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Improving outcomes in urological cancers: The impact of ''multidisciplinary team meetings''

Peter L. Acher*, Anthony J. Young, Russell Etherington-Foy, Philip J. McCahy, Anthony M. Deane

William Harvey Hospital, Department of Urology, Ashford, Kent, TN24 0L2, UK

KEYWORDS
Multidisciplinary;
Clinical governance;
Cancer

Abstract *Introduction:* In order to improve the outcomes of urological cancers, guidelines published by the National Institute of Clinical Excellence encourage the management of cancer patients by specific Multi-Disciplinary Teams (MDTs) with discussion of cancer patients at MDT Meetings. The aim of this prospective study was to examine the changes in management resulting from review at MDT Meetings in our unit.
Methods: Over a six month period 124 cancer cases were discussed at 10 meetings. Prior to the meetings consultants completed a form stating their proposed management and whether they thought this would be changed after discussion. At the meeting histological, radiological and clinical data were reviewed and a collective decision about the optimal treatment was made. Any changes were recorded.
Results: Two of 124 cases had their clinical management changed as a result of the meeting. These were identified (amongst 10 others) as potential 'change cases' prior to the meeting. Four changes were made to histological reports and 1 to radiology; none of these affected clinical management.
Conclusion: Discussion of cancer cases at MDMs made no difference to the clinical management in over 98% of cases. Consultants correctly identified cases requiring discussion, indicating that a selective rather than blanket approach would be appropriate. This has the potential to reduce the considerable costs involved without affecting patient care.

* Corresponding author. Fax: +44 207 1886787.
E-mail address: peter.acher@gstt.nhs.uk (P.L. Acher).

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Introduction

UK Guidelines by the National Institute for Clinical Excellence (NICE) published in the document *Improving outcomes in urological cancers* promote the formation of local Multidisciplinary Teams (MDTs) made up of designated specialists to collectively manage all cases of urological cancer (both new and existing).[1] It is noted that although urological malignancies account for 11.7% of cancer deaths[2] urological services have lagged behind other specialities in forming co-ordinated MDTs.[1] The guidelines encourage regular MDT meetings where relevant information is gathered and cases are discussed with a view to making collective evidence-based decisions.[1] However, there is a lack of evidence supporting the idea that MDT meetings will improve cancer outcomes in urology.[1]

The aim of this prospective study was to examine the impact of MDT meetings in a District General Hospital with respect to changes in management resulting from case review.

Methods

MDT meetings in our unit occupy one session each fortnight and are attended by three consultants in urology, a lead clinician, a pathologist, a radiologist, an oncologist, two urology nurse practitioners and junior staff. Meetings were analysed prospectively over a period of 6 months. Prior to each meeting, individual consultants were requested to complete a pro forma for each case under their care to be discussed stating the patient's details and diagnosis, the consultant's own management plan and whether he thought this had potential to be changed. At each meeting one of the authors recorded any changes made to pathology or radiological reports following MDT review and compared the agreed management plan for each case to that proposed by the clinician.

Results

During the study 124 urological cancer cases were discussed; consultants identified 12 of these as potential ''case changes'' prior to the meetings. There were two clinical management changes as a result of MDT discussion, both of which were from the ''case change'' group (see Table 1).

There were four histological and one radiological report changes (see Table 1); none of these had any alteration on clinical management.

Conclusion

It appears that the vast majority of newly diagnosed urological cancer cases do not require discussion at an MDT meeting, and those that do benefit can be filtered out by consultants in advance. Whilst it may be the case that a longer study would have revealed more pertinent management changes, possibly from larger numbers of diagnostic reviews, we feel that this is unlikely and the discussion of every single case not justified.

Table 1 Changes arising from the meetings

Change	Notes
Histological	
1. Grade 2 to Grade 3 bladder cancer[a]	86-year-old male — inoperable tumour
2. Grade 1 to Grade 2 bladder cancer[a]	77-year-old male (T1 tumour) — undergoing surveillance and intravesical chemotherapy
3. Gleason 3 + 5 to 4 + 5 prostate cancer[a]	85-year-old male — undergoing hormone manipulation
4. Gleason 2 + 2 to 3 + 2 prostate cancer[a]	66-year-old male — suitable for radical prostatectomy
Radiological	
1. Renal cyst[a,b]	Reported as benign but queried by Urologist. Later considered benign therefore no management change
Management	
1. Radiotherapy cf symptomatic treatment[b]	84-year-old male with locally advanced bladder cancer; Outcome — death from cardiac causes 2 months later
2. Regular review cf surgery[b]	24-year-old male with a suspicious testicular lesion on USS; Outcome — continues to be under review 12 months later

[a] Made no difference to management.
[b] Identified by consultants as possible ''case changes'' prior to the meetings.

Multidisciplinary team management (with regular meetings) is a fundamental pillar of *Improving outcomes in urological cancers* and is becoming more widespread across a variety of specialities[1] indeed the concept has been described as a fourth cancer treatment modality after surgery, chemotherapy and radiotherapy.[3] The knowledge that a panel of specialists discuss every cancer case is reassuring both to patients and clinicians alike[4] and will be amongst patient expectations increasingly so in the future.[5] This can be seen as part of the movement towards a consultant-delivered service.

By working together, all modalities can be considered from the outset allowing improved planning and preventing any compromise later on in a patient's treatment.[4] The administrative aspect has potential to facilitate auditing and monitoring of local services, brings together all aspects of patient care and prevents loss of follow-up, forming a ''co-ordination'' mechanism[6] which improves feedback and ultimately, clinical outcomes.[7] There is also a highly educational value to be attached for all attendees.[8]

There are, however, hurdles to overcome particularly in terms of funding and manpower,[4,9,10] the latter necessitating co-ordination with other cancer groups. To date, few centres have been allocated extra resources for meetings; ours has been fortunate to receive a dedicated session every 2 weeks. Specialist uropathologists and uroradiologists reviewing all relevant cases prior to meetings could reduce meeting times without compromising patient care. Attendance at these sessions inevitably takes time away from the provision of other services such as clinics or operating lists.

The introduction of MDT meetings is an expensive exercise: NICE have calculated this to be £6.4 million on a national scale to cover co-ordinators, additional staff time and additional consultant sessions.[1] The results of this study suggest that the costs are not well defensible.

Our study shows that consultants are quite capable of identifying cases that require discussion with other team members. The small number of management changes as a result of MDT meeting (less than 2% of cases discussed) had been recognised in this manner; adopting a targeted approach could make savings on resources without adversely affecting patient care provided all cancer management decisions are continued to be brought to the attention of a consultant. The low rate of changes may well be cited as a measure of the success of MDT meetings: an advantage that would not be lost.

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Exploring the impact of uro-oncology multidisciplinary team meetings on patient outcomes: A systematic review

Blake Askelin [a,c] · Alica Hind [a,c] · Catherine Paterson [a,b]

Affiliations & Notes · Article Info

Abstract

Purpose

Multidisciplinary team (MDT) meetings are mainstay clinical management globally. Clinical guidelines state that patients should be considered for MDT review, but evidence has identified that within the specialty of uro-oncology not all patients are reviewed by an MDT. This systematic review aimed to understand the impact of uro-oncology MDT meetings on patient outcomes, to explore how patient engagement is incorporated in the process, and

Methods

A systematic review was reported according to PRISMA guidelines. Electronic databases (MEDLINE, CINAHL and PsychINFO) were searched in EBSCOhost from January 2010 to March 2021, using a range of key search words. Studies were assessed for inclusion according to a pre-defined eligibility criteria. Data extraction and quality assessment was undertaken. The findings were tabulated, and a narrative synthesis undertaken.

