoledronic acid (Zol).



CI, confidence interval. Fig. 3B.10



Zol, zoledronic acid. Fig. 3B.11

Zol is a bisphosphonate tested as a bone-protecting agent at two doses (8 mg and 4 mg) vs placebo in a phase III trial in CRPC patients (Saad et al, 2002).

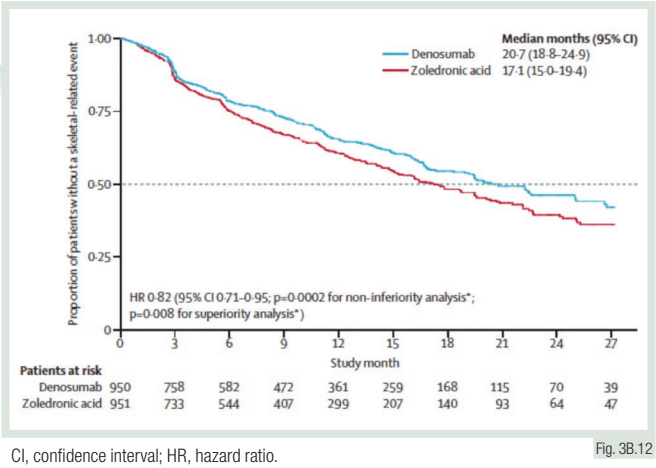
At 24-month follow-up, fewer patients on Zol (4 mg) compared with placebo had experienced skeletal-related events (SREs) (38% vs 49%), and time to first SRE was 488 vs 321 days.

Dose must be adjusted to creatinine clearance. Calcium and vitamin D should be supplemented. Osteonecrosis of the jaw (ONJ) is a complication of bisphosphonate treatment.

Denosumab is a human antibody against the RANK ligand. In a phase III clinical trial, it was compared with Zol in CRPC patients (Fizazi et al, 2011).

Median time to first SRE was significantly longer with denosumab (20.7 vs 17.1 months). ONJ occurred in 2% of patients, vs 1% on Zol.

Denosumab is associated with severe hypocalcaemia (13%) and is therefore recommended in combination with calcium and vitamin D supplementation.



CI, confidence interval; HR, hazard ratio. Fig. 3B.12

REVISION QUESTIONS

1. What is the mechanism of action of radium-223?
2. What is the main benefit of bisphosphonate treatment in CRPC patients?
3. Why does denosumab have to be administered with calcium and vitamin D supplementation?

Sequencing of therapies, staging and treatment monitoring

Disease monitoring is carried out in CRPC patients to evaluate the anti-tumour activity of treatments and identify potential complications early.

The Prostate Cancer Working Group (PCWG) gave recommendations for clinical trials that treatment changes should not be based on rising PSA alone.

Bone metastases in CRPC patients are mostly non-measurable and difficult to monitor because, in the first weeks of novel treatment, flares can occur (in bone scans and CT scans).

Suggested frequency of assessment for commonly used measures in metastatic prostate cancer clinical trials

Measure*	PCWG2 Frequency (2008)	PCWG3 Frequency (2015)†
Clinical		
Symptoms/ performance status	Every cycle	Retained
Blood-based markers		
PSA	By cycle (every 3 or 4 weeks)	Retained
ALP, LDH	By cycle (every 3 or 4 weeks)	Retained
Serum chemistry, CBC	Not addressed	By cycle (every 3 to 4 weeks)
Circulating tumour cells	Not addressed	By cycle (every 3 to 4 weeks) if available
Imaging		
Bone scans	Every 12 weeks	Every 8 to 9 weeks for first 24 weeks, then every 12 weeks†
CT/MRI	Every 12 weeks	Every 8 to 9 weeks for first 24 weeks, then every 12 weeks†
Patient-reported outcomes	Not addressed	By cycle (every 3 to 4 weeks)
Analgesic consumption (opioids/no opioids)	Not addressed	By cycle (every 3 to 4 weeks)

Fig. 3B.13

*All measures should be assessed at baseline to determine changes over time.
†There may be exceptions to these suggestions: in nonmetastatic castration-resistant prostate cancer trials, for example, imaging assessment intervals of 16 weeks are advised. Likewise, in long-term responders (>2 to 3 years of clinical benefit and no signs of clinical or biomarker progression), reduced frequency of imaging is reasonable, such as every 16 to 24 weeks (4 to 6 months).

ALP, alkaline phosphatase; CBC, complete blood count; CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG2 or 3, Prostate Cancer Clinical Trials Working Group 2 or 3; PSA, prostate-specific antigen.

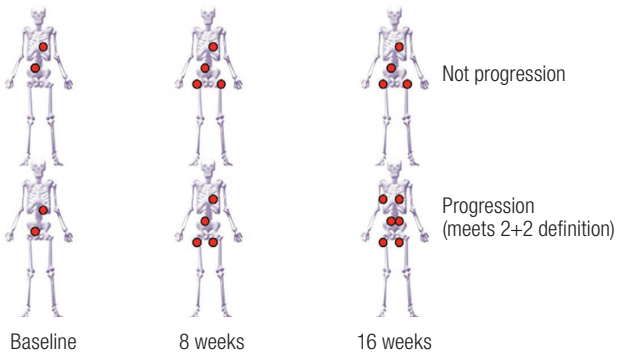


Fig. 3B.14

Appearance of new lesions on a bone scan within 12 weeks of treatment in the absence of progression of soft tissue disease, PSA or clinical progression, may indicate a flare reaction.

Soft tissue disease can be assessed by CT scans. Although considered uncommon, up to 50% of patients with CRPC develop visceral metastases.

Malignant spinal cord compression is a complication with high morbidity and mortality. Development of new bone pain and/or neurological symptoms should prompt rapid evaluation by magnetic resonance imaging (MRI) of the whole spine.

The experts of the Advanced Prostate Cancer Consensus Conference (APCCC) recommend that two out of three criteria are met before systemic treatment is discontinued in men with advanced PC.

These three criteria are: PSA progression, radiographic progression and clinical progression. Unequivocal soft tissue progression (e.g. new liver metastases) requires consideration of a biopsy to rule out secondary malignancy or small-cell/neuroendocrine differentiation.

Prostate cancer – defining progression

Generally 2 out of 3 criteria should be fulfilled:

Criteria	Caution!
1. PSA progression	• Can rise in the first 9-12 weeks of a new treatment, PSA rise on radium is common • Not reliable in very advanced disease • PSA can be low in relation to tumour volume (aggressive variants!)
2. Radiographic progression	• 90% of patients with advanced prostate cancer have bone metastases • Flare on bone scintigraphy is common • Increasing sclerosis on CT scans often misinterpreted as progression • Epidural tumour difficult to appreciate on CT • Malignant superscan not uncommon in advanced disease
3. Clinical progression	• Bone pain in elderly patients with advanced prostate cancer can also have other causes (e.g. degenerative disease, osteoporosis…)

CT, computed tomography; PSA, prostate-specific antigen.

Fig. 3B.15

REVISION QUESTIONS

1. Why is monitoring of disease activity important?
2. What are the recommended modalities for monitoring of disease activity?
3. What are the criteria for definition of progression in advanced PC?

Summary: Treatment of castration-resistant prostate cancer

- For men with M0 CRPC, three treatment options (enzalutamide, apalutamide and darolutamide) have shown a significant improvement in time to radiographic progression vs placebo
- Rising PSA on ADT in the presence of castrate levels of testosterone indicates CRPC
- For CRPC, two ChT agents (docetaxel first-line and cabazitaxel second-line) have been shown to prolong mOS
- Two novel endocrine agents, AA and enzalutamide, also prolong mOS in ChT-naïve and in ChT pre-treated patients
- Radium-223 is an alpha-pharmaceutical prolonging mOS in patients with bone-predominant, symptomatic metastatic CRPC without visceral metastases. Radium-223 can no longer be combined with AA because of an increased risk of fractures and, in patients receiving radium-223, a bone-protecting agent is strongly recommended
- Two bone-protecting agents (Zol and denosumab) have both been shown to significantly prolong time to first SRE
- Monitoring of disease activity is challenging in CRPC; it should be better performed at regular intervals and should NOT rely on PSA only

Further Reading

Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011; 377:813–822.

Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: the report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. Eur Urol 2018; 73:178–211.

Saad F, Gleason DM, Murray R, et al; Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002; 94:1458–1468.

Sartor O, de Bono JS. Metastatic prostate cancer. N Engl J Med 2018; 378:645–657.

Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 2016; 34:1402–1418.

4 Staging and treatment of localised bladder cancer

Staging and treatment of non-muscle-invasive bladder cancer

Transurethral resection of bladder tumours includes the removal of the tumour with additional resection biopsies of the lateral margins and a deep detrusor biopsy.

The use of fluorescence-based resection techniques improves tumour visualisation and the detection of carcinoma *in situ* (CIS). *En bloc* resection can be performed whenever technically feasible and may facilitate staging by pathologists.

In patients with a high-grade (G3) and/or invasive (pT1) bladder cancer at primary diagnosis, a transurethral resection of bladder tumour (TURBT) should be performed with a second resection within 2-6 weeks.

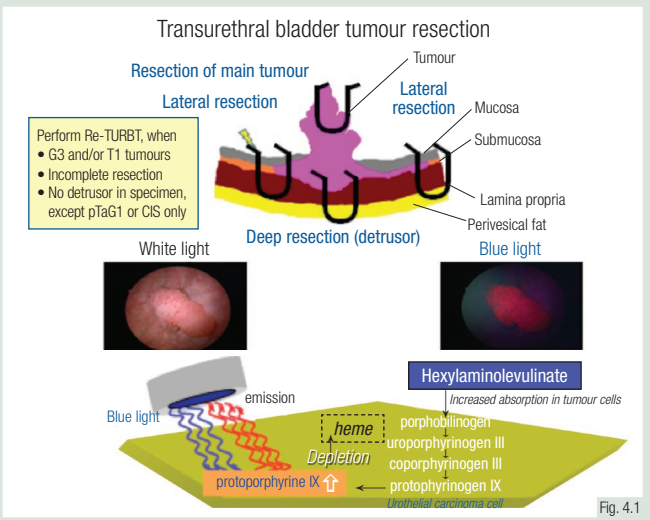


Fig. 4.1

CIS, carcinoma *in situ*; TURBT, transurethral resection of bladder tumour.

EORTC risk stratification in NMIBC

Site	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥8	6	3
Tumour diameter		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 recurrence/year	2	2
>1 recurrence/year	4	2
T category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Tumour grade (WHO 1973)		
G1	0	0
G2	1	0
G3	2	5
TOTAL SCORE	**0-17**	**0-23**

Recurrence score	Probability of recurrence at 1 year (%, 95% CI)	Probability of recurrence at 5 years
0	15 (10-19)	31 (24-37)
1-4	24 (21-26)	46 (42-49)
5-9	38 (35-41)	62 (58-65)
10-17	61 (55-67)	78 (73-84)

Progression score	Probability of progression at 1 year (%, 95% CI)	Probability of progression at 5 years
0	0.2 (0-0.7)	0.8 (0-1.7)
2-6	1 (0.4-1.6)	6 (5-8)
7-13	5 (4-7)	17 (14-20)
14-23	17 (10-24)	45 (35-55)

Low Risk
Intermediate Risk
High Risk

Fig. 4.2

CI, confidence interval; CIS, carcinoma *in situ*; EORTC, European Organisation for Research and Treatment of Cancer; NMIBC, non-muscle-invasive bladder cancer; WHO, World Health Organization.

The European Organisation for Research and Treatment of Cancer (EORTC) risk tables for non-muscle-invasive bladder cancer (NMIBC) enable risk assessment for intravesical recurrence and progression.

The EORTC scoring system is based on the six most significant clinical and pathological risk factors.

These include the number of tumours, tumour size, prior recurrence rate, T-category, presence of concomitant CIS and tumour grade.

Low-risk patients should be treated with a single postoperative chemo-instillation within 24 hours after TURBT.

Intermediate-risk patients should be offered intravesical adjuvant instillation with either mitomycin C or Bacillus Calmette-Guérin (BCG) and intravesical instillation for a maximum of 12 months.

High-risk patients should be offered intravesical BCG immunotherapy. In those with extensive/multifocal T1G3 with associated CIS or BCG non-responders, radical cystectomy should be considered as a feasible option. Hyperthermia may increase efficacy of intravesical chemotherapy (ChT) and is currently being investigated in clinical trials. Checkpoint inhibitors are currently investigated in clinical trials as an option for BCG-unresponsive patients.

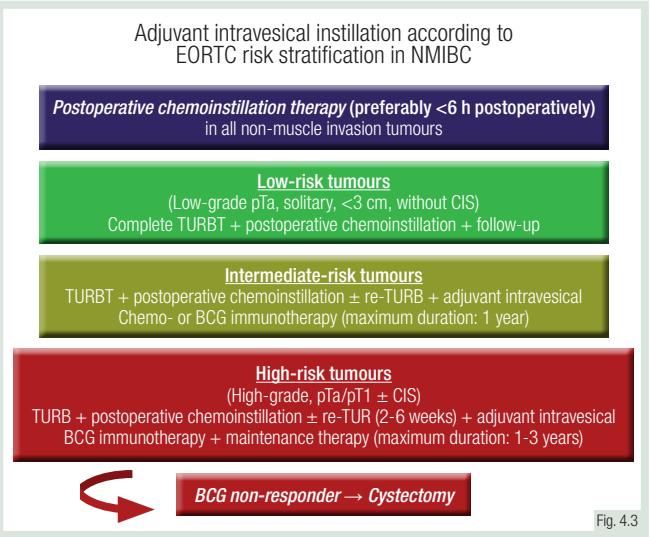


Fig. 4.3

BCG, Bacillus Calmette-Guérin; CIS, carcinoma *in situ*; EORTC, European Organisation for Research and Treatment of Cancer; NMIBC, non-muscle-invasive bladder cancer; TUR, transurethral resection; TURB, transurethral resection of bladder; TURBT, transurethral resection of bladder tumour.

REVISION QUESTIONS

1. Can *en bloc* resection be performed for treatment of NMIBC?
2. Should patients with intermediate-risk bladder cancer receive adjuvant BCG immunotherapy?
3. What is the preferable time interval for administration of postoperative early chemo-instillation?

Treatment of muscle-invasive bladder cancer

In men, standard open radical cystectomy (RC) includes the removal of the bladder, prostate and seminal vesicles.

In women, standard open RC includes the removal of the tumour-bearing bladder, uterus, distal ureters and anterior vaginal wall.

To maintain urinary continence and sexual function after RC, the urethra- and external genitalia-supplying autonomous nerves can be spared in both men and women.

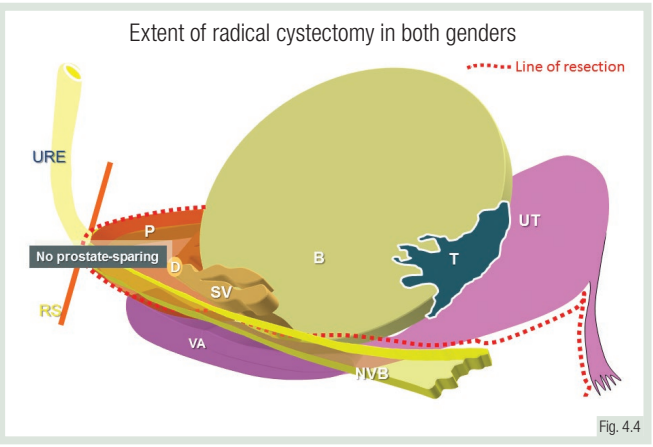


Fig. 4.4

B, bladder; D, duct; NVB, neurovascular bundle; P, prostate, RS, resection; SV, seminal vesicles; T, tumour; URE, urethra; UT, uterus; VA, vagina.

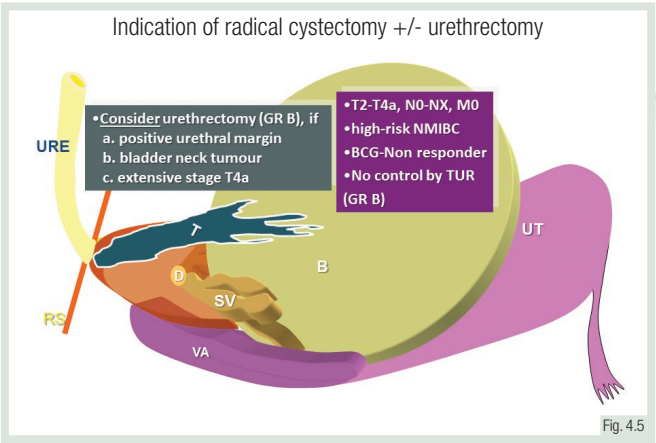


Fig. 4.5

B, bladder; BCG, Bacillus Calmette-Guérin; D, duct; NMIBC, non-muscle-invasive bladder cancer; RS, resection; SV, seminal vesicles; T, tumour; TUR, transurethral resection; URE, urethra; UT, uterus; VA, vagina.

Indications for RC include: pathologically confirmed muscle-invasive bladder cancer (MIBC) (T2-4a N0-NXM0), NMIBC at high risk of progression, lack of response to BCG treatment and transurethrally uncontrollable NMIBC.

In men and women, urethrectomy should be performed at RC in cases of concomitant urethral malignancy, positive urethral margin status and bladder neck involvement.

Urethrectomy should also be considered with curative cystectomy where an orthotopic neobladder is not possible.

Recent randomised trials have shown equivalent oncological and perioperative outcomes for robotic-assisted RC (RARC) compared with open RC (ORC).

Prospective trials have shown no statistically significant differences in recurrence patterns and recurrence-free survival (RFS).

RARC is an alternative to ORC when performed by an experienced surgeon. There are insufficient data to recommend total intracorporeal urinary diversion.

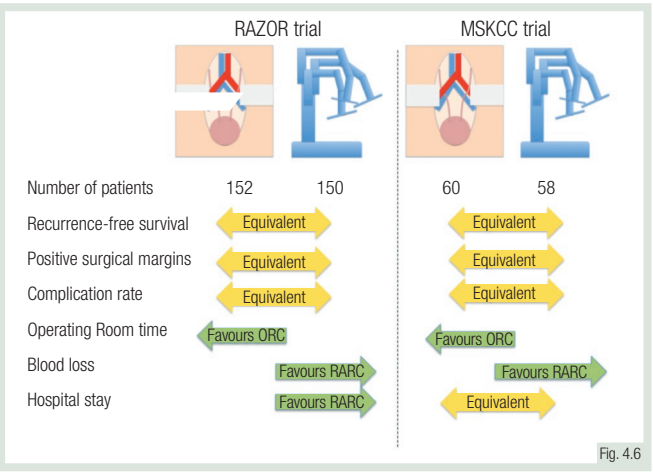


Fig. 4.6

MSKCC, Memorial Sloan Kettering Cancer Center; ORC, open radical cystectomy; RARC, robotic-assisted radical cystectomy.

REVISION QUESTIONS

1. What are the indications for RC in bladder cancer?
2. Should the prostate and seminal vesicle be removed at RC in male patients?
3. Does RARC provide equivalent oncological outcomes compared with ORC?

Lymph node dissection at radical cystectomy

Bilateral pelvic lymph node dissection (PLND) is an integral part of RC.

Standard PLND should be defined as the removal of all lymphatic tissues around the common iliac, external iliac internal iliac and obturator region bilaterally.

An extended PLND includes the removal of all lymphatic tissue in the presacral region up to the aortic bifurcation. A super-extended PLND includes all the tissue up to the inferior mesenteric artery.

Indication and extent of lymphadenectomy at RC

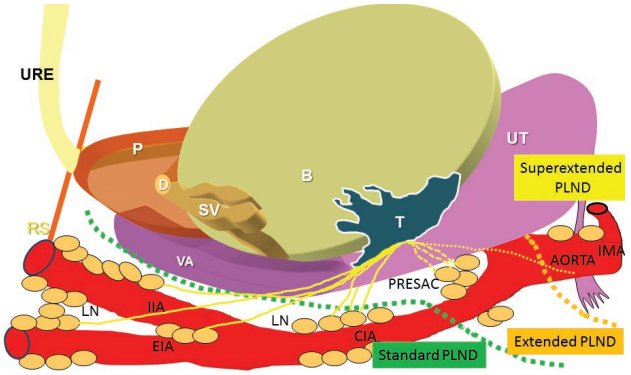


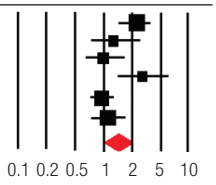
Fig. 4.7

B, bladder; CIA, common iliac artery; D, duct; EIA, external iliac artery; IIA, internal iliac artery; IMA, inferior mesenteric artery; LN, lymph node; P, prostate; PLND, peritoneal lymph node dissection; RC, radical cystectomy; RS, resection; T, tumour; SV, seminal vesicles; URE, urethra; UT, uterus; VA, vagina.

Indication and extent of lymphadenectomy at RC

Probability of positive lymph nodes: extended vs. standard lymph node dissection (random effects)

Study	Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	p-value	
Dhar	2.31	1.54	3.45	0.00	
Poulsen	1.36	0.68	2.73	0.38	
Abol-Eneim	1.00	0.63	1.58	1.00	
Holmer	2.86	1.37	6.01	0.01	
Simone	0.94	0.71	1.25	0.67	
Jensen	1.12	0.72	1.74	0.61	
OVERALL	1.39	0.96	2.01	0.08	



CI, confidence interval; RC, radical cystectomy.

Fig. 4.8

From a diagnostic perspective, the more lymph nodes removed, the higher the probability of detecting at least one positive lymph node.

A meta-analysis has shown that an extended PLND increases the probability of detecting positive nodes at RC.

The number of removed lymph nodes is a surrogate marker for the meticulousness of lymph node dissection. However, the number of lymph nodes may also depend on individual anatomy and pathological documentation.

An extended PLND is associated with improved 5-year RFS after RC.

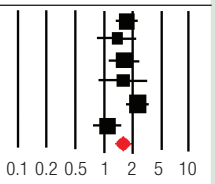
Most studies investigating the impact of lymph node dissection on survival are hampered due to their retrospective design and different definitions of an extended PLND.

The optimal extent (standard vs extended vs super-extended) has not been defined thus far.

Indication and extent of lymphadenectomy at RC

5-year recurrence-free survival rates: extended vs. standard lymph node dissection (random effects)
Red diamond represents the overall estimated effect size (odds ratio). A value more than 1 indicates a benefit of an extended LND

Study	Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	p-value	
Dhar	1.76	1.29	2.40	0.00	
Poulsen	1.28	0.70	2.33	0.42	
Abol-Eneim	1.65	1.10	2.47	0.02	
Holmer	1.62	0.83	3.15	0.16	
Simone	2.30	1.75	3.04	0.00	
Jensen	1.09	0.75	1.59	0.65	
OVERALL	1.63	1.27	2.07	0.00	



CI, confidence interval; LND, lymph node dissection; RC, radical cystectomy.

Fig. 4.9

REVISION QUESTIONS

1. What is a 'standard' PLND in MIBC?
2. Does the removal of more lymph nodes improve the accuracy of pathological nodal staging?
3. Is an 'extended' PLND associated with improved RFS?

Urinary diversion after radical cystectomy and multimodality treatment

Patients should be fully informed about all types of urinary diversion after RC. The final decision should be based on a broad consent between the patient and the treating surgeon.

Various types of continent and incontinent diversions exist. Lower urinary tract reconstruction using the terminal ileum is frequently employed.

Contraindications for orthotopic bladder substitution are: a positive urethral margin, renal insufficiency, hepatic insufficiency, complex urethral strictures, urinary incontinence due to intrinsic sphincter deficiency, and physical and mental impairments precluding self-catheterisation.

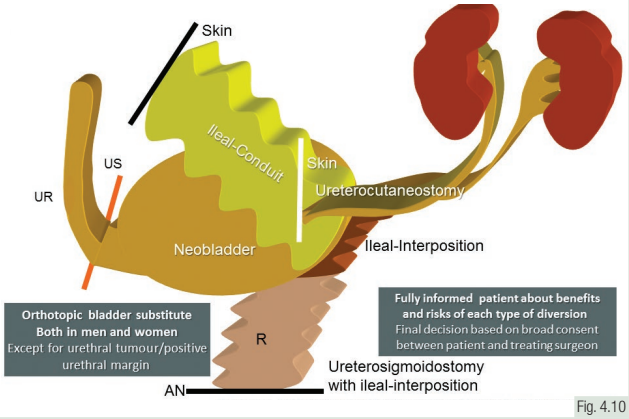


Fig. 4.10

AN, anus; R, rectum; UR, urethra; US, urethral sphincter.

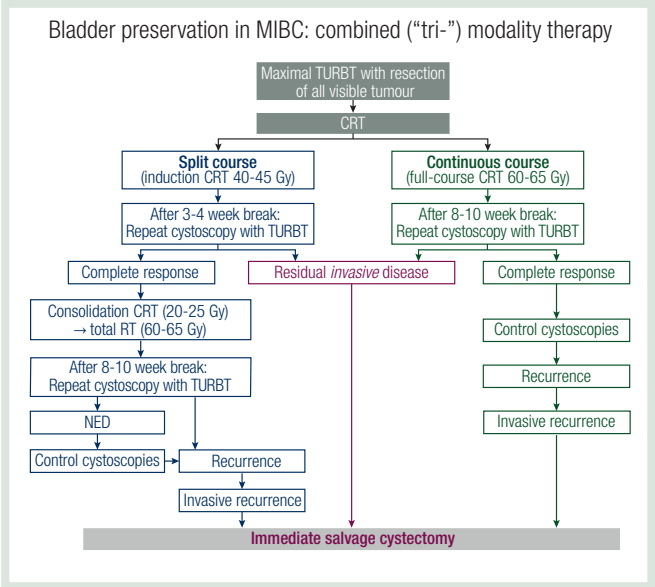


Fig. 4.11

CRT, chemoradiotherapy; NED, no evidence of disease; RT, radiotherapy; TURBT, transurethral resection of bladder tumour.

A multimodality bladder-preserving treatment with maximal TURBT followed by chemoradiotherapy (CRT) ('triple-therapy') may be offered as an alternative to RC, depending on disease characteristics.

A maximal TURBT (stage T0) before initiation of CRT exerts a strong impact on long-term outcomes. Male gender, organ-confined disease and absence of upper tract dilatation represent further factors with better prognostic impact.

In case of incomplete response or treatment failure, salvage cystectomy is recommended.

In a randomised trial, synchronous ChT with fluorouracil and mitomycin C combined with radiotherapy (RT) (i.e. CRT) significantly improved locoregional control of bladder cancer compared with RT alone.

Whereas CRT was associated with improved locoregional control, there was no significant difference in median overall survival (OS) rates between the groups (48% for CRT vs 35% for RT, p = 0.16).

Grade 3/4 adverse events were slightly more common in the CRT arm than in the RT group (36% vs 27.5%, p = 0.07).

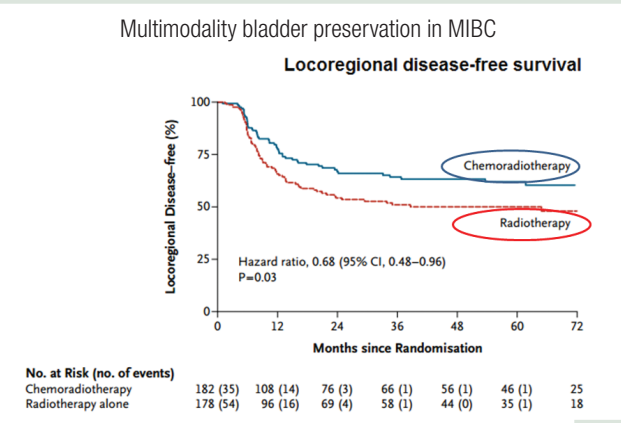


Fig. 4.12

CI, confidence interval; MIBC, muscle-invasive bladder cancer.

REVISION QUESTIONS

1. Is an orthotopic neobladder recommended in patients with glomerular filtration rate <45 mL/min?
2. Is a T0 stage prior to CRT associated with improved bladder-preservation rates?
3. Is RT alone oncologically equivalent to CRT?

Perioperative chemotherapy and survival after cystectomy

Neoadjuvant cisplatin-based ChT is recommended in patients with T2-T4a cN0M0 bladder cancer. It improves 5-year OS by 5%-8%.

Patients who respond well to neoadjuvant treatment, especially those who show a complete response (pT0N0), show a major improvement in OS.

Currently, both molecular subtypes and presence of deleterious mutations in DNA-repair-genes are discussed as potential predictors of response to neoadjuvant ChT.

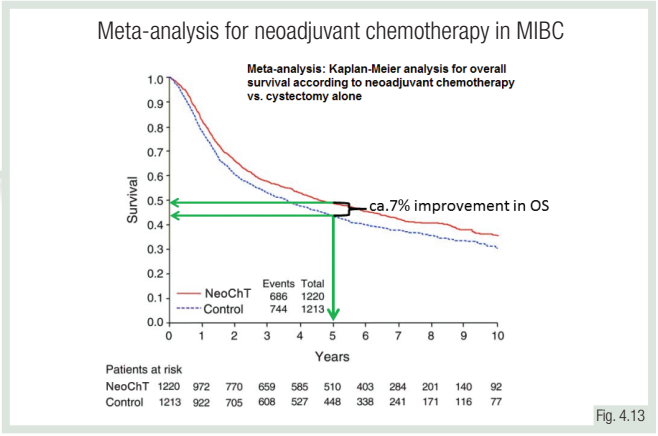


Fig. 4.13

MIBC, muscle-invasive bladder cancer; NeoChT, neoadjuvant chemotherapy; OS, overall survival.

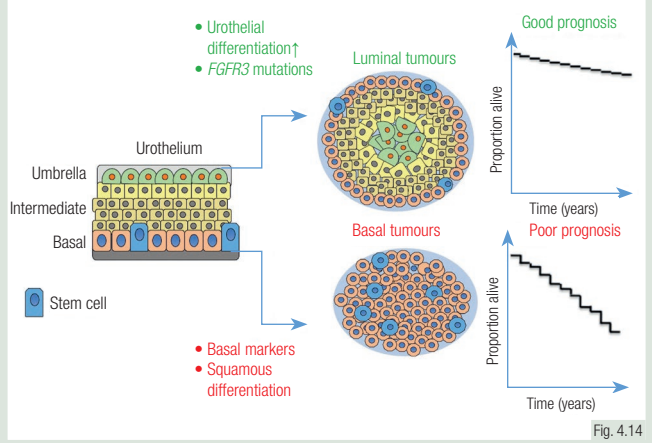


Fig. 4.14

FGFR3, fibroblast growth factor receptor 3.

Phase II trials show high pathological response rates after neoadjuvant ChT in patients with deleterious mutations in DNA-repair genes.

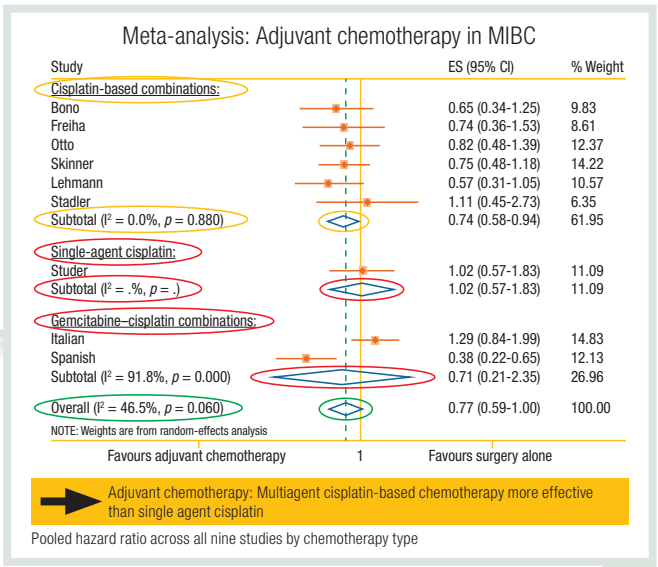
Based on gene expression profiles, several molecular subtypes of bladder cancer have been identified. First data suggest that patients with basal tumours may have a more pronounced benefit from neoadjuvant ChT.

Further validation of these factors in prospective clinical trials is needed before including them in clinical decision algorithms.

Adjuvant cisplatin-based combination ChT may be offered to patients with pT3/4 and/or pN+ disease if no neoadjuvant ChT has been given.

The meta-analyses for adjuvant ChT are flawed by methodological limitations (i.e. limited patient numbers, poor accrual).

Adjuvant ChT should not be considered for patients who are ineligible for cisplatin-based ChT.



CI, confidence interval; ES, effect size; MIBC, muscle-invasive bladder cancer.

Fig. 4.15

REVISION QUESTIONS

1. Does a pT0N0 stage at RC exert an impact on long-term oncological outcomes?
2. Are there potential predictive markers for selecting patients who may benefit from neoadjuvant ChT?
3. Can carboplatin-based ChT in pT2N0R0 bladder cancer be recommended as adjuvant treatment?

Summary: Staging and treatment of localised bladder cancer

- Optimising TURBT by implementing new techniques such as photodynamic diagnostics or *en bloc* resection is essential for improvement of treatment efficacy and probably long-term outcome
- A broad variety of instillation therapies exist for patients with NMIBC. Further modifications of instillation therapies (e.g. hyperthermia-assisted ChT) may lead to improved efficacy
- Recent evidence suggests equivalent oncological outcomes for patients treated with RARC compared with ORC
- The indications for RC are: T2-4a N0-NXM0 bladder cancer
- Currently, a standard PLND at RC is recommended
- RT should be performed in combination with maximal TURB and ChT, to improve long-term outcome of patients unfit for cystectomy
- Neoadjuvant ChT is recommended in cisplatin-eligible patients with T2-T4a cN0M0
- Molecular subtypes and alterations in DNA damage-repair genes are promising predictive markers for identification of optimal candidates for neoadjuvant cisplatin-based ChT

Further Reading

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5 Treatment of metastatic bladder cancer and upper tract transitional cell carcinoma

Diagnosis and presentation of metastatic bladder cancer

Approximately 5%-10% of patients with muscle-invasive bladder cancer (MIBC) present initially with metastatic disease.

Approximately 50% of patients with MIBC, originally staged as non-metastatic (T2-T4N0M0), relapse after radical treatment.

Relapses consist mainly of distant metastases. Local recurrence occurs in nearly 30% of patients.

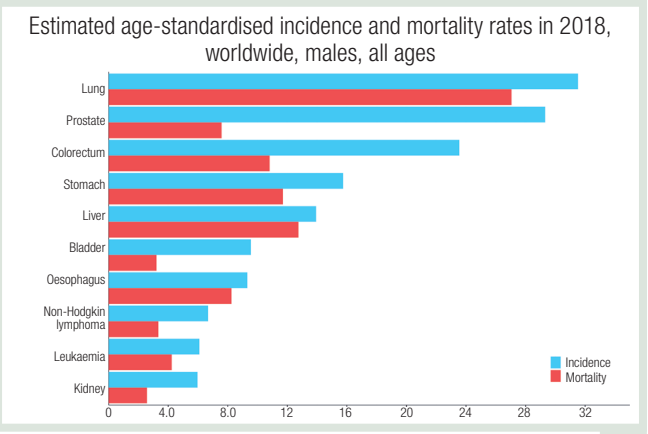


Fig. 5.1

Sites and frequency of metastatic lesions of bladder cancer ($n = 150$)		
Site	**No.**	**%**
Lymph nodes	104	69
Bone	71	47
Lung	55	37
Liver	39	26
Peritoneum	24	16
Pleura	17	11
Soft tissue	14	9
Adrenal	10	7
Brain	7	5
Urethra, penis	4	3
Intestine	4	3
Spleen	2	1
Pericardium	2	1
Heart	1	<1
Kidney	1	<1
Pancreas	1	<1
Scrotum	1	<1
Vagina	1	<1
Ethmoid sinus	1	<1

Fig. 5.2

Lymph nodes, bones, lung, liver and peritoneum are the most common sites of bladder cancer metastasis.

Preoperative computed tomography (CT) has a low sensitivity for detecting microscopic nodal dissemination.

Fluorodeoxyglucose-positron emission tomography (FDG-PET)-CT can add further value to the staging procedure, providing high specificity but medium sensitivity.

In case of progressive symptomatic metastatic cancer, oncological palliative treatment should be considered.