Results

373 articles were screened, and seven studies were included. The studies were conducted in a range of international countries which provided an overview of uro-oncology MDTs in different healthcare contexts. The following themes were identified: 1) MDT and clinical outcomes, 2) structure and format, 3) patient engagement in the process, and 4) barriers and facilitators.

Conclusion

Cancer care is constantly being challenged due to complex newer therapies, including multimodality treatments, and newer emergent broader considerations such as, oncogeriatrics, genetic counselling, and survivorship issues which should have a central place for consideration in the MDT.

Keywords

Multidisciplinary teams · Cancer · Genitourinary · Review · Systematic · Patient outcomes · Decision-making · Cancer care

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Exploring Clinical Decision-Making among the Uro-oncology Multidisciplinary Team: A Qualitative Study

Blake Askelin [a], Alicia Hind [b], Catherine Paterson [c]

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Abstract

Objective

The aim of this qualitative study was to understand the clinical decision-making process among the genitourinary oncology (GU) multidisciplinary team (MDT) and how patients are engaged in the process.

Data Sources

A qualitative descriptive study design was conducted and has been reported according to the Consolidated Criteria for Reporting Qualitative Studies (COREQ). Members of the GU MDT were recruited from a metropolitan tertiary hospital and cancer regional center in Australia serving a population of 550,000. Semistructured interviews were conducted, and the audiorecordings were transcribed; an inductive thematic analysis was used to provide insight from multiple perspectives.

Conclusion

Three themes emerged: (1) the role and scope of the uro-oncology MDT, (2) lack of person-centered clinical decision-making, and (3) the barriers and facilitators. Amid the COVID-19 pandemic, the MDT discussions transitioned to virtual application, which was found to be convenient and efficient and improved attendance. The GU cancer MDT had a prominent biomedical focus that lacked person-centered considerations. Additional research is needed to explore how person-centered outcomes can be incorporated into the clinical decision-making process.

Implication for Nursing Practice

The GU MDT is increasingly important in the care of uro-oncology patients. There appears to be barriers to the implementation of person-centered discussions in the MDT. The effective delivery of multidisciplinary care is contingent on an appropriate mechanism for collaborative communication between all MDT members and patients given the limited involvement of the patient in the MDT itself.

Introduction

Multidisciplinary team (MDT) meetings are a mandatory and central part of cancer services globally. Cancer MDT meetings are generally held on a weekly basis and are considered the gold standard for cancer care.[1] Although not always obligatory, MDTs are widely implemented internationally but with varying uptake of patient referrals from clinicians.[2] The fundamental aim of cancer MDT meetings are to improve individual patient treatment outcomes through discussions held by cancer health care professionals representative of nurses, radiation oncologists, medical oncologists, surgeons, pathologists, and radiologists.[3] Timely discussions

between MDT clinical experts serves the purpose to deliberate on all clinical treatment options and to develop personalized evidence-informed care recommendations that consider each individual patient's preferences and needs.[2]

Internationally, cancer MDT meetings are held with all common tumor streams as a health care professional alliance guided by their willingness to agree on evidence-based clinical decisions and to coordinate the delivery of care throughout the cancer trajectory and support patients to take an active role.[4] Research studies have shown that given the specialties of cancer MTDs,5, 6, 7 each tumor-specific MDT will have their own barriers and facilitators that affect patient outcomes.[2] There is also disparity globally as to whether patients are viewed as part of the MDT or even invited to attend the MDT meeting.

The uro-oncology MDT aims to optimize the clinical management of penile, bladder, prostate, testicular, and kidney cancer.[8] However, evidence has underscored that within the specialty of uro-oncology,[2] not all patients are reviewed by an MDT, with a distinct lack of patient engagement in the process. Research has shown that when patients are discussed in the MDT meeting, it increases the opportunity for patients to consider taking part in clinical trials; often patients experience changes to management plans from those initially advised to them by their individual treating clinician.9, 10, 11 Consequently, a significant number of patients affected by GU cancers may receive suboptimal clinical management due to not having access to a timely MDT clinical review and not receiving MDT-informed changes to clinical management.[2] This is a very important area for future research to understand the complexities (such as public and private hospital settings) and the decision-making process of clinicians who do not refer their patients for an MDT meeting discussion and, importantly, why other patients are referred.

Decision-making is a fundamental process of choosing between alternatives[12] to information that is gathered, interpreted, and evaluated in order to select an evidence-based choice of action in health care.[13] The cognitive continuum theory[14,15] is a decision-making theory that has be widely applied in different health care professional groups,[16] including cancer.[17] The importance of clinical decision-making processes among the uro-oncology MDT members is central; cancer care and treatments are constantly being challenged due to complex and multimodality therapy,[18] and newer, broader emergent considerations, such as geriatric oncology,[19] genetic counseling, and addressing unmet survivorship care issues in uro-oncology,20, 21, 22, 23, 24 are currently not being addressed within existing MDT GU cancer services. There is a lack of understanding on how patients are engaged in the MDT discussion to address their individual care needs and preferences for treatment,[2] taking into consideration quality of life considerations (urinary,

bowel, sexual function, social situation) and the psychosocial impact of cancer. Therefore, the aim of this qualitative study was to understand the clinical decision-making process among the uro-oncology MDT and how patients are engaged in the process.

Section snippets

Study Design

A qualitative descriptive study design[25] was chosen to gain insight into GU MDT health care professionals' clinical decision-making experiences. Qualitative descriptive design was considered appropriate for an in-depth examination, through semistructured individual interviews.[26] The study has been reported according to the consolidated criteria for reporting qualitative studies (COREQ) 32-item checklist (see Supplementary Table 1 for a completed checklist).[27] …

Setting

The setting was a metropolitan …

Findings

A total of five participants consented to the study representative of radiation oncology, medical oncology, and specialist nurses; see Table 3 for participant characteristics. Participant response for the project was lower than expected despite optimization of all

recruitment strategies. The ongoing COVID-19 pandemic and subsequent challenges of staffing were problematic for cancer services and likely affected recruitment. No participants withdrew consent, and there were no direct refusals to …

Theme 1: The Role and Scope of the MDT

The uro-oncology MDT discussions were carried out weekly at 7 a.m. each Thursday morning. The discussions were generally 1 hour in length and were capped to discuss a total of only 10 uro-oncology patients at each session. Participants reported that occasionally the MDT may increase the length of the discussion time to facilitate another case review or to come to consensus in challenging or difficult cases. The weekly uro-oncology MDT had on average 20 to 25 health care professionals from …

Theme 2: Lack of Person-Centered Clinical Decision-Making

The decision to refer a patient to the uro-oncology MDT for a case discussion was the sole responsibility of the treating consultant, specialist, or team. In the private hospital setting, the referral was primarily driven by the consultant, whereas in the public hospital settings, referrals are driven by the treating team, consultant, or specialist. For a patient to be referred to the uro-oncology MDT, a referral form was required to be completed and submitted at least 2 days before the …