Palliation is mainly systemic therapy and palliative radiotherapy but can, in selected patients, be surgical.

The Bajorin prognostic model in untreated metastatic patients includes two factors (Karnofsky performance score [KPS] <80, presence of visceral metastasis) and three risk groups.

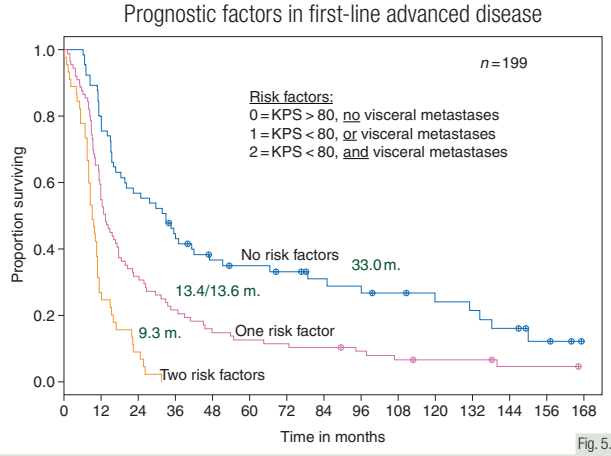


Fig. 5.3

KPS, Karnofsky performance score.

REVISION QUESTIONS

1. What is the percentage of relapses of metastases in radically treated patients?
2. What are the three most common sites of metastatic dissemination?
3. How can the prognosis be predicted by clinical data?

First-line treatment in metastatic bladder cancer

Before the introduction of effective chemotherapy (ChT), patients with metastatic urinary bladder cancer (mUBC) rarely had a median survival >3-6 months.

Cisplatin combination therapies are the primary choice for treatment in fit patients, since they are superior to single-drug cisplatin treatments in terms of response rates and survival.

Cisplatin combination therapies are more toxic.

Results for survival and disease-free survival overall and for trials grouped by chemotherapy type			
Endpoint: Overall survival			
Chemotherapy type	Single agent platinum	Platinum-based combination	All trials
Number of patients/events	261/376	1430/2433	1691/2890
HR (95% CI)	1.15 (0.9-1.47)	0.86 (0.77-0.95)	0.89 (0.81-0.98)
Effect p-value	0.26	0.003	0.022
Absolute benefit at 5 yrs (95% CI)	-5% (-14% to 4%)	5% (2% to 9%)	4% (0% to 7%)
Interaction p-value		0.029	
Endpoint: Disease-free survival			
Chemotherapy type	Single agent platinum	Platinum-based combination	All trials
Number of patients/events	166/217	1618/2629	1847/2846
HR (95% CI)	1.14 (0.83-1.55)	0.78 (0.71-0.86)	0.81 (0.74-0.89)
Effect p-value	0.42	<0.0001	<0.0001
Absolute benefit at 5 yrs (95% CI)	-5% (-16% to 7%)	9% (5% to 12%)	8% (4% to11%)
Interaction p-value		0.024	

CI, confidence interval; HR, hazard ratio. Fig. 5.4

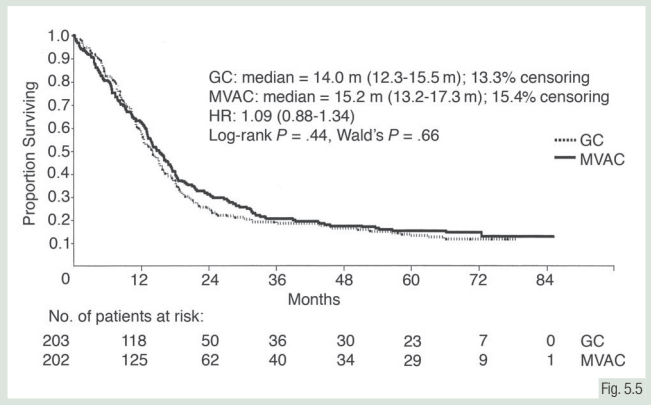


Fig. 5.5

GC, gemcitabine/cisplatin; HR, hazard ratio; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin.

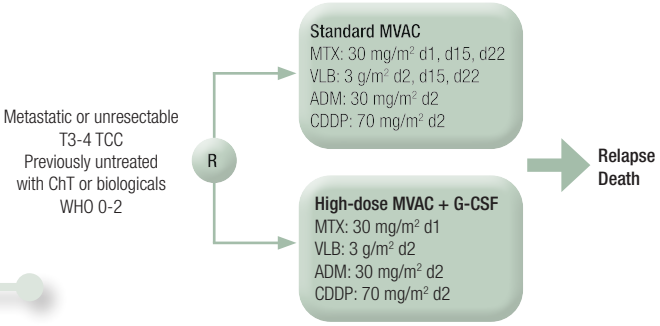
Two combinations are mainly used for first-line therapy: methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) or gemcitabine/cisplatin (GC).

MVAC vs GC has, in a phase III trial, displayed similar results in terms of response rates (46% vs 49%) and survival (14.8 vs 13.8 months).

GC shows less toxicity compared with MVAC. Common toxicities seen with these combinations are neutropaenia, alopecia, nausea, emesis and mucositis.

Approximately 20% of patients treated with high-dose-intensity MVAC (HD-MVAC) have a long-term survival.

HD-MVAC must be administered together with granulocyte colony-stimulating factor (G-CSF) to allow recovery of bone marrow between doses.



Dose intensity			
	MVAC Q14 days mg/m²	HD-MVAC Q14 days mg/m²	Dose intensity
Methotrexate (MTX)	45	30	0.7x
Vinblastine (VLB)	4.5	3	0.7x
Doxorubicin (ADM)	15	30	2.0x
Cisplatin (CDDP)	35	70	2.0x

ChT, chemotherapy; G-CSF, granulocyte colony-stimulating factor; HD-MVAC, high-dose MVAC; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; R, relapse; TCC, transitional cell carcinoma; WHO, World Health Organization. Fig. 5.6

REVISION QUESTIONS

1. How do cisplatin combination therapies compare with single-drug cisplatin treatments?
2. Which cisplatin combination therapy is considered to be less toxic?
3. Name two facts that make HD-MVAC a good treatment option.

First-line, second-line and novel treatment options in metastatic bladder cancer

Immunotherapy is associated with class-specific toxicities, distinct from those of ChT.

All organ systems in the body can be affected by the therapy. Close surveillance of patients is of utmost importance.

Vinflunine is approved in Europe for platinum-refractory patients.

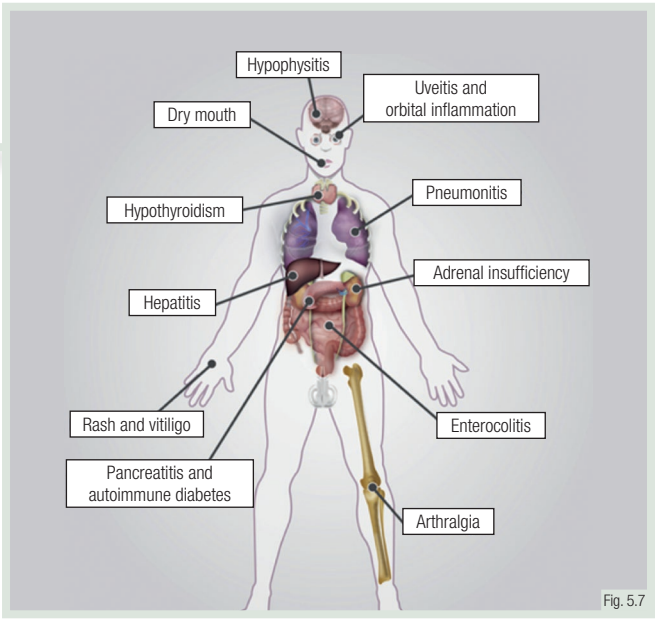


Fig. 5.7

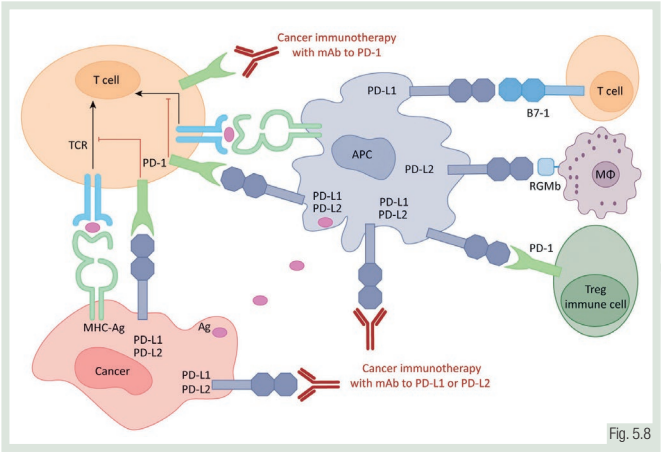


Fig. 5.8

Ag, antigen; APC, antigen-presenting cell; mAb, monoclonal antibody; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1/2, programmed death-ligand 1/2; RGMb, repulsive guidance molecule b; TCR, T cell receptor; Treg, T regulatory cell.

Immunotherapy is a new life-prolonging option in metastatic urothelial cancer. Three agents are approved in Europe so far: pembrolizumab, atezolizumab and nivolumab.

The approved agents are monoclonal antibodies (mAbs) targeting programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1). They work by restoring the anti-tumour activity of the immune system. Response rates vary between 13% and 21%.

No robust biomarker exists as of today to predict response to treatment. PD-L1 has been tested with variable success.

Second-line: five PD-(L)1 inhibitors (three in Europe, pembrolizumab, atezolizumab and nivolumab) are approved so far after failure on ChT. Pembrolizumab is the only one that demonstrated overall survival (OS) benefit in a phase III trial (KEYNOTE-045).

OS was 10.3 months in the pembrolizumab arm vs 7.4 months in the ChT arm. ChT was investigators' choice of docetaxel, paclitaxel or vinflunine.

There was no significant difference in progression-free survival (PFS). The toxicity profile was in favour of immunotherapy.

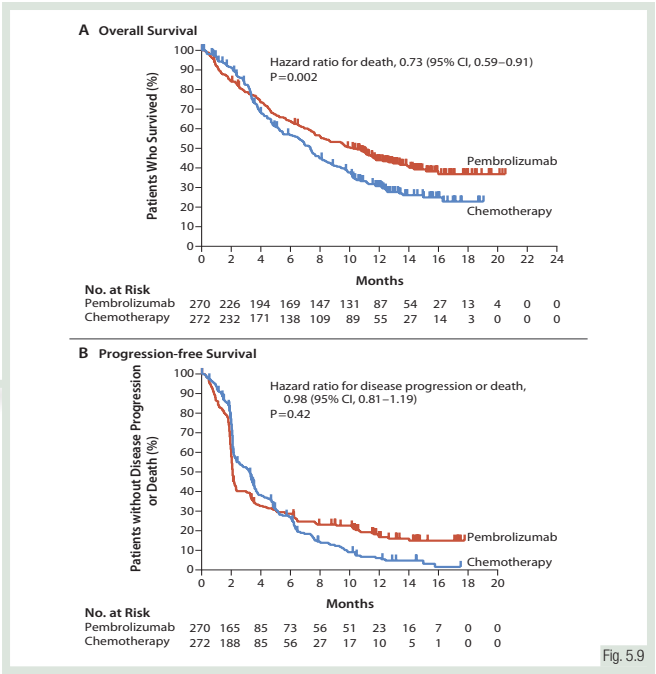


Fig. 5.9

CI, confidence interval.

First-line, second-line and novel treatment options in metastatic bladder cancer (continued)

Patients responding to immunotherapy often show an early response to treatment, but it may take several months before a significant response is obtained according to RECIST (Response Evaluation Criteria in Solid Tumours) 1.1.

Erdafitinib is a pan-FGFR (fibroblast growth factor receptor) tyrosine kinase inhibitor (TKI), recently Food and Drug Administration (FDA)-approved, based on data from an ongoing phase II study for patients progressing on platinum (NCT02365597). Approval is restricted to patients with certain FGFR alterations.

Enfortumab vedotin, an antibody-drug conjugate targetting cancers that express Nectin-4, has shown effect in urothelial cancer and FDA approval has been applied for.

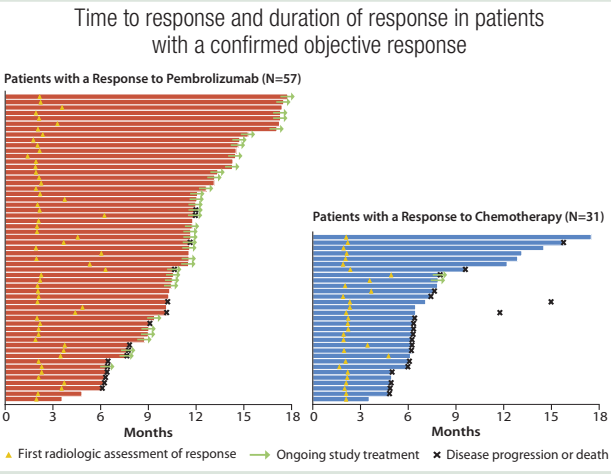


Fig. 5.10

REVISION QUESTIONS

1. What kind of toxicities are induced by immunotherapy?
2. Long-term survival can be seen in a subset of patients: what percentage of patients survive for 5 years?
3. How soon can immunotherapy induce a response?

Treatment in cisplatin-unfit patients

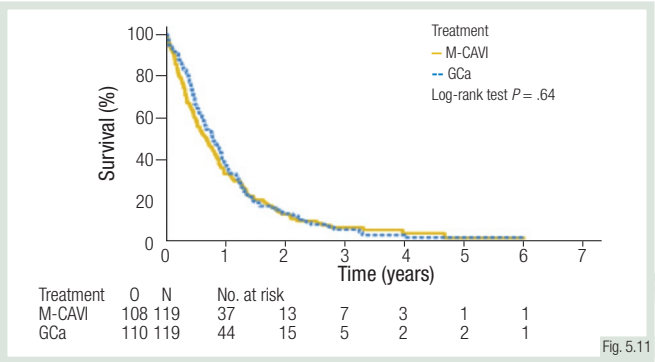


Fig. 5.11

GCa, gemcitabine/carboplatin; M-CAVI, methotrexate/carboplatin/vinblastine; O, observed number of deaths.

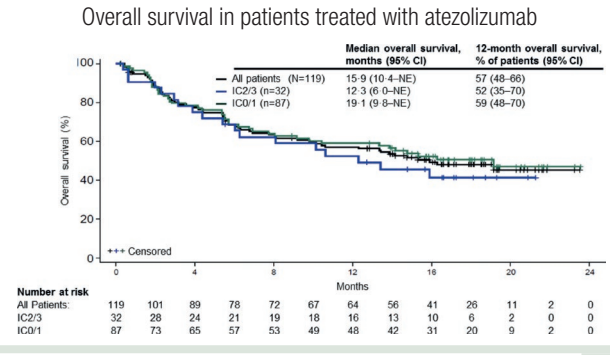
More than 50% of patients with urothelial cancer and metastatic disease are unfit for cisplatin ChT.

Unfit patients have the following criteria: glomerular filtration rate (GFR) <60 mL/min, hearing loss, neuropathy grade ≥2 and New York Heart Association (NYHA) grade >2. Other criteria may also apply.

The best ChT regimen regarding both effect and toxicity is carboplatin in combination with gemcitabine.

Two agents are approved in the first-line setting for cisplatin-unfit patients: atezolizumab and pembrolizumab. So far, only phase II data is available. Phase III studies are ongoing.

At the time of publication, the use of these agents in first-line is restricted by the European Medicines Agency (EMA) to patients with high expression of PD-L1.



CI, confidence interval; IC, tumour-infiltrating immune cell; NE, not estimable; PD-L1, programmed death-ligand 1.

Fig. 5.12

REVISION QUESTIONS

1. How do you define unfit vs fit patients for cisplatin ChT?
2. In cisplatin-unfit patients, what is the chemotherapeutic regimen of choice?
3. In short, describe how immunotherapy works.

Bone metastatic disease, complications and palliation in metastatic bladder cancer

The prevalence of bone metastatic disease in patients with metastatic bladder cancer is 30%-40%.

Bisphosphonates reduce and delay skeletal-related events.

The human mAb denosumab is as effective as bisphosphonates, and is easier to administer to patients with reduced renal function.

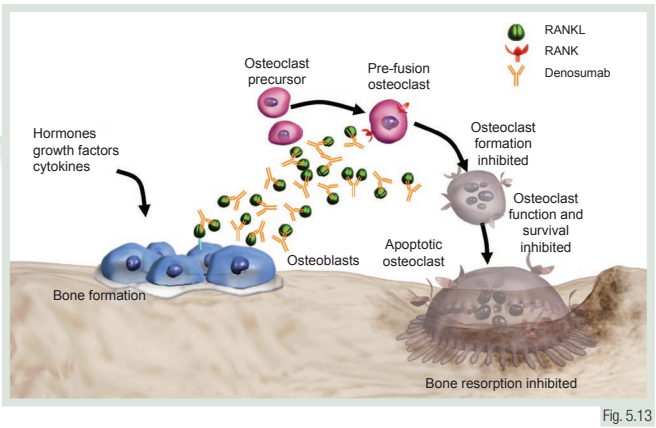


Fig. 5.13

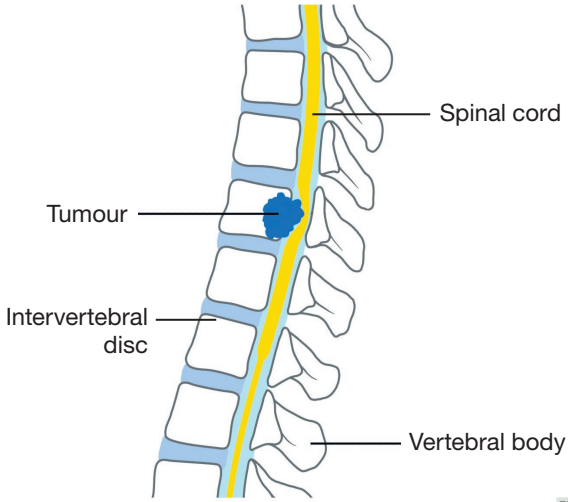


Fig. 5.14

Palliative one-dose (8 Gy) or fractionated radiation (4 Gy × 5) are equally effective treatment options for pain relief or pathological fractures risk reduction.

A few patients require surgery or radiotherapy in case of impending spinal compression.

The major symptoms of spinal compression are neurological symptoms and/or severe pain. Evaluation with magnetic resonance imaging (MRI) of the whole spine needs to be performed immediately and, if diagnosis is confirmed, rapid surgery is recommended.

In metastatic bladder cancer, health-related quality of life (HRQoL) is reduced, due to associated micturition problems, bleeding and pain.

Repeated bleeding in an uncystectomised metastatic patient can form an indication for palliative transurethral resection of the bladder (TURB) or haemostyptic radiation.

Repeated bleeding or severe local symptoms in an uncystectomised metastatic patient can, in selected cases, be treated with an ileal conduit.

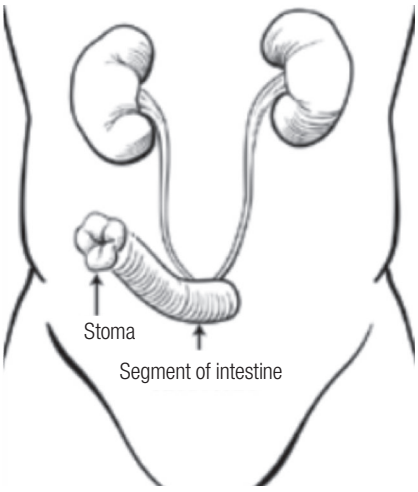


Fig. 5.15

REVISION QUESTIONS

1. What is the difference between bisphosphonates and denosumab in terms of efficacy in the reduction and delay of skeletal-related events?
2. What palliative radiation regimens exist for pain relief or when there is a risk of pathological fractures?
3. Mention two urological surgical procedures that can be considered palliative in selected uncystectomised patients with metastatic urinary bladder cancer.

Upper tract transitional cell carcinoma

Urothelial tumours of the ureter or renal pelvis, also known as upper tract tumours (UTTs), account for 5% of all urothelial carcinomas. 95% have transitional cell carcinoma (TCC) histology. Urothelial tumours are the third commonest malignancy in patients with Lynch syndrome.

The most common presenting symptom is haematuria; however, incidental diagnosis also occurs. Patients with UTT have a 25%-75% risk of developing a TCC recurrence in the bladder.

Peak incidence is in the eighth and ninth decades of life, and men are twice as likely to be affected as women. UTTs are more commonly invasive at diagnosis and can be multifocal. Invasive tumours have a low rate of cure.

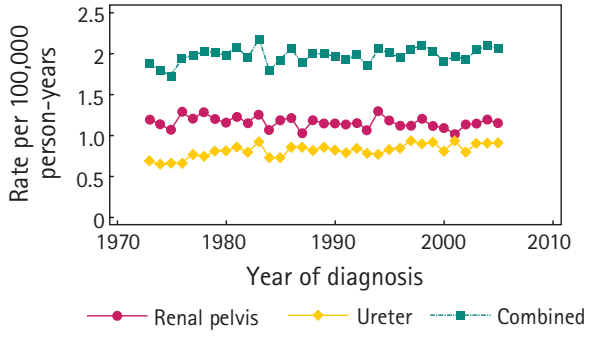
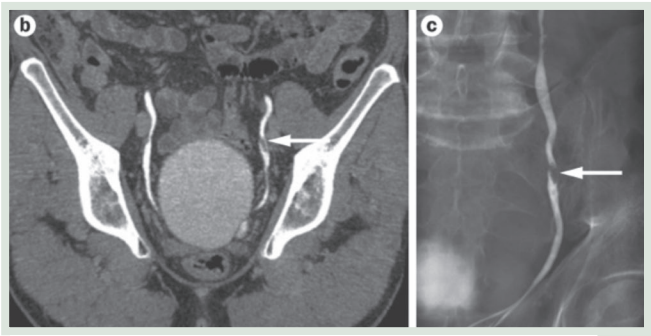


Fig. 5.16



Left, CT coronal reconstruction demonstrating a mass in the left pelvic ureter. Right, Retrograde ureteropyelography.
CT, computed tomography.

Fig. 5.17

CT urography is the most accurate imaging test, though magnetic resonance (MR) urography may be used in patients who cannot undergo CT urography.

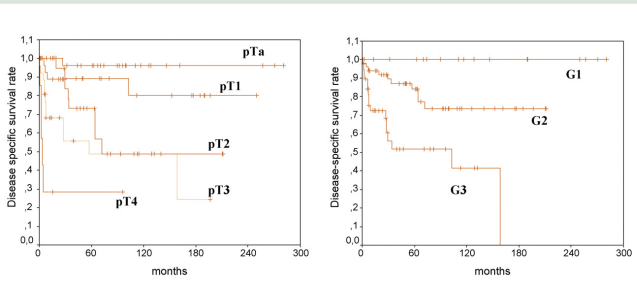
Flexible ureteroscopy is used to visualise and biopsy the upper tract. Urine cytology is helpful, because a positive test is highly suggestive of UTT if bladder cystoscopy is normal.

Despite these investigations, the sensitivity and specificity of preoperative imaging, biopsy and cytology may be as low as 75%.

Tumour, node, metastasis (TNM) staging of UTTs is similar to that of bladder carcinoma. Tumour stage and grade are the most important prognostic factors. Staging should include cystoscopy to exclude concurrent bladder lesions.

Additional adverse prognostic factors include (lympho)-vascular invasion, location of the tumour, multifocality, hydronephrosis, raised inflammatory markers, variant histology and smoking.

Traditionally, systemic treatment for UTTs has been based on data from bladder TCC studies, though UTTs show higher rates of microsatellite instability and therefore may exhibit different biological behaviour.



Author	No. of patients	Prognostic factor
Langner	190	Vascular invasion (lymphatic + venous)
Akdogan	72	Ureteral location
van der Poel	149	Proximal ureteral location
Kikuchi	173	Lymphovascular invasion
Novara	269	Tumour multifocality; previous or concomitant bladder cancer
Hong	86	Lymphovascular invasion
Wu	72	Vascular invasion, tumour location
Miyata	125	Intratumour lymphatic vessels
Langner	190	Extensive tumour necrosis
Langner	190	Infiltrative invasion pattern
Saito	130	Preoperative C-reactive protein level

Fig. 5.18

REVISION QUESTIONS

1. What are the common presenting features of UTT?
2. Which procedures are needed to make an accurate diagnosis of UTT?
3. Name three prognostic factors of UTT.

Upper tract transitional cell carcinoma (continued)

Nephroureterectomy with bladder cuff excision is indicated in non-metastatic disease, or a nephron-sparing procedure for low-grade disease. In high-grade cases, lymphadenectomy is inconsistently recommended in the absence of level I evidence.

If concurrent investigation of the bladder shows invasive bladder cancer, cystectomy or chemoradiotherapy is also required. Non-invasive bladder disease requires local therapy and appropriate follow-up.

Post-operative recurrence in the bladder is common, occurring at a median time ranging from 25 to 88 months. A single dose of intravesical mitomycin C reduced bladder recurrence incidence by 11% in absolute terms in the ODMIT-C study.

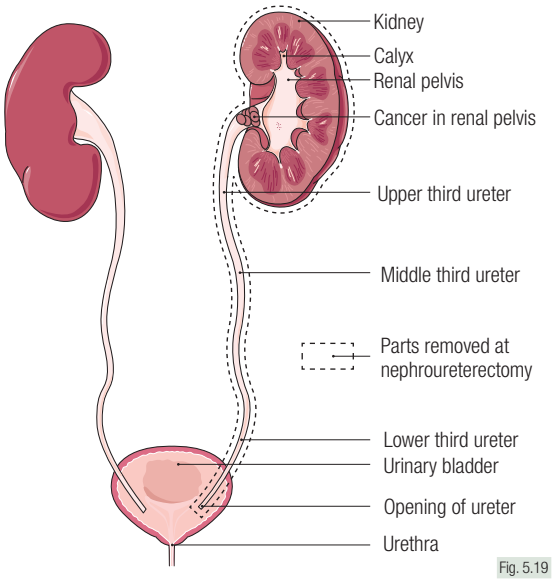


Fig. 5.19

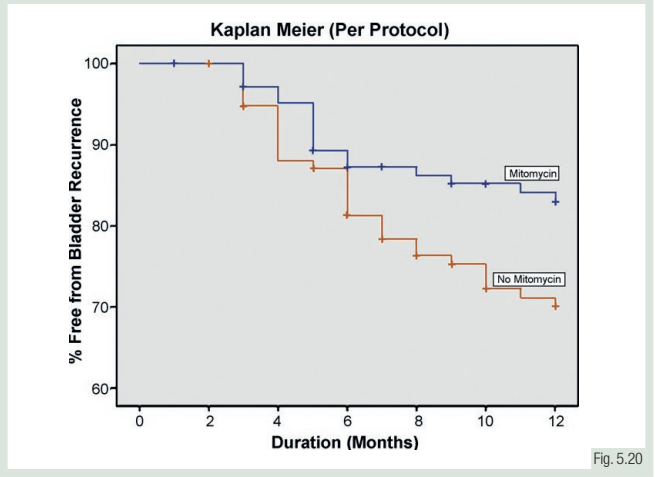


Fig. 5.20

In the phase III POUT study, adjuvant platinum-based ChT increased disease-free survival in pT2-T4 or pN1 disease, supporting older registry data.

Despite the predictable decline in renal function following nephroureterectomy, carboplatin was shown to be safe and effective in patients with lower estimated glomerular filtration rates (eGFRs). Although neoadjuvant ChT avoids predicted post-operative decline in eGFR, there is only limited, retrospective evidence for this and a risk of overtreatment exists in lower-risk patients with pT1 disease.

Treatment of metastatic UTTs is based on data from bladder cancer trials in which UTT patients were included. Regimens are usually platinum-based, such as aMVAC (accelerated methotrexate/vinblastine/doxorubicin/cisplatin), or gemcitabine + cisplatin/carboplatin.

First-line therapy is usually with ChT. Pembrolizumab and atezolizumab are licensed for platinum-ineligible patients with high PD-L1 expression (combined positive score [CPS] ≥10 or immune cell [IC] >5%).

Second-line therapy can be with ChT or pembrolizumab regardless of CPS (see page 33). The delay to disease response with immunotherapy may limit its use in the deteriorating patient.

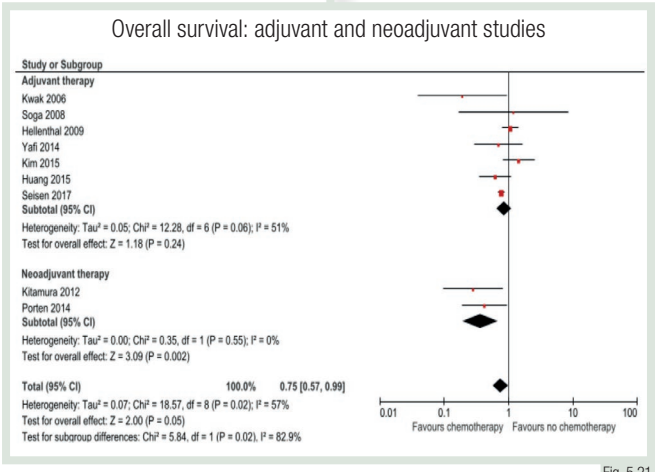


Fig. 5.21

CI, confidence interval.

REVISION QUESTIONS

1. In a patient with a small UTT mass in the left kidney pelvis without radiological evidence of metastasis, name two surgical procedures that could be performed.
2. What is the median survival of metastatic UTT patients treated with platinum-containing regimens?
3. What systemic treatment options are available for metastatic UTT?

Summary: Treatment of metastatic bladder cancer and upper tract transitional cell carcinoma

- mUBC relapse is high (~50%) even after radical treatment. Preoperative CT has a low sensitivity for detecting nodal dissemination. Node-positive cancer is most often a post-cystectomy finding
- Local relapses and/or overt metastatic disease post-cystectomy must be treated in case of symptomatic manifestations, and not upfront
- There is an improved survival and objective response for cisplatin combination therapy. GC and MVAC are equally efficient, but GC therapy is less toxic
- Survival outcome depends on patient-related factors and comorbidity. The absence of visceral metastases improves outcome
- Treatment with cisplatin is recommended in fit patients, with carboplatin combinations and immunotherapy (in PD-L1-positive patients) as treatment options for cisplatin-unfit patients
- Bisphosphonates or denosumab are optional for the treatment of bone metastases
- Immunotherapy has shown OS benefit in second-line treatment
- Palliative one-dose or fractionated radiation are equally effective for pain relief and reducing the risk of pathological fractures
- UTTs account for 5% of all urothelial carcinomas; TCC is the most common histology
- Nephroureterectomy is indicated in non-metastatic TCC, with extended lymph node dissection in high-grade disease; nephron-sparing surgery may be considered in low-grade, limited disease. Adjuvant ChT should be considered
- Treatment of advanced or metastatic UTT follows guidelines for metastatic bladder cancer

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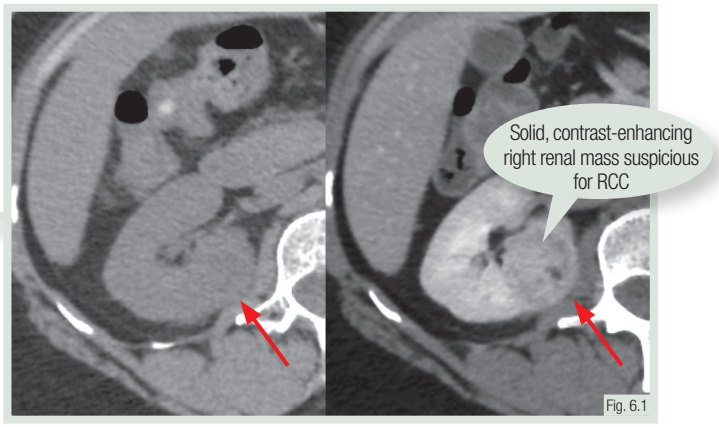
6 Staging and treatment of localised renal cell cancer

Diagnosis and staging

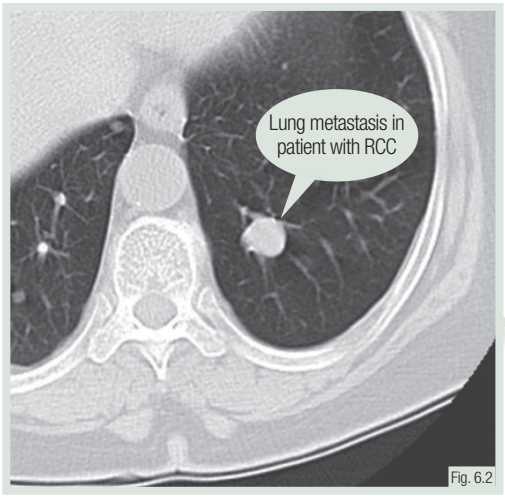
Most localised renal tumours are currently diagnosed incidentally when abdominal imaging (ultrasound, computed tomography [CT], magnetic resonance imaging [MRI]) is performed for other medical reasons.

Triphasic abdominal CT is generally used to characterise renal masses. The diagnosis of malignancy is based on the presence of contrast enhancement (≥15 HU).

MRI can provide additional information when the results of CT are indeterminate. It is also recommended in patients allergic to CT contrast medium and during pregnancy.



RCC, renal cell carcinoma.



RCC, renal cell carcinoma.

Most renal tumours can be diagnosed accurately using imaging alone. Ultrasound- or CT-guided percutaneous renal tumour biopsy (RTB) can be used in selected cases to histologically characterise renal tumours and aid in treatment decisions.

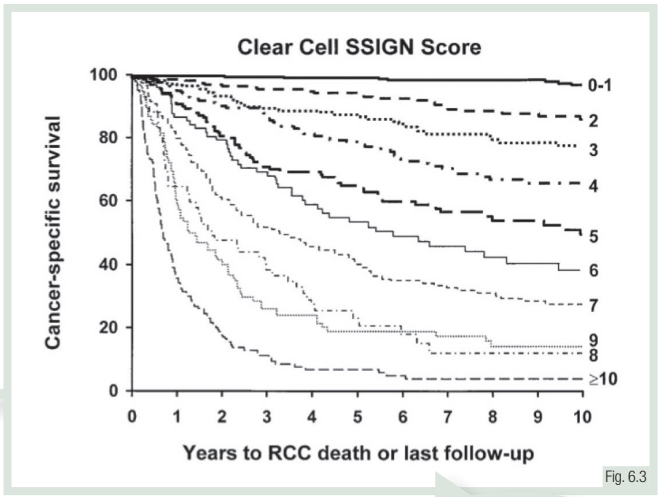
Multiphasic contrast-enhanced CT of chest and abdomen is the gold standard for staging renal tumours. MRI can be used to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.

Since most bone and brain metastases are symptomatic at diagnosis, routine bone or brain imaging is not recommended, as there is no evidence that early detection prolongs survival.

The 2018 TNM (tumour, node, metastasis) classification is recommended to define renal tumour stage (see Appendix 2, page 97). Its prognostic value has been confirmed in single- and multi-institutional studies.

The prognosis of some stages of the 2018 TNM classification (pT2b and pT3a, pT3c and pT4) may overlap. The accuracy of the classification of nodal disease is currently questioned.

Integrated prognostic models (e.g. Stage, Size, Grade and Necrosis [SSIGN] and University of California Los Angeles Integrated Staging System [UISS]) and anatomical classification systems of renal tumours (e.g. PADUA [Preoperative Aspects and Dimensions Used for Anatomical classification] and RENAL [Radius, Exophytic/endophytic, Nearness, Anterior/posterior, Location] nephrometry) are useful for patient counselling and treatment planning.



RCC, renal cell carcinoma; SSIGN, Stage, Size, Grade and Necrosis.

Stratification of cancer-specific survival of renal tumours after radical nephrectomy using the SSIGN score

REVISION QUESTIONS

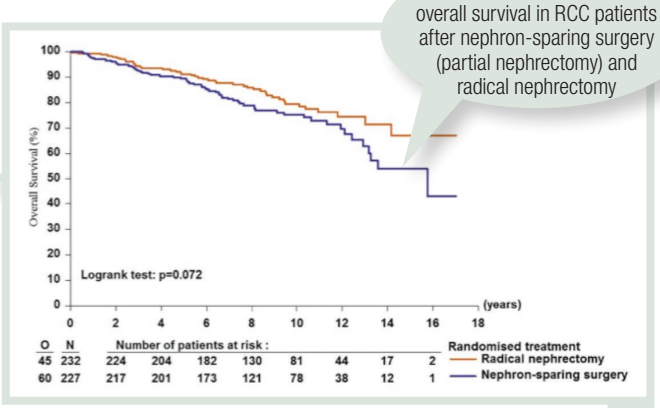
1. How are most renal tumours diagnosed?
2. Which is the appropriate imaging technique to diagnose renal cancer?
3. Which is the current staging system for renal tumours?

Surgical treatment

Surgery is the recommended curative treatment for localised renal tumours.

For clinically localised renal tumours, partial nephrectomy (PN) achieves similar oncological outcomes and better preserves postoperative renal function when compared with radical nephrectomy (RN).

PN is recommended for cT1 tumours and should be favoured over RN whenever technically feasible.



Kaplan-Meier estimates for overall survival in RCC patients after nephron-sparing surgery (partial nephrectomy) and radical nephrectomy

Fig. 6.4

O, observed number of deaths; RCC, renal cell carcinoma.

Characteristics	LRN	ORN
No. patients	36	37
Age	67.8 ± 12.8	61.1 ± 12.7
Sex		
Male	23 (64%)	23 (62%)
Female	13 (36%)	14 (38%)
ASA		
ASA 1	–	3 (8%)
ASA 2	20 (56%)	21 (57%)
ASA 3	16 (44%)	13 (35%)
ASA 4	–	–
Clinical stage		
cT1a	15	9
cT1b	21	20
cT2	0	8
Pathological stage		
pT1a	12	9
pT1b	17	20
pT2	0	8
pT3	4	
No. surgeons	6	12
Cases performed by		
Attending/Head of Department	36 (100%)	31 (84%)
Residents	–	6 (16%)
Operative time (min)	146 ± 42	113 ± 48
Length of hospital stay (days)	7.2 ± 2.9	9.1 ± 3.5
Blood loss (ml)	231 ± 153	424 ± 361

ASA, American Society of Anesthesiologists; LRN, laparoscopic RN; ORN, open RN; RN, radical nephrectomy.

Fig. 6.5

Laparoscopic RN (LRN) is associated with lower blood loss, lower morbidity and shorter hospital stays, compared with open RN.

LRN is recommended for patients with localised renal tumours not treatable by PN and for patients with cT2 tumours.

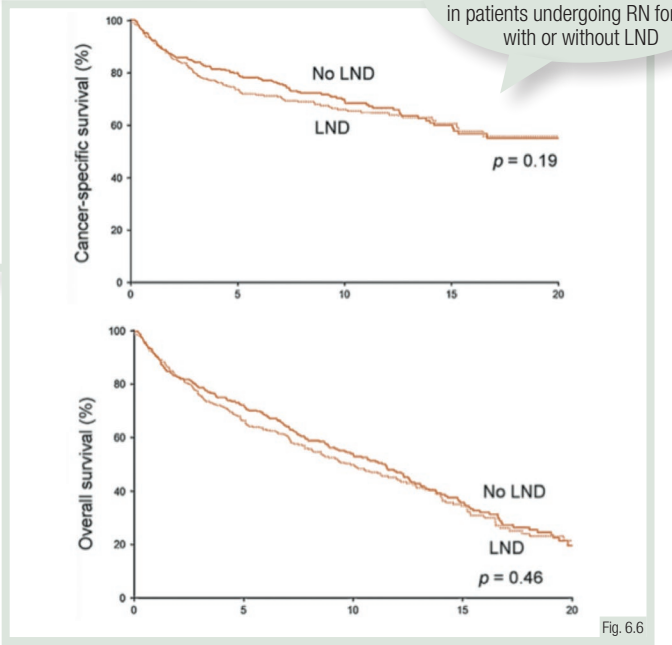
Ipsilateral adrenalectomy is not routinely recommended during RN since it does not provide a survival advantage.

Comparison of perioperative outcomes of laparoscopic RN (LRN) and open RN (ORN), showing shorter hospital stay and lower blood loss in the laparoscopic group.

Lymph node dissection (LND) is not routinely recommended during RN for localised renal tumours without clinical evidence of lymph node metastases, since it was not shown to provide a survival advantage.

LND can be performed for staging purposes in patients with non-metastatic renal tumours and clinically enlarged lymph nodes. However, the survival benefit in this setting is unclear.

At present, adjuvant tyrosine kinase inhibitor (TKI) therapy is generally not recommended after nephrectomy. Trials testing immunotherapy in the adjuvant setting are ongoing.



Kaplan-Meier curves showing no difference in cancer-specific survival and overall survival in patients undergoing RN for RCC with or without LND

Fig. 6.6

LND, lymph node dissection; RCC, renal cell carcinoma; RN, radical nephrectomy.

REVISION QUESTIONS

1. What is the recommended treatment for clinically localised renal tumours?
2. When is laparoscopic RN indicated for localised renal tumours?
3. Is LND routinely indicated during RN?

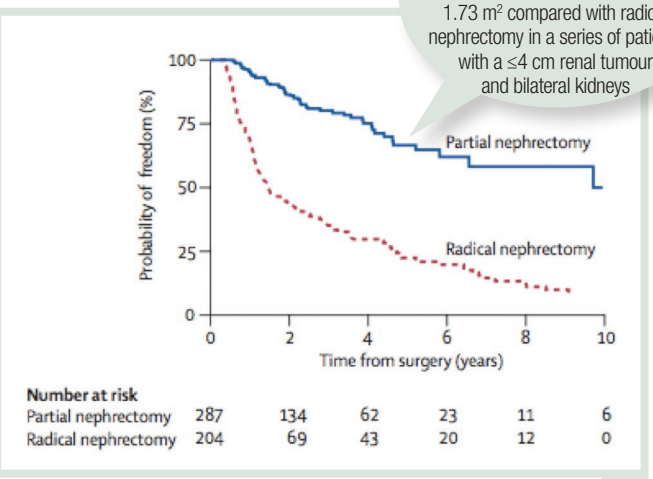
Partial nephrectomy – Nephron-sparing surgery

Nephron-sparing surgery (NSS) aims to completely remove renal tumours with negative surgical margins, while preserving the maximal amount of healthy renal parenchyma.

Several studies have shown that NSS is associated with a considerably lower risk of developing significant chronic renal failure compared with RN.

NSS was shown to be associated with a lower risk of cardiovascular events compared with RN, while its association with improved overall survival (OS) is debated.

Partial nephrectomy allows a significantly higher probability of freedom from new onset of GFR <60 mL/min per 1.73 m² compared with radical nephrectomy in a series of patients with a ≤4 cm renal tumour and bilateral kidneys



GFR, glomerular filtration rate. Fig. 6.7

A multicentre series of 660 partial nephrectomies performed in solitary kidneys under cold or warm ischaemia. On multivariate analysis, the strongest predictors of early and late renal function were preoperative GFR and percentage of healthy parenchyma preserved

	Postop GFR		
	β Estimate (95% CI)		p Value
Age (per 1-yr increase]	-0.1	(-0.3, -0 01)	0.04
Male	-2.6	(-5.4, 0.2)	0.07
Black (vs white/other]	-1.8	(-7.3, 3.8)	0.5
Preop GFR (per 1 ml/min/1.73 m² increase)	0.6	(0.6, 0.7)	<0.00001
Yrs with solitary kidney before PN:			
1-20 (vs less than 1)	0.2	(-3.5, 3.9)	0.9
Greater than 20 (vs less than 1)	1.4	(-2.8, 5.6)	0.5
Radiographic tumour size (per 1 cm increase)	0.2	(0 06, 0.4)	0.006
Polar (vs interpolar)	1.5	(-2.0, 5.1)	0.4
Central (vs peripheral)	-1.3	(-4.5, 2.0)	0.4
Multifocal (vs unifocal)	-1.9	(-5.7, 1.8)	0.3
Most experienced surgeons	-5.7	(-10 8, -0.5)	0.03
Time of surgery:			
1998-2001 (vs 1980-1997)	0.4	(-6.1, 6.9)	0.9
2002-2009 (vs 1980-1997)	-2.5	(-10.1, 5.1)	0.5
Ischaemia time (per 1 min increase)	-0.01	(-0.1, 0.01)	0.08
Warm ischaemia (vs cold)	2.6	(-3.5, 8.7)	0.4
Interaction (ischaemia time * ischaemia type)	-0.2	(-0.4, 0.1)	0.1
% Parenchyma preserved (per increase in 1 unit)	0.2	(0.1, 0.3)	<0.0001
Propensity score to undergo PN-CI	0.8	(-9.2, 10.8)	0.8

CI, confidence interval; GFR, glomerular filtration rate; PN, partial nephrectomy. Fig. 6.8

PN is generally performed with temporary interruption of the arterial blood flow to the kidney, in order to minimise bleeding and favour a safe tumour excision.

Preoperative renal function and the amount of healthy renal tissue preserved are the main independent predictors of long-term renal function after PN.

Warm ischaemia time (WIT) is a significant modifiable predictor of postoperative renal function. Efforts should be made to avoid prolonged WITs (>25 minutes). Cold ischaemia should be employed when longer ischaemia is expected.

NSS can be performed either with an open, laparoscopic or robot-assisted approach.

Laparoscopic PN is a valuable alternative to open PN in centres with laparoscopic expertise.

In meta-analyses robot-assisted PN is associated with shorter WIT and lower rates of positive margins, complications and conversion to RN, compared with laparoscopic PN.

Outcomes	WMD or RR (95% CI)	p Value	Favours
Periop safety:			
Conversion to laparoscopic/open surgery	0.36 (0.22 to 0.61)	<0.001	RPN
Conversion to radical nephrectomy	0.44 (0.18 to 1.09)	0.08	RPN
Complications (Clavien 1 or greater)	0.84 (0.73 to 0.95)	0.007	RPN
Major complications (Clavien 1 or greater)	0.71 (0.52 to 0.95)	0.023	RPN
Periop effectiveness:			
Operative time	-12.19 (-37.37 to 12.98)	0.34	Similar
EBL	-24.55 (-57.89 to 8.78)	0.15	Similar
Hospital LOS	-0.22 (-0.47 to 0.04)	0.10	Similar
WIT	-4.34 (-6.17 to -2.51)	<0.001	RPN
Periop functional:			
Change in eGFR	-2.10 (-8.17 to 3.96)	0.50	Similar
Oncological:			
Positive margins	0.53 (0.39 to 0.72)	<0.001	RPN

CI, confidence interval; EBL, estimated blood loss; eGFR, estimated glomerular filtration rate; LOS, length of stay; RPN, robot-assisted partial nephrectomy; RR, relative risk; WIT, warm ischaemia time; WMD, weighted mean difference. Fig. 6.9

REVISION QUESTIONS

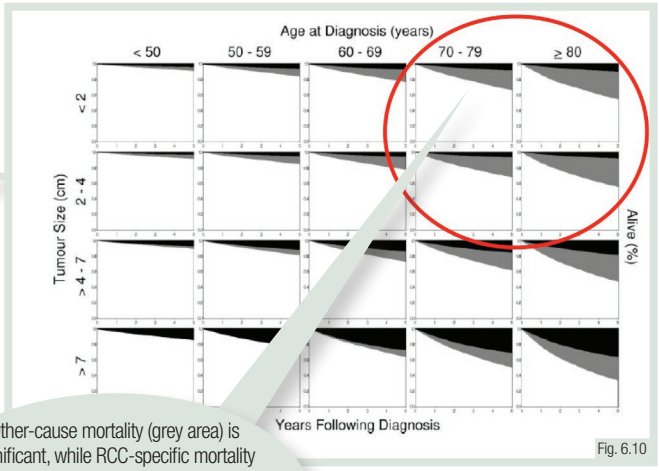
1. What are the advantages of PN compared with RN?
2. What are the independent predictors of long-term renal function after PN?
3. What are the possible surgical approaches to perform NSS?

Non-surgical management – Ablative treatments

Small renal tumours are histologically heterogeneous. A significant proportion are benign tumours (20%-25%) or low-grade RCCs with a relatively indolent behaviour.

Non-RCC-related mortality is significant after surgical treatment of localised renal tumours in elderly patients and patients with comorbidities.

Population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared with non-surgical management, but this is not confirmed in patients >75 years old.



Other-cause mortality (grey area) is significant, while RCC-specific mortality (black area) is rare in the 5 years following surgery for localised <4 cm renal tumours in elderly patients, providing a rationale for non-surgical treatment in patients with limited life expectancy

Fig. 6.10

RCC, renal cell carcinoma.

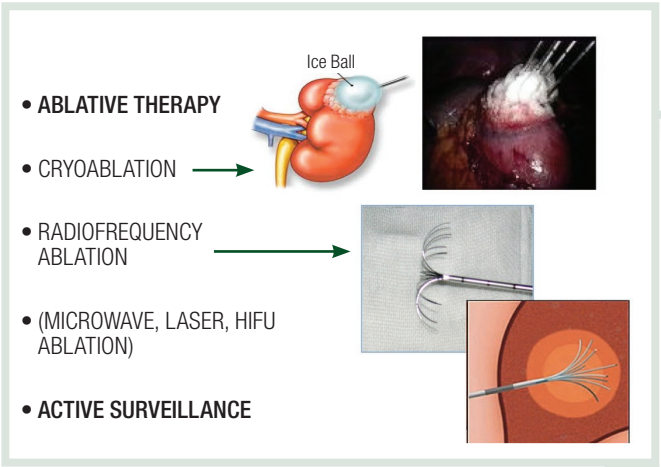


Fig. 6.11

HIFU, high-intensity focused ultrasound.

Cryoablation and radiofrequency ablation are established techniques for minimally invasive ablation of renal tumours. Other techniques using microwaves, high-intensity focused ultrasound (HIFU) and laser energy are currently considered experimental.

Ablative therapies can be offered to elderly and/or comorbid patients with small renal masses (<4 cm) and a limited life expectancy, and to patients who refuse surgical treatment.

RTB is recommended before or during ablation for histological characterisation of the tumour. Treatment success is generally defined as a lack of contrast enhancement and a reduction in tumour size after ablation.

There are no randomised studies comparing the outcomes of ablative therapies and NSS. Low-quality studies suggest a higher local recurrence rate and a lower complication rate for ablative therapies compared with PN.

Ablative techniques can be performed either with a percutaneous or laparoscopic-assisted approach. Percutaneous ablation can be performed under local anaesthesia as a short-stay procedure.

Due to the low quality of the available data, no definite recommendation can be made on the ideal ablation technique for small renal tumours.

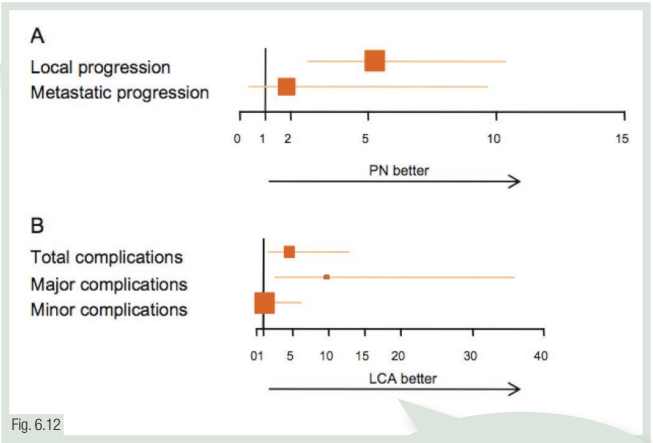


Fig. 6.12

LCA, laparoscopic cryoablation; PN, partial nephrectomy.

Results of a cumulative analysis of observational studies on oncological outcomes and perioperative complications of laparoscopic cryoablation (LCA) and partial nephrectomy

REVISION QUESTIONS

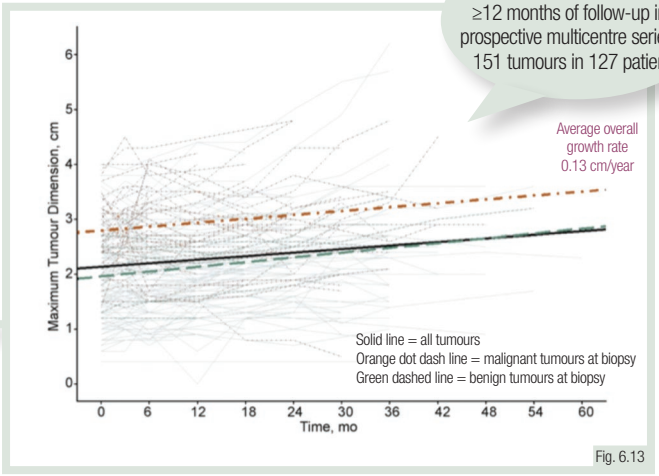
1. What is the rationale for non-surgical management of localised renal tumours?
2. What are the established techniques for ablation of renal tumours?
3. Which is the ideal ablative technique for localised renal tumours?

Active surveillance – Percutaneous renal tumour biopsy

Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (ultrasound, CT, or MRI) with delayed intervention reserved for tumours that show clinical progression during follow-up.

Active surveillance can be offered to elderly and/or comorbid patients with small renal masses and limited life expectancy.

In active surveillance cohorts, the growth rate of small renal masses is slow in most cases. Progression to metastatic disease is rare (1%-2%).

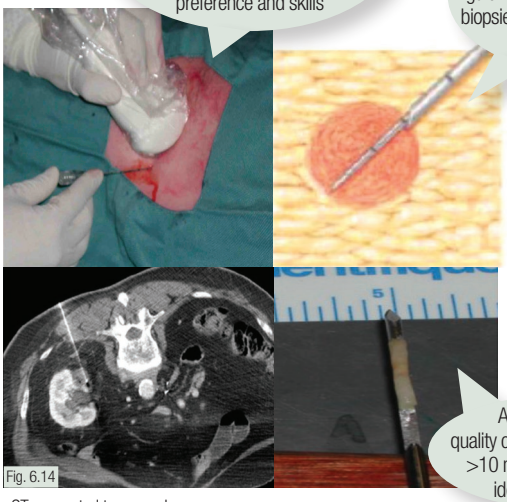


Growth patterns of small renal masses with ≥12 months of follow-up in a prospective multicentre series of 151 tumours in 127 patients

Fig. 6.13

Percutaneous renal tumour biopsy is performed with ultrasound or CT guidance, depending on tumour location, patient body habitus, and operator preference and skills

Coaxial technique: approach to the tumour with a guiding cannula and subsequent biopsies through the cannula after removal of the stylet



At least two good quality cores (non-fragmented, >10 mm in length) should ideally be obtained

Fig. 6.14

CT, computed tomography.

Percutaneous RTB is recommended in patients in whom non-surgical management is pursued.

RTBs can be performed under local anaesthesia and have a low complication rate. Core biopsy and fine needle aspiration can be obtained. Core biopsy should be favoured for solid renal masses.

Tumour seeding of RTB is anecdotal. To avoid the risk of this complication, the biopsy should always be performed through a coaxial cannula.

Adequate biopsy cores have a high diagnostic yield (80%-100%) with good accuracy for the diagnosis of malignancy and tumour histotype.

Differential diagnosis between renal oncocytoma and chromophobe RCC and assessment of tumour grade are challenging on RTBs.

Due to intra-tumour heterogeneity of renal tumours, further studies are needed to define the ideal RTB pattern (number and location of biopsies).

	No. of tumours biopsied	Diagnostic biopsies, %	Accuracy for malignancy, %	Accuracy for RCC subtyping, %	Accuracy for grading, %
Neuzillet et al	88	91	92	92	69.8
Shannon et al	235	78	100	98	NR
Schmidbauer et al	78	97	Sensitivity 93.5 Specificity 100	91	76
Lebret et al	119	79	86	86	46/74
Maturen et al	152	96	Sensitivity 97.7 Specificity 100	NR	NR
Volpe et al	100	84	100	100	66.7/75
Wang et al	110	90.9	100	96.6	NR
Veltri et al	103	100	NR	93.2	NR
Leveridge et al	345	80.6	99.7	88	63.5

NR, not reached; RCC, renal cell carcinoma.

Fig. 6.15

Diagnostic outcomes of percutaneous renal core biopsies of renal masses in large series at experienced centres

REVISION QUESTIONS

1. What is the definition of active surveillance of renal tumours?
2. What are the indications for active surveillance of small renal tumours?
3. What are the current indications of percutaneous renal tumour biopsy?

Summary: Staging and treatment of localised renal cell cancer

- Contrast-enhanced, multiphasic abdominal CT and MRI are the most appropriate imaging modalities for the diagnosis and staging of renal tumours
- Chest CT is recommended for staging assessment of the lungs and mediastinum
- RTB is recommended before ablative therapy and systemic therapy without previous pathology, and in patients who are candidates for active surveillance
- The use of the current TNM classification system is recommended for staging renal tumours
- Surgery is the gold standard therapeutic approach for localised renal tumours
- NSS is recommended in patients with clinical T1 renal tumours whenever technically feasible
- Ipsilateral adrenalectomy and LND are not recommended for localised renal tumours without clinical evidence of adrenal or lymph node invasion
- Adjuvant systemic treatment is currently not recommended after surgical treatment for non-metastatic renal tumours
- Laparoscopic RN should not be performed in patients with T1 tumours, for whom PN is indicated, while it is recommended for patients with T2 tumours and localised renal masses not treatable by NSS
- Active surveillance, cryoablation and radiofrequency ablation can be offered to elderly and/or comorbid patients with small renal masses and limited life expectancy

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7 Treatment of metastatic renal cell cancer

Understanding the molecular background of the disease and development of novel agents

Renal cell carcinoma (RCC) is a group of kidney tumours, each with a different epithelial origin and a different genetic background.

The clear cell type is the most common and is characterised by loss or mutation of the von Hippel-Lindau *(VHL)* tumour-suppressor gene.

VHL loss leads to intracellular increase of hypoxia-inducible factor alpha (HIF-α) followed by the induction of hypoxia-inducible genes.

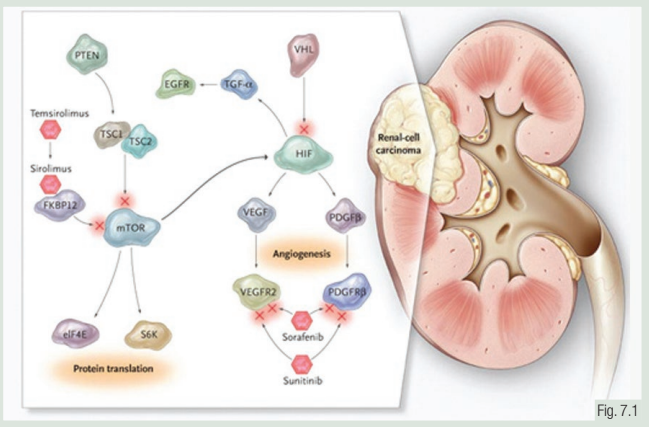


Fig. 7.1

EGFR, epidermal growth factor receptor; eIF4E, eukaryotic translation initiation factor 4E; HIF, hypoxia-inducible factor; mTOR, mammalian target of rapamycin; PDGFβ, platelet-derived growth factor beta; PDGFRβ, PDGF receptor beta; PTEN, phosphatase and tensin homologue; S6K, S6 kinase; TGF-α, transforming growth factor alpha; TSC1 and TSC2, tuberous sclerosis complex 1 and 2; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2; VHL, von Hippel-Lindau.

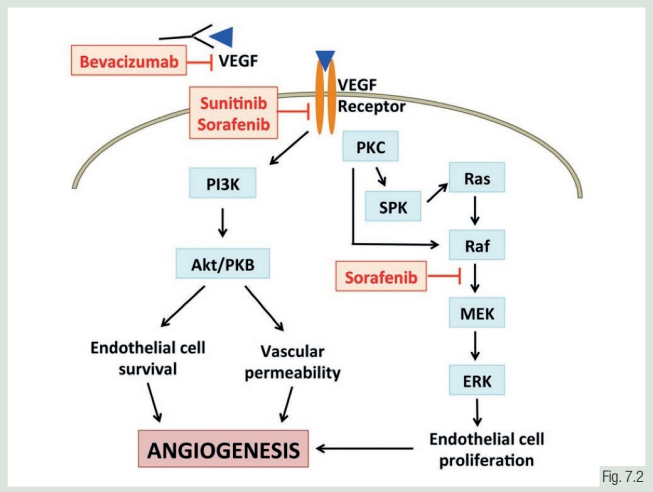


Fig. 7.2

ERK, extracellular signal-regulated kinase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; SPK, sphingosine kinase; VEGF, vascular endothelial growth factor.

Targeted agents such as vascular endothelial growth factor (VEGF) inhibitors and mammalian target of rapamycin (mTOR) inhibitors hinder HIF-α-induced expression of growth factor signalling at different sites of endothelial and/or tumour cells.

Their primary mode of action is anti-angiogenesis.

More recently, it has been recognised that immune checkpoints play a crucial role in cancer.

Several steps within the cancer immunity cycle can be hijacked by the tumour. As a result, the body's own immune system can no longer eliminate the tumour.

Several therapeutic strategies have been developed to restore the efficiency of the immune system; among these are programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) immune checkpoint inhibitors.

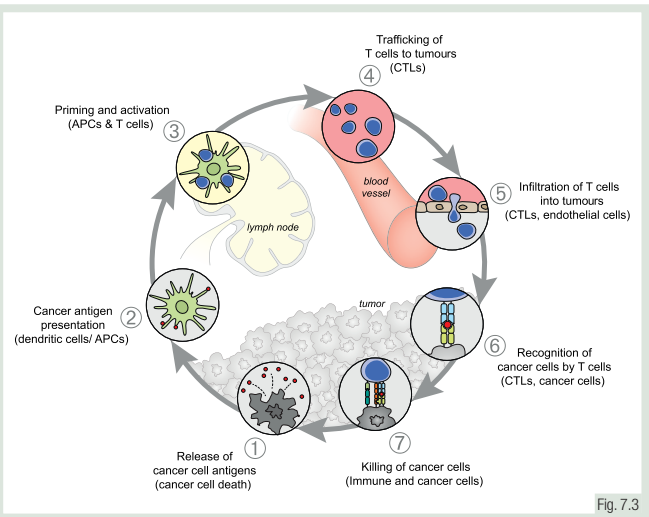


Fig. 7.3

APC, antigen presenting cell; CTL cytotoxic T-lymphocyte.

REVISION QUESTIONS

1. What is the genetic background of the most common type of RCC?
2. What is the mode of action of targeted agents and where do they exhibit their function?
3. Is cancer an immunological problem?

Risk group classifications and role of surgery

Treatment selection in metastatic RCC (mRCC) is based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group classification.

Patients can be classified into three risk groups: favourable (0 risk factors), intermediate (1-2 risk factors) or poor risk (3 or more risk factors).

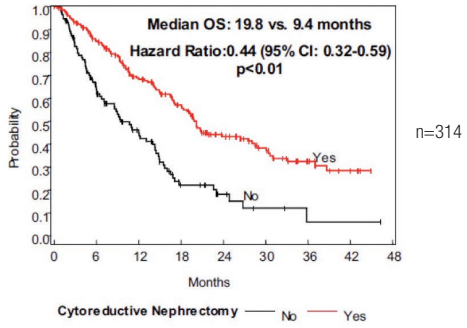
Risk factors include: time from diagnosis (of primary tumour) to treatment for metastatic disease, low haemoglobin, Karnofsky performance score (KPS) <80%, increased corrected calcium, neutrophilia and thrombocytosis.

Era of targeted agents: IMDC risk group classification: Association overall survival with six factors

	Original model n=564		Validation n=849	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
KPS <80%	2·51 (1·92–3·29)	<0·0001	2·08 (1·71–2·55)	<0·0001
<1 year from diagnosis to treatment	1·42 (1·09–1·84)	0·0098	1·27 (1·05–1·53)	0·0122
Haemoglobin concentration <lower limit of normal	1·72 (1·31–2·26)	0·0001	1·69 (1·38–2·06)	<0·0001
Calcium concentration >upper limit of normal	1·81 (1·29–2·53)	0·0006	1·45 (1·10–1·92)	0·0087
Neutrophil count >upper limit of normal	2·42 (1·72–3·39)	<0·0001	1·64 (1·31–2·05)	<0·0001
Platelet count >upper limit of normal	1·49 (1·09–2·03)	0·0121	1·60 (1·28–2·01)	<0·0001

CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance score. Fig. 7.4

The impact of cytoreductive nephrectomy on survival of patients with mRCC receiving targeted therapy: a retrospective analysis



Marginal benefit for
-Patients in the poor risk group (p = 0.06)
-Patients with Karnofsky performance score less than 80% (p = 0.08)

Fig. 7.5

CI, confidence interval; mRCC, metastatic renal cell carcinoma; OS, overall survival.

Based on the results of two randomised trials from the cytokine era, cytoreductive nephrectomy has been the standard-of-care (SoC) for decades.

This is no longer the case: the CARMENA trial is a randomised phase III study investigating whether surgery is still necessary in the era of targeted agents in mRCC patients with intermediate or poor risk.

The primary endpoint of the CARMENA trial was overall survival (OS); patients were randomised to cytoreductive nephrectomy followed by sunitinib or sunitinib alone.

OS in patients receiving sunitinib alone was not inferior to that in patients treated with surgery followed by sunitinib.

The OS of patients treated with sunitinib alone vs sunitinib + surgery was 18.4 vs 13.9 months, respectively (stratified hazard ratio [HR] for death: 0.89, 95% confidence interval [CI] 0.71-1.10).

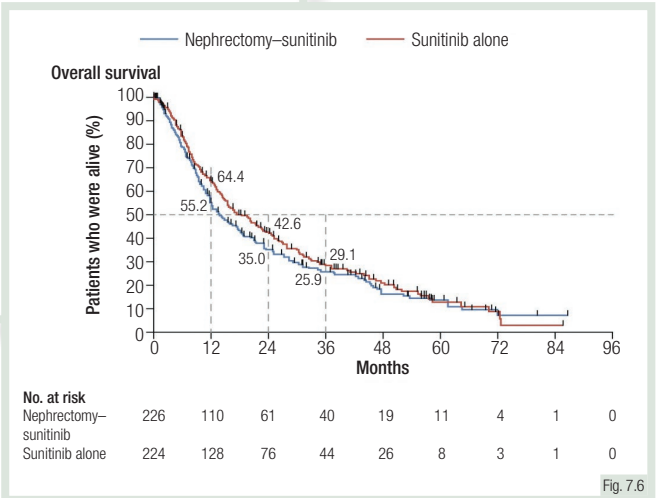


Fig. 7.6

REVISION QUESTIONS

1. Which factors are considered in the IMDC score when classifying patients into risk groups?
2. Is cytoreductive nephrectomy still SoC in the context of VEGF inhibitors?
3. Does this apply to all IMDC risk groups?

First-line treatment for clear cell (and non-clear cell) RCC with favourable prognosis

The European Society for Medical Oncology (ESMO) guidelines recommend the use of axitinib in combination with pembrolizumab for patients of all IMDC risk categories (IA) and the combination of nivolumab + ipilimumab for patients with intermediate or poor IMDC (IA).

These agents were approved based on their superiority over the former SoC interferon alpha (IFNα) alone (sunitinib and bevacizumab trial) or placebo (pazopanib trial).

In 2017, the European Medicines Agency (EMA) approved another anti-angiogenic agent: tivozanib, a highly potent inhibitor of VEGF receptor (VEGFR) 1,2,3 signalling.

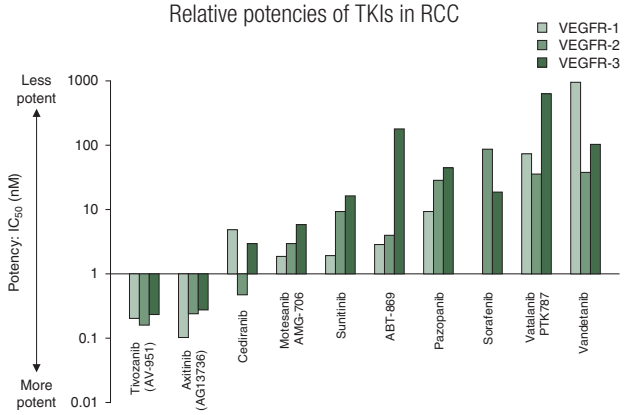


Fig. 7.7

RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

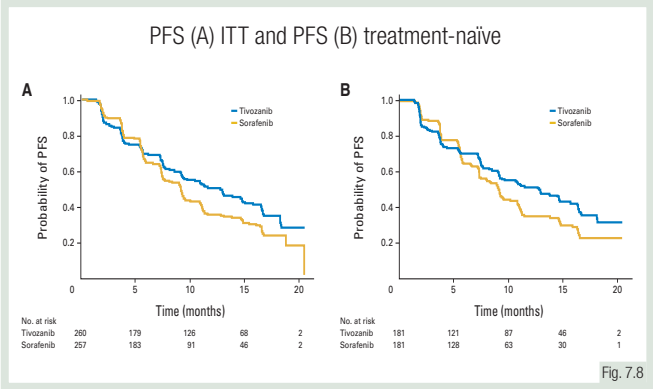


Fig. 7.8

ITT, intention to treat; PFS, progression-free survival.

The randomised phase III trial TIVO-1 compared tivozanib with sorafenib in VEGF inhibitor-naïve patients.

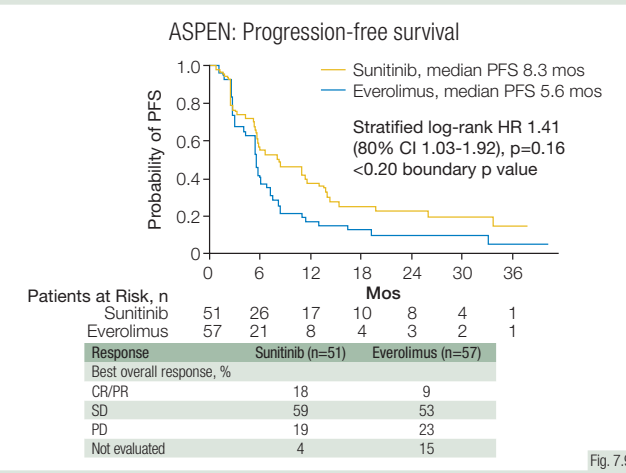
The primary endpoint, progression-free survival (PFS), was significantly longer in patients receiving tivozanib than in sorafenib patients (11.9 vs 9.1 months, HR 0.797; 95% CI 0.639-0.93, p = 0.042).

Tivozanib appears to have a favourable toxicity profile.

Sunitinib is still recommended as the SoC in patients with non-clear cell histology.

The ASPEN trial compared sunitinib with everolimus in patients with different non-clear cell histology: the median PFS was significantly longer in patients assigned to sunitinib (8.3 vs 5.6 months, stratified log-rank HR 1.41, p = 0.16, < 0.20 boundary p-value).

Ideally, patients with non-clear cell histology should be included in a clinical trial.



Response	Sunitinib (n=51)	Everolimus (n=57)
Best overall response, %		
CR/PR	18	9
SD	59	53
PD	19	23
Not evaluated	4	15

Fig. 7.9

CI, confidence interval; CR, complete response; HR, hazard ratio; mos, months; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

REVISION QUESTIONS

1. What are the treatment options for patients with favourable risk?
2. Is there any new VEGF inhibitor beyond sunitinib, pazopanib and bevacizumab?
3. What are the key advantages of tivozanib?

First-line treatment for clear cell RCC with intermediate or poor prognosis

CheckMate 214 was a randomised phase III trial comparing combined checkpoint inhibitor therapy (nivolumab/ipilimumab) with sunitinib in patients with intermediate and poor prognosis.

Combined immune checkpoint blockade was associated with a statistically significant benefit in OS and overall response rate (ORR).

Furthermore, PFS was numerically prolonged.