Barriers

Several barriers to the uro-oncology MDT were expressed by the participants: (1) attendance issues, (2) late or incomplete referrals, (3) the virtual discussion itself, and (4) personality conflicts. Attendance issues were reported by the participants to be infrequent and generally did not affect patients; however, nonattendance was perceived to be problematic when a health discipline or specialist perspective and input were required in the decision-making processes for consensus outcomes.
“This …

…

Discussion

This qualitative study set out to understand the clinical decision-making processes among the uro-oncology MDT members and how patients are engaged in the process. There were several clinically valuable new insights and multiple factors within the uro-oncology MDT that affect patient engagement in the process. The MDT has a biomedical focus that overshadows person-centered principles of holistic care.[20,21,24,28] There is no psychosocial representation from allied health disciplines with …

Limitations

There are several limitations of this research to point out. First, the small sample size was reflective of recruitment challenges during the peak of the COVID-19 pandemic. This study was conducted with a single-site uro-oncology MDT but was representative of servicing a total population of 550,000 patients in Australia. It is acknowledged that recruitment bias is possible because we were unable to capture reasons for nonparticipation due to ethical approval restrictions. Patients who agreed to …

Conclusion

This study provides further evidence to support the fact that uro-oncology MDTs continue to have a solely biomedical focus and do not consider the holistic care needs of patients. Specialist nurses reported a lack of participation despite their significant role in patient advocacy for people living with cancer. The clinical focus of the uro-oncology MDT dominates care perspectives and evidently the whole person is not being treated by the cancer MDT, resulting in reduced quality of life and may …

Declarations

Ethics approval was given by HREC University of Canberra (Project ID 11535). Consent to participate and for publication was given by written informed consent. …

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this report. …

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Author Contributions

BA provided methodology, validation, formal analysis, and writing review and editing. AH provided methodology, validation, formal analysis, and writing review and editing. CP provided conceptualization, methodology, validation, formal analysis, writing review and editing, and supervision. …

Recommended articles

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Cancer centers of excellence for the multidisciplinary management of urologic cancers: The intersection between education, research, and healthcare

Daniel Andrés Nieva-Posso [1], Philippe E Spiess [2 3 4], Herney Andrés García-Perdomo [1 5]

Affiliations

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Abstract

Urologic cancers are among the leading causes of morbidity and mortality in the world, representing more than 10% of the total number of new cancer cases worldwide. These complex diseases are linked to several issues related to their diagnosis, management, monitoring, and treatment - issues that require multidisciplinary solutions that encompass and manage patients as complex entities. In response to this, the so-called cancer centers of excellence (CCEs) emerged, defined as multidisciplinary institutions specialized in the diagnosis, management, monitoring, and treatment of specific diseases, including cancer. Different institutions, such as the European Association of Urology

(EAU), have proposed and encouraged its consolidation, especially for the management of prostate cancer. These institutions must be composed of three areas: healthcare, education, and research, which have complementary interactions and relationships, stimulating research and problem-solving from a multidisciplinary approach and also covering elements of basic sciences and mental health. The implementation of these CCEs has brought positive results; therefore, it is necessary to stimulate their implementation with a uro-oncologic approach.

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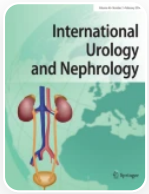

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Miguel Gil, João Guerra, Vanessa Andrade, Mariana Medeiros, Thiago Guimarães, Rui Bernardino, Gil Falcão, Fernando Calais da Silva & Luís Campos Pinheiro

Abstract

Purpose

Multidisciplinary team (MDT) conferences are currently the standard of care in cancer patients' management. Despite evidence supporting benefits to the majority of malignancies, a paucity of data exists examining the impact in urinary and male genital cancers. This study aims to evaluate the impact of MDT conferences in urologic cancer practice.

Methods

Clinical plans discussed in urologic MDT conferences in Centro Hospitalar Universitário de Lisboa Central between January 2019 and December 2019 were retrospectively analysed. Clinical plans were categorized as accepted, changed, rejected (cases that had to be re-presented to the MDT because of insufficient staging or administrative issues) or no plan. MDT conferences' impact was assessed according to type of consultation, referral medical specialty and primary tumour type.

Results

710 clinical plans were discussed at the MDT conferences. 61.8% were accepted, 10.6% were changed, 16.5% were rejected and 11.1% of cases referred to MDT discussion had no defined clinical plan. First consultations had a higher rate of accepted clinical plans (63.4%) versus subsequent consultations (56.4%). Referrals by the urology specialty had the highest rate of acceptances (64.3%). On the stratification by primary tumour site, testicular cancer had the highest acceptance rate (70.3%), whereas bladder cancer had the lowest (47.8%).

Conclusions

MDT conferences had an important impact in the management of 38.2% of cases. Therefore, all patients with urologic malignancies should be referred to MDT review to ensure optimal clinical care.

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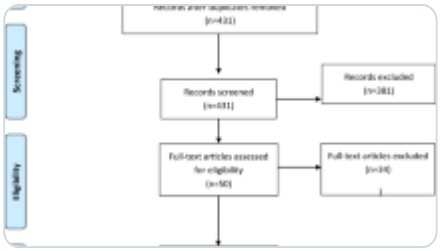

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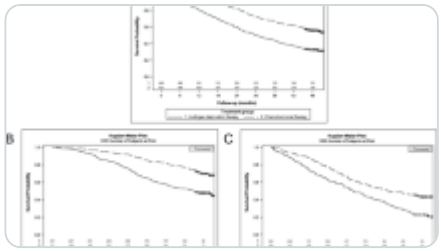

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Author information

Authors and Affiliations

Urology Department, Centro Hospitalar Universitário de Lisboa Central, EPE, Rua José António Serrano, 1150-199, Lisbon, Portugal

Miguel Gil, João Guerra, Vanessa Andrade, Mariana Medeiros, Thiago Guimarães, Rui Bernardino, Gil Falcão, Fernando Calais da Silva & Luís Campos Pinheiro

Corresponding author

Correspondence to Miguel Gil.

Ethics declarations

Conflict of interest

The authors report no conflict of interest.

Ethical approval

The study was conducted according to the ethical principles of the Declaration of Helsinki.

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Implementation rates of uro-oncology multidisciplinary meeting decisions

Ned Kinnear*, Riley Smith*, Derek B. Hennessey*, Damien Bolton*† and Shomik Sengupta*†

*Department of Urology, Austin Health, Heidelberg, Vic., Australia, and †Department of Surgery, University of Melbourne, Heidelberg, Vic., Australia

Objectives

To assess implementation rates of the consensus plans made at the uro-oncology multidisciplinary meeting (MDM) of an Australian tertiary centre, and analyse obstacles to implementation.

Methods

A retrospective review was performed of all patients discussed at the uro-oncology MDM at our institution between 1 January and 30 June 2015. Rates of referral for MDM discussion after a new histological diagnosis of malignancy, categorised by tumour type, were assessed. Patient records were interrogated to confirm MDM plan implementation, with the outcomes examined being completion of MDM plan within 3 months and factors preventing implementation.