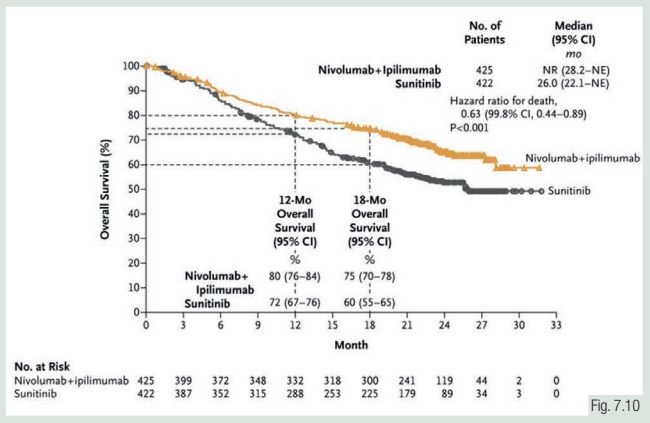


Fig. 7.10

CI, confidence interval; NE, not estimable; NR, not reached;

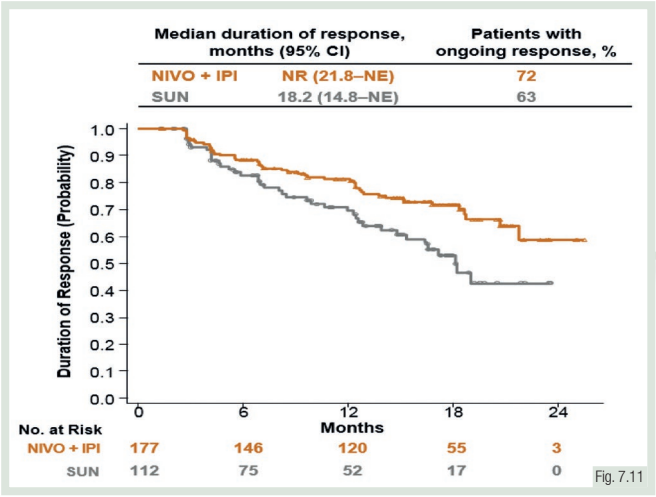


Fig. 7.11

CI, confidence interval; IPI, ipilimumab; NE, not estimable; NIVO, nivolumab; NR, not reached; SUN, sunitinib.

The quality of response was highlighted by the long duration of response and the high rate of complete responders.

The highest response rates were observed in PD-L1-positive patients.

In contrast, PFS and ORR were significantly improved with sunitinib in favourable-risk patients.

In 2019, the KEYNOTE-426 phase III trial testing axitinib plus pembrolizumab showed OS benefit vs sunitinib in untreated RCC patients across all risk groups, independent of PD-L1 expression. The JAVELIN Renal 101 study testing axitinib plus avelumab vs sunitinib reported improved PFS in PD-L1-positive patients.

The MET-AXL and VEGF inhibitor cabozantinib is another option in first-line treatment, as well as in patients with primary or secondary resistance to VEGF inhibitors.

In the randomised phase II CABOSUN trial, treatment with cabozantinib was shown to provide a statistically significant improvement in PFS and ORR when compared with sunitinib in intermediate- or poor-risk patients.

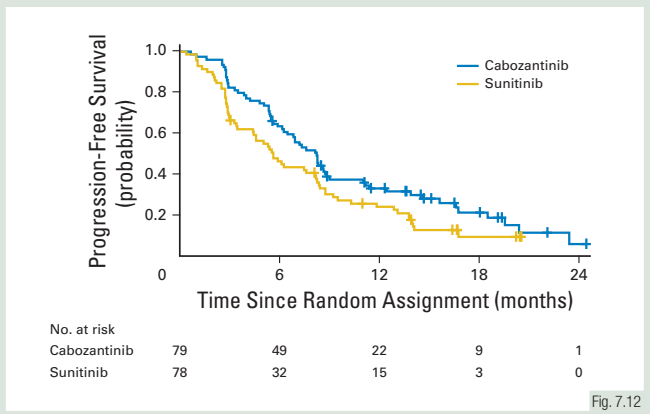


Fig. 7.12

REVISION QUESTIONS

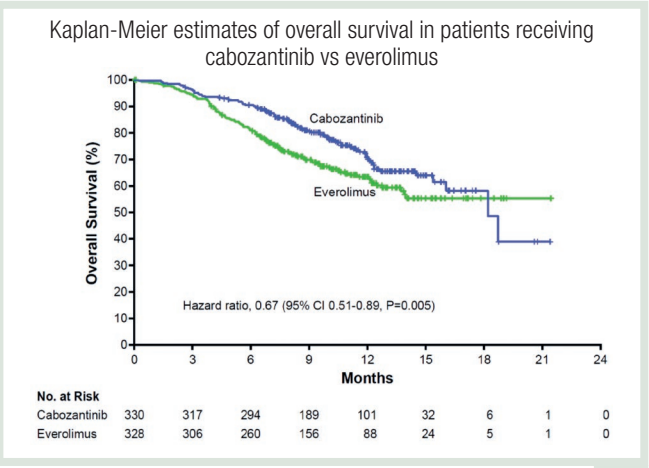
1. Are VEGF inhibitors SoC in patients with intermediate-poor risk?
2. What are the best treatment options for this patient population and which strategy has the highest evidence level?
3. Is cabozantinib just another tyrosine kinase inhibitor (TKI)? Does it have specific properties that may address VEGF inhibitor resistance?

Second-line treatment for clear cell RCC

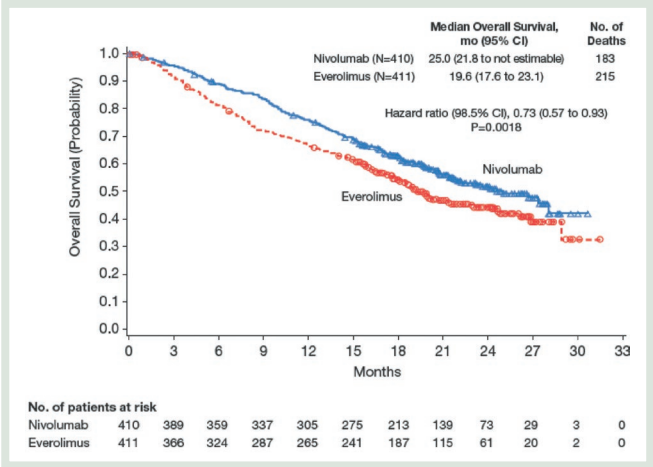
The METEOR trial compared cabozantinib with the former SoC everolimus in patients who had previously failed one or two VEGF inhibitors.

Patients assigned to cabozantinib experienced significantly improved OS, PFS and ORR rates when compared with everolimus patients.

Cabozantinib is currently considered an SoC in patients failing first-line VEGF inhibitors.



CI, confidence interval. Fig. 7.13



CI, confidence interval. Fig. 7.14

Another option after failure of VEGF inhibitor first-line treatment is the PD-1 immune checkpoint inhibitor, nivolumab.

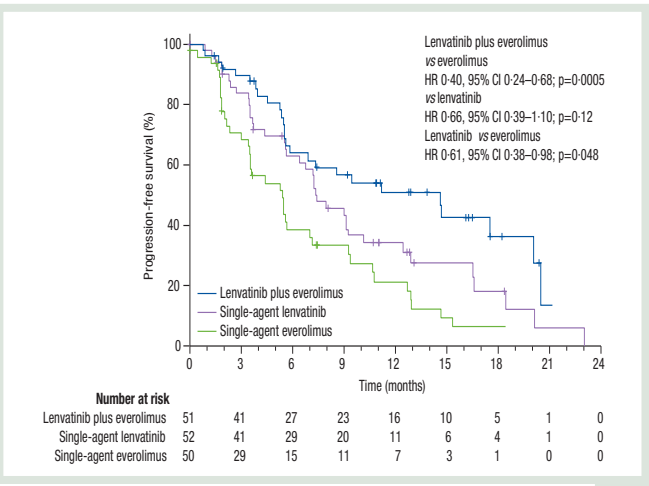
CheckMate 025 was a randomised phase III trial comparing nivolumab with everolimus in previously treated patients. OS was significantly longer and ORR significantly higher in nivolumab patients.

The superiority of nivolumab over everolimus was shown regardless of PD-L1 expression.

The fibroblast growth factor (FGF) is another target that has been linked to resistance to VEGF inhibitors.

In a randomised phase II trial, the combination of the FGF-VEGF inhibitor lenvatinib and the mTOR inhibitor everolimus was shown to be superior in terms of PFS and ORR when compared with everolimus or lenvatinib alone in patients who failed first-line VEGF inhibitors.

At the time of writing, there are no phase III trials comparing these new second-line strategies, and no trials that address intermediate-poor risk patients who have progressed on the new first-line strategies (nivolumab/ipilimumab and cabozantinib).



CI, confidence interval; HR, hazard ratio. Fig. 7.15

REVISION QUESTIONS

1. Which agent was shown to provide three positive endpoints in a randomised phase III trial in second line?
2. What are the current new SoC options in second line?
3. Do they all have the same level of evidence?

Summary: Treatment of metastatic renal cell cancer

- The role of cytoreductive nephrectomy in the context of VEGF inhibition has changed: it is no longer considered SoC in intermediate- and poor-risk patients
- The IMDC risk groups model facilitates the classification of patients into specific risk groups: favourable, intermediate and poor
- For patients with clear cell histology and favourable risk, first-line treatment recommendations include either sunitinib or bevacizumab + IFNα, pazopanib or tivozanib
- Patients with non-clear cell histology should be included in a clinical trial
- For patients with clear cell histology, intermediate- and poor-risk, the new SoC is the combination of nivolumab/ipilimumab; cabozantinib is another option
- In second-line after failure of VEGF inhibitors, three different strategies exist: nivolumab, cabozantinib or lenvatinib + everolimus
- Nivolumab and cabozantinib have a higher evidence level than lenvatinib + everolimus; no phase III trial has yet compared these second-line strategies
- No trials have yet been conducted to examine patients who have failed first-line nivolumab/ipilimumab or first-line cabozantinib

Further Reading

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8 Staging and treatment of stage I testicular cancer

Diagnosis, staging and prognosis

Clinical stage I is the most frequent presentation of testicular cancer, as 85% of seminomas and 60% of non-seminomas are clinical stage I.

A standard staging procedure requires a computed tomography (CT) scan of the thorax/abdomen/pelvis taken before orchiectomy and blood samples including the tumour markers: human chorionic gonadotropin (hCG), alpha-foetoprotein (AFP) and lactate dehydrogenase (LDH), taken before and after orchiectomy. Positron emission tomography (PET)-CT should not be used routinely in the staging of testicular cancer.

If stage is uncertain (e.g. small lymph nodes but with suspicion of pathology), the staging procedure may be repeated at 6-8 weeks.

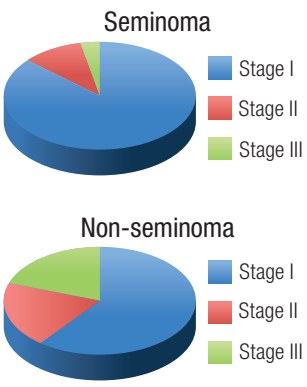


Fig. 8.1

	Seminoma	Non-seminoma
Local treatment	None	RPLND, for teratoma only, especially with somatic transformation
Systemic treatment	Carboplatin x 1, AUC7	BEP x 1
	Surveillance	Surveillance
Cure rate short term (5 years)	99%	99%
Overall survival (20 years+)	Not known	Not known
Morbidity (20 years+)	Not known	Not known

AUC, area under the curve; BEP, bleomycin/etoposide/cisplatin; RPLND, retroperitoneal lymph node dissection.

Fig. 8.2

The prognosis of stage I testicular cancer is excellent. Given correct management, the 5-year survival rate should be close to 100%.

However, treatment with radiotherapy (RT) or salvage chemotherapy (ChT) may induce late effects such as secondary cancers or cardiovascular disease, resulting in reduced survival 10-50 years after treatment.

Based upon presence or absence of lymphovascular invasion (LVI) in the primary tumour, patients with stage I non-seminoma can be classified into risk categories. Patients without LVI have a low risk of relapse (20%), while patients with LVI present a high risk of relapse (50%).

In stage I seminoma, risk factors are more controversial, as different studies return divergent results. Most studies find that invasion of tumour cells in the rete testis and/or tumour size ≥4 cm imply a higher relapse rate. With one or both of these risk factors the relapse rate is 20%-30%. Patients with no risk factors have a low risk of relapse of ~5%.

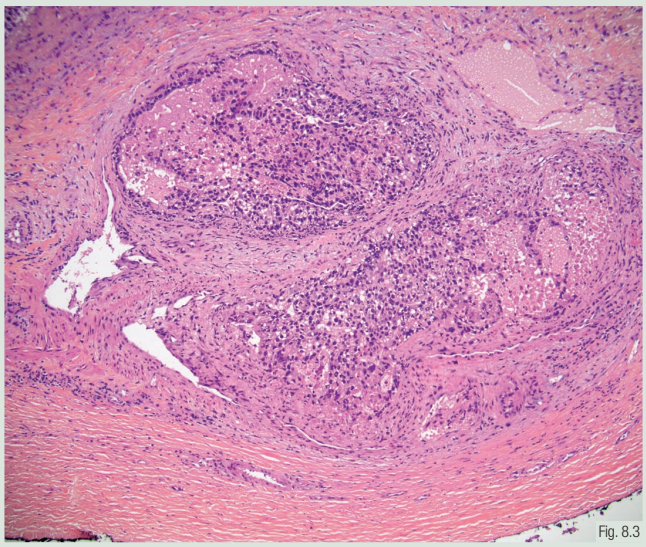


Fig. 8.3

REVISION QUESTIONS

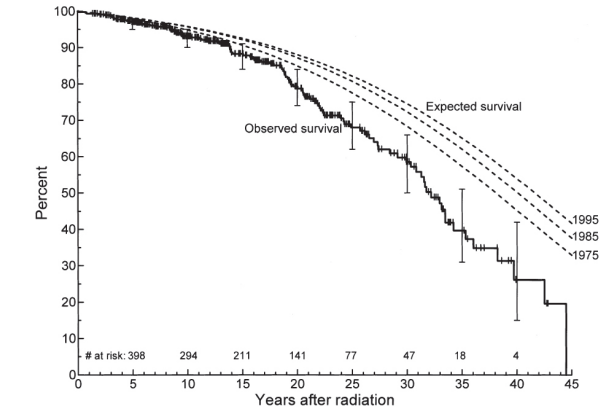
1. What differentiates high-risk disease from low-risk disease in stage I seminoma and non-seminoma?
2. In case of active treatment, what are the possible late effects?
3. Is PET-CT indicated for the initial staging of testicular cancer?

Management options

All treatment strategies in clinical stage I disease result in excellent short-term survival. However, treatment differs regarding short- and long-term toxicity.

What affects the survival and morbidity in the long term is the late toxicity of any treatment for metastatic disease or adjuvant treatment given.

Salvage treatment may induce: secondary cancers, cardiovascular disease, pulmonary toxicity, nephrotoxicity, neurotoxicity, decreased fertility, hypogonadism, fatigue and anxiety.



Note: the 15–20-years delay before survival is affected

Fig. 8.4

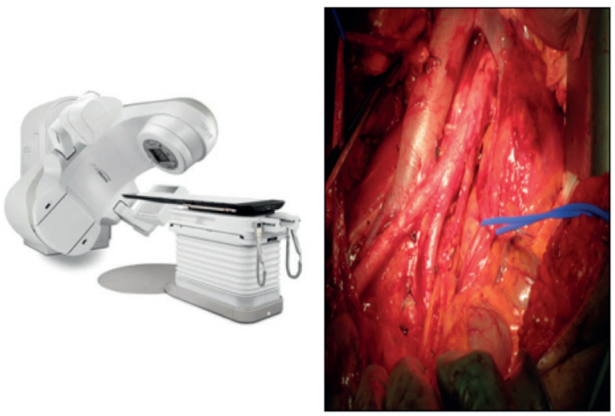


Fig. 8.5

Traditionally, adjuvant RT was used extensively in stage I seminoma treatment but it has been removed from most guidelines due to concerns of secondary cancer induction.

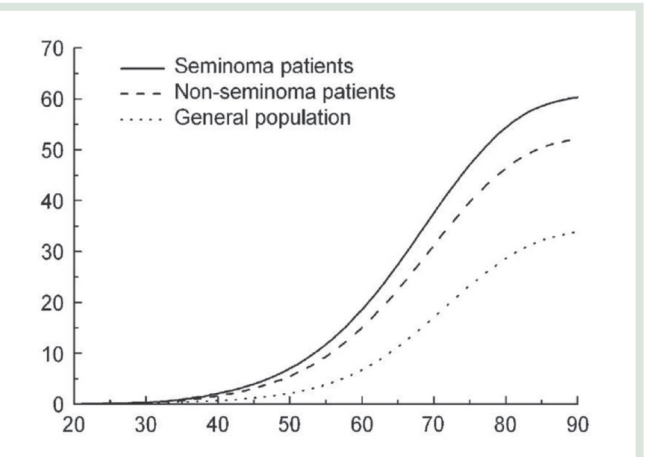
The optimal management of stage I testicular cancer has for many years been an area of controversy, with no unified consensus.

In stage I non-seminoma, retroperitoneal lymph node dissection (RPLND) was a mainstay of treatment. Nowadays, it is rarely used in Europe.

Management of stage I testicular cancer must be balanced between two concerns:

1. As few patients as possible should be exposed to salvage treatment
2. As few patients as possible should be exposed to unnecessary adjuvant treatment.

Any management option presents advantages and disadvantages, therefore the patients should be actively involved in decisions related to the management of their disease.



Risk of second solid non-germ cell cancer at age of 70 when treated for seminoma at age 20 is 40% as compared with 20% in the general population

Fig. 8.6

REVISION QUESTIONS

1. What is the prognosis of stage I testicular cancer?
2. What concerns need to be balanced when deciding management of stage I testicular cancer?
3. Why should the patient take part in decisions related to disease management?

Surveillance

Most patients are cured by orchiectomy alone. Large studies have shown that surveillance is a safe management option for patients with stage I testicular cancer.

However, different risk groups render the picture more complex:

- 50% of high-risk non-seminomas will relapse without adjuvant treatment
- 20%-30% of high-risk seminomas will relapse without adjuvant treatment.

Relapse rates during surveillance		
	Seminoma	Non-seminoma
Unselected	16%	25%
Low-risk	5%	15%
High-risk	20%-30%	50%

Note the large difference in the risk of relapse following surveillance

Fig. 8.7

	Risk factor	Management
Non-seminoma	Vascular invasion present	1 x BEP Active surveillance (optional) RPLND (rarely)
	Vascular invasion absent	Active surveillance 1 x BEP (optional) RPLND (very rarely)
Seminoma	Primary tumour ≥4 cm and/or rete testis invasion	Carboplatin x 1-2 Active surveillance (optional)
	Primary tumour <4 cm without rete testis invasion	Active surveillance Carboplatin x 1-2 (optional)

Fig. 8.8

BEP, bleomycin/etoposide/cisplatin; RPLND, retroperitoneal lymph node dissection.

Surveillance protocols require compliant patients, close monitoring with imaging, tumour markers and clinical examination for 5-10 years.

In most guidelines, active surveillance is the recommended management option in low-risk non-seminoma.

In high-risk non-seminomas and in all patients with seminoma, both surveillance and adjuvant ChT are possible management options.

Even if surveillance is recommended as the preferred management of all stage I testicular cancers in many guidelines, there are also disadvantages to surveillance, especially in patients with a high risk for relapse or compliance problems.

Figure 8.9 shows the mode of relapse detection in 1954 Danish seminoma patients on active surveillance. Almost all relapses were detected by imaging.

Presence of specific microRNA appears to be linked to the presence, i.e. relapse, of testicular cancer. Therefore, the sensitivity of, and dependence on, imaging may radically change in the future.

Patient care should be individualised and based on the risk of relapse, including late effects of salvage therapy.

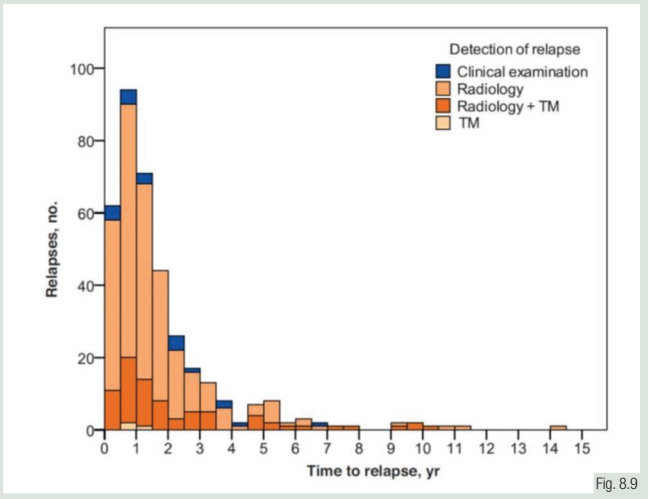


Fig. 8.9

TM, Tumour markers.

REVISION QUESTIONS

1. What is the main advantage of surveillance?
2. What are the disadvantages of surveillance?
3. Which patients do you consider most eligible for surveillance?

Adjuvant chemotherapy

The aim of adjuvant ChT is to reduce the risk of relapse, sparing the patient the burden of salvage ChT, which is known to induce serious late effects.

When adjuvant treatment is chosen, it should always be preceded by a discussion of the potential trade-offs of the different possible management strategies.

Adjuvant ChT does not abolish the need for monitoring following treatment, as there is a risk of relapse.

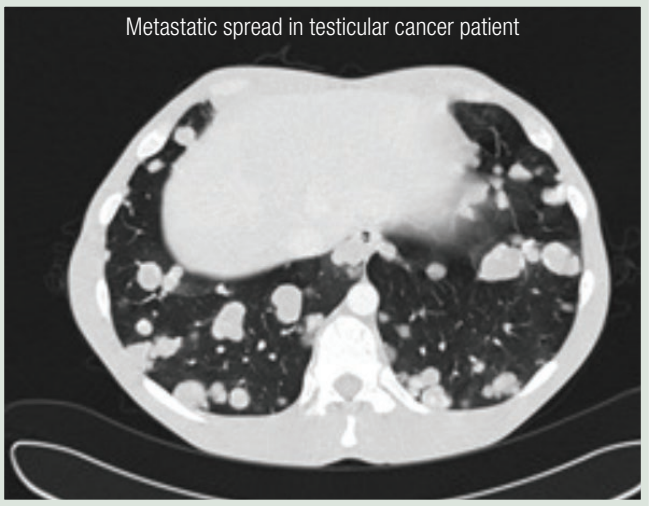


Fig. 8.10

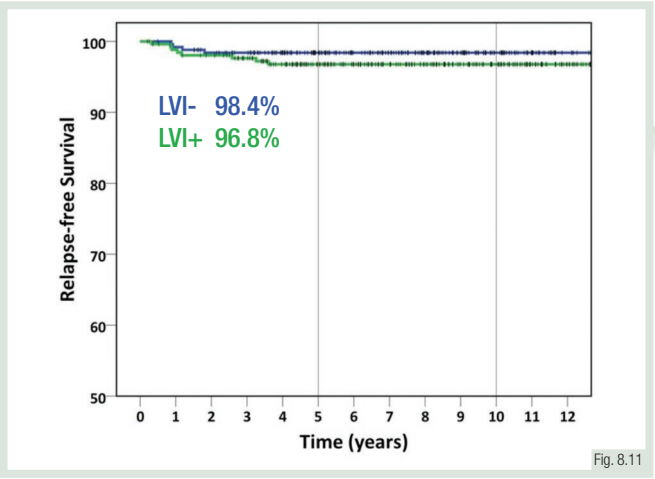


Fig. 8.11

LVI+, lymphovascular invasion-positive; LVI-, lymphovascular invasion-negative.

One course of adjuvant bleomycin/etoposide/cisplatin (BEP) is a standard treatment option in high-risk non-seminoma, reducing the risk of relapse by 90%-95%.

Most guidelines do not consider it as a treatment option in low-risk non-seminoma patients, but some groups offer these patients adjuvant BEP based upon the patient's preference.

So far, there are no reports on late effects of one course of adjuvant BEP but is it too soon to firmly conclude.

In stage I seminoma, the standard adjuvant ChT is one course of adjuvant carboplatin (AdjC). The dose is based on exact uncorrected values of glomerular filtration rates (GFR) assessed by chromium-51 labelled ethylenediamine tetraacetic acid (^{51}Cr-EDTA) or a comparable technique.

One course of AdjC reduces the risk of relapse by 60%-70%.

The risk of relapse in seminoma without risk factors is too low to justify AdjC, according to a 2018 consensus (Honecker et al, 2018). In patients presenting one or both risk factors, AdjC is a standard treatment option together with surveillance. No increase in late effects from 1 course of AdjC has been reported so far.

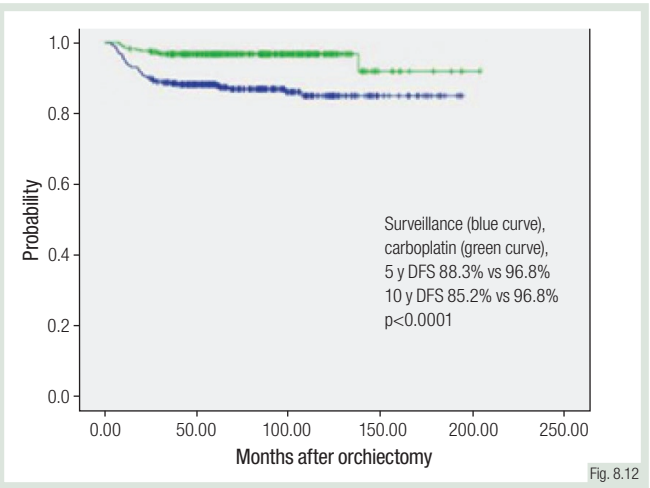


Fig. 8.12

DFS, disease-free survival.

REVISION QUESTIONS

1. What kind of adjuvant ChT is given in stage I non-seminoma and seminoma?
2. What is the number needed to treat with adjuvant ChT in the different risk groups to prevent one relapse?
3. Does adjuvant ChT increase the risk of late effects?

Comparison of relapse rates and treatment burden between adjuvant chemotherapy and active surveillance

Relapse rates during active surveillance of unselected patients are ~25%, resulting in 250/1000 patients requiring salvage treatment.

This number is 111 among 1000 patients treated by a risk-adapted approach of BEP x 1 for LVI-positive (LVI+) and active surveillance for LVI-negative (LVI-).

Estimated treatment burden for 1000 non-seminoma CSI patients

	All		LVI+		LVI–		Risk adapted	
	AS	BEP	AS	BEP	AS	BEP	AS	BEP
# Patients	1000	1000	1000	1000	1000	1000	666	334
Relapses	250	21	500	32	150	16	100	11
# BEP cycles	750	1063	1500	1096	450	1054	667	
# Salvage Tx	250 25%	21 2.1%	500 50%	32 3.2%	150 15%	16 1.6%	111 11%	

Fig. 8.13

Salvage Tx usually 3-4 BEP +/- RPLND.
AS, acute surveillance; BEP, bleomycin/etoposide/cisplatin; CSI, clinical stage I; LVI+, lymphovascular invasion-positive; LVI-, lymphovascular invasion-negative; RPLND, retroperitoneal lymph node dissection; Tx, treatment.

Follow-up schedules for seminomas and non-seminomas

There is little evidence on which follow-up schedule would provide the highest detection rate of still small and thereby highly curable recurrences while limiting the follow-up appointments to a minimum, to ensure compliance and avoid unnecessary examinations. These schedules were critically discussed at the 2018 ESMO (European Society for Medical Oncology) Consensus Conference on testicular germ cell cancer (Level of evidence: V; strength of recommendation: B; level of consensus >90%).

Recommended minimal follow-up for seminoma stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)					
Modality	**Year 1**	**Year 2**	**Year 3**	**Years 4+5**	**After 5 years**
Tumour markers +/- doctor visit	2 times	2 times	2 times	1 time	Further management according to survivorship care plan
Chest X-ray	0	0	0	0	
Abdominal CT/MRI	2 times	2 times	1 at 36m	1 at 60m	
Recommended minimal follow-up for non-seminoma stage I on active surveillance					
Modality	**Year 1**	**Year 2**	**Year 3**	**Years 4+5**	**After 5 years**
Tumour markers +/- doctor visit	4 times	4 times	2 times	1-2 times	Further management according to survivorship care plan
Chest X-ray	2	2	1 if LVI+	At 60m if LVI+	
Abdominal CT/MRI	2 times	At 24m	At 36m (optional)	At 60m (optional)	
Recommended minimal follow-up for non-seminoma after adjuvant treatment					
Modality	**Year 1**	**Year 2**	**Year 3**	**Years 4+5**	**After 5 years**
Tumour markers +/- doctor visit	4 times	4 times	2 times	2 times	Further management according to survivorship care plan
Chest X-ray	1-2	1	1	1	
Abdominal CT/MRI	1-2 times	At 24m	1 at 36m (optional)	1 at 60m (optional)	
Thorax CT	–	–	–	–	

Fig. 8.14

CT, computed tomography; LVI+, lymphovascular invasion-positive; m, months; MRI, magnetic resonance imaging.

According to a population-based analysis, very late relapse after 5 years occurs in 0.5% of patients. Thus, the aim of follow-up after 5 years shifts to the detection of the late side effects of treatment. Because patients with testicular germ cell cancer (TGCC) receiving >1 line of treatment for disseminated disease have a greatly increased risk of late toxicity and death (from causes other than TGCC), life-long follow-up has been suggested for these patients.

REVISION QUESTIONS

1. What is the relapse risk of non-seminoma patients with vascular invasion?
2. How important do you consider the patient's compliance with the follow-up schedule?
3. Should this question be addressed during the shared decision-making on the choice of active surveillance versus adjuvant ChT?

Summary: Staging and treatment of stage I testicular cancer

- When correctly managed, survival in stage I testicular cancer should be 99%-100%
- There is a risk of late onset, long-term morbidity and reduced survival in patients treated with RT or salvage ChT
- Management of clinical stage I testicular cancer should be based upon unbiased presentation of risks of relapse and management options, respecting the patient's preferences
- Surveillance is the preferred management option in low-risk non-seminoma
- In high-risk non-seminoma, both 1 course of adjuvant BEP and surveillance are possible management options
- In seminoma, both 1 course of AdjC or surveillance are possible management options

Further Reading

Aparicio J, Maroto P, García del Muro X, et al. Prognostic factors for relapse in stage I seminoma: a new nomogram derived from three consecutive, risk-adapted studies from the Spanish Germ Cell Cancer Group (SGCCG). Ann Oncol 2014; 25:2173–2178.

Beyer J, Albers P, Altena R, et al. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. Ann Oncol 2013; 24:878–888.

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9 Treatment of metastatic germ cell tumours

Metastatic seminoma

Seminoma is the most chemosensitive solid cancer. Cisplatin-based chemotherapy (ChT) cures most patients with metastatic disease.

Only 25% of patients with seminoma have extra-testicular dissemination, and among them only 5% have dissemination above the retroperitoneal lymph nodes.

Patients with moderately enlarged metastatic lymph nodes in the retroperitoneum (stage IIA) can be treated with either radiotherapy (RT) or ChT. Patients with clinical stage IIB disease should receive ChT.

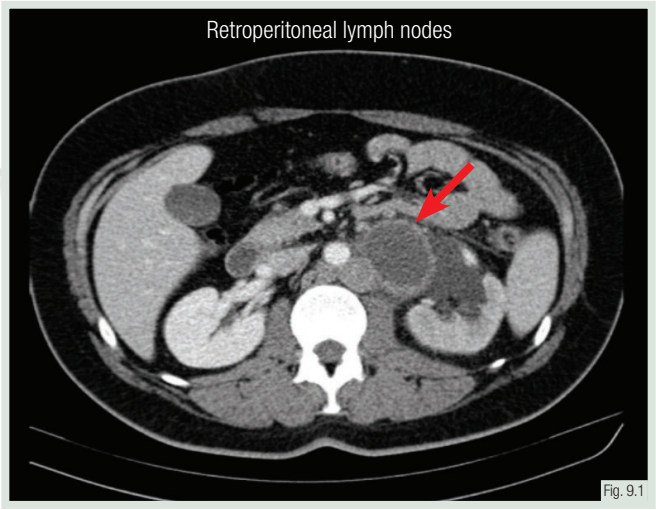


Fig. 9.1

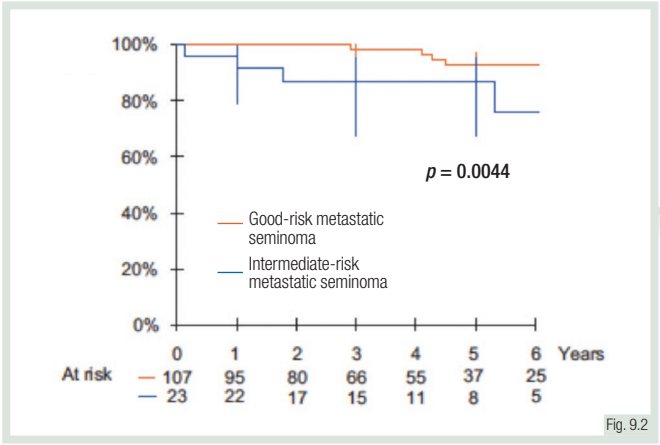


Fig. 9.2

Consensus guidelines recommend cisplatin/etoposide x 4 cycles (4 EP) or bleomycin/etoposide/cisplatin x 3 cycles (3 BEP) for most metastatic seminomas.

Current treatment leads to a cure rate of >90% in patients with metastatic seminoma.

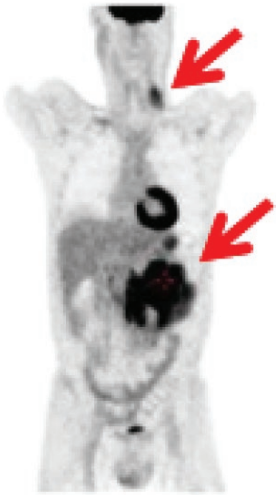
Patients with intermediate prognosis should be treated with 4 cycles of BEP, or 4 cycles of VIP (cisplatin/etoposide/ifosfamide) + granulocyte colony-stimulating factor (G-CSF) in bleomycin-unfit patients.

The management of patients with seminoma and post-ChT residual masses has changed over the last two decades, with reduced use of surgery.

Immediate surgical resection of residual masses after completion of ChT should not be proposed in metastatic seminoma. A fluorodeoxyglucose positron emission tomography (FDG-PET) scan is recommended at least 8 weeks after day 21 of the last ChT cycle, specifically if the tumour mass is >3 cm.

Surveillance is advised when a complete metabolic response (CMR) is achieved. Resection by an experienced surgeon should be considered in the absence of a CMR (especially if confirmed on a second FDG-PET).

Positive FDG-PET scan showing viable residual tumour after chemotherapy



FDG, fluorodeoxyglucose; PET, positron emission tomography.

Fig. 9.3

REVISION QUESTIONS

1. Is metastatic seminoma a curable disease?
2. What is the first-line treatment to administer in metastatic seminoma?
3. What is recommended if residual masses persist after first-line treatment?

Good-prognosis disseminated non-seminomatous germ cell tumours

Good-prognosis advanced non-seminomatous germ cell tumours (NSGCTs) are defined by the International Germ Cell Cancer Collaborative Group (IGCCCG) as: testis or retroperitoneal primary cancer, absence of non-pulmonary visceral metastasis, and alpha-foetoprotein (AFP) <1000 ng/mL, human chorionic gonadotropin (hCG) <5000 UI/L and lactate dehydrogenase (LDH) <1.5 × normal.

Prognosis (IGCCCG)	Proportion of patients	5-year OS/PFS	Non-seminoma	Seminoma
Good	56%	92% / 89%	Testis or retroperitoneal primary No non-pulmonary visceral metastases Low tumour markers: - AFP <1000 ng/mL - and hCG <1000 ng/mL (<5000 UI/L) - and LDH <1.5 x normal level	No non-pulmonary visceral metastases
Intermediate	28%	80% / 75%	Testis or retroperitoneal primary No non-pulmonary visceral metastases Intermediate tumour markers: - AFP 1000–10 000 ng/mL - and hCG 1000–10 000 ng/mL (5000–50 000 UI/L) - and LDH 1.5–10 x upper normal level	Presence of non-pulmonary visceral metastases
Poor	16%	48% / 41%	Primary mediastinal NSGCT and/or Presence of non-pulmonary visceral metastases (liver, brain, bone) and/or High tumour markers: - AFP >10 000 ng/mL - and/or hCG >10 000 ng/mL (> 50 000 UI/L) - and/or LDH >10 x normal level	

Fig. 9.4

AFP, alpha foetoprotein; hCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group; LDH, lactate dehydrogenase; NSGCT, non-seminomatous germ cell tumour; OS, overall survival; PFS, progression-free survival.

The BEP regimen combines cisplatin 20 mg/m²/day intravenous (i.v.) x 5 days, etoposide 100 mg/m²/day i.v. × 5 days, bleomycin 30 mg/day i.v. or intramuscular (i.m.) on day 1, 8 and 15, every 3 weeks.

The primary objective of first-line ChT is to induce tumour marker (hCG and AFP) normalisation, with or without shrinkage of metastases.

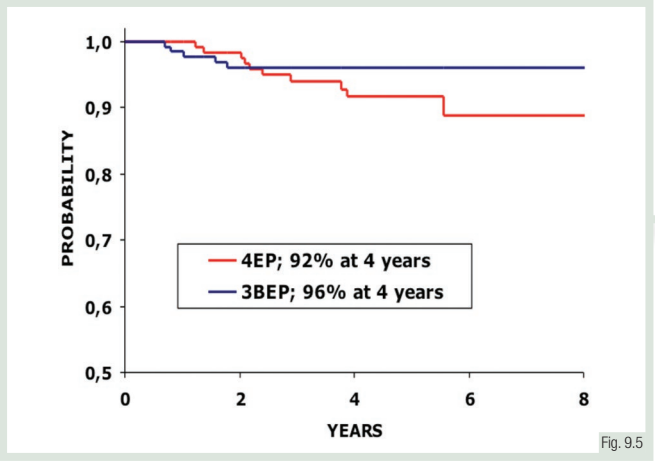


Fig. 9.5

BEP, cisplatin/etoposide/bleomycin; EP, cisplatin/etoposide.

The preferred regimen for good-risk metastatic NSGCTs is 3 cycles of the BEP regimen.

The only randomised trial (GETUG T93BP) to compare 3 BEP vs 4 EP in NSGCTs reported fewer deaths in the 3 BEP arm. In NSGCTs, 4 EP should be used only if there is a contraindication to bleomycin.

Modification of the BEP regimen (3 days instead of 5) and attempts to replace cisplatin by carboplatin have failed in randomised trials.

Patients with clinical stage IIA and normal serum tumour markers should have a repeated computed tomography (CT) scan ~8 weeks after surgery or a biopsy to confirm metastatic disease.

Post-ChT surgery should be performed by an experienced surgeon in case of residual masses >1 cm and tumour marker normalisation. Residual masses contain necrosis in 50%, teratoma in 40% and viable cancer in 10%. Multiple sites (e.g. retroperitoneal lymph nodes, lungs) can be resected.

Complete resection should be attempted, specifically if teratoma or viable cancer remains. Post-surgery ChT is discussed only in some cases with residual viable cancer.

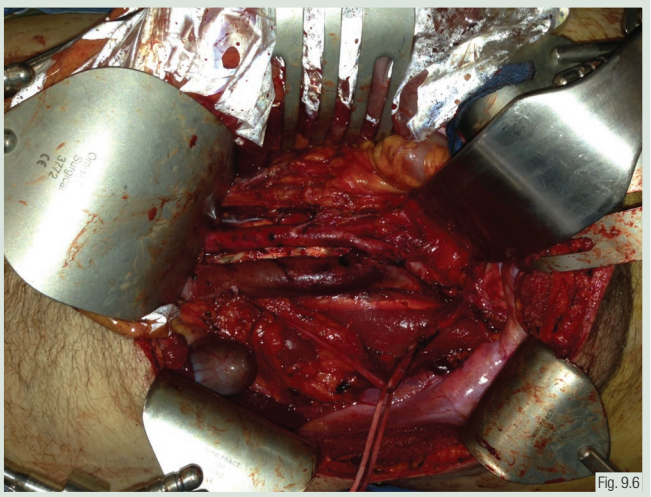


Fig. 9.6

REVISION QUESTIONS

1. How is good-prognosis metastatic NSGCT defined in the international classification?
2. What is the standard ChT regimen for good-prognosis NSGCTs?
3. Should post-ChT surgery be performed in the case of residual masses in NSGCTs?

Intermediate-prognosis disseminated non-seminoma – specific situations in germ cell tumours

Intermediate-prognosis NSGCT is defined by the IGCCCG as a testicular or retroperitoneal primary site, with absence of non-pulmonary visceral metastases, and AFP 1000-10 000 ng/mL or hCG 5000-50 000 UI/L or LDH 1.5–10 × normal.

Standard ChT consists of 4 cycles of BEP (or 4 cycles of VIP + G-CSF if bleomycin is contraindicated), followed by resection of residual masses.

No significant benefit was found when paclitaxel was added to 4 BEP.

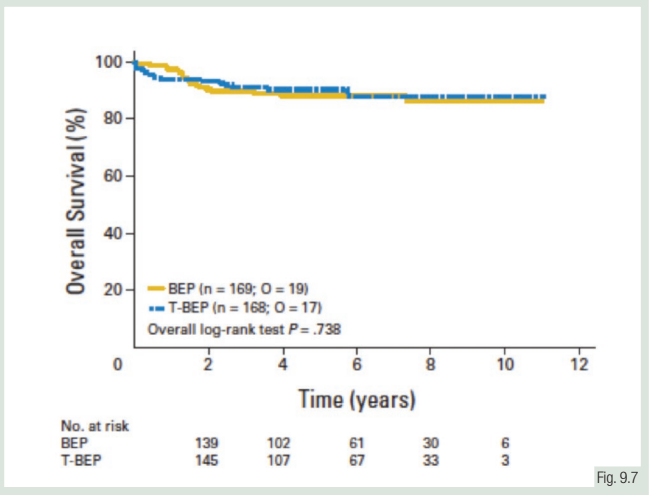


Fig. 9.7

BEP, bleomycin/etoposide/cisplatin; T-BEP, paclitaxel + BEP.

CT coronal reconstruction demonstrating bilateral masses from growing teratoma

Teratoma

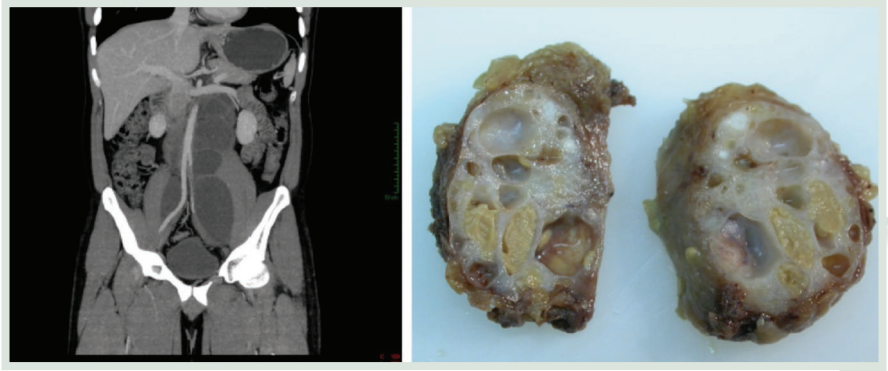


Fig. 9.8

CT, computed tomography.

Growing teratoma syndrome (GTS) is defined as an increase in tumour size, during or after ChT, that contains only teratoma.

The main risks related to GTS are:
- local complications
- the potential to metastasise
- malignant transformation

The treatment of choice for GTS is complete surgery.

Teratoma with malignant transformation (TMT) is a unique and rare phenomenon of GCTs with a non-GCT component (e.g. sarcoma, adenocarcinoma, primitive neuroectodermal tumour [PNET]). TMT carries a poor prognosis and its management is usually based on adapted ChT associated with surgical resection of the residual masses.

A higher incidence of acute thromboembolic events (TEEs) has been reported in patients with GCTs treated with cisplatin-based ChT.

Preventive anticoagulation therapy using low-molecular-weight heparin (LMWH) is under evaluation.

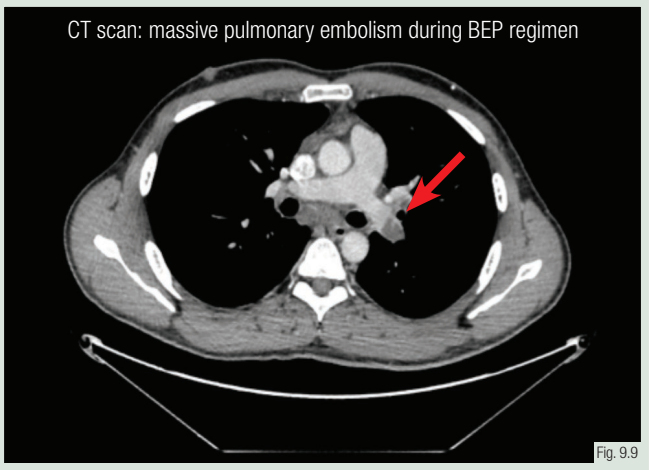


Fig. 9.9

BEP, bleomycin/etoposide/cisplatin; CT, computed tomography.

REVISION QUESTIONS

1. How is intermediate-prognosis metastatic NSGCT defined by the IGCCCG?
2. What is the standard treatment for intermediate-prognosis metastatic NSGCTs?
3. What is the standard treatment for GTS?

Poor-prognosis disseminated non-seminomatous germ cell tumours

Poor-prognosis advanced NSGCTs are defined by the presence of at least one of the following criteria:

- Non-pulmonary visceral metastases
- A primary mediastinal NSGCT
- Any of the following serum tumour marker levels:
  - hCG >50 000 UI/L
  - AFP >10 000 ng/mL
  - LDH >10 × normal

In 1987, 4 cycles of BEP were shown to be superior to 4 cycles of PVB (cisplatin/vinblastine/bleomycin). 4 cycles of VIP are not superior to 4 BEP (William SD, NEJM 1987).

According to the IGCCCG, patient outcome remains poor: 5-year progression-free survival (PFS) is 41% and 5-year overall survival (OS), 48%.

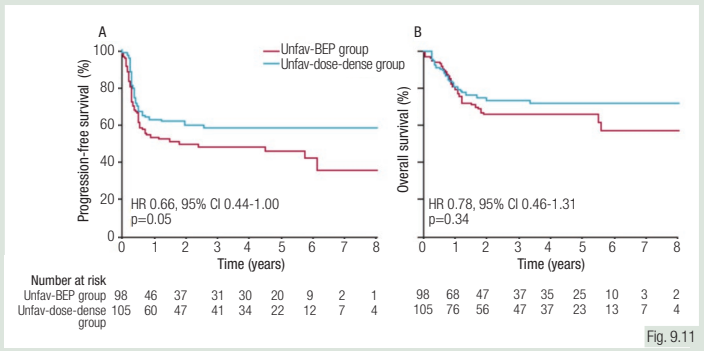


Fig. 9.11

BEP, bleomycin/etoposide/cisplatin; CI, confidence interval; HR, hazard ratio.

Patients with extensive lung metastases and very high hCG levels at presentation are at high risk of acute respiratory distress syndrome and death during induction ChT. Immediate referral to a well-trained team and dose reduction should be performed.

In a randomised trial, treatment in a centre with a small accrual was associated with a 20% reduction in cure rates (Collette L, J Natl Cancer Inst, 1999). Referral of all patients with metastatic GCTs to a well-trained team is strongly recommended.

Primary mediastinal NSGCT is a distinct entity with a poorer prognosis, a clear association with Klinefelter syndrome and ~10% risk of leukaemia containing a *12p* isochromosome. Considering its lower chemosensitivity, post-treatment surgery is strongly recommended irrespective of marker status.

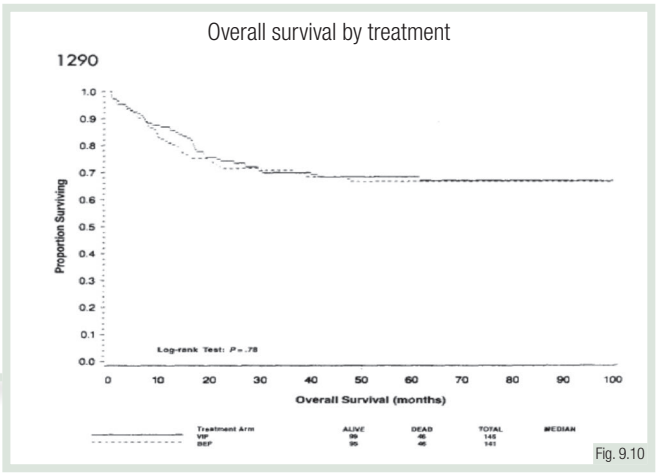


Fig. 9.10

BEP, bleomycin/etoposide/cisplatin; VIP, cisplatin/etoposide/ifosfamide.

In patients with poor-risk NSGCTs, tumour marker decline assessed at baseline and after only 1 cycle of ChT correlates strongly with outcome. A calculator tool or mobile app can be downloaded at: https://www.gustaveroussy.fr/calculation-tumor/NSGCT.html

GETUG-13 established that patients with a favourable tumour marker decline after 1 cycle of BEP are likely to achieve cure in >80% of cases if BEP is continued.

It also demonstrated that ChT intensification after 1 cycle significantly reduces the risk of progression and death in patients with unfavourable tumour marker decline. This strategy translates into a 34% reduction in the risk of death or progression (and overall, a survival rate >75% in poor-risk NSGCTs).

CT scan showing extensive bilateral lung metastases from choriocarcinoma

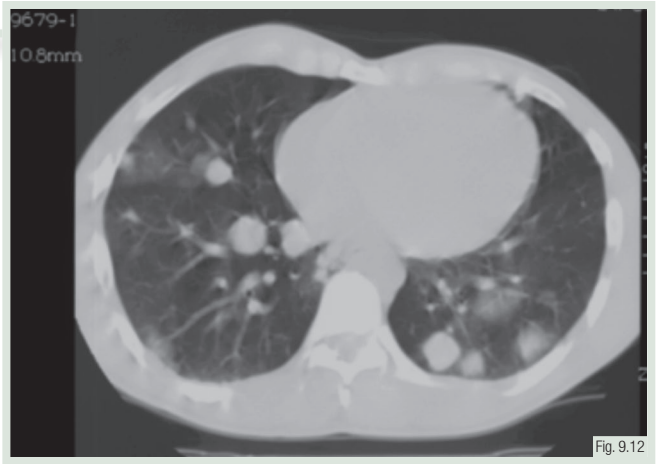


Fig. 9.12

CT, computed tomography.

REVISION QUESTIONS

1. How is poor-prognosis advanced NSGCT defined by the IGCCCG?
2. What is the role of an early tumour marker decline in the management of poor-risk NSGCTs?
3. What is the current standard treatment for poor-prognosis NSGCTs?

Salvage chemotherapy

Approximately 75% of patients with metastatic GCTs achieve a continuous complete response (CR). For patients who relapse or progress, a multicentre international retrospective analysis defined a prognostic score (the International Prognostic Factors Study Group [IPFSG]). It is strongly recommended to refer these patients to high-volume centres.

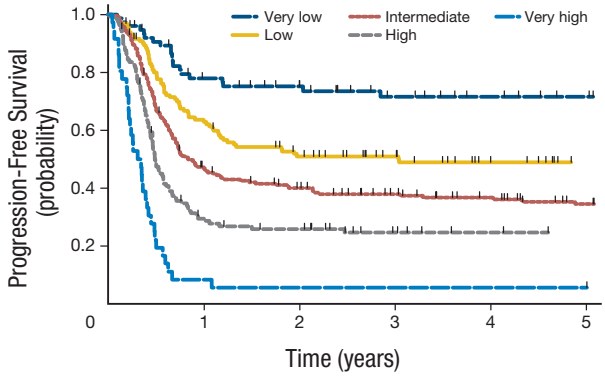


Fig. 9.13

Only one phase III trial (IT94) directly compared salvage standard-dose ChT vs high-dose ChT (HDCT), and no improvement in PFS or OS was demonstrated.

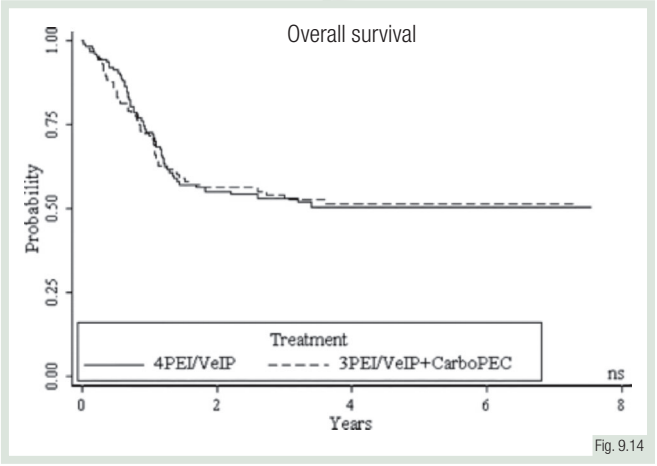


Fig. 9.14

CarboPEC, high-dose carboplatin/etoposide/cyclophosphamide; PEI, cisplatin/ifosfamide/etoposide; VeIP, vinblastine/ifosfamide/cisplatin.

The preferred conventional-dose ChT (CDCT) regimens are: cisplatin/ifosfamide/paclitaxel (TIP), cisplatin/ifosfamide/gemcitabine (GIP), vinblastine/ifosfamide/cisplatin (VeIP) and VIP. Salvage ChT should be used with G-CSF support.

The most widely used HDCT is the TI-CE regimen, composed of 2 cycles of conventional doses of paclitaxel/ifosfamide, followed by 3 cycles of high-dose carboplatin/etoposide.

Salvage ChT should be followed by surgical resection of residual masses, if tumour markers are normalised.

When possible, patients should be included in the prospective, randomised phase III TIGER trial, comparing CDCT (TIP) and HDCT (TI-CE).

HDCT can still cure patients who have failed several lines of ChT and should be considered on an individual basis.

If HDCT is being used, a sequential regimen is preferred (rather than a single-cycle HDCT regimen), because the risk of a toxicity-related death is reduced.

'Desperate' surgery can (rarely) be associated with the cure of patients with chemorefractory GCTs and may be discussed on an individual basis.

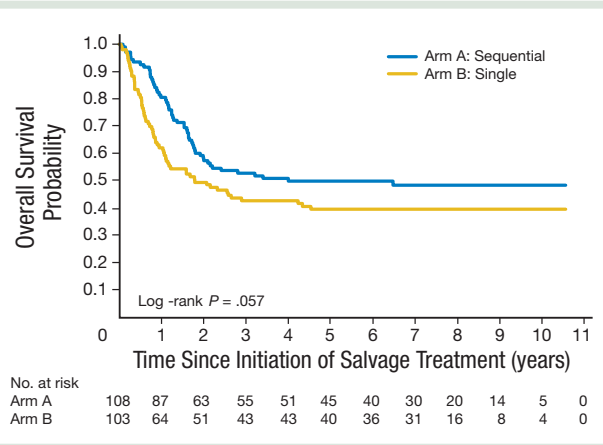


Fig. 9.15

REVISION QUESTIONS

1. How is the level of risk defined in GCTs in the salvage setting?
2. What are the two main options for salvage ChT in GCTs?
3. Is the number of cases treated in a hospital or by a physician important for a patient's chance of cure?

Summary: Treatment of metastatic germ cell tumours

- GCTs are the most chemosensitive solid cancer. Cisplatin-based ChT cures most patients with metastatic dissemination
- Prognostic factors have been established and the IGCCCG classification should be used before decision-making
- Standard ChT for good-prognosis metastatic NSGCT is 3 cycles of BEP. In good-prognosis metastatic seminoma, either 4 EP or 3 BEP can be administered
- Standard ChT for intermediate GCTs is 4 cycles of BEP (or 4 cycles of VIP + G-CSF)
- Patients with poor-prognosis NSGCTs should receive 1 cycle of BEP with an assessment of the serum tumour marker decline 3 weeks later:
  - Patients with a favourable decline should be treated with a total of 4 BEP (or VIP)
  - Patients with an unfavourable decline should receive treatment intensification (e.g. a dose-dense regimen + G-CSF)
- After completion of ChT for GCT, residual masses should be resected (if the primary was a NSGCT) or assessed with FDG-PET (if the primary was a pure seminoma)
- Patients failing first-line ChT are still potentially curable and should be considered for either salvage CDCT with G-CSF support, or HDCT plus a stem cell transplant
- Centralisation of patients with metastatic GCTs in expert centres is strongly recommended and is already mandatory in some countries
- Adequate therapy for GCTs includes multidisciplinary teams involving experts on fertility preservation, emotional and socioeconomic support, palliative care and survivorship issues to meet the needs of all patients

Further Reading

Beyer J, Albers P, Altena R, et al. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. Ann Oncol 2013; 24:878–888.

Collette L, Sylvester RJ, Stenning SP, et al. Impact of the treating institution on survival of patients with “poor-prognosis” metastatic nonseminoma. European Organization for Research and Treatment of Cancer Genito-Urinary Tract Cancer Collaborative Group and the Medical Research Council Testicular Cancer Working Party. J Natl Cancer Inst 1999; 91:839–846.

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Williams SD, Birch R, Einhorn LH, et al. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 1987; 316:1435-1440.

B

More advanced knowledge

10 Hereditary kidney cancer syndromes

Criteria and genetic testing

5%-8% of early-stage and 16% of advanced renal cell carcinomas (RCCs) are hereditary. Hereditary RCC syndromes are suggested by family history, age of onset and presence of other lesions.

Germline mutations in tumour suppressor genes (*von Hippel-Lindau [VHL], BAP1, FH, FLCN, PTEN, TSC1, TSC2,* etc.) or proto-oncogenes (*MET*) can predispose to RCC.

Hereditary RCC syndromes have effective cancer screening recommendations to find early-stage tumours, starting as early as 2 years old. Diagnosis and screening are essential for disease management.

Referral criteria for genetic counselling

- RCC ≤46 yrs old
- Bilateral/multifocal lesions
- Family history of RCC
- Family/personal history of other tumours* or pneumothorax/lung cysts
- Family/personal history of dermatology disease (angiofibroma, fibrofolliculoma, leiomyomata, melanoma)

Fig. 10.1

*Retinal/central nervous system haemangioma, pancreatic cysts/tumours, neuroendocrine tumours, melanoma, mesothelioma, phaeochromocytoma/paraganglioma, endolymphatic sac tumours, uterine fibroids (young)

RCC, renal cell carcinoma.

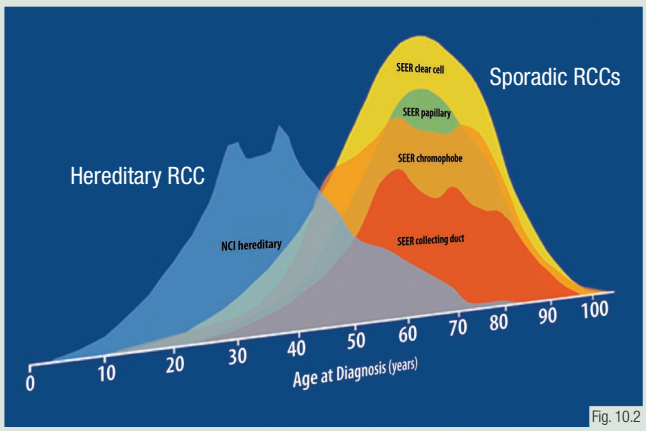

Fig. 10.2

NCI, National Cancer Institute; RCC, renal cell carcinoma; SEER, Surveillance, Epidemiology and End Results.

Median age of RCC diagnosis for hereditary RCC is 37 years; 70% of hereditary RCC tumours would be found in the lowest decile (≤46 years old) of all RCC tumours, if all young patients were screened.

A global survey of kidney cancer organisations found that inherited RCC is one of the top 10 concerns of RCC patients around the world.

The most common hereditary RCC is VHL disease. VHL patients are heterozygous for the *VHL* gene in every cell, but homozygous in the tumour through somatic loss-of-function mutation of the second allele.

Some centres screen a gene panel for comprehensive and cost-effective targeted deep sequencing (next-generation sequencing).

Patients should be referred to a clinical geneticist for germline DNA testing and family counselling. First-degree relatives may also be at risk.

If hereditary RCC is diagnosed, care should be transferred to an academic hospital, preferably an expert centre for hereditary cancer syndromes.

Suggested gene panel for DNA sequencing

BAP1	*MET*	*SDHB*	*TP53*
FH	*MITF*	*SDHC*	*TSC1*
FLCN	*PTEN*	*SDHD*	*TSC2*
HNF1B	*SDHA*	*SMARCB1*	*VHL*

VHL, von Hippel-Lindau.

Fig. 10.3

REVISION QUESTIONS

1. Is the contribution of germline predisposing mutations in RCC significant?
2. At what age should one consider an RCC to possibly be hereditary?
3. What other symptoms in the patient and/or their first-degree relatives are relevant to determine the need for genetic testing for a hereditary RCC syndrome?

Clinical presentation, biology

VHL syndrome affects 1/36 000 people; 20% of patients are *de novo*. Early manifestations include retinal/central nervous system (CNS) haemangiomas and phaeochromocytomas.

The majority of hereditary RCC cases have characteristic extra-renal lesions, which are syndrome-specific, of which many manifest before RCC.

More than 20% of patients with metastatic non-clear cell RCC show a germline mutation, of which half have the potential to direct systemic therapy.

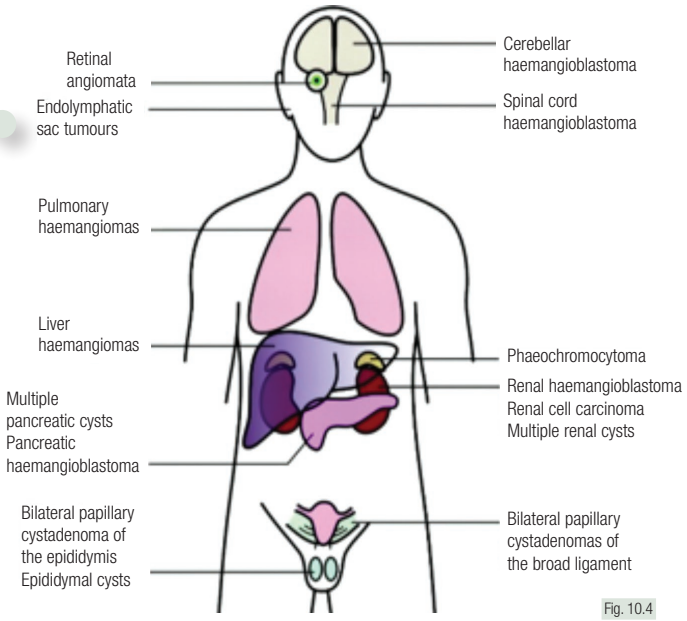

Fig. 10.4

Standard screening examinations include computed tomography (CT) scan and magnetic resonance imaging (MRI). Positron emission tomography (PET) scans can also be used to detect subclinical lesions.

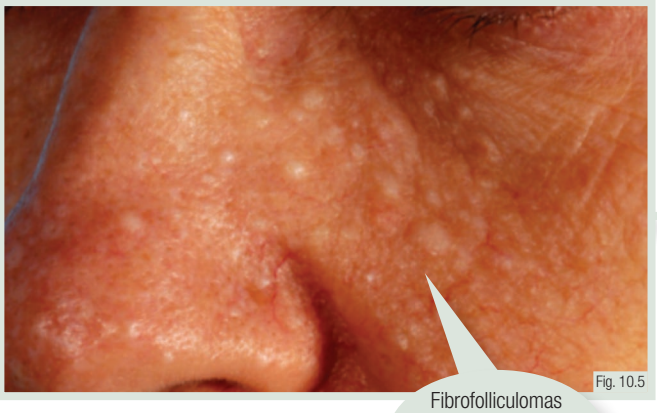
Fig. 10.5

Fibrofolliculomas and/or pneumothorax indicate Birt-Hogg-Dubé syndrome

Characteristic skin lesions, such as fibrofolliculomas in patients with Birt-Hogg-Dubé (BHD) syndrome (shown here), can facilitate differential diagnosis.

Unlike most cancers, pathways and genes affected in patients with hereditary RCC syndromes are the same as those in patients with sporadic RCCs.

Many genes mutated in hereditary RCC syndromes (red boxes) encode proteins linked to oxygen and nutrient sensing in the renal epithelium.

Studying hereditary RCC syndromes justified the development of mTOR (mammalian target of rapamycin) inhibitors and hypoxia-inducible factor (HIF)-target antagonists (e.g. vascular endothelial growth factor [VEGF] receptor tyrosine kinase inhibitors).

Further molecular understanding of rare hereditary RCC syndromes may contribute to new therapeutic strategies for sporadic RCC. There are few animal models available.

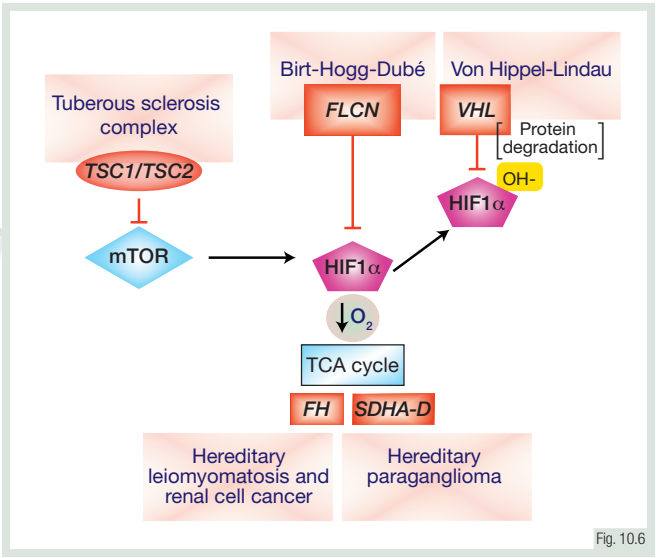

Fig. 10.6

mTOR, mammalian target of rapamycin; SDHA-D, succinate dehydrogenase A-D; TCA, tricarboxylic cycle; TSC, tuberous sclerosis complex.

REVISION QUESTIONS

1. Are hereditary RCCs distinct from sporadic RCCs?
2. What are the advantages of a 'watch and wait' strategy in patients with hereditary RCC?
3. How is it possible to prevent metastasis in a hereditary RCC patient?

Surgical management and surveillance

Patients with hereditary kidney cancer syndromes require repeated interventions. Appropriately timed nephron-sparing approaches are recommended.

Except for hereditary leiomyomatosis and RCC (HLRCC) and succinate dehydrogenase (SDH) syndromes, surveillance until the largest solid tumour reaches 3 cm diameter is recommended to reduce interventions.

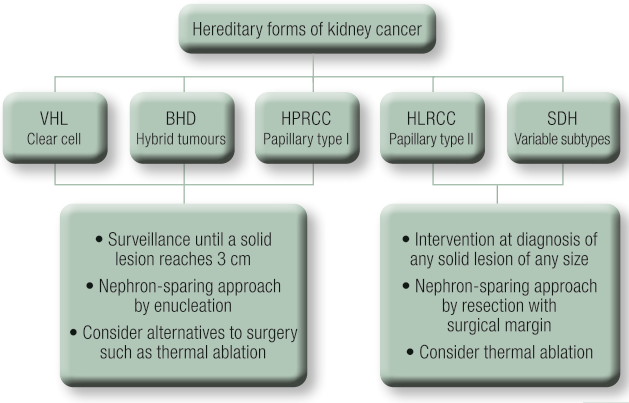

Fig. 10.7

BHD, Birt-Hogg-Dubé; HLRCC, hereditary leiomyomatosis and renal cell cancer; HPRCC, hereditary papillary renal cell cancer; SDH, succinate dehydrogenase; VHL, von Hippel-Lindau.

Hereditary disease	Germline mutation	RCC subtype
von Hippel-Lindau	*VHL*	ccRCC
Birt-Hogg-Dubé	*FLCN*	Chromophobe, oncocytoma, pRCC, ccRCC, hybrid tumours
Tuberous sclerosis	*TSC1* *TSC2*	ccRCC, anaplastic RCC, angiomyolipoma
Hereditary papillary RCC (HPRCC)	*MET*	pRCC type I
Hereditary leiomyomatosis and renal cell cancer (HLRCC)	*FH*	pRCC type II, collecting duct carcinoma
Succinate dehydrogenase RCC	*SDHA, SDHB, SDHC, SDHD*	Distinct; cuboidal cells with bubbly eosinophilic cytoplasm
Cowden syndrome	*PTEN, SDHB, SDHD, PIK3CA, AKT1*	pRCC type I, ccRCC, chromophobe
Rhabdoid tumour predisposition syndrome	*SMARCB1, SMARCA4*	Malignant rhabdoid tumours
Tumour predisposition syndrome	*BAP1*	ccRCC
Microphthalmia-associated RCC	*MITF*	ccRCC, pRCC

Fig. 10.8

ccRCC, clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma; RCC, renal cell carcinoma; VHL, von Hippel-Lindau.

For nephron-sparing surgery in VHL, BHD and hereditary papillary RCC (HPRCC), the goal of removing all solid tumours in that renal unit must be balanced against the loss of renal function. This does not apply to HLRCC and SDH, which require complete and immediate resection.

To date, there are 10 known hereditary RCC syndromes; they are associated with specific germline mutations, RCC histology and comorbidities.

Although not hereditary, somatic fusion translocations of *TFE3* and *TFEB* may affect 15% of patients with RCC ≤45 years old and 20%-45% of children and young adults with RCC. Diagnosis can be made with dual fluorescence chromosome imaging.

Active surveillance for VHL, BHD and HPRCC should be customised to the individual and follow the growth kinetics, size and location of the tumours rather than a standard fixed interval.

Regular screening for both renal and extra-renal lesions should follow international guidelines for that syndrome. Multidisciplinary and coordinated care should be offered where appropriate.

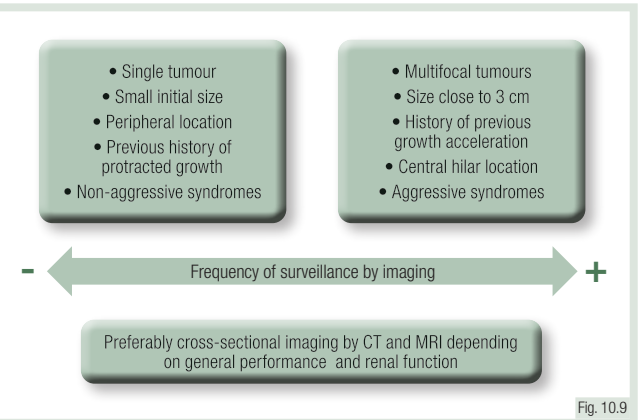

Fig. 10.9

CT, computed tomography; MRI, magnetic resonance imaging.

REVISION QUESTIONS

1. Is active surveillance recommended in hereditary kidney cancer syndromes?
2. Should tumours in patients with HLRCC syndrome be removed only at 3 cm diameter or larger?
3. Is nephrectomy the treatment of choice in multifocal hereditary kidney cancer?

Summary: Hereditary kidney cancer syndromes

- 5%-8% of early-stage RCCs are hereditary; but 16% of all advanced RCCs have a relevant germline mutation
- 20% are *de novo*, the first in their family
- In RCC patients <46 years or with bilateral/multifocal lesions, inherited RCC syndrome should be considered
- Extra-renal disease: dermatological lesions, phaeochromocytomas, CNS/retinal lesions, pancreatic cysts/tumours, pneumothorax or lung cysts, uterine fibroids, paraganglioma
- Germline genetic testing is performed on non-tumour material (e.g. blood) by a clinical geneticist
- RCC histology is linked to specific syndromes
- Diagnosis is important for timely entry into tumour-detection screening programmes
- The genes affected in hereditary RCC syndromes are relevant in sporadic RCC
- It is important to apply appropriately timed nephron-sparing surgery
- Surgery is recommended at 3 cm, except for HLRCC and SDH syndromes

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11 Epidemiology, risk factors, screening and predisposition genes for prostate cancer

Prevalence and risk factors in prostate cancer

Age-standardised rates (ASRs) for prostate cancer (PC) incidence and mortality vary widely across different regions of the world.

Mortality and incidence rates tell us, per region, what risk a man diagnosed with PC has of dying.

The USA has the highest incidence and the lowest mortality; Russia shows an inverse relationship. One possible explanation could be that screening in the USA is more widespread.