Results

During the enrolment period, from 291 uro-oncological procedures, 240 yielded malignant histology of which 160 (67%) were discussed at the MDM. Overall, 202 patients, including 32 females, were discussed at the uro-oncology MDM. MDM consensus plans were implemented in 184 (91.1%) patients. Reasons for deviation from the MDM plan included delay in care, patient deterioration or comorbidities, patient preference, consultant decision, loss to follow-up, and change in patient scenario due to additional new information.

Conclusion

The MDM is increasingly important in the care of uro-oncology patients, with about two-thirds of new diagnoses currently captured. There appear to be few barriers to the implementation of consensus plans, with nearly all patients undergoing the recommended management.

Keywords

multi-disciplinary, multi-disciplinary meeting, MDM, urology, oncology, implementation

Introduction

A patient with cancer will need input from a range of medical specialties and allied health professionals. Such multidisciplinary care (MDC) allows clinicians with a range of expertise to collaborate in patient care. This brings to bear a broader knowledge base and promotes balanced decision making [1]. MDC may also enhance patient understanding and improve survival [2–4].

Formal provision of such inter-disciplinary care may be variously structured as multidisciplinary meetings (MDM), multidisciplinary care clinics, and tumour boards [1]. MDC has existed in the USA for >50 years [5], and has since been endorsed in the UK [6], Europe [7], Africa [8], and Asia [9]. In Australia, MDC became government policy in 1997 [10] and is now well recognised as best practice [11,12].

The global movement towards MDC is also true of urological malignancies [2,3,13–18]. Recent research has focused on the impact of these uro-oncology MDMs on patient care. Studies at our centre [19] and elsewhere [17,20–22] reveal that MDMs change 2–32% of management plans.

However, there is scant evidence regarding the rate at which these plans are then implemented [15,23]. Literature on the Australian experience is limited [24], but suggests high rates of adherence. We therefore aimed to assess rates of deviation from the consensus plans of our institutional uro-oncology MDM.

Methods

Our institutional uro-oncology MDMs have been held weekly since 2007 [19]. Patients are referred for discussion from both Austin Health and private practices. These cases are presented before an audience of urologists, medical oncologists, radiation oncologists, pathologists, radiologists, nuclear medicine physicians, urology nurse specialists, and trainees from the various specialties.

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With institutional Human Research Ethics Committee approval (LNR/16/Austin/333), all cases discussed at the MDM between 1 January and 30 June 2015 were enrolled. This period was chosen to allow sufficient follow-up to ascertain whether the MDM plan had been implemented, even allowing for delays.

Urological oncological procedures performed during the study period were also collated to assess the proportion discussed at MDMs. Cases of prostate biopsy were reviewed, and patients with benign histology were excluded. The proportion of patients undergoing an oncological procedure who were subsequently discussed at a MDM was examined overall and by tumour type.

The consensus plan developed for each patient at the MDM was determined from a database prospectively maintained through the North Eastern Melbourne Integrated Cancer Service. Hospital records were interrogated to assess whether MDM consensus plans were implemented within 3 months and reasons for non-implementation. MDM consensus plans could involve one or more recommendations. In addition to surveillance by that specialty, a plan of referral to the outpatient clinic of medical oncology, radiation oncology or urology could involve recommendation to commence chemotherapy or hormonal therapy, radiotherapy or surgery, respectively. All aspects of the plan needed to occur within 3 months for implementation to be assessed as complete.

Results

Patients

In all, 202 patients were discussed at the uro-oncology MDM during the enrolment period, of whom 32 (15.8%) were female. The median (interquartile range [IQR]) age was 68 (59–74) years and 50 (24.8%) patients had metastasis. In order of frequency, patients discussed at MDM had malignancies of the prostate (86 patients), bladder (47), kidney (46) and testes (17). Six patients had tumours of other urological organs, including the penis or adrenals, or had urological organs invaded by tumours of other viscera.

Capture of eligible cases

Within the enrolment period, 291 oncological urological procedures producing histological specimens were performed. Excluding 51 cases of prostate biopsy with benign histology, 240 patients were eligible for presentation at the MDM, of whom 160 (66.7%) were discussed. Uro-oncological procedures, categorised by tumour type and procedure, are outlined in Table 1. This shows that almost all newly diagnosed uro-oncology patients are discussed at a MDM, with the exceptions being bladder tumours resected cystoscopically (around one-third), prostate cancer treated by radical prostatectomy (just over half), and renal tumours treated by nephrectomy (about three-quarters).

Table 1 Capture of eligible cases from urology operating lists for multidisciplinary meeting discussion.

Procedure	Eligible, *n*	Discussed, *n* (%)	Rao et al. [19], %
Prostate cancer on biopsy	57	54 (95)	31
Radical prostatectomy	26	15 (58)	26
Nephrectomy	37	27 (73)	23
Orchidectomy	10	9 (90)	60
TURBT	90	35 (38)	23
Cystectomy	6	6 (100)	83
Other	14	14 (100)	n/a
Sub-total	240	160 (67)	
Discussed without recent surgery	–	42 (–)	
Total, *n*		202 (–)	120

TURBT, transurethral resection of bladder tumour or bladder biopsy. Other: includes adrenalectomy and retroperitoneal lymph node dissection. n/a: not applicable.

MDM plans

MDM consensus plans could involve one or more recommendations per patient, with only integer values possible. Among the 202 patients discussed, their plans comprised a total of 297 recommendations, representing on average 1.5 recommendations per patient [median (IQR) 1 (1–2)]. Plans most commonly directed patients towards further specialist consultation. There were 216 such referrals in total, representing 72.7% of all plans. In all, 105, 56 and 54 patients were referred to the outpatient clinics of urology, medical oncology, and radiation oncology, respectively. For eight patients, their follow-up occurred in private practice or with their regional public hospital service. Surgery was planned for 36 patients. Three patients were recommended for enrolment in clinical trials at Austin Health. Thirteen patients had other recommendations in their consensus plans, distinct from previous categories. These consisted of seven patients referred for consultation with a specialty not present at the uro-oncology MDM, three patients recommended for nephrostomy tube insertion or change, two patients requiring re-examination of their histology by a pathologist, and one patient booked for liver biopsy. Full details on patient demographics, tumour types, and MDM consensus plans are summarised in Table 2.

Implementation of MDM plans

MDM consensus plans failed to be fully implemented within a 3 month time-frame in 18 (8.9%) patients. Reasons are given in Table 3, and included system delays in five patients, patient deterioration or comorbidities in four, patient

Table 2 Patient demographics by MDM plan implementation status.