	Incidence		Mortality		Ratio mortality/incidence
	N	ASR	N	ASR	%
World	1,276,106	29.3	350,989	7.6	27.5
Europe	449,761	62.1	107,315	11.3	23.8
North America	234,278	73.7	32,686	18.1	13.9
Russian Fed.	40,060	39.4	14,324	13.6	35.7
Asia	297,215	11.5	118,427	4.5	39.8

Source: GLOBOCAN 2018, International Agency for Research on Cancer (IARC).
ASR, age-standardised rate.

Fig. 11.1

	Age			
	20-29	30-39	40-49	≥50
Caucasian males (Sakr)				
N men	7	23	22	–
N (%) cancers	0 (0)	7 (30)	7 (32)	–
Black males (Sakr)				
N men	28	32	28	–
N (%) cancers	0 (0)	8 (25)	10 (36)	–
Caucasian males (ref 14 in Sakr)				
			<50	≥50
N men			30	180
N (%) cancers			0 (0)	69 (38)

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Fig. 11.2

PC is found at autopsy at a higher prevalence than when diagnosed clinically, and much earlier in life.

PC prevalence in autopsy specimens from men without clinical evidence of the disease is strongly age-dependent.

Across the world the prevalence of non-diagnosed PC seems similar, although the disease is more frequent clinically in Afro-Caribbean > Caucasian > Asian men.

Besides age and race, family history is a well-established risk factor for PC. First-degree relatives of PC patients have twice the risk of developing the disease compared with the general population, rising to fourfold if the PC is diagnosed before the age of 60 and increasing the more relatives are affected.

PC is one of the most inheritable cancers, with 57% of the risk attributed to genetic factors.

Environmental and lifestyle factors are also determinants of PC risk but have not yet been well characterised.

Risk factors for prostate cancer	
Unmodifiable	Modifiable
Race	Body mass index
Age	Diet
Family history	Smoking
Germline mutations	

Fig. 11.3

REVISION QUESTIONS

1. Which areas of the world have the highest mortality rates for clinically diagnosed PC?
2. Autopsy prevalence of PC is higher than clinical incidence. What is the difference in percentage in different populations?
3. Which factors are most important in the pathogenesis of PC: inheritance or environmental factors?
4. In Fig. 11.3, do you see any risk factors that could be used in practice to decrease the incidence of aggressive PC?

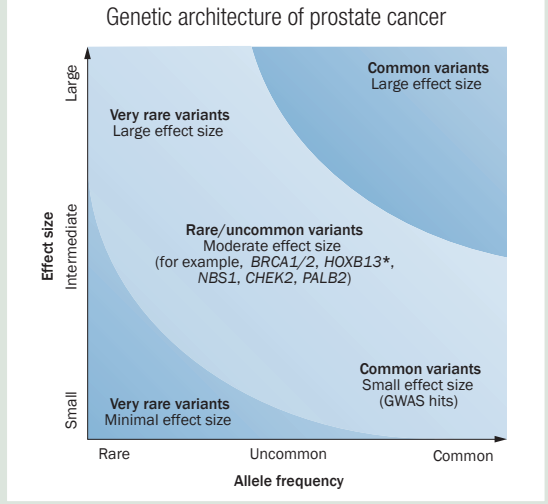
Prostate cancer predisposition genes

Genome-wide association studies (GWAS) have identified >100 common variants (single-nucleotide polymorphism [SNP]) associated with PC risk, which could explain ~30% of the genetic variance of PC.

Pathogenic variants in genes of high/moderate penetrance, such as *BRCA2, BRCA1,* confer increased lifetime risk of PC.

BRCA2 mutation carriers have a 36% lifetime risk of developing PC. These mutations have been associated with aggressive forms of the disease and carriers older than 40 should undergo annual PC screening.

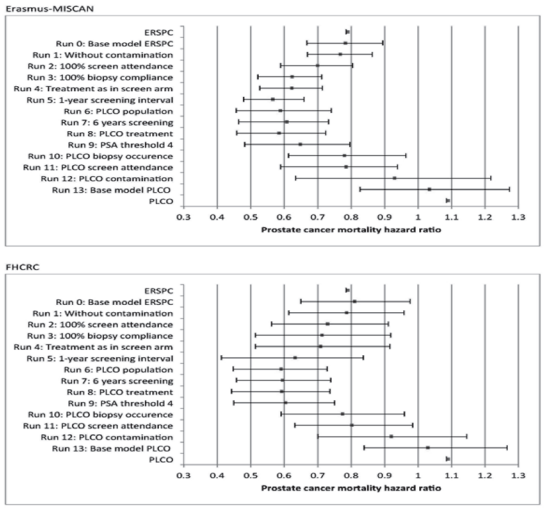
Genetic testing should be considered in men with metastatic PC, even in the absence of a family history of cancer, as several studies have shown that 12% of patients with advanced disease harbour a germline mutation in DNA repair genes.



GWAS, genome-wide association studies.

Fig. 11.4

Screening in prostate cancer



The observed mortality reductions in both trials are sensitive to protocol and practice settings and the efficacy of both trials is not necessarily inconsistent

Fig. 11.5

ERSPC, European Randomized Study of Screening for Prostate Cancer; FHCRC, Fred Hutchinson Cancer Research Center; MISCAN, MIcrosimulation SCreening ANalysis; PLCO, Prostate, Lung, Colorectal and Ovarian; PSA, prostate-specific antigen.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) and the prostate segment of the Prostate, Lung, Colorectal and Ovarian (PLCO) study are the largest PC screening trials.

In 2018, re-analysis of the data including statistical modelling showed that after differences in implementation and settings are accounted for, the ERSPC and PLCO study provide compatible evidence that screening reduces PC mortality. The models projected 19%-21% mortality reduction in ERSPC and 6%-8% mortality reduction in PLCO.

However, the use of a prostate-specific antigen (PSA) cut-off value (3 ng/mL) as an indication for biopsy is not only associated with the detection of clinically insignificant cancers but may miss some high-grade PCs, even in men with a normal rectal examination.

Numbers (percentages) of prostate cancers and high-grade cancers by PSA level in the Prostate Cancer Prevention Trial

PSA level, ng/mL	N	No. of prostate cancers (%)	No. of high-grade prostate cancers (Gleason ≥7) (%)
0-1	1963	217 (11.1)	19 (1.0)
1.1-2	1640	337 (20.5)	43 (2.6)
2.1-3	775	205 (26.5)	44 (5.7)
3.1-4	510	153 (30.0)	48 (9.4)
4.1-6	481	234 (48.6)	70 (14.6)
>6	150	65 (43.3)	33 (22.0)
Total	**5519**	**1211 (21.9)**	**257 (4.7)**

PSA, prostate-specific antigen.

Fig. 11.6

REVISION QUESTIONS

1. What could be the cancer-risk implications for the relatives of a PC patient found to carry a pathogenic *BRCA2* mutation?
2. If screening was introduced, how could the information on modifiable and non-modifiable factors be used to design more effective policies than in the population-based ERSPC trial?
3. Which PSA cut-off value would you use to recommend a biopsy to your patients?

Screening in prostate cancer (continued)

After a follow-up period of 16 years, the ERSPC trial showed a significant relative PC mortality reduction of 20% in intention-to-screen analyses. PC mortality risk was reduced by 25% in men screened once and 48% in those screened twice.

Fig. 11.7 shows the development in 4-year periods of the 21% relative difference in PC mortality seen in ERSPC with truncated 13-year follow-up.

PC mortality was identical during the initial 4 years. The difference develops during years 4-8 and reaches its maximum of 28% during the 8-12-year period.

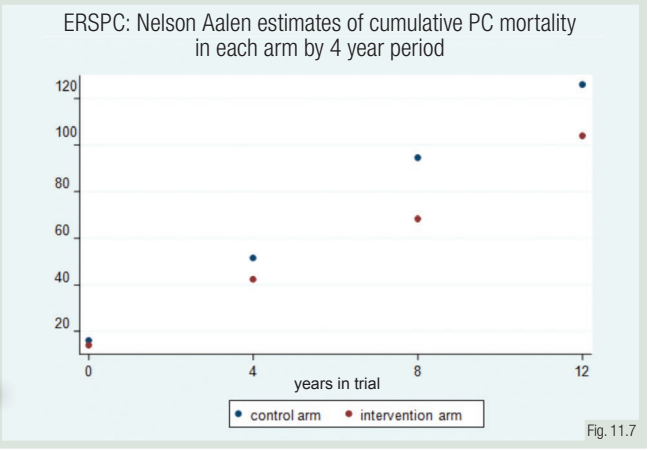


Fig. 11.7

ERSPC, European Randomized Study of Screening for Prostate Cancer; PC, prostate cancer.

Lead-time and over-detection by screening in the MISCAN prostate model (results from the Rotterdam ERSPC trial)

Screening	Mean lead-time* years	% Detection of clinical cancer	Over-detection	
			% detection	% increase lifetime risk
Single screen test at age:				
55	12.3	17	27	6
65	9.5	44	47	38
75	6.0	38	56	47
Screening with regular interval:				
55-67, annual	12.3	81	50	80
55-67, 4-year interval	11.2	70	48	65

**Time elapsed from screen-detection to either clinical diagnosis or death from other causes in the situation without screening*

Fig. 11.8

ERSPC, European Randomized Study of Screening for Prostate Cancer; MISCAN, Microsimultation SCreening ANalysis.

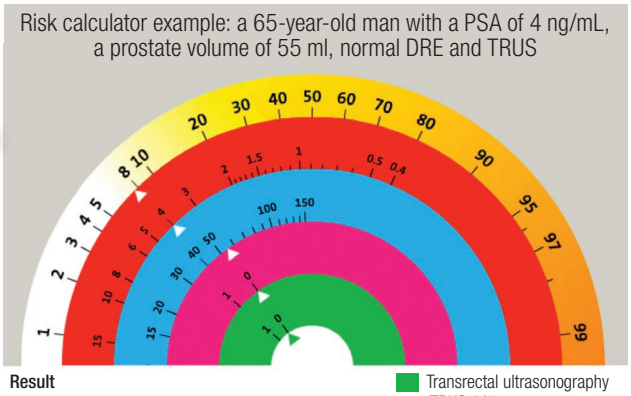
The number needed to invite (NNI) and number needed to diagnose (NND) were 781 and 27 (1410 and 48 after 8 years), respectively.

Men considering PC screening need to understand lead time and overdiagnosis. Lead time is the time by which screening advances the diagnosis, a consequence of the fact that PC is detectable many years before symptoms appear. Overdiagnosis is the detection of cancer which may not become symptomatic or kill.

Both are influenced by the age that screening starts and ends in relation to life expectancy and the number of screening tests applied (screening interval). In addition, overdiagnosis can be restricted by applying risk stratification prior to biopsy. This can be achieved by a multivariable risk calculator or imaging techniques like magnetic resonance imaging (MRI) (see Chapter 2).

The Rotterdam Prostate Cancer Risk Calculator (RPCRC) is based on data from participants in the Rotterdam section of the ERSPC trial who were biopsied during the initial screening round.

In the multivariable analysis of risk factors, the outcomes of PSA, digital rectal examination (DRE), transrectal ultrasound (TRUS) and prostatic volume were significant predictors of a positive biopsy.



DRE, digital rectal examination; PSA, prostate-specific antigen.

Fig. 11.9

REVISION QUESTIONS

1. What are the risks of using a fixed PSA cut-off value to determine the need for prostate biopsies?
2. What do we need to know to use the RPCRC risk calculator to avoid unnecessary biopsies, knowing that we will always miss some cancers?
3. Despite upfront risk stratification, PC overdiagnosis will exist. How can we diminish the harm of these potentially over-diagnosed cancers?

Summary: Epidemiology, risk factors, screening and predisposition genes for prostate cancer

- Incidence and mortality of PC show strong geographical variations
- Initiation of PC occurs early in life and precedes clinical diagnosis by >20 years
- Risk factors of PC include family history, age, race, body mass index and heavy smoking
- Some pathogenic genetic variants (i.e. *BRCA2*) increase the risk of PC but are also relevant for screening and treatment indications
- The risk of developing biopsy-detectable PC over time is PSA-dependent
- Validated risk calculators help to identify men who harbour indolent PC and should be used to avoid overdiagnosis
- The ERSPC trial showed a 27% PC mortality reduction in screened men with 13 years of follow-up. The NND to avoid one PC death decreased from 48 to 27 with 9 and 13 years of follow-up, respectively. The incidence of PC was 1.4-fold higher in the screening arm after 16-year follow-up

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12 Rare genitourinary tract tumours (prostate, kidney, bladder, testis, adrenal glands and penis)

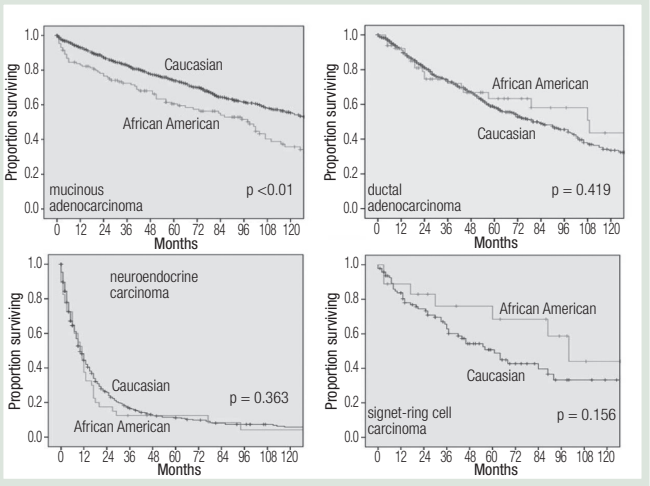
Prostate and kidney tumours

Compared with acinar adenocarcinoma (AdC), other prostate tumours are very rare (less than 1%). Mucinous and signet-ring cell AdCs are rare variants of acinar AdC.

Ductal AdC is the second most common AdC subtype, after acinar AdC. Among other tumour types, neuroendocrine (small cell) carcinoma predominates.

Prognosis is best in mucinous adenocarcinoma, intermediate in ductal adenocarcinoma and signet-ring cell carcinoma, and poorest in small cell carcinoma.

Survival in rare variants of prostate cancer (SEER data)



Incidence of rare variants of prostate cancer (SEER data)

Histology	Incidence rate (in cases per million per year)
Mucinous	0.61
Ductal	0.49
Signet cell	0.08
Neuroendocrine	0.35
Adenosquamous	0.03
Adenocarcinoma	586.0

SEER, Surveillance, Epidemiology, and End Results.

Fig. 12.1

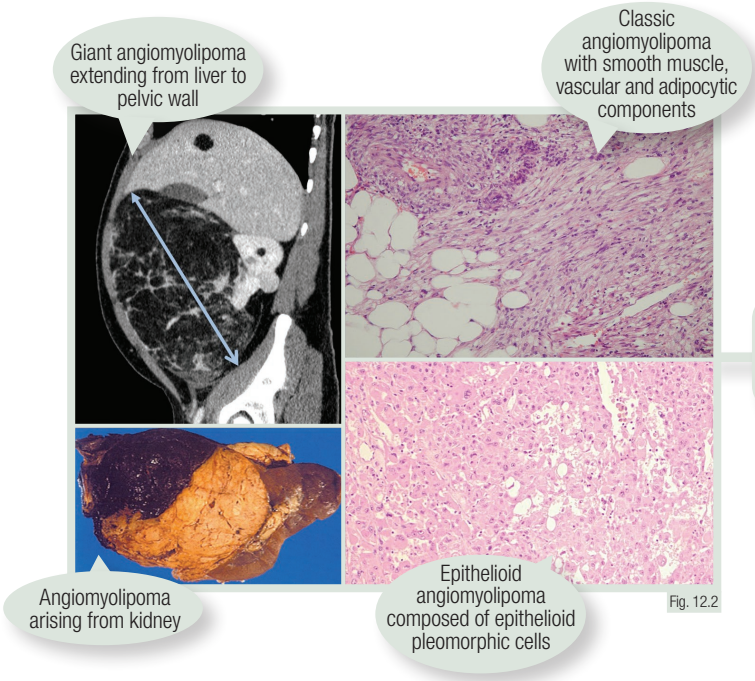


Fig. 12.2

Angiomyolipomas are predominantly benign tumours composed of vascular, smooth muscle and fat elements, comprising 0.7%-2% of renal tumours.

80% of angiomyolipomas are sporadic; 20% are seen in association with tuberous sclerosis or pulmonary lymphangioleiomyomatosis.

Sporadic tumours occur mostly in females (female:male ratio 4:1) and at an older age (median 43 years), compared with inherited tumours (median age 10 years).

Adult Wilms' tumours account for <10% of Wilms' tumour cases, with an incidence rate of less than 0.2 per million per year.

Although adult patients more often present with localised disease, their long-term outcome is significantly worse than for paediatric patients.

Better results are reported when adult patients are treated according to paediatric protocols; a standardised approach based on experience in paediatric patients is recommended.

Survival probability for paediatric and adult Wilms' tumours and estimated 5-year survival for different age groups (SEER data)

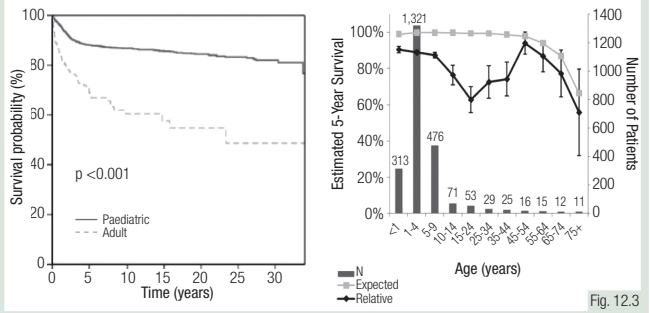


Fig. 12.3

SEER, Surveillance, Epidemiology, and End Results.

REVISION QUESTIONS

1. Which of the rare variants/types of prostate cancer carries the worst prognosis?
2. Which genetic syndromes are associated with increased incidence of angiomyolipoma?
3. What treatment principles should be applied to adult Wilms' tumours?

Bladder and testicular tumours

Squamous cell carcinomas (SCCs) comprise 2%-7% of bladder cancers in developed countries, and historically up to 75% in endemic areas of schistosomiasis.

Incidence of schistosoma-related bladder cancer is decreasing; non-bilharzial SCCs are caused by chronic infection and irritation.

Prognosis in non-bilharzial SCC is analogous to urothelial cancers; treatment is predominantly surgical.

Incidence of squamous cell vs transitional cell carcinoma of the bladder

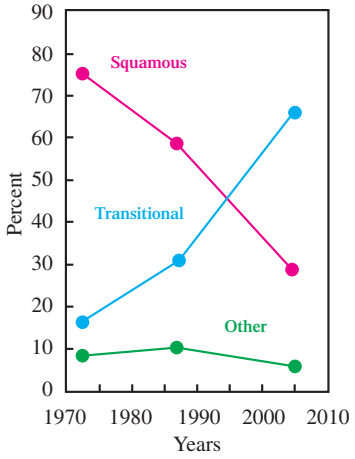


Fig. 12.4

Overall survival in urachal vs non-urachal tumours

MD Anderson diagnostic criteria for urachal carcinoma

1. Location in the bladder dome or elsewhere in the bladder midline
2. Sharp demarcation between tumour and normal epithelium

Supportive criteria:

- enteric-type histology
- absence of urothelial dysplasia
- absence of cystitis cystica or glandularis transitioning to the tumour
- absence of primary adenocarcinoma of other organ

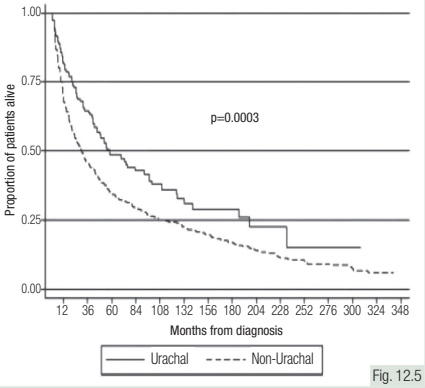


Fig. 12.5

Bladder AdCs include urachal (~10%) and non-urachal tumours (~90%). Urachal cancers occur at a younger age, more often in females and are of lower grade.

Despite more frequent metastatic presentation, prognosis is better than in non-urachal tumours. Treatment involves surgery (partial cystectomy).

Diagnostic criteria include location in the bladder dome or elsewhere in the midline and sharp demarcation between tumour and normal epithelium.

Spermatocytic tumours are rare and differ from classical seminomas by later age of onset and lack of relation to testicular development disorders.

Spermatocytic tumours do not arise from germ cell neoplasia *in situ* (GCNIS), do not occur in association with other germ cell tumours and do not arise outside the testes.

Most patients present with slow, painless testicular enlargement, which may involve both testes. Metastatic spread is extremely rare.

Seminoma	Spermatocytic seminoma
50% of germ cell tumours	2% of germ cell tumours
Age: 30-40 years	Age: 50-60 years
Extra-testicular sites possible	Occurs only in testis
Increased incidence in undescended testis	No obvious epidemiological pattern
Increased serum markers (beta-hCG LDH) possible	Normal serum markers
Arising from germ cell neoplasia *in situ* (GCNIS)	Not associated with GCNIS
Risk of metastases (mostly nodal)	No metastatic potential
Prognosis related to stage (generally favourable)	Favourable prognosis

hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.

Fig. 12.6

REVISION QUESTIONS

1. What is the aetiology of non-bilharzial bladder SCC?
2. What is the prognosis in urachal AdCs?
3. What is the prognosis in spermatocytic tumours?

Testicular and adrenal tumours

Leydig cell tumours account for 1%-3% of testis tumours. Approximately 10% are malignant. Prognosis is very good in benign cases and unfavourable in malignant tumours.

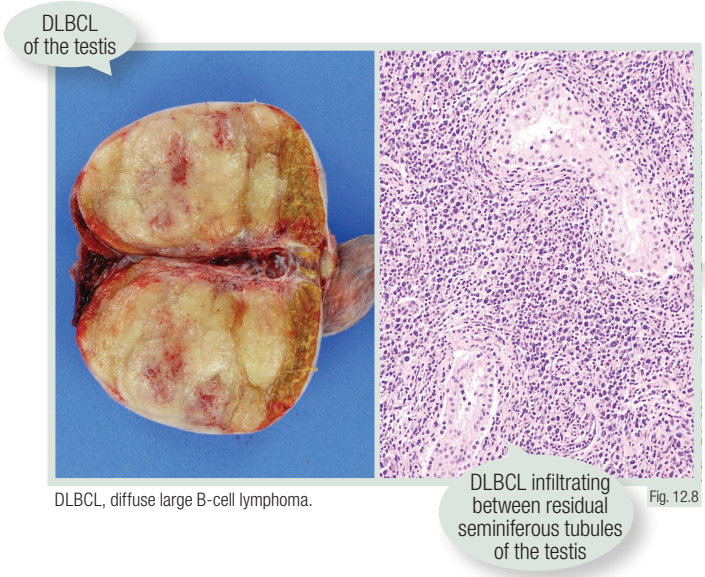
Leydig cell tumours occur mostly in boys of 5-10 years (due to excess testosterone secreted by the tumour, they often present with precocious puberty) or in men of 30-60 years.

Sertoli cell tumours comprise <1% of testicular tumours. Due to excess oestrogen production, they often present with progressive feminisation. Approximately 10% are malignant.

Sex cord–stromal tumours (WHO 2016 classification)
Leydig cell tumour
Malignant Leydig cell tumour
Sertoli cell tumour
Malignant Sertoli cell tumour
Large cell calcifying Sertoli cell tumour
Intratubular large cell hyalinising Sertoli cell neoplasia
Granulosa cell tumour
Adult granulosa cell tumour
Juvenile granulosa cell tumour
Tumours in the fibroma-thecoma group
Mixed and unclassified sex cord–stromal tumours
Mixed sex cord–stromal tumour
Unclassified sex cord–stromal tumour
Tumours containing both germ cell and sex cord–stromal elements
Gonadoblastoma

Fig. 12.7

WHO, World Health Organization.



DLBCL, diffuse large B-cell lymphoma.

Fig. 12.8

Testicular lymphomas comprise 2% of testis tumours, but are the most frequent testicular tumours in men of 60-80 years. The testes may be involved in 5% of extra-testicular lymphomas.

In adults, 80% are diffuse large B-cell lymphoma (DLBCL). In children, secondary involvement from Burkitt's lymphoma, DLBCL, or lymphoblastic lymphoma is the most frequent.

Prognosis is poor, relapses often include the contralateral testis and central nervous system (CNS). Aggressive treatment involving chemotherapy (ChT) with rituximab, radiotherapy (RT) and CNS prophylaxis is warranted.

Adrenal tumours are rare, usually benign, and rarely require intervention. Some of them secrete hormones and require endocrinological care.

The most common adrenal tumours are adrenocortical adenomas usually found incidentally on computed tomography (CT). Malignant adrenal tumours include adrenocortical carcinomas (ACs) and malignant phaeochromocytomas (PHs).

Endocrine-producing tumours may cause symptoms related to hormone overproduction (Cushing's syndrome, Conn's disease, noradrenaline secretion, virilisation and feminisation). Endocrine work-up is essential prior to intervention.

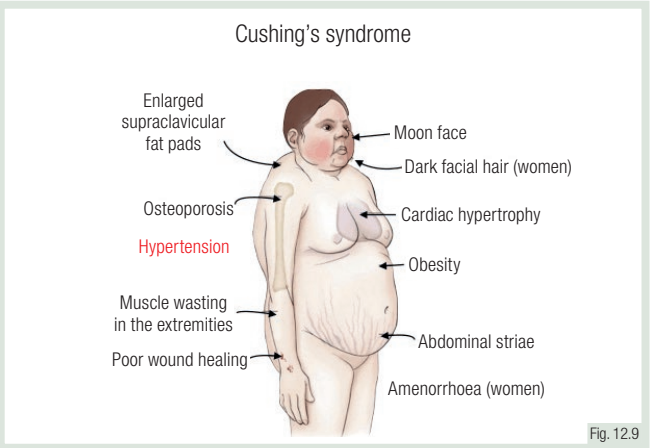


Fig. 12.9

REVISION QUESTIONS

1. Which hormones are secreted by Leydig cell tumours?
2. What is the most common histology of testicular lymphoma?
3. What is the differential diagnosis in a patient with an adrenal incidentaloma and cushingoid appearance?

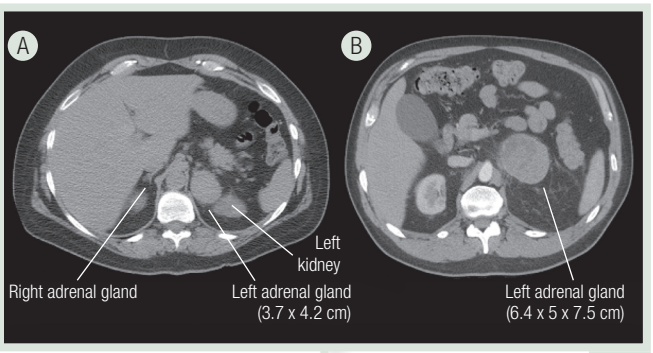
Adrenal tumours (continued)

A significant proportion of malignant adrenal tumours is associated with hereditary syndromes and requires consideration for genetic testing.

ACs may be related to Beckwith-Wiedemann syndrome, familial adenomatous polyposis coli or Li-Fraumeni syndrome.

PHs may be related to multiple endocrine neoplasia type 2 (MEN 2), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1) or hereditary paraganglioma syndrome.

CT images showing adrenal tumours. (A) Showing smooth borders and homogeneous interior versus (B) a malignant slightly heterogeneous mass with slightly indistinct medial border.



CT, computed tomography.

Fig. 12.10

Fig. 12.11

Cross-sectional imaging (CT/magnetic resonance imaging [MRI]) can usually distinguish between benign and malignant tumours as well as AC and PH.

PHs secrete catecholamines that may precipitate life-threatening hypertension. Typical symptoms include headaches, palpitations, diaphoresis and severe hypertension. The tumour is malignant in 10% of cases.

Imaging for PH includes CT, MRI, fluorodeoxyglucose-positron emission tomography (FDG-PET) or ^{123}I metaiodobenzylguanidine (MIBG) scintigraphy.

In patients with a suspected PH, biopsy should be avoided. Endocrine work-up and management prior to surgery are essential to prevent an adrenergic crisis.

Surgery is the mainstay of treatment of malignant adrenal tumours and should be performed wherever complete resection can be achieved. Lymph node dissection may improve the outcome.

Clear resection margins are associated with a better outcome for malignant tumours, but relapses after surgery are common and the 5-year survival rate is less than 50%.

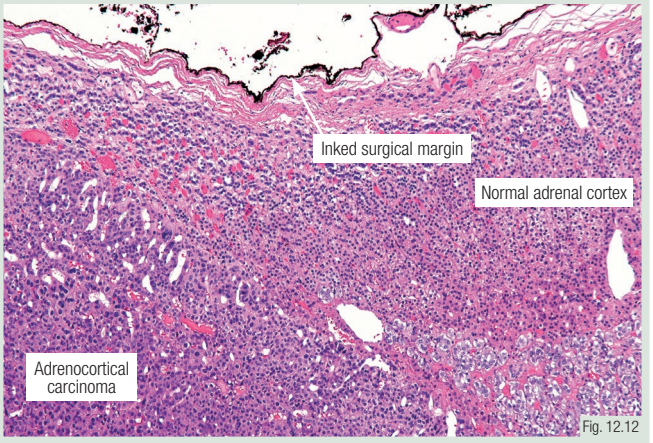


Fig. 12.12

REVISION QUESTIONS

1. Name the hereditary syndromes associated with malignant adrenal tumours.
2. What are the imaging modalities of choice, and why, in a patient with a high clinical suspicion for PH?
3. What are the risks of a tumour biopsy in a patient with PH?

Adrenal tumours and penile cancer

Tumour bed RT for incomplete resections and adjuvant ChT (mitotane) for more aggressive ACs should be considered after surgery.

Patients with metastatic AC have a poor outcome. Mitotane alone or in combination with other drugs (etoposide, doxorubicin, cisplatin) is used. Surgery to the primary in metastatic disease is controversial but may help control symptoms.

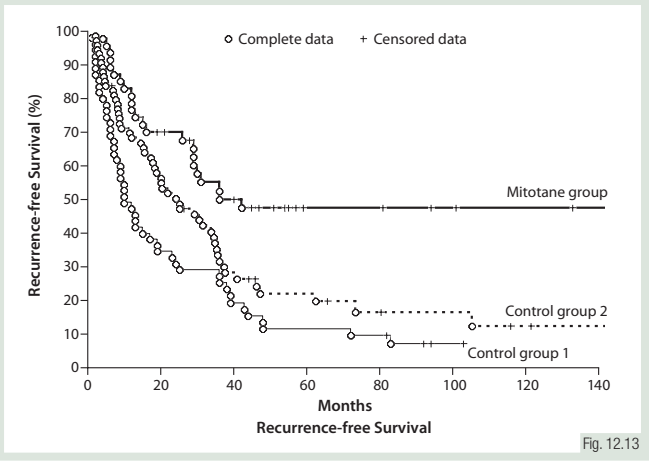


Fig. 12.13

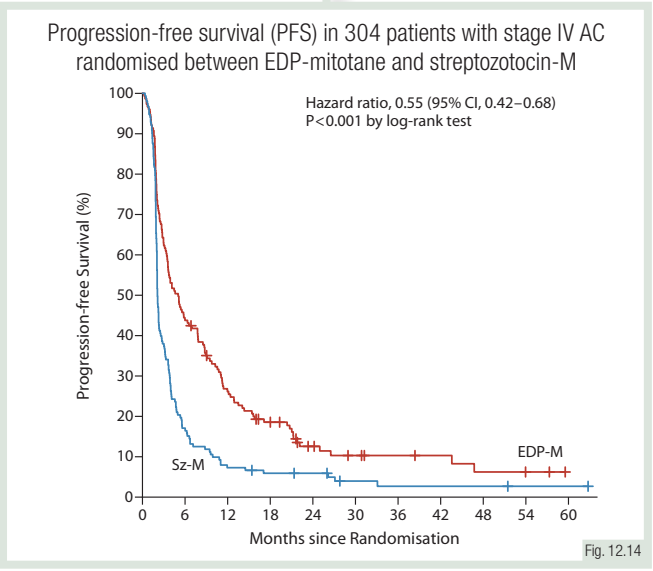


Fig. 12.14

AC, adrenocortical carcinoma; CI, confidence interval; EDP, etoposide/doxorubicin/cisplatin; M, mitotane; Sz-M, streptozotocin plus mitotane.

Treatment of metastatic PH focuses on control of catecholamine secretion. MIBG imaging is used to determine treatment and patients with high uptake are offered MIBG treatment.

Penile cancer is rare in the Western world, with an incidence of <1/100 000 in Europe. More than 95% are SCCs. Rare subtypes include: verrucous, basaloid, warty, papillary and sarcomatoid carcinoma.

Human papillomavirus (HPV)-16 and -18 are involved in carcinogenesis and HPV DNA is detected in almost 50% of SCC cases, mostly in basaloid and warty subtypes.

Physical examination is used for assessment of size, number, location and morphology of penile lesion(s), and their relationship to other structures. MRI can help assess local invasion.

Palpable inguinal lymphadenopathy is present at diagnosis in 30%-60% of cases and is strongly correlated with the stage and long-term outcome.

Palpable lymph node (LN) metastases should be confirmed by cytology and/or histology. In cases of clinically negative LNs, dynamic sentinel lymph node biopsy (DSNB) is recommended.

Staging for locoregional and distant disease includes CT, MRI and FDG PET-CT. In patients with skeletal symptoms, a bone scan should be performed.

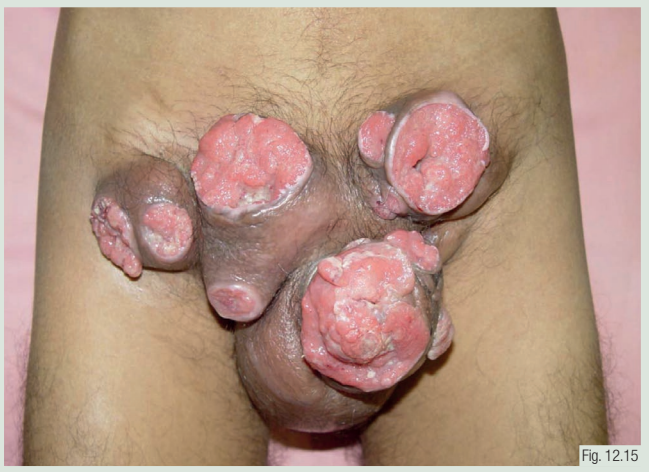


Fig. 12.15

REVISION QUESTIONS

1. Name a palliative treatment for metastatic AC and PH.
2. What are the aetiological factors of penile cancer?
3. In cases of non-palpable LNs, what is the preferred approach to assess the presence of LN disease in penile cancer?

Penile cancer (continued)

For small-volume and superficial penile lesions, conservative treatments such as circumcision, wide local excision and epithelial ablative techniques are used.

Brachytherapy is also recommended as the initial treatment for invasive T1, T2 and selected T3 stage penile cancers.

Poorly differentiated or more advanced tumours are better managed by partial penectomy. Total penectomy with perineal urethrostomy should be reserved for bulky T3 or T4 tumours involving the base of the penis.

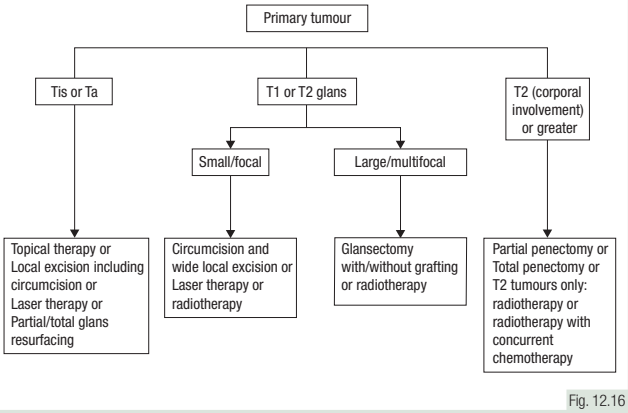
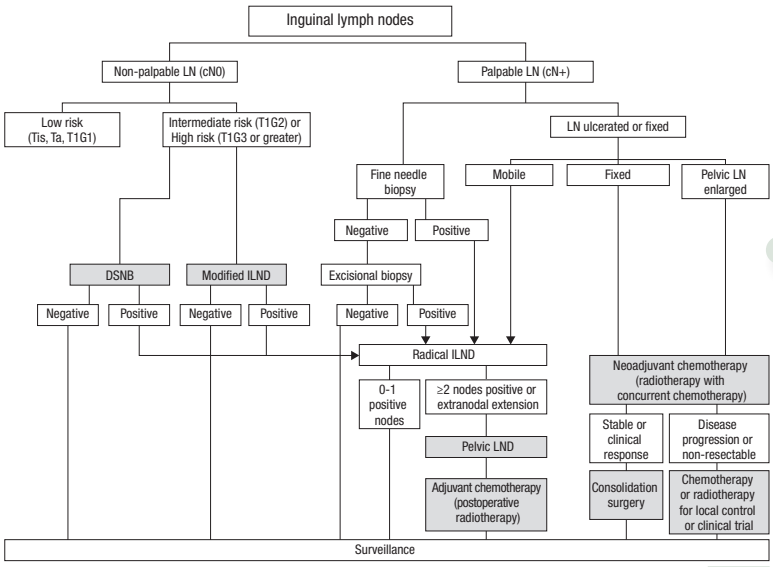


Fig. 12.16



DSNB, dynamic lymph node biopsy; ILND, inguinal lymph node dissection; LN, lymph node; LND, lymph node dissection.
Fig. 12.17

All patients with histologically proven LN metastases should undergo radical inguinal lymph node dissection.

Cisplatin-based neoadjuvant ChT, followed by radical surgery, is advised in non-resectable or recurrent LN metastases. A few small heterogeneous series show benefit from adjuvant ChT in pN2-3 patients.

Adjuvant inguinal RT following radical inguinal lymphadenectomy in patients with high-risk features does not decrease the risk of relapse and is not recommended.

The prognosis of patients with metastatic disease is poor (0% at 5 years). Short-term palliation can be obtained with combination ChT using cisplatin and 5-fluorouracil, gemcitabine, paclitaxel or ifosfamide.

Epidermal growth factor receptor (EGFR) overexpression is common, and some activity of monoclonal antibodies targeting EGFR (panitumumab and cetuximab) has been reported in small patient series.

Most squamous carcinomas express programmed death-ligand 1 (PD-L1), which is associated with high-risk clinicopathological features and poor clinical outcome. Immunotherapy trials are ongoing.

Reported studies of ≥10 patients receiving chemotherapy for advanced penile cancer

Author	Line of therapy	Regimen	Design	*N*	Clinical response *N* (%)	Median PFS	Median OS
Gagliano et al	First	Cisplatin	Phase II trial	26	4 (15.4)	NR	4.7 months
Haas et al	First	BMP	Phase II trial	40	13 (32.5)	NR	28 weeks
Dexeus et al	First	BMP	Retrospective[a]	14	10 (72)	NR	NR
Corral et al	First	BMP	Phase II trial[b]	30	16 (55)	NR	11.5 months
Di Lorenzo et al	First	CF	Retrospective	25	8 (32)	20 weeks	8 months
Theodore et al	First	CI	Phase II trial	28	8 (30.8)	NR	NR
Di Lorenzo et al	Second	Paclitaxel[c]	Phase II trial	25	5 (20)	11 weeks	23 weeks

[a]Twelve of the 14 patients had penile primary site.
[b]Trial enrolled patients with squamous cell carcinoma of the penis, scrotum, bladder, renal pelvis, ureter, or urethra.
[c]Paclitaxel every 3 weeks

BMP, bleomycin/methotrexate/cisplatin; CF, cisplatin/5-fluorouracil; CI, cisplatin/irinotecan; NR, not reported; OS, overall survival; PFS, progression-free survival.
Fig. 12.18

REVISION QUESTIONS

1. What is the indication for total penectomy?
2. What is the most feasible therapeutic approach for non-resectable LN disease?
3. Which ChT schedule is recommended for metastatic penile cancer?

Summary: Rare genitourinary tract tumours (prostate, kidney, bladder, testis, adrenal glands and penis)

- Rare GU cancers should be managed in high-volume centres

Rare prostate, kidney, bladder and testis tumours

- Rare prostate cancers: mucinous and ductal are the most common; small cell has the poorest prognosis
- Bladder SCCs are often endemic and associated with schistosoma infection; non-bilharzial cases are usually caused by prolonged irritation
- Urachal bladder AdCs are rare (~10%), occur at younger age and are associated with better prognosis
- Spermatocytic tumours have a later onset. There is no association with other germ cell tumours and they are associated with an extremely low risk of metastases
- Sex cord tumours may cause symptoms related to the secretion of testosterone (Leydig cell tumour) or oestrogens (Sertoli cell tumour); about 10% are malignant
- Testicular lymphomas, mostly DLBCLs, have a poor prognosis. Treatment includes RT and CNS prophylaxis, besides ChT and rituximab (which are the mainstay of lymphoma treatment)

Malignant adrenal tumours

- The most common malignant adrenal tumours are ACs followed by adrenal PHs. The backbone of curative treatment is surgery
- Some tumours are hormonally active and may require endocrinological care

Penile cancer

- SCC accounts for more than 95% of penile cancer cases. It is strongly associated with HPV, mostly HPV-16 and HPV-18
- For superficial penile lesions, conservative treatment is the main approach. Total penectomy should be performed for bulky T3 or T4 tumours

Further Reading

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New drugs and novel treatment strategies for prostate cancer

13

Molecular subtypes and druggable pathways

Molecular profiling studies have identified several prostate cancer (PC) subtypes, such as *ETS* fusion-positive, structural variation-driven subtypes, or those with DNA damage repair defects (DDRd).

Druggable genes and pathways are commonly identified: DNA damage repair (DDR)-deficient tumours, an immunogenic subtype (with mismatch repair or CDK12 defects) and types driven by aberrations activating the PI3K, Wnt or MAPK pathways.

Next-generation sequencing of primary but preferably metastatic sites can guide precision medicine in patients with metastatic castration-resistant PC (mCRPC), with putative actionable alterations found in over 80% of cases.

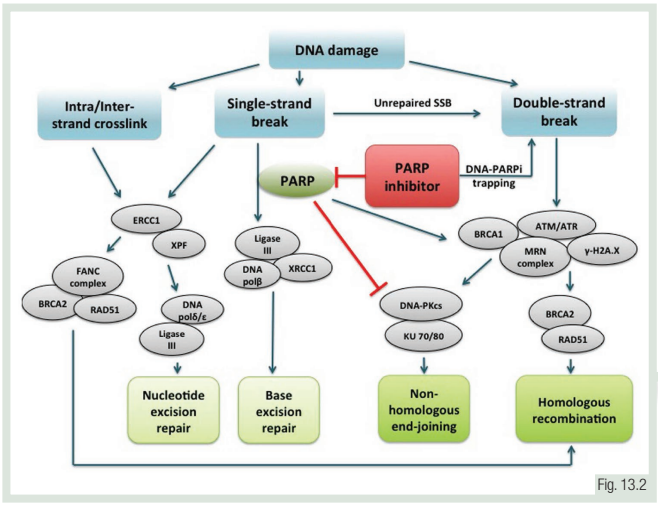


Fig. 13.2

ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; DNA polβ/δ/ε, DNA polymerase beta/delta/epsilon; FANC, Fanconi anaemia; γ-H2A.X, gamma-histone H2A member X; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; SSB, single-strand break.

Phosphatase and tensin homologue (PTEN) suppresses tumour growth by inhibiting AKT signalling. PI3K and AKT inhibitors are evaluated alone or in combination trials.

PI3K activation, an early PC event, facilitates development of resistance to agents targeting androgen receptor (AR) signalling. Ipatasertib, an AKT inhibitor, has shown activity in phase II trials, in combination with abiraterone acetate (AA) in PTEN loss tumours. Phase III trials are ongoing.

Other future targets include cyclin-dependent kinase (CDK), Wnt, RAF kinases, insulin-like growth factor 1 receptor (IGF-1R) and epithelial-to-mesenchymal transition (EMT).

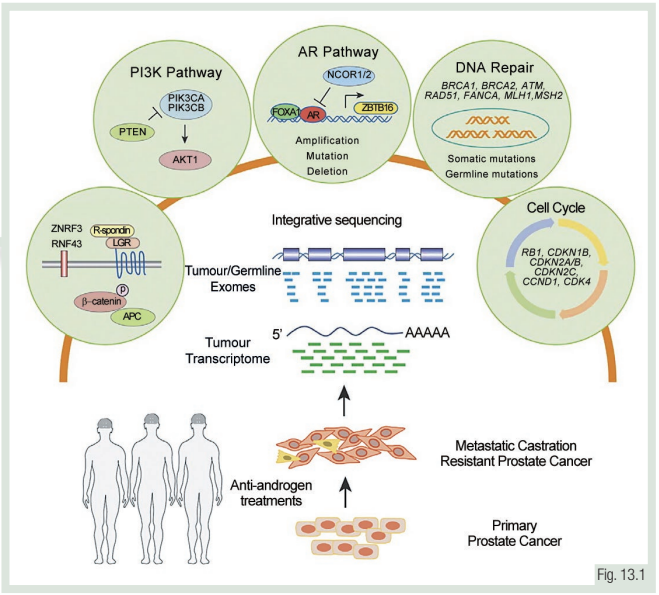


Fig. 13.1

APC, antigen-presenting cell; AR, androgen receptor; ATM, ataxia telangiectasia mutated; FANC, Fanconi anaemia; PTEN, phosphatase and tensin homologue.

Olaparib is an inhibitor of DNA repair protein PARP (poly[ADP-ribose] polymerase). In the absence of homologous DNA repair, double-strand breaks accumulate, leading to cell death.

Functional homologous repair deficiency is commonly seen in BRCA-carrier PC, with somatic bi-allelic inactivation or with defects in alternative DDR genes, such as *ATM, CHEK, PALB2, RAD51, CDK12*. Responses to PARP inhibitors vary regarding defect and alleles inactivated.

Targeting PARP in DDR-deficient tumours has a cytotoxic effect while sparing surrounding normal tissue (dubbed synthetic lethality).

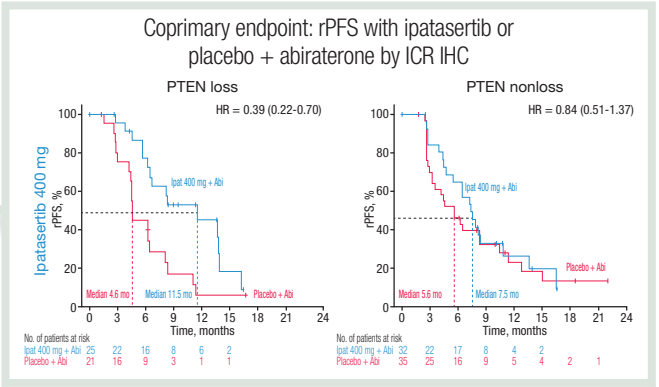


Fig. 13.3

Abi, abiraterone; HR, hazard ratio; ICR, Institute of Cancer Research; IHC, immunohistochemistry; Ipat, ipatasertib; PTEN, phosphatase and tensin homologue; rPFS, radiographic progression-free survival.

REVISION QUESTIONS

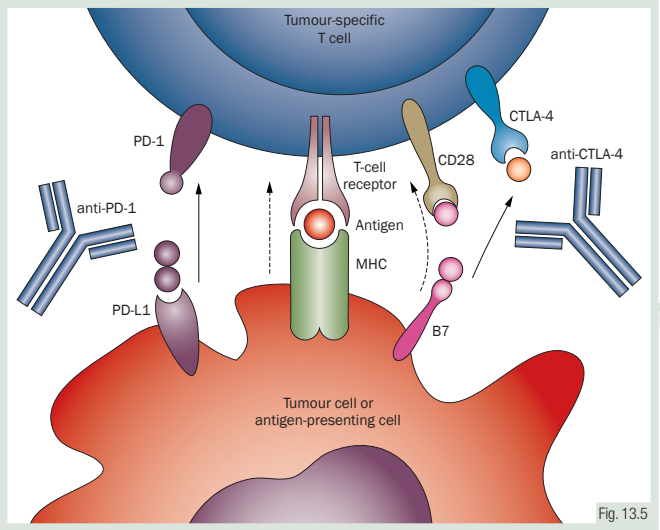
1. How does PTEN loss lead to enhanced PI3K activity?
2. Explain the concept of synthetic lethality through PARP inhibition.
3. Which pathways are involved in PC growth and progression?

Immuno-oncology agents

Sipuleucel-T was the first approved autologous cellular immunotherapy in PC. Alternative agents to boost or reactivate the immune system are being studied extensively in mCRPC and include cancer vaccines, antibody conjugates and T cell checkpoint inhibition in monotherapy or combinational studies.

Prostvac-VF/PSA-TRICOM (prostate-specific antigen-T cell costimulatory molecule) is a poxvirus-based vaccine composed of a vector with the PSA gene, and granulocyte-macrophage colony stimulating factor (GM-CSF). A phase III trial did not show overall survival (OS) benefit.

Tasquinimod modulates the tumour microenvironment, targeting the immunomodulatory protein S100A9 and angiogenesis. In phase III no OS benefit was seen.

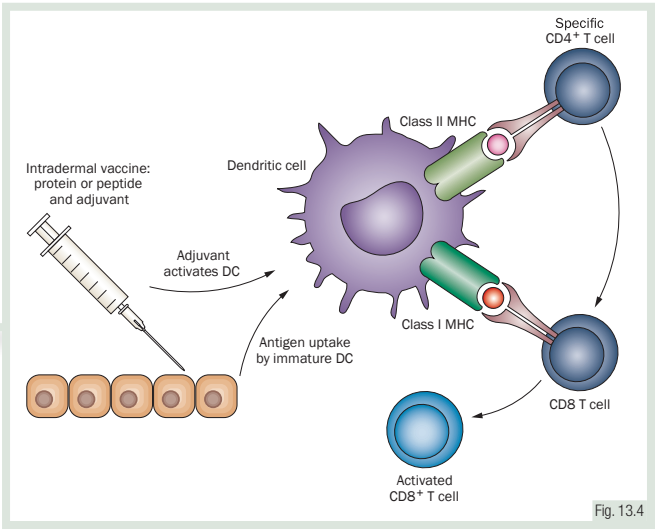


CTLA-4, cytotoxic T-lymphocyte antigen 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Antibody drug conjugates (ADCs) show promise, e.g. the anti-prostate specific membrane antigen (PSMA) antibody linked to the anti-mitotic agent MMAE (monomethyl auristatin E).

Several radioligand therapies (RLTs) with ^{177}lutetium-labelled PSMA ligands (PSMA-RLTs) are currently used to treat mCRPC patients.

PSA responses can be seen in heavily pre-treated patients, while the toxicity profile is mostly acceptable (haematological toxicities, xerostomia, fatigue and nausea).

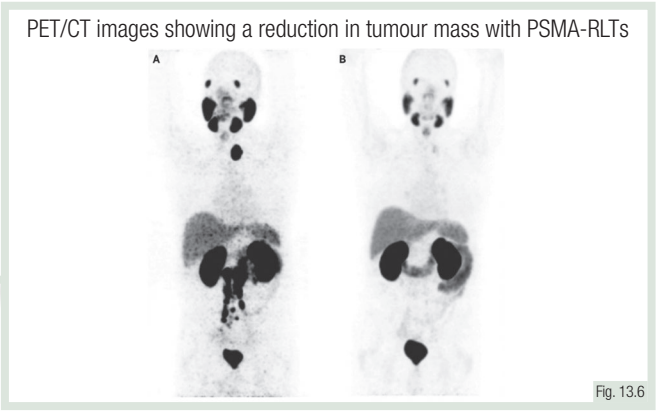


DC, dendritic cell; MHC, major histocompatibility complex.

Ipilimumab, a human monoclonal antibody (mAb) inhibiting the cytotoxic T-lymphocyte antigen 4 (CTLA-4) checkpoint, offered promising results in phase I/II, but yielded negative phase III results in unselected patients, both pre- and post-chemotherapy (ChT).

Pembrolizumab, programmed cell death protein 1 (PD-1) immune checkpoint inhibitor (ICI), showed objective responses in ~6% of unselected patients and clinical benefits in ~10% of patients. Small series have shown increased responsiveness to ICIs in patients with an immunogenic subtype.

Multiple combinatory trials are ongoing with CTLA-4 and PD-1/PD-L1 ICIs, or with combinations of ICI with enzalutamide, radium-223, taxane ChT and PARP inhibitors.



CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

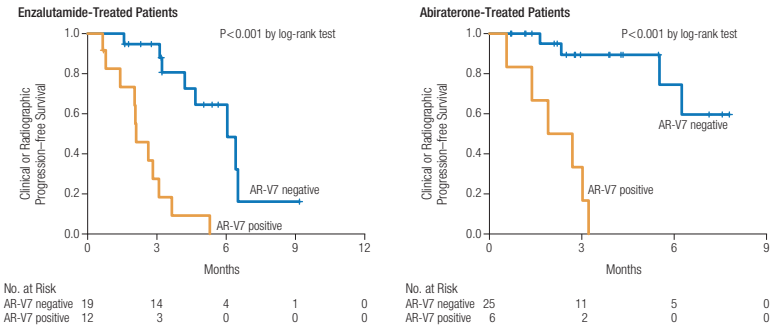
REVISION QUESTIONS

1. How can we reactivate T cells and which side effects can be expected?
2. What is the mechanism of action of viral tumour vaccines?
3. Explain how the therapeutic efficacy is increased with ADCs while limiting systemic side effects.

Androgen signalling and novel targets

Androgen signalling remains a key target in most advanced PCs. Novel AR antagonists include apalutamide (ARN-509), darolutamide (ODM-201), with VT-464 being a more specific CYP17 inhibitor, and galeterone (TOK-001) having dual action. AR-degrading drugs like AZD3514 inhibit AR signalling through AR nuclear translocation and decreasing AR levels.

Cross-resistance between agents remains a major issue.



AR-V7, androgen receptor-splice variant 7.

Fig. 13.7

AR amplification, AR mutations and constitutive active splice variants lacking the ligand-binding domain may be responsible for primary and acquired resistance to androgen signalling agents.

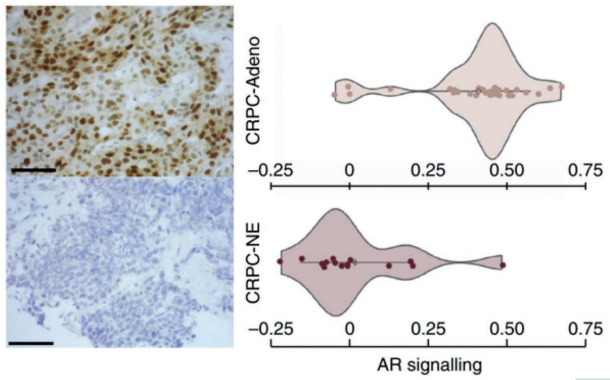


Fig. 13.8

AR, androgen receptor; CRPC-Adeno, castration-resistant prostate adenocarcinoma; CRPC-NE, neuroendocrine castration-resistant prostate cancer.

Agents specifically targeting the N-terminal domain (NTD) of the AR, or drugs that may be active in AR-splice variant 7 (AR-V7)-positive cancers, are strongly sought after. EPI-001, EPI-506 and galeterone have all been discontinued from further development.

Targeting a molecular chaperone of the AR decreases AR signalling, e.g. heatshock protein HSP27 with OGX-427 or HSP90 with AT13387 or STA90-90.

Since the use of second-generation agents targeting AR signalling, prevalence of neuroendocrine PC (NEPC) has increased. N-MYC plays a key role in NEPC formation in inducing a transcriptional program, shutting down AR signalling. Alisertib, targeting Aurora A kinase (AURKA) overexpression, showed some activity in NEPC, and trials targeting the activated histone methyltransferase EZH2 (GSK126) are ongoing.

Histone deacetylase (HDAC) is overexpressed in 5% of PCs. HDAC inhibitors (HDACis) vorinostat and panobinostat alter histone and non-histone protein function such as PI3K activity.

Novel bone-targeting agents (atrasentan, targeting the endothelin-A receptor and dasatinib, targeting SRC family kinases) have failed to show OS benefit. Bisphosphonates and agents targeting the RANK ligand in men with mCRPC decrease incidence of skeletal-related events (SREs) but do not appear to increase OS.

Many putative practice-changing trials are ongoing in the metastatic hormone-sensitive PC (HSPC) setting, with trials combining radiotherapy, novel endocrine agents, ChT, PARP inhibitors and immunotherapy.

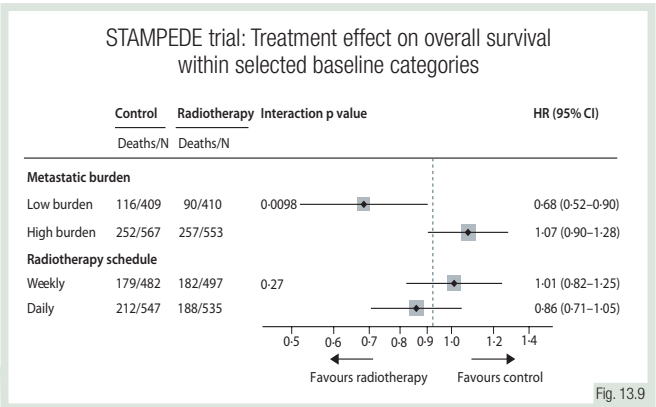


Fig. 13.9

CI, confidence interval; HR, hazard ratio.

REVISION QUESTIONS

1. Explain the differences in action between the classical CYP17 inhibitor AA and galeterone.
2. How could the alternative AR-V7 cause resistance to AA?
3. Why do a proportion of advanced mCRPCs progress with a low PSA and aggressive disease?

Summary: New drugs and novel treatment strategies for prostate cancer

- Next-generation sequencing has led to an improved understanding of primary PC and evolutionary routes for mCRPC
- Activation of the PI3K pathway is a likely resistance mechanism to CYP17 inhibitors or AR antagonists, and is commonly seen in PC
- Trials with a myriad of agents targeting PI3K, AKT and downstream targets are in progress
- PARP inhibitors are a novel treatment option for selected PC patients with defects in DNA repair, including those with BRCA alterations or 'BRCAness'
- Novel immunotherapeutic agents include cancer vaccines, antibody conjugates and T cell checkpoint modulation with CTLA-4 and PD-1/PD-L1 inhibitors
- Despite treatment with AA or enzalutamide, all PCs ultimately progress; however, most remain androgen-dependent
- More potent AR antagonists or CYP17 inhibitors have been developed, some with multiple modes of action including targeting of androgen-splice variants
- A proportion of advanced adenocarcinomas of the prostate differentiate into aggressive neuroendocrine tumours
- Novel drugs targeting specific neuroendocrine markers are in development

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New drugs and novel treatment strategies for kidney cancer

14

New drugs in clear cell renal cell carcinoma

New vascular endothelial growth factor receptors (VEGFRs) and immune checkpoint inhibitors (ICIs) have vastly improved outcomes of patients with renal cell carcinoma (RCC).

Treatment of second-line metastatic clear cell RCC (ccRCC) relies on the anti-programmed cell death protein 1 (PD-1) nivolumab and the VEGFR/MET inhibitor cabozantinib.

Combinations of ICIs with or without VEGFR-directed therapies are becoming the standard-of-care in the first-line metastatic setting.

Standard-of-care in second-line therapy for metastatic clear cell renal cell carcinoma

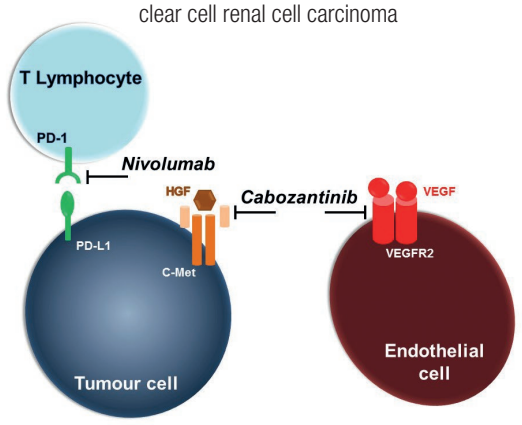

Fig. 14.1

HGF, hepatocyte growth factor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

Results of phase III immunotherapy combinations in first-line metastatic ccRCC

Trial and agents	Primary endpoints	ORR Primary endpoint population		PFS Primary endpoint population	OS Primary endpoint population
CheckMate 214 Nivolumab + ipilimumab vs sunitinib	ORR PFS OS in intermediate / poor-risk patients (N=847)	42% vs 27%		*Median* 11.6m (95% CI 8.7-15.5) vs 8.4m (95% CI 7.0-10.8)	*Median* NR (95% CI 28.2-NE) vs 26m (95% CI 22.1-NE)
IMMotion 151 Atezolizumab + bevacizumab vs sunitinib	PFS in patients with PD-L1+ tumours (N=362) OS in ITT (N=915)	PD-L1 + 43% vs 35%	ITT 37% vs 33%	*Median* 11.2m (95% CI 8.9-15.0) vs 7.7m (95% CI 6.8-9.7)	*Median* 33.6m (95% CI 29.0-NE) vs 34.9m (95% CI 27.8-NE)
Javelin Renal 101 Avelumab + axitinib vs sunitinib	PFS OS in patients with PD-L1+ tumours (N=560)	55% vs 26%		*Median* 13.8m (95% CI 11.1-NE) vs 7.2m (95% CI 5.7-9.7)	Not available
Keynote 426 Pembrolizumab + axitinib vs sunitinib	PFS OS in unselected patients (N=861)	59% vs 36%		*Median* 15.1m (95% CI 12.6-17.7) vs 11.1m (95% CI 8.7-12.5)	*12-months OS rate* 89.9% (95% CI 86.4-92.4) vs 78.3 (95% CI 73.8-82.1)

Fig. 14.2

ccRCC, clear cell renal cell carcinoma; CI, confidence interval; ITT, intention to treat; m, months; NE, not estimated; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1+, programmed death-ligand 1-positive; PFS, progression-free survival.

Frontline combinations of anti-PD-1 pembrolizumab plus VEGFR-inhibitor axitinib, and nivolumab plus anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) ipilimumab, improved overall survival (OS) over sunitinib, respectively, in unselected patients and in intermediate/poor-risk patients (according to the International Metastatic Renal Cell Carcinoma Database Consortium [IMDC] risk groups).

ICIs and VEGF(R)-inhibitor combinations avelumab/axitinib and atezolizumab/bevacizumab improved first-line progression-free survival (PFS) over sunitinib in patients with programmed death-ligand 1 (PD-L1)-positive tumours.

Upfront cabozantinib as monotherapy can be an option for intermediate- or poor-risk patients in the first-line setting. Several other immune checkpoints are involved in RCC immune escape and are potential therapeutic targets.

New compounds inhibit the checkpoints T cell immunoglobulin and mucin domain 3 (TIM-3) and lymphocyte-activation gene 3 (LAG-3), or activate pro-inflammatory checkpoints OX40 and 4-1BB.

These new therapies are currently being evaluated in ongoing clinical trials in combination with PD-1/PD-L1 inhibitors.

Selection of targetable immune checkpoints in renal cell carcinoma

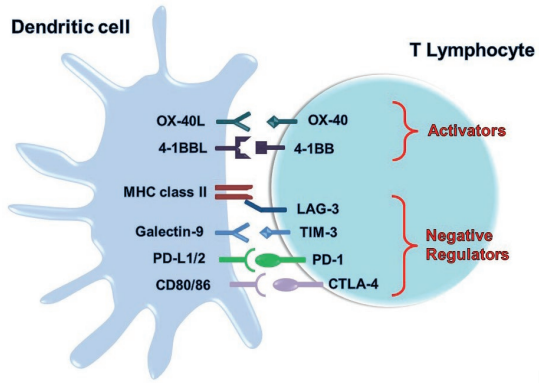

Fig. 14.3

CTLA-4, cytotoxic T-lymphocyte antigen 4; LAG-3, lymphocyte-activation gene 3; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1/2, programmed death-ligand 1/2; TIM-3, T cell immunoglobulin and mucin domain 3.

REVISION QUESTIONS

1. Which population benefits from the combination of nivolumab plus ipilimumab in the frontline metastatic setting?
2. Which combination of ICI and VEGFR-directed therapy demonstrated OS benefit over sunitinib in the first-line setting?
3. Mention three immune checkpoints potentially involved in the regulation of RCC anti-tumour immunity.

Novel treatment strategies

No systemic therapy for localised RCC is currently recommended.

Several studies failed to demonstrate OS benefit for adjuvant VEGFR-targeted therapies in high-risk patients, with negative results for sorafenib, axitinib, pazopanib and sunitinib.

Various ICIs are being evaluated as adjuvant therapies in RCC, including nivolumab, nivolumab/ipilimumab, atezolizumab, pembrolizumab, durvalumab and durvalumab/tremelimumab.

Phase III clinical trials with immune checkpoint inhibitors in the localised setting

Experimental arms	Setting	Mechanism of action	Primary endpoints	Clinical trial identification
Nivolumab + ipilimumab	Adjuvant	Anti-PD-1 + anti-CTLA4	DFS	NCT03138512
Nivolumab	Localised, perioperative	Anti-PD-1	RFS	NCT03055013
Pembrolizumab	Adjuvant	Anti-PD-1	DFS	NCT03142334
Durvalumab +/- tremelimumab	Adjuvant	Anti-PD-L1 +/- anti-CTLA-4	DFS OS in high-risk patients	NCT03288532
Atezolizumab	Adjuvant	Anti-PD-L1	DFS	NCT03024996

CTLA-4, cytotoxic T-lymphocyte antigen 4; DFS, disease-free survival; OS, overall survival; PD-1, programmed cell death protein 1; RFS, recurrence-free survival.

Fig. 14.4

Principles of treatment intensification using immune checkpoint inhibitors in advanced clear cell renal cell carcinoma

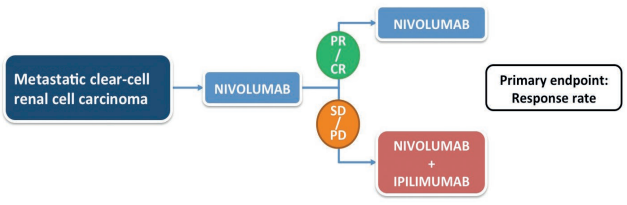

Fig. 14.5

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Numerous phase I and II trials are investigating immunotherapy-based combinations in the neoadjuvant setting.

In the metastatic setting, rescue strategies are being evaluated, with addition of ipilimumab to nivolumab in the absence of response to nivolumab single-agent.

Trials of sequential radiotherapy (RT) and immunotherapy are ongoing, based on the premise that RT might elicit immunogenic cell death.

The race for biomarkers

A genomic assay based on the expression of 16 genes has been externally validated to predict the risk of relapse in localised ccRCC.

Contrary to other solid tumours, PD-L1 expression and tumour mutation burden are not robust predictors of outcomes to ICIs in the metastatic setting.

Frameshift insertions and deletions are associated with neoantigen expression and might represent promising biomarkers of response to ICIs.

Biomarkers investigated in immune checkpoint inhibitors trials in renal cell carcinoma

Biomarker	Methods	Clinical relevance in mRCC
PD-L1 expression	Immunohistochemistry	+/-
CD8+ lymphocytes infiltration	Immunohistochemistry	+/-
Insertions and deletions	DNA sequencing	+/-
Mutational load	DNA sequencing	-
Gene expression profiling	RNA sequencing	+/-
Circulating biomarkers	Circulating tumour cells Cell-free circulating tumour DNA	Unknown

mRCC, metastatic renal cell carcinoma; PD-L1, programmed death-ligand 1.

Fig. 14.6

REVISION QUESTIONS

1. Are adjuvant VEGFR-tyrosine kinase inhibitors recommended in high-risk localised RCC?
2. Have molecular classifications been implemented in clinical practice for metastatic RCC?
3. Is PD-L1 a robust biomarker for ICI activity in RCC?

The race for biomarkers (continued)

Tumour infiltration by CD8+ T lymphocytes is another candidate biomarker reported to be associated with improved outcomes in patients treated with ICIs.

Immune and angiogenic gene expression signatures may help identify subgroups of responders to VEGFR-targeted agents or immunotherapy-based regimens.

Randomised trials based on transcriptomic profiling are under investigation (BIONIKK trial, NCT02960906).

Principles of investigated personalised therapy according to gene expression signatures

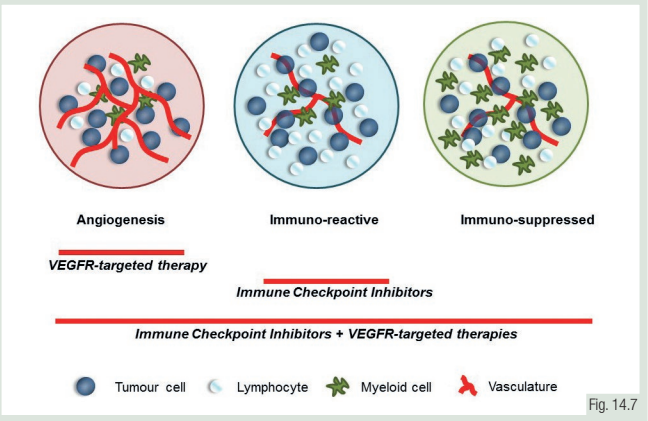

Fig. 14.7

VEGFR, vascular endothelial growth factor receptor.

The case of non-clear cell renal cell carcinoma

Main oncogenic alterations in non-clear cell renal cell carcinoma

Non-clear cell carcinoma subtype	Papillary Type 1	Papillary Type 2	Chromophobe	Collecting Duct	Medullary	Translocation
Main oncogenic alterations	MET activation Cell cycle Chromatin remodelling TERT		Metabolism *TP53* mTOR TERT Chromosomal aberrations	Immune response Cell cycle Metabolism Hippo Chromatin remodelling	*SMARCB1* loss	*MITF* fusion
	MAPKs	Metabolism Hippo NRF2-ARE Methylation				

Fig. 14.8

ARE, antioxidant response element; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; TERT, telomerase reverse transcriptase.

Molecular characterisation of non-ccRCC revealed several distinct entities in tumours that may share similar histological features.

MET activation has been reported to be a prominent alteration in both type 1 and 2 papillary carcinomas.

Oncogenic events across non-ccRCCs include deregulation of tumour metabolism, cell cycle, *TP53*, Hippo pathway, NRF2 pathway and chromatin remodeling genes.

Agents targeting MET are evaluated in ongoing clinical trials in papillary RCC.

ICIs have shown substantial antitumour activity in non-ccRCC, but outcomes may vary depending on histological subtypes.

Cabozantinib demonstrated clinical activity in retrospective non-ccRCC cohorts, requiring prospective assessments.

Response to pembrolizumab in non-clear cell renal cell carcinoma by histology in the phase II trial KEYNOTE-427

Best overall response	Overall N=165	Papillary n=118	Chromophobe n=21	Unclassified n=26
Partial or complete response	25%	25%	10%	35%
Stable disease	32%	35%	48%	8%
Progressive disease	37%	34%	43%	46%
Not available	6%	6%	0%	11%

Fig. 14.9

REVISION QUESTIONS

1. Do papillary and chromophobe RCCs harbour similar molecular alterations?
2. Which molecular alteration predominantly affects papillary RCCs?
3. Name an ICI that has been prospectively evaluated in non-ccRCC.