	Implemented	Not implemented	Total
Number of patients (%)	184 (91.1)	18 (8.9)	202 (100.0)
Female, *n* (%)	31	1	32 (15.8)
Male, *n* (%)	153	17	170 (84.2)
Age, years, median (IQR)	68 (59–74)	67.5 (63.25–75)	68 (59–74)
N (%)			
Metastasis	47	3	50 (24.8)
Non-metastatic	137	15	152 (74.2)
Tumour type			
Bladder	40	7	47 (23.3)
Kidney /ureter	43	3	46 (22.8)
Prostate	78	8	86 (42.6)
Testis	17	0	17 (8.4)
Other*	6	0	6 (3.0)
MDM plan†			
Medical oncology clinic‡	53	4	57 (28.2)
Radiation oncology clinic§	46	8	54 (26.7)
Urology clinic	98	7	105 (52.0)
Surgery	29	7	36 (17.8)
Imaging	16	4	21 (10.4)
Private/ rural follow-up	8	0	8 (4.0)
Enrolment in clinical trial	3	0	3 (1.5)
Other	12	1	13 (6.4)

**'Other' includes malignancies of urological viscera such as the penis, adrenal gland or retroperitoneal lymph node metastases, as well as involvement of urological organs by tumours of other viscera, such as the bowel. †MDM plan may include more than one of the listed options. ‡Medical oncology clinic may include commencement of chemotherapy and/ or hormonal therapy. §Radiation oncology clinic may include commencement of radiotherapy.*

Table 3 Reasons for non-implementation of MDM consensus plan.

Reason for deviation from MDM plan	Present study, *n* (%)	De Ieso et al. [23], %
Consultant decision	2 (11)	22.9
Patient deterioration or comorbidities	4 (22)	33.3
Patient preference	4 (22)	31.2
Delay*	5 (28)	6.3
New (re-staging) information	1 (6)	6.3
Lost to follow-up	2 (11)	n/a
Total, *n*	18	48

**All delayed plans in our study were eventually implemented. n/a: not applicable.*

preference in four, consultant decision in two, lost to follow-up in two, and new information on re-staging imaging scans in one patient. For the patients who had delays, all plans were implemented within 12 months of discussion at the MDM.

Discussion

MDC has become the standard of care for patients with cancer [1,6,10,11]. MDMs have flourished in the management of urological malignancy [13,18–21,25–27], particularly of the prostate [2,3,14–17,28,29]. Studies have shown that these MDMs change the clinician's initial management plan in 2–32% of cases (Table 4) [17,18–22]. However, there is a paucity of literature about how frequently these consensus plans are enacted.

The outcomes of an Italian prostate cancer MDM over 6 years were published by Magnani et al. [15], who reported that 6% of consensus plans were changed subsequently during patient–clinician consultations. Patient numbers were not stated. De Ieso et al. [23] detailed the decision outcomes of 551 patients with solid tumours and lymphoma discussed in an MDM in the UK. Divergence from the MDM consensus plan occurred in 48 (8.7%) cases. Implementation rates from patients presented over 3 months at a selection of surgical oncology MDMs at our institution were published previously [24]; for the 160 patients with evaluable data, the retrospective audit found only 5% of plans were not enacted.

The present study represents the largest assessment in Australasia of the implementation rates of consensus plans formulated in an MDM, uro-oncological or otherwise. The deviation rate of 8.9% is similar to the small number of similar existing studies. The causes for altering the plans are also similar (Table 3). A small deviation rate is to be expected, as during the time taken to present the patient at a MDM and then discuss this plan in outpatient clinic with the patient, there may be changes in patient preference, health or the clinical scenario.

Continued efforts are required to minimise MDM non-implementation rates and most efficiently use meeting time, as the administration and staffing costs of MDMs are significant, and may exceed AUD$15 000 per month [23]. Referrals to the MDM must be economical. Inefficient referral of patients with less complex clinical scenarios [18,21] or incomplete staging information [15,21,24] is well

Table 4 Studies describing rates of management plan change by a uro-oncology MDM.

Reference	Year	Country	MDM scope	Total *N*	*N* with modified plan (%)
Sundi et al. [17]	2015	USA	Prostate	647	66 (10.2)
Rao et al. [19]	2014	Australia	Uro-oncology	120	32 (26.7)
Kurpad et al. [20]	2011	USA	Uro-oncology	269	87 (32.3)
Sooriakumaran et al. [21]	2009	UK	Uro-oncology	87	11 (12.6)
Acher et al. [22]	2005	UK	Uro-oncology	124	2 (1.6)

documented. Furthermore, in health systems with multiple MDMs of overlapping scope or arranged in a hierarchy, patients may be discussed at up to five separate meetings [23]. Strategies to improve the efficiency of MDM referral should therefore include institutional protocols for the management of straightforward cases and efforts to increase the accuracy of presented patient data.

Increased involvement of allied health professionals during the MDM may further reduce non-implementation rates. Allied health professionals report often having useful information to add to MDM discussion about patient psychosocial state, but having difficulty in contributing, due to perceptions of lack of time or respect for their input [30]. Structured methods of regularly involving allied health staff in meeting dialogue may be beneficial.

Similarly, greater patient involvement may help reduce plan deviation due to causes found commonly in the present study such as system delays, patient preference, and unreported significant comorbidities. However, how best to involve the patient remains an area for debate [18,31]. Australian governmental guidelines recommend patients with cancer 'participate as members of the multidisciplinary team in treatment planning' [32]. However, MDC exists in different formats across Australia, so the method of patient involvement varies.

Clinicians are often averse to patients being present during the MDM, due to concerns that it would be confronting for patients, provoke anxiety, constrain the dynamics of frank MDM discussion [30], and be less comfortable for all parties than subsequent one-on-one discussion [14]. Testing these apprehensions, Choy et al. [33] involved 30 well-educated English speaking patients with breast cancer in postoperative MDM discussion of their cases, and compared their experience to matched patients who did not attend. Involved patients tended to feel better informed, had no measurable change in anxiety scores, and would recommend the experience to others. However, most clinicians reported that they had to modify their language, and did not find patient involvement to have a positive impact on the MDM. Considering this, the most appropriate approach may be greater efforts to understand patient wishes before the MDM, followed by the common practice, as currently structured at our institution [19] and elsewhere [3,16,17,20,23], of patients consulting with clinicians and discussing MDM plans solely in one-on-one settings.

It is well accepted that not all patients with cancer require MDM discussion [33]. We found that 67% of patients undergoing a uro-oncological procedure demonstrating malignant histology were discussed at the MDM. This rate appears to strike a reasonable balance between the availability of MDM care and the provision of stream-lined protocol-driven care for straightforward cases. We have previously proposed selection criteria that may help guide the inclusion of patients in uro-oncology MDMs to maximise potential management impact [19]. These include need for multi-modal treatment, recurrent or metastatic disease, potential patient eligibility for a clinical trial, rare tumours, and cases with diagnostic uncertainty. Daily practice at our institution also includes many malignancies that do not meet these criteria, and are thus routinely managed in uro-oncology outpatient clinic, in accordance with evidence-based guidelines.

MDC remains relatively new in Australia and its reception amongst urologists has been mixed [34]. An effective multidisciplinary team will cross-refer patients to its constituent specialties. In a previous study [19] of our institution's uro-oncology MDM, published in 2014, 33% of MDM patients were cross-referred between specialties. An even greater proportion of inter-disciplinary referrals are evidenced in this more recent analysis. These findings should reassure those involved in the care of patients with urological malignancies of the growing commitment to MDC. This collaborative approach of urologists, and their fundamental role in common malignancies, such as prostate cancer, should also support future campaigns to raise public awareness of the profession [35].

Effective discussion at MDMs requires thorough collection of patient information. These high-quality data may be suitable for national aggregation in existing national cancer registries, such as the newly founded Prostate Cancer Outcomes Registry-Australia and New Zealand [36]. Challenges to enrolling MDMs nationwide would include ethical considerations including distribution of patient information, perceived threat to clinical independence from national review, and administrative burden if automatic digital linkage were problematic. However, international experience has shown that such a system may hold great opportunities. These include harnessing national knowledge-base and the pooling of uncommon malignancies, enabling publication of both consensus protocols and population-scale studies, respectively [37]. An additional significant benefit may be greater adherence to evidence-based guidelines and subsequent improved patient outcomes [2,4].

Limitations of the present study include its retrospective nature, moderate size, and single-institution focus. Additionally, some malignancies will be discussed within the enrolment period but have their oncological procedure beyond it, which will affect the expected ratios of related procedures, such as transurethral resection of bladder tumour and cystectomy.

In summary, the present study shows that most urological oncology patients are managed with multidisciplinary input, and the rates of non-implementation of recommendations are low. Incremental improvement may stem from increasing

patient information accuracy and allied health involvement. MDMs may support national oncological registries, and their collegiality may benefit public awareness campaigns of relevant specialists for specific malignancies. Further studies are required to confirm and build on these findings.

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Conflicts of interest

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Correspondence: Shomik Sengupta, 292 Springvale Road, Glen Waverley, Victoria 3150, Australia.

e-mail: senguptaurology@gmail.com

Abbreviations: IQR, interquartile range; MDC, multidisciplinary care; MDM, multidisciplinary meeting.

Future Oncology ›
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Research Article

Uro-Oncologic Patient Management During the COVID-19 Pandemic: Survey Findings from an Italian Oncologic Hub

Stefano Luzzago, Francesco A Mistretta, Enza Dossena, Gianna Comandi, Giovanni Petralia, Dario Di Trapani, ...show all

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Abstract

Aim: Patient and worker satisfaction at an oncologic hub during the COVID-19 pandemic has never been reported. We addressed this topic. **Methods:** We conducted a survey to test the views of patients (n = 64) and healthcare professionals (n = 52) involved with our operative protocol. **Results:** A moderate/severe grade of concern due to the COVID-19 emergency was recorded in 63% of patients versus 75% of hospital staff. High/very high versus low satisfaction grade about preventive strategies to reduce the risk of SARS-CoV-2 contagion was identified in the patients compared with the hospital staff group. **Conclusion:** Surgical treatment at a hub center of uro-oncologic patients coming from spoke centers is well accepted and should, therefore, be recommended. Preventive strategies to reduce the risk of SARS-CoV-2 contagion in hospital staff members should be implemented.

Lay abstract

COVID-19 pandemic represents a credible solution for management of non-deferrable uro-oncologic patients. Specifically, surgical treatment at a hub center of patients coming from spoke centers is well accepted by both patients and hospital staff members. Moreover, collaboration between healthcare workers from spoke and hub centers generates minimal levels of anxiety, while potentially being associated with clinical, surgical and scientific improvement. This said, a more specific focus on recommended strategies to reduce the risk of SARS-CoV-2 contagion at oncologic hub hospitals is warranted.

Keywords:: COVID-19 oncology service SARS-CoV-2 surgical oncology urological cancer

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at:
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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved. Stefano Luzzago had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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British Journal of Hospital Medicine, VOL. 80, NO. 12 | Symposium on Multidisciplinary Team Working

Multidisciplinary team management of patients with urological cancer

CN Molokwu ✉, T Naqvi, D Tyson

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Abstract

Several specialist teams are involved in the management of patients with urological cancer. These specialists have been brought together as a multidisciplinary team to discuss, plan and deliver care to patients in an effective, patient-centred approach. This article discusses the benefits of this approach and ways in which multidisciplinary team working can be optimized.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

C. Parker[1], E. Castro[2], K. Fizazi[3], A. Heidenreich[4], P. Ost[5], G. Procopio[6], B. Tombal[7] & S. Gillessen[8,9,10], on behalf of the ESMO Guidelines Committee*

[1]Royal Marsden Hospital, Sutton, UK; [2]Department of Medical Oncology, Virgen de la Victoria University Hospital, Institute of Biomedical Research in Málaga, Malaga, Spain; [3]Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Saclay, Villejuif, France; [4]Department of Urology, Uro-Oncology, Robot-Assisted and Specialized Urologic Surgery, University Hospital of Cologne, Cologne, Germany; [5]Department of Radiation Oncology, Ghent University Hospital, Ghent, Belgium; [6]Department of Medical Oncology 1, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; [7]Institut de Recherche Clinique, Université Catholique de Louvain, Brussels, Belgium; [8]Oncology Institute of Southern Switzerland, Bellinzona; [9]Faculty of Biomedical Sciences, USI, Lugano, Switzerland; [10]Division of Cancer Medicine, University of Manchester, Manchester, UK

Available online 25 June 2020

Key words: chemotherapy, hormone therapy, prostate cancer, radiotherapy, surgery

SCREENING AND EARLY DETECTION

Subclinical prostate cancer is common in men >50 years. Population-based screening of men aged between 55 and 69 years, using prostate-specific antigen (PSA) testing, has been evaluated.[1] After a median follow-up of 16 years, the European screening trial demonstrated a 25% relative reduction in prostate cancer mortality. However, 570 men needed to be invited for screening and 18 patients needed to be treated to prevent one death from prostate cancer, and there was no effect on overall survival (OS).

Risk-adapted early detection of prostate cancer using a baseline PSA has been evaluated in retrospective cohort studies. Men with a PSA >1 ng/ml at 40 years or >2 ng/ml at 60 years are at increased risk of prostate cancer metastasis or death from prostate cancer.[2]

Recommendations

- Population-based PSA screening of men for prostate cancer reduces prostate cancer mortality at the expense of overdiagnosis and overtreatment and is not recommended [I, C].
- Early PSA testing (baseline PSA followed by risk-adapted follow-up) can be offered to men >50 years, men >45 years with a family history of prostate cancer, African-Americans >45 years and *BRCA1/2* carriers >40 years [III, B].
- Testing for prostate cancer in asymptomatic men should not be done in men with a life expectancy <10 years [I, E].

DIAGNOSIS AND PATHOLOGY

The risk of clinically significant prostate cancer is related to age, ethnicity, family history, PSA level, free/total PSA ratio and findings on digital rectal examination.[3] Physicians are encouraged to use risk calculators incorporating these factors.[4] Multiparametric magnetic resonance imaging (mpMRI) is recommended before prostate biopsy.[5–7] Targeted transperineal biopsies, in comparison with systematic transrectal biopsies, result in an increased detection rate of clinically significant prostate cancer, a decreased detection rate of clinically insignificant prostate cancer and fewer adverse events.[5] When mpMRI is positive [i.e. Prostate Imaging—Reporting and Data System (PI-RADS) ≥3], targeted ± systematic biopsy should be done. When mpMRI is negative (i.e. PI-RADS ≤2), and clinical suspicion of prostate cancer is low, the biopsy can be omitted. Diagnostic work-up is shown in Figure 1.