Summary: New drugs and novel treatment strategies for kidney cancer

- New VEGFR-targeted therapies and ICIs have improved the outcome of patients with metastatic ccRCC
- Combination therapies are becoming standard-of-care in the first-line metastatic ccRCC setting, as pembrolizumab/axitinib and nivolumab/ipilimumab demonstrated improved OS over sunitinib in all-comers and in intermediate/poor-risk patients
- Rescue strategies/therapies to overcome resistance to ICIs in subsets of patients with metastatic disease are an unmet need
- Adjuvant therapy with VEGFR inhibitors does not provide consistent benefit and is currently not recommended. Immunotherapy trials are ongoing
- PD-L1 expression is not, to date, a robust predictor of response to ICIs in RCC
- Molecular stratification of patients in upcoming clinical trials can help elaborate more efficient therapeutic strategies
- ICIs and cabozantinib showed interesting activity in patients with non-clear cell histology
- The heterogeneous molecular landscape of non-ccRCC provides opportunities for biomarker-driven trials

Further Reading

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New drugs and novel treatment strategies for urothelial carcinoma

15

New treatment combinations for urothelial carcinoma

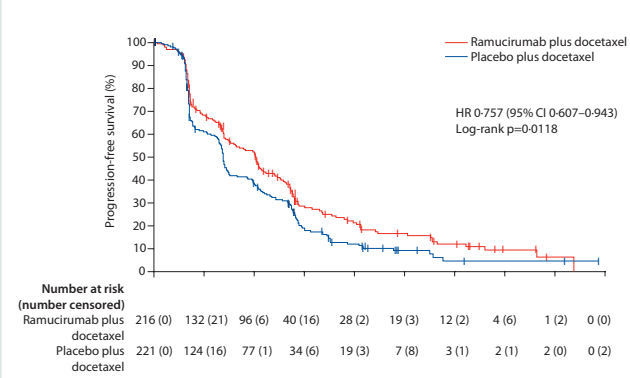
Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) inhibit anti-tumour immunity at different stages of the cancer immunity cycle: CTLA-4 is involved at the priming phase, PD-1 acts during the effector phase.

Nivolumab/ipilimumab combination was tested in a randomised phase I/II study which included 208 patients with metastatic urothelial carcinoma (UC) previously treated with platinum-based chemotherapy (ChT).

This combination was associated with significant anti-tumour activity (overall response rate [ORR] of 26%-38.5% and complete response [CR] rate of 2.9%-3.8%). Most responses occurred early and were maintained.

Responses	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg (n=26)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n=104)
Confirmed ORR, % (95% CI)	38.5 (20.2-59.4)	26.0 (17.9-35.5)
Best overall response, %		
Complete response	3.8	2.9
Partial response	34.6	23.1
Stable disease	19.2	25.0
Progressive disease	26.9	41.3

CI, confidence interval; ORR, objective response rate. Fig. 15.1



CI, confidence interval; HR, hazard ratio. Fig. 15.2

Vascular endothelial growth factor receptors (VEGFRs) 1 and 2 and their ligand, vascular endothelial growth factor (VEGF), are important mediators of tumour angiogenesis and contribute to the pathogenesis and progression of UC.

Ramucirumab is a monoclonal antibody (mAb) against VEGFR-2. In a phase III trial, ramucirumab/docetaxel improved progression-free survival (PFS) and ORR compared with placebo/docetaxel in patients with platinum-refractory metastatic UC. However, no improvement in overall survival (OS) was seen.

In a phase III trial, bevacizumab, a VEGF inhibitor, plus cisplatin/gemcitabine improved PFS compared with cisplatin/gemcitabine alone in first-line metastatic patients but failed to improve OS.

Resistance to immunotherapy occurs through immune escape mechanisms activated by multiple immune-inhibitory receptors and tyrosine kinase receptors.

Several studies are investigating the role of combining an immune checkpoint inhibitor (ICI) with a multi-TKI (tyrosine kinase inhibitor) in UC. Cabozantinib is a multi-TKI targeting VEGFR-2, MET and AXL.

A phase I trial of cabozantinib/nivolumab or cabozantinib/nivolumab/ipilimumab showed significant efficacy (ORR 38%, CR rate 10%). Both combinations were safe and well tolerated.

	Total N	SD % (N)	PR % (N)	CR % (N)	ORR % (N)
All Naïve	26	38% (8/21)	27% (6/21)	10% (2/21)	38% (8/21)
CaboNivo	15	33% (4/12)	42% (5/12)	8% (1/12)	50% (6/12)
CaboNivolpi	11	44% (4/9)	11% (1/9)	11% (1/9)	22% (2/9)
Refractory ICI CaboNivo	7	57% (4/7)	29% (2/7)	0	29% (2/7)

CaboNivo, cabozantinib/nivolumab; CaboNivolpi, cabozantinib/nivolumab/ipilimumab; CR, complete response; ICI, immune checkpoint inhibitor; ORR, objective response rate; PR, partial response; SD, stable disease. Fig. 15.3

REVISION QUESTIONS

1. At what level do CTLA-4 and PD-1 act in the cancer immunity cycle?
2. What is the role of VEGFR in tumour pathogenesis?
3. What is the purpose of combining an ICI with a TKI?

New drugs for the treatment of urothelial carcinoma

Dysregulation of the fibroblast growth factor receptor (FGFR) pathway due to mutations, amplifications and gene fusions has been described in several solid tumours including UCs.

The presence of these alterations might confer sensitivity to FGFR inhibitors. Inhibition of FGFR signalling can result in anti-proliferative activity and an anti-angiogenic effect.

FGFR3 has been shown to harbour activating mutations in 38%-66% of non-invasive UCs and in 15%-20% of invasive UCs, fusions in 2%-3% and amplifications in 3%-5% of UCs.

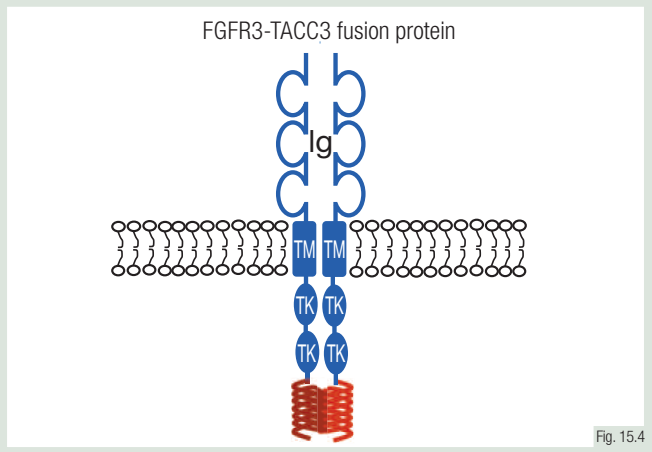


Fig. 15.4

FGFR3, fibroblast growth factor receptor; Ig, immunoglobulin; TK, tyrosine kinase domain; TM, transmembrane domain.

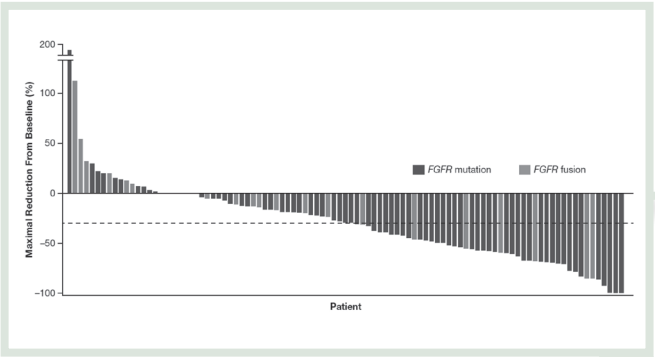


Fig. 15.5

FGFR, fibroblast growth factor receptor.

Erdafitinib, an oral, pan-FGFR (1-4) inhibitor, was investigated in a phase II trial in patients with treatment-naïve or previously treated metastatic UC with *FGFR* fusions or mutations.

The trial showed promising efficacy with an ORR of 40%, CR rate of 3% and median OS of 13.8 months. Erdafitinib was well tolerated with most adverse events (AEs) being of grade 1 or 2.

Other FGFR inhibitors are being investigated as monotherapy, such as rogaratinib (ORR 24%) and vofatamab (B-701), as well as in combination with ChT and immunotherapy.

Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) which consists of a mAb targeting nectin-4 linked to monomethyl auristatin E, a microtubule-disrupting ChT.

Nectin-4 is a cell adhesion molecule highly expressed in UC. The ADC mechanism delivers the ChT directly to the cancer cell, minimising toxicity.

EV showed promising anti-tumour activity in a phase I trial in previously treated metastatic UC, with an ORR of 41%, a median OS of 14 months and a manageable toxicity profile. A phase II trial confirmed similar results (ORR 44%) in ChT- and ICI-previously treated patients.

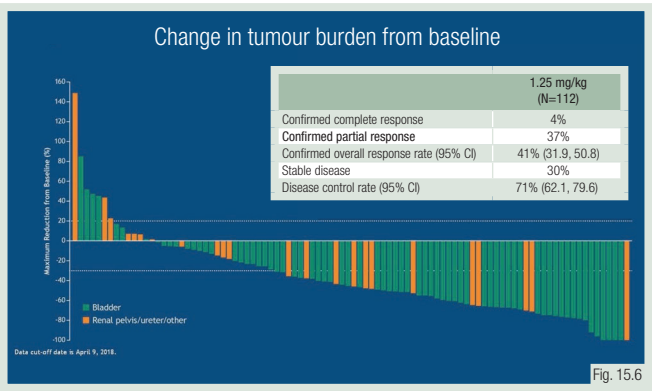


Fig. 15.6

CI, confidence interval.
Disease control rate = complete response + partial response + stable disease

REVISION QUESTIONS

1. How frequent are alterations of the FGFR pathway in UC?
2. How active are the FGFR inhibitors in UC?
3. What is an ADC?

Future directions

The Cancer Genome Atlas (TCGA) project analysed a cohort of 412 patients with localised or metastatic UC. It identified altered pathways amenable for therapeutic intervention in 69% of patients.

It also suggested a high somatic mutation rate, mainly driven by the APOBEC-mediated mutagenesis, to be a potential predictive biomarker for immunotherapy.

The study identified five expression-based distinctive molecular subtypes, each with different developmental mechanisms and therapeutic potential.

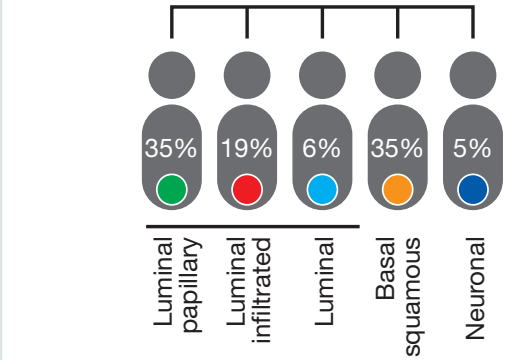


Fig. 15.7

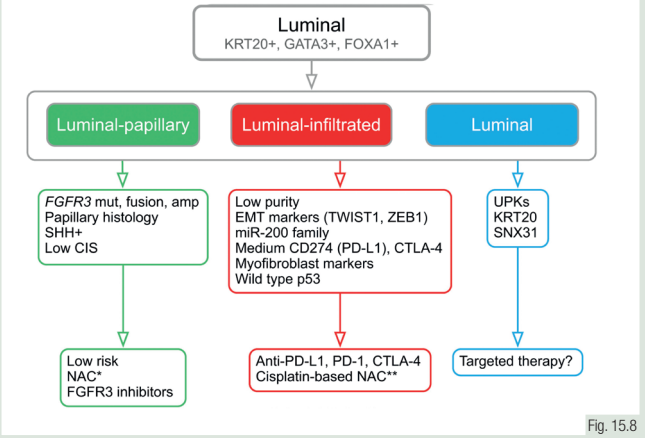


Fig. 15.8

*Low predicted likelihood of response, based on preliminary data

**Low response rate

amp, amplification; CIS, carcinoma *in situ*; CTLA-4, cytotoxic T-lymphocyte antigen 4; EMT, epithelial-mesenchymal transition; FGFR3, fibroblast growth factor receptor 3; mut, mutation; NAC, neoadjuvant chemotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SHH, sonic hedgehog; UPK, uroplakin.

1. Luminal-papillary subtype: characterised by *FGFR3* alterations and papillary histology. It might not need neoadjuvant ChT and could benefit from *FGFR3* inhibitors.

2. Luminal-infiltrated subtype: enriched on immune markers. It could benefit from programmed death-ligand 1 (PD-L1) inhibitors. ChT could be used but a low response rate is expected.

3. Luminal subtype: characterised by high expression of luminal markers (uroplakins). It could benefit from ChT and/or therapies targeting specific molecular alterations.

4. Basal-squamous subtype: it has the strongest immune expression signature. It could benefit from ChT and from PD-L1 inhibition.

5. Neuronal subtype: characterised by the expression of neuroendocrine markers and high proliferative status. It has poor prognosis and could benefit from etoposide/platinum.

Although the value of this molecular sub-classification needs to be prospectively validated in future clinical trials, it opens a window of opportunities for the personalised treatment of UC.

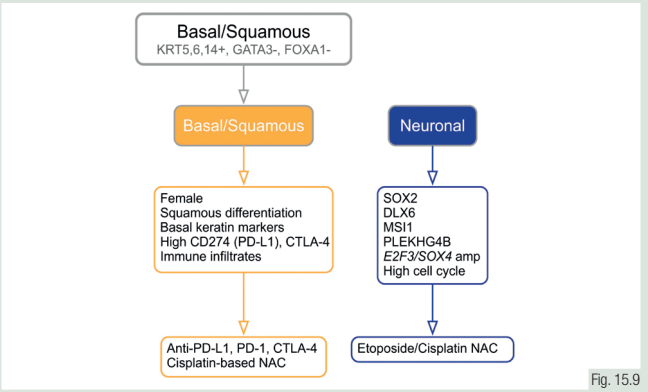


Fig. 15.9

amp, amplification; CTLA-4, cytotoxic T-lymphocyte antigen 4; NAC, neoadjuvant chemotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

REVISION QUESTIONS

1. What could potentially indicate a high mutation burden in UC?
2. What are the five molecular subtypes of UC in the TCGA?
3. Which subtypes could potentially benefit from immunotherapy?

Summary: New drugs and novel treatment strategies for urothelial carcinoma

- There are several new treatment combinations currently under investigation for metastatic UC
- Nivolumab/ipilimumab showed significant anti-tumour activity in a randomised phase I/II study
- Ramucirumab/docetaxel improved PFS and ORR in a phase III trial compared with docetaxel alone
- Cabozantinib/nivolumab or cabozantinib/nivolumab/ipilimumab showed promising anti-tumour activity
- The FGFR pathway is frequently altered in UC and might confer sensitivity to FGFR inhibitors
- Erdafitinib, an FGFR inhibitor, showed an ORR of 40% in a phase II trial with FGFR-altered UC
- Enfortumab is an ADC targeting nectin-4 linked to monomethyl auristatin E
- Enfortumab showed promising anti-tumour activity and manageable toxicity in both phase I and phase II trials
- TCGA discovered that UC is characterised by a high somatic mutation rate
- TCGA project identified five distinctive expression-based molecular subtypes

Further Reading

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Appendix 1: WHO Classification of Tumours, 4th Edition, Volumes 8 and 10

(WHO Classification of Tumours of the Urinary System and Male Genital Organs; WHO Classification of Tumours of Endocrine Organs)

Tumours of the kidney

Renal cell tumours

- Clear cell renal cell carcinoma
- Multilocular cystic renal neoplasm of low malignant potential
- Papillary renal cell carcinoma
- Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma
- Chromophobe renal cell carcinoma
- Collecting duct carcinoma
- Renal medullary carcinoma
- MiT family translocation renal cell carcinomas
- Succinate dehydrogenase-deficient renal carcinoma
- Mucinous tubular and spindle cell carcinoma
- Tubulocystic renal cell carcinoma
- Acquired cystic disease-associated renal cell carcinoma
- Clear cell papillary renal cell carcinoma
- Renal cell carcinoma, unclassified
- Papillary adenoma
- Oncocytoma

Metanephric tumours

- Metanephric adenoma
- Metanephric adenofibroma
- Metanephric stromal tumour

Nephroblastic and cystic tumours occurring mainly in children

- Nephrogenic rests
- Nephroblastoma
- Cystic partially differentiated nephroblastoma
- Paediatric cystic nephroma

Mesenchymal tumours

Mesenchymal tumours occurring mainly in children

- Clear cell sarcoma
- Rhabdoid tumour
- Congenital mesoblastic nephroma
- Ossifying renal tumour of infancy

Mesenchymal tumours occurring mainly in adults

- Leiomyosarcoma (including renal vein leiomyosarcoma)
- Angiosarcoma
- Rhabdomyosarcoma
- Osteosarcoma
- Synovial sarcoma
- Ewing sarcoma
- Angiomyolipoma
- Epithelioid angiomyolipoma
- Leiomyoma
- Haemangioma
- Lymphangioma
- Haemangioblastoma
- Juxtaglomerular cell tumour
- Renomedullary interstitial cell tumour
- Schwannoma
- Solitary fibrous tumour

Mixed epithelial and stromal tumour family

- Adult cystic nephroma
- Mixed epithelial and stromal tumour

Neuroendocrine tumours

- Paraganglioma

Renal haematopoietic neoplasms

Germ cell tumours

Metastatic tumours

Tumours of the urinary tract

Infiltrating urothelial carcinoma

- Nested, including large nested
- Microcystic
- Micropapillary
- Lymphoepithelioma-like
- Plasmacytoid / signet ring cell / diffuse
- Sarcomatoid
- Giant cell
- Poorly differentiated
- Lipid-rich
- Clear cell

Non-invasive urothelial neoplasms

- Urothelial carcinoma *in situ*
- Non-invasive papillary urothelial carcinoma, low-grade
- Non-invasive papillary urothelial carcinoma, high-grade
- Papillary urothelial neoplasm of low malignant potential
- Urothelial papilloma
- Inverted urothelial papilloma
- Urothelial proliferation of uncertain malignant potential
- Urothelial dysplasia

Squamous cell neoplasms

- Pure squamous cell carcinoma
- Verrucous carcinoma
- Squamous cell papilloma

Glandular neoplasms

- Adenocarcinoma
- Villous adenoma

Urachal carcinoma

Tumours of Müllerian type

Neuroendocrine tumours

- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma
- Well-differentiated neuroendocrine tumour
- Paraganglioma

Melanocytic tumours

- Malignant melanoma
- Naevus
- Melanosis

Mesenchymal tumours

- Rhabdomyosarcoma
- Leiomyosarcoma
- Angiosarcoma
- Inflammatory myofibroblastic tumour
- Perivascular epithelioid cell tumour
- Solitary fibrous tumour
- Leiomyoma
- Haemangioma
- Granular cell tumour
- Neurofibroma
- Other mesenchymal tumours

Haematopoietic and lymphoid tumours

- Lymphoma
- Plasmacytoma

Carcinoma of Skene, Cowper and Littre glands

Metastatic tumours

Epithelial tumours of the upper urinary tract

Epithelial tumours arising in a bladder diverticulum

Urothelial tumours of the urethra

Tumours of the prostate

Acinar adenocarcinoma

Prostatic intraepithelial neoplasia, high-grade

Intraductal carcinoma

Ductal adenocarcinoma

Urothelial carcinoma

Squamous neoplasms

- Adenosquamous carcinoma
- Squamous cell carcinoma

Basal cell carcinoma

Neuroendocrine tumours

- Neuroendocrine cells in usual prostate adenocarcinoma
- Adenocarcinoma with Paneth cell–like neuroendocrine differentiation
- Well-differentiated neuroendocrine tumour
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma

Mesenchymal tumours

- Stromal tumour of uncertain malignant potential and stromal sarcoma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Leiomyoma
- Other mesenchymal tumours

Haematolymphoid tumours

- Lymphoma
- Leukaemia

Miscellaneous tumours

Metastatic tumours

Seminal vesicle tumours

- Adenocarcinoma
- Squamous cell carcinoma
- Mixed epithelial and stromal tumours
- Cystadenoma
- Mesenchymal tumours
- Miscellaneous seminal vesicle tumours
- Metastatic tumours

Tumours of the testis and paratesticular tissue

Germ cell tumours

Germ cell tumours derived from germ cell neoplasia *in situ*

Germ cell neoplasia in situ
Tumours of a single histological type (pure forms)
- Seminoma

Non-seminomatous germ cell tumours
- Embryonal carcinoma
- Yolk sac tumour, postpubertal-type
- Trophoblastic tumours
  - Choriocarcinoma
  - Non-choriocarcinomatous trophoblastic tumours
- Teratoma, postpubertal-type
- Teratoma with somatic-type malignancy

Non-seminomatous germ cell tumours of more than one histological type
- Mixed germ cell tumours

Germ cell tumours of unknown type
- Regressed germ cell tumours

Germ cell tumours unrelated to germ cell neoplasia *in situ*

- Spermatocytic tumour
- Teratoma, prepubertal-type
- Mixed teratoma and yolk sac tumour, prepubertal-type
- Yolk sac tumour, prepubertal-type

Sex cord-stromal tumours

Pure tumours
- Leydig cell tumour
- Sertoli cell tumour, NOS
- Large cell calcifying Sertoli cell tumour
- Intratubular large cell hyalinizing Sertoli cell neoplasia
- Granulosa cell tumour
  - Adult granulosa cell tumour
  - Juvenile granulosa cell tumour
- Tumours in the fibroma-thecoma group

Mixed and unclassified sex cord-stromal tumours
Emerging entity

Tumour containing both germ cell and sex cord-stromal elements

- Gonadoblastoma

Miscellaneous tumours of the testis and paratesticular tissue

- Ovarian epithelial-type tumours
- Juvenile xanthogranuloma
- Haemangioma

Haematolymphoid tumours

- Diffuse large B-cell lymphoma
- Follicular lymphoma, NOS
- Extranodal NK/T-cell lymphoma, nasal-type
- Plasmacytoma
- Myeloid sarcoma
- Rosai-Dorfman disease

Tumours of collecting ducts and rete testis

- Adenoma
- Adenocarcinoma

Tumours of paratesticular structures

- Adenomatoid tumour
- Mesothelioma
- Epididymal tumours
  - Cystadenoma
  - Papillary cystadenoma
  - Adenocarcinoma
- Squamous cell carcinoma
- Melanotic neuroectodermal tumour
- Nephroblastoma
- Paraganglioma

Mesenchymal tumours of the spermatic cord and testicular adnexa

- Adipocytic tumours
- Smooth muscle tumours
- Skeletal muscle tumours
- Fibroblastic/myofibroblastic tumours
- Nerve sheath tumours
- Other mesenchymal tumours of the spermatic cord and testicular adnexa

Metastatic tumours

Tumours of the penis

Malignant epithelial tumours

Squamous cell carcinoma
Non-HPV-related squamous cell carcinomas
- Squamous cell carcinoma, usual type
- Pseudohyperplastic carcinoma
- Pseudoglandular carcinoma
- Verrucous carcinoma
- Carcinoma cuniculatum
- Papillary carcinoma, NOS
- Adenosquamous carcinoma
- Sarcomatoid squamous cell carcinoma
- Mixed squamous cell carcinoma

HPV-related squamous cell carcinoma
- Basaloid squamous cell carcinoma
- Papillary-basaloid carcinoma
- Warty carcinoma
- Warty-basaloid carcinoma
- Clear cell carcinoma
- Lymphoepithelioma-like carcinoma
- Other rare carcinomas

Precursor lesions

- Penile intraepithelial neoplasia
- Extramammary Paget disease

Melanocytic lesions

Mesenchymal tumours

Penile lymphomas

Metastatic tumours

Tumours of the adrenal cortex

Adrenal cortical carcinoma
Adrenal cortical adenoma
Sex cord-stromal tumours
Adenomatoid tumour
Mesenchymal and stromal tumours
- Myelolipoma
- Schwannoma

Haematolymphoid tumours
Secondary tumours

Tumours of the adrenal medulla and extra-adrenal paraganglia

Phaeochromocytoma
Extra-adrenal paragangliomas
- Head and neck paragangliomas
- Sympathetic paraganglioma

Neuroblastic tumours of the adrenal gland
Composite phaeochromocytoma
Composite paraganglioma

Abbreviations:
HPV, human papillomavirus; NK, natural killer; NOS, not otherwise specified; WHO, World Health Organization.

Appendix 2: UICC TNM Classification of Malignant Tumours, 8th edition (2018)*

Urinary Bladder: Urothelial Carcinomas

Primary Tumour (T)

T Category	T Criteria
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Urothelial carcinoma *in situ*: 'flat tumour'
T1	Tumour invades lamina propria (subepithelial connective tissue)
T2	Tumour invades muscularis propria **pT2a** Tumour invades superficial muscularis propria (inner half) **pT2b** Tumour invades deep muscularis propria (outer half)
T3	Tumour invades perivesical soft tissue **pT3a** Tumour invades perivesical soft tissue microscopically **pT3b** Tumour invades perivesical soft tissue macroscopically (extravesical mass)
T4	Extravesical tumour directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall **T4a** Extravesical tumour invades diectly into prostatic stroma, seminal vesicles, uterus, vagina **T4b** Extravesical tumour invades pelvic wall, abdominal wall

T Suffix	Definition
(m)	Select if synchronous primary tumours are found in single organ

Regional Lymph Node (N)

N Category	N Criteria
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

N Suffix	Definition
(sn)	Select if regional lymph node metastasis identified by SLN biopsy only
(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only

Distant Metastasis (M)**

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis **cM1a** Distant metastasis limited to lymph nodes beyond the common iliacs **cM1b** Non-lymph-node distant metastasis
pM1	Distant metastasis, microscopically confirmed **pM1a** Distant metastasis limited to lymph nodes beyond the common iliacs, microscopically confirmed **pM1b** Non-lymph-node distant metastases, microscopically confirmed

Histologic Grade (G)

G	G Definition
LG	Low-grade
HG	High-grade

Urinary Bladder: Squamous Cell Carcinoma and Adenocarcinoma

Primary Tumour (T)

T Category	T Criteria
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Urothelial carcinoma *in situ*: "flat tumour"
T1	Tumour invades lamina propria (subepithelial connective tissue)
T2	Tumour invades muscularis propria **pT2a** Tumour invades superficial muscularis propria (inner half) **pT2b** Tumour invades deep muscularis propria (outer half)
T3	Tumour invades perivesical soft tissue **pT3a** Tumour invades perivesical soft tissue microscopically **pT3b** Tumour invades perivesical soft tissue macroscopically (extravesical mass)
T4	Extravesical tumour directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall **T4a** Extravesical tumour invades directly into prostatic stroma, seminal vesicles, uterus, vagina **T4b** Extravesical tumour invades pelvic wall, abdominal wall

T Suffix	Definition
(m)	Select if synchronous primary tumours are found in single organ

Regional Lymph Node (N)

N Category	N Criteria
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

N Suffix	Definition
(sn)	Select if regional lymph node metastasis identified by SLN biopsy only
(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only

Distant Metastases (M)**

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis **cM1a** Distant metastasis limited to lymph nodes beyond the common iliacs **cM1b** Non-lymph-node distant metastases
pM1	Distant metastasis, microscopically confirmed **pM1a** Distant metastasis limited to lymph nodes beyond the common iliacs, microscopically confirmed **pM1b** Non-lymph-node distant metastases, microscopically confirmed

Histologic Grade (G)

G	G Definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

*Used with the permission of the Union for International Cancer Control (UICC), Geneva, Switzerland. The original source for this material is the UICC TNM Classification of Malignant Tumours, Eighth Edition (2018) published by Wiley and Sons.

**The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

Abbreviations:
ENE, extranodal extension; FNA, fine needle aspiration; SLN, sentinel lymph node.

Prostate Cancer

Primary Tumour (T)

Clinical T (cT)

T Category	T Criteria
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour that is not palpable **T1a** Tumour incidental histological finding in 5% or less of tissue resected **T1b** Tumour incidental histological finding in more than 5% of tissue resected **T1c** Tumour identified by needle biopsy found in one or both sides, but not palpable
T2	Tumour is palpable and confined within prostate **T2a** Tumour involves one-half of one side or less **T2b** Tumour involves more than one-half of one side but not both sides **T2c** Tumour involves both sides
T3	Extraprostatic tumour that is not fixed or does not invade adjacent structures **T3a** Extraprostatic extension (unilateral or bilateral) **T3b** Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

T Suffix	Definition
(m)	Select if synchronous primary tumours are found in single organ

Pathological T (pT)

T Category	T Criteria
T2	Organ confined
T3	Extraprostatic extension **T3a** Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck **T3b** Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Note: There is no pathological T1 classification.
Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

T Suffix	Definition
(m)	Select if synchronous primary tumours are found in single organ

Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No positive regional lymph nodes
N1	Metastases in regional lymph node(s)

N Suffix	Definition
(sn)	Select if regional lymph node metastasis identified by SLN biopsy only
(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only

Distant Metastasis (M)**

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis **cM1a** Non-regional lymph node(s) **cM1b** Bone(s) **cM1c** Other site(s) with or without bone disease
pM1	Distant metastasis, microscopically confirmed **pM1a** Non-regional lymph node(s), microscopically confirmed **pM1b** Bone(s), microscopically confirmed **pM1c** Other site(s) with or without bone disease, microscopically confirmed

Note: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.

Histologic Grade Group (G)

Grade Group (G)	Gleason score	Gleason pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Penile Cancer

Primary Tumour (T)

T Category	T Criteria
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ* (Penile intraepithelial neoplasia [PeIN])
Ta	Non-invasive localised squamous cell carcinoma
T1	Glans: Tumour invades lamina propria Foreskin: Tumour invades dermis, lamina propria, or dartos fascia Shaft: Tumour invades connective tissue between epidermis and corpora regardless of location All sites with or without lymphovascular invasion or perineural invasion and is or is not high grade **T1a** Tumour is without lymphovascular invasion or perineural invasion and is not high grade (i.e., grade 3 or sarcomatoid) **T1b** Tumour exhibits lymphovascular invasion and/or perineural invasion or is high grade (i.e., grade 3 or sarcomatoid)
T2	Tumour invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion
T3	Tumour invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion
T4	Tumour invades into adjacent structures (i.e., scrotum, prostate, pubic bone)

T Suffix	Definition
(m)	Select if synchronous primary tumours are found in single organ

Regional Lymph Node (N)

Clinical N (cN)

N Category	N Criteria
cNX	Regional lymph nodes cannot be assessed
cN0	No palpable or visibly enlarged inguinal lymph nodes
cN1	Palpable mobile unilateral inguinal lymph node
cN2	Palpable mobile ≥2 unilateral inguinal nodes or bilateral inguinal lymph nodes
cN3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral

N Suffix	Definition
(sn)	Select if regional lymph node metastasis identified by SLN biopsy only
(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only

Abbreviations:
FNA, fine needle aspiration; SLN, sentinel lymph node.

Penile Cancer (continued)

Pathological N (pN)

N Category	N Criteria
pNX	Lymph node metastasis cannot be assessed
pN0	No lymph node metastasis
pN1	≤2 unilateral inguinal metastases, no ENE
pN2	≥3 unilateral inguinal metastases or bilateral metastases, no ENE
pN3	ENE of lymph node metastases or pelvic lymph node metastases

Distant Metastasis (M)**

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Histologic Grade (G)

G Category	G Criteria
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated/high grade

Kidney Cancer

Primary Tumour (T)

T Category	T Criteria
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤7 cm in greatest dimension, limited to the kidney **T1a** Tumour ≤4 cm in greatest dimension, limited to the kidney **T1b** Tumour >4 cm but ≤7 cm in greatest dimension limited to the kidney
T2	Tumour >7 cm in greatest dimension, limited to the kidney **T2a** Tumour >7 cm but ≤10 cm in greatest dimension, limited to the kidney **T2b** Tumour >10 cm, limited to the kidney
T3	Tumour extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia **T3a** Tumour extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia **T3b** Tumour extends into the vena cava below the diaphragm **T3c** Tumour extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

T Suffix	Definition
(m)	Select if synchronous primary tumours are found in single organ

Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

N Suffix	Definition
(sn)	Select if regional lymph node metastasis identified by SLN biopsy only
(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only

Distant Metastasis (M)**

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Histologic Grade (G)

G Category	G Criteria
GX	Grade cannot be assessed
G1	Nucleoli absent or inconspicuous and basophilic at 400x magnification
G2	Nucleoli conspicuous and eosinophilic at 400x magnification, visible but not prominent at 100x magnification
G3	Nucleoli conspicuous and eosinophilic at 100x magnification
G4	Marked nuclear pleomorphism and/or multinucleate giant cells and/or rhabdoid and/or sarcomatoid differentiation

Testicular Cancer

Primary Tumour (T)

Clinical T (cT)

T Category	T Criteria
cTX	Primary tumour cannot be assessed
cT0	No evidence of primary tumour
cTis	Germ cell neoplasia *in situ*
cT4	Tumour invades scrotum with or without vascular/lymphatic invasion

Note: Except for Tis confirmed by biopsy and T4, the extent of the primary tumour is classified by radical orchiectomy. TX may be used for other categories of clinical staging.

T Suffix	Definition
(m)	Select if synchronous primary tumours are found in single organ

Pathological T (pT)

pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour
pTis	Germ cell neoplasia *in situ*
pT1	Tumour limited to testis (including rete testis invasion) without lymphovascular invasion **pT1a*** Tumour smaller than 3 cm in size **pT1b*** Tumour 3 cm or larger in size
pT2	Tumour limited to testis (including rete testis invasion) with lymphovascular invasion OR Tumour invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion
pT3	Tumour directly invades spermatic cord soft tissue with or without lymphovascular invasion
pT4	Tumour invades scrotum with or without lymphovascular invasion

*Subclassification of pT1 applies only to pure seminoma.

T Suffix	Definition
(m)	Select if synchronous primary tumours are found in single organ

Regional Lymph Node (N)

Clinical N (cN)

N Category	N Criteria
cNx	Regional lymph nodes cannot be assessed
cN0	No regional lymph node metastasis
cN1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension OR Multiple lymph nodes, none larger than 2 cm in largest dimension

Abbreviations:
ENE, extranodal extension; FNA, fine needle aspiration; SLN, sentinel lymph node.

cN2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension OR Multiple lymph nodes, any one mass larger than 2 cm but not larger than 5 cm in greatest dimension
cN3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

N Suffix	Definition
(sn)	Select if regional lymph node metastasis identified by SLN biopsy only
(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only

Pathological N (pN)

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension and less than or equal to five nodes positive, none larger than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension; or more than five nodes positive, none larger than 5 cm; or evidence of extranodal extension of tumour
pN3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

Distant Metastasis (M)**

M Category	M Criteria
cM0	No distant metastases
cM1	Distant metastases **cM1a** Non-retroperitoneal nodal or pulmonary metastases **cM1b** Non-pulmonary visceral metastases
pM1	Distant metastases, microscopically confirmed **pM1a** Non-retroperitoneal nodal or pulmonary metastases, microscopically confirmed **pM1b** Non-pulmonary visceral metastases, microscopically confirmed

Histologic Grade (G)

Germ cell tumours are not graded.

Adrenal Cancer

Primary Tumour (T)

T Category	T Criteria
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤5 cm in greatest dimension, no extra-adrenal invasion
T2	Tumour >5 cm, no extra-adrenal invasion
T3	Tumour of any size with local invasion, but not invading adjacent organs
T4	Tumour of any size that invades adjacent organs (kidney, diaphragm, pancreas, spleen, or liver) or large blood vessels (renal vein or vena cava)

T Suffix	Definition
(m)	Select if synchronous primary tumours are found in single organ

Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional node metastasis
N1	Metastasis in regional lymph node(s)

N Suffix	Definition
(sn)	Select if regional lymph node metastasis identified by SLN biopsy only
(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only

Distant Metastasis (M)**

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Histologic Grade (G)

G Category	G Criteria
LG	Low grade (≤20 mitoses per 50 HPF)
HG	High grade (>20 mitoses per 50 HPF); *TP53* or *CTNNB* mutation

Abbreviations:
FNA, fine needle aspiration; HPF; high-power field; SLN, sentinel lymph node.

Appendix 3: Definition of regional lymph nodes

Kidney:

The regional lymph nodes include the hilar, abdominal para-aortic, and paracaval nodes

Urinary bladder:

The regional lymph nodes are the pelvic nodes along and below the bifurcation of the common iliac arteries

Prostate:

The regional lymph nodes include the pelvic nodes below the bifurcation of the common iliac arteries

Penile:

The regional lymph nodes are the superficial and deep inguinal and the pelvic nodes

Adrenal:

The regional lymph nodes are the hilar, abdominal para-aortic, and paracaval nodes

Testis:

The regional lymph nodes are the abdominal para-aortic (periaortic), preaortic, interaortocaval, precaval, paracaval, retrocaval, and retroaortic nodes. Nodes along the spermatic vein should be considered regional. The intrapelvic nodes and the inguinal nodes are considered regional after scrotal or inguinal surgery

Image sources

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Index

Note: Abbreviations used in the index are listed on pages xii-xiii

A

B

C

D

E

F

G

H

M

N

O

P

R

S

T

U

V

W

Y

Z

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