Recommendations

- mpMRI should be carried out before prostate biopsy [I, B].
- A prostate cancer risk calculator and/or mpMRI should be used to confirm the indication for biopsy in men with elevated PSA [III, C].
- Transperineal biopsies are recommended, rather than transrectal ultrasound-guided biopsies [III, B].
- Each biopsy should be reported individually and evaluated using the International Society of Urological Pathology Consensus recommendations [II, B].[8]

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

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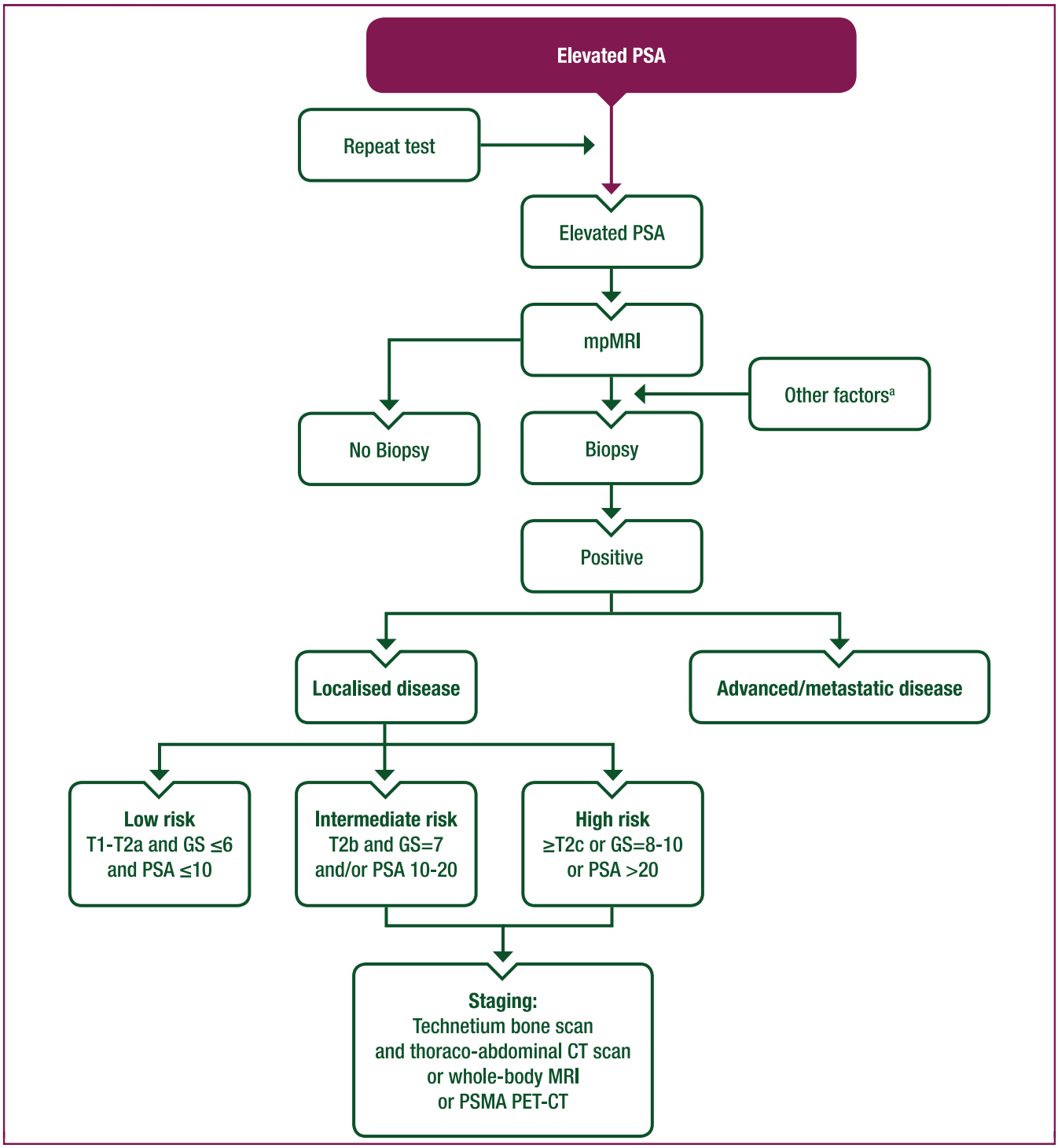

Figure 1. Diagnostic work-up and staging for prostate cancer.
CT, computed tomography; DRE, digital rectal examination; GS, Gleason score; mpMRI, multi-parametric magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.
[a] In addition to PSA level and MRI results, the decision to biopsy or not should be made in light of DRE findings, ethnicity, age, comorbidities, free/total PSA, history of previous biopsy and patient values.

STAGING AND RISK ASSESSMENT

Staging and risk assessment are presented in supplementary Tables S1 and S2, available at *Annals of Oncology* online. Patients who are not suitable for treatment with curative intent, by virtue of poor general health, do not normally require staging investigations. Magnetic resonance imaging (MRI) provides T staging[9] and can inform surgical technique with respect to nerve-sparing and wide excision of areas of potential extra-prostatic extension. Men with low-risk disease [T1/2, Gleason score (GS) $\leq$6, PSA $\leq$10][10] do not require further imaging. Within the low-risk category, percentage of positive cores, length of core involvement, PSA density and a lower free/total PSA ratio are positively associated with risk of understaging.

Men with intermediate- or high-risk disease[10] should have imaging for nodal or metastatic disease. Whole-body MRI, choline-positron emission tomography-computed tomography (PET-CT)[11] and prostate-specific membrane antigen (PSMA)-PET-CT[12,13] have better sensitivity and specificity than CT or bone scan but have not been shown to improve clinical outcomes. The evidence regarding PET and whole-body MRI in this setting is not adequate to make a recommendation concerning their use. Patients with localised disease on routine imaging should not be denied radical local treatment solely because metastatic lesions are identified on novel imaging techniques.

Recommendations

- Localised disease should be classified as low-, intermediate- or high-risk as a guide to prognosis and therapy [III, A].
- Patients with intermediate-risk disease should be staged for metastases using MRI or CT (abdomen and pelvis) and bone scan [III, B].
- Patients with high-risk disease should be staged for metastases using CT (chest, abdomen and pelvis) and bone scan [III, B].

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

There is no consensus regarding optimum management of localised disease (Table 1 and Figures 2 and 3). Patients should be informed of the benefits and harms of the different options. Given the range of treatment options and their side-effects, men should be offered the opportunity to consult with both a urologist and a radiation oncologist. Men should be counselled that treatment of prostate cancer may cause sexual dysfunction, infertility, bowel and urinary problems.

Watchful waiting with delayed hormone therapy for symptomatic progression is an option for men who are not suitable for, or unwilling to have, treatment with curative intent. Active surveillance is a strategy of close monitoring, typically using PSA, repeat biopsies and MRI, keeping curative treatment for those with evidence of disease progression. There is no good evidence comparing different methods of active surveillance.[14]

Curative options include radical prostatectomy (RP), external beam radiotherapy (RT) and low-dose-rate brachytherapy. Two randomised, controlled trials (RCTs) have compared RP and watchful waiting.[15,16] The Scandinavian Prostate Cancer Group (SPCG) Study 4 accrued 695 men during the 1990s, at a time when PSA testing was not routinely carried out, and may not be applicable to screen-detected cancers. After a mean follow-up of 29 years, the risk of death from prostate cancer was 20.4% and 31.6% in the RP and the watchful waiting groups, respectively. RP increased the rate of erectile dysfunction (80% versus 45%), and urinary leakage (49% versus 21%),[15] but these rates may not be generalisable to high-volume surgical centres.

Table 1. Stage-matched therapeutic strategies

Localised disease	Low risk	Active surveillance Brachytherapy RP Radical RT
	Intermediate risk	RP Radical RT ± neoadjuvant ADT Brachytherapy Active surveillance
	High risk	Long-term ADT + radical RT ± neoadjuvant docetaxel RP + pelvic lymphadenectomy
Locally advanced disease		Neoadjuvant ADT + radical RT + adjuvant ADT ± neoadjuvant docetaxel RP + pelvic lymphadenectomy
M0 CRPC	High risk	ADT + apalutamide ADT + darolutamide ADT + enzalutamide
Metastatic disease	Hormone-naive	ADT + abiraterone ADT + docetaxel ADT + enzalutamide ADT + apalutamide RT for low volume ADT alone for frail patients who cannot tolerate the above treatments Bone health agent
	Castration-resistant (first line)	Abiraterone Docetaxel Enzalutamide ^{223}Ra for patients unfit for above treatments (and bone-only metastases)
	Second line or post-docetaxel	Abiraterone Cabazitaxel Enzalutamide ^{223}Ra

^{223}Ra, radium-223; ADT, androgen deprivation therapy; M0 CRPC, non-metastatic castration-resistant prostate cancer; RP, radical prostatectomy; RT, radiotherapy.

The PIVOT trial recruited 731 North American men between 1994 and 2002.[16] They were more representative of men with PSA-detected cancer, but had a remarkably high rate of comorbidity. No significant difference was seen in OS between RP and watchful waiting [hazard ratio (HR) 0.88; 95% confidence interval (CI) 0.71—1.08]. In the low-risk subgroup of 296 men, the risk of death from prostate cancer was <3% at 12 years, with no significant benefit for surgery. Indeed, the trend both in terms of prostate cancer-specific mortality (HR 1.48; 95% CI 0.42—0.54) and overall mortality (HR 1.15; 95% CI 0.80—1.66), favoured watchful waiting rather than surgery. However, the high overall mortality rate of ~50% at 10 years illustrates the recruitment of men with significant comorbidities.

ProtecT is a prospective randomised clinical phase III trial comparing active therapy (RP or RT) versus active monitoring (repeat biopsy in men with a PSA rise of >50% from the baseline value).[17] The trial recruited 1643 men with localised prostate cancer; after a median follow-up of 10 years there was no statistically significant difference in terms of cancer-specific survival, which was 99% in all three arms. However, there was a statistically significant increase in the frequency of skeletal metastases and the need for androgen deprivation in the active monitoring arm.

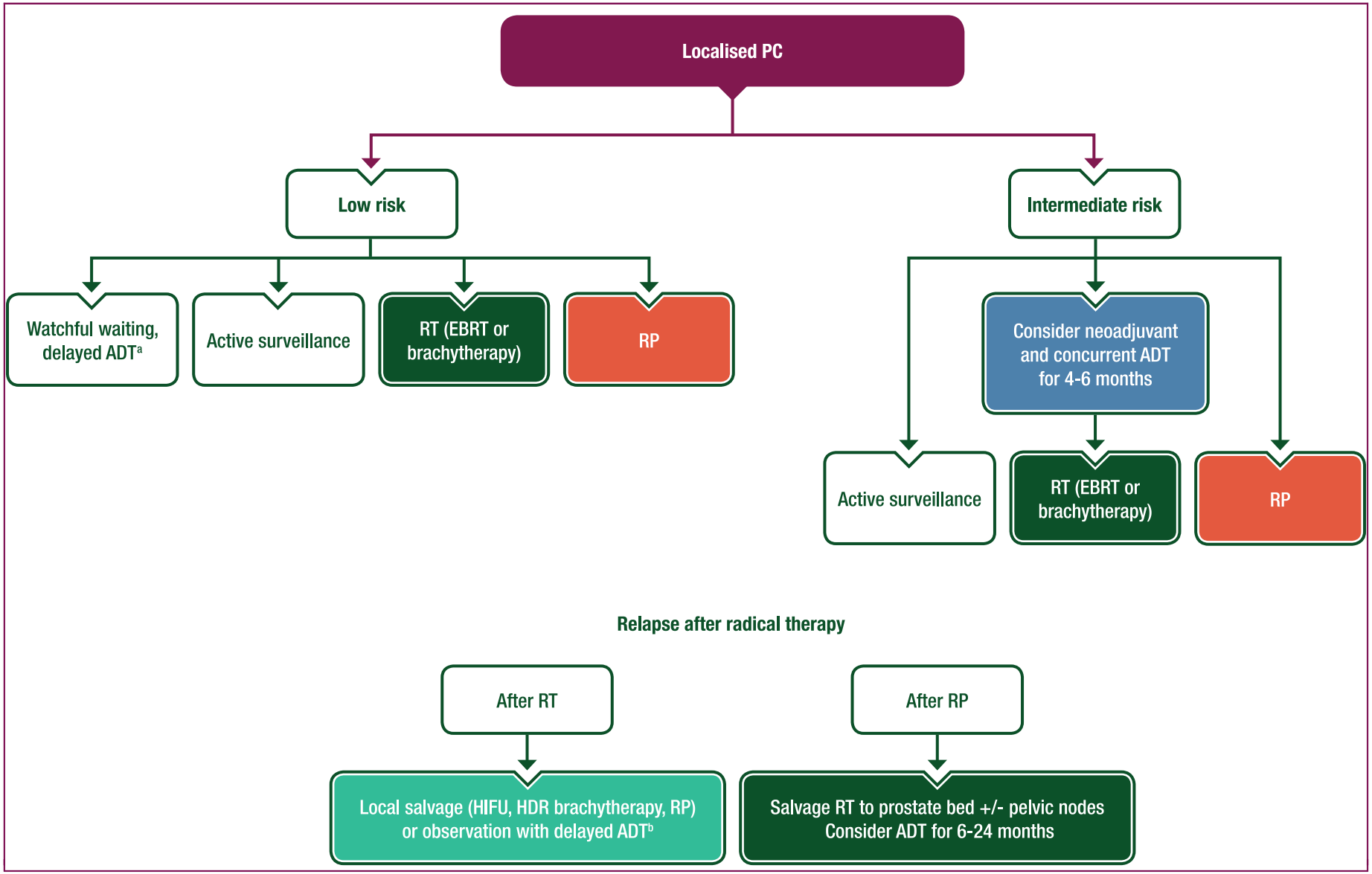

Figure 2. Localised prostate cancer treatment algorithm.
ADT, androgen deprivation therapy, EBRT, electron beam radiotherapy; HDR, high-dose rate; HIFU, high-intensity focused ultrasound; PC, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy: RT, radiotherapy.
[a] Also suitable for localised/locally advanced disease if patient not suitable for (or unwilling to have) radical treatment.
[b] For men with biochemical relapse and symptomatic local disease, proven metastases or a PSA doubling time of <3 months.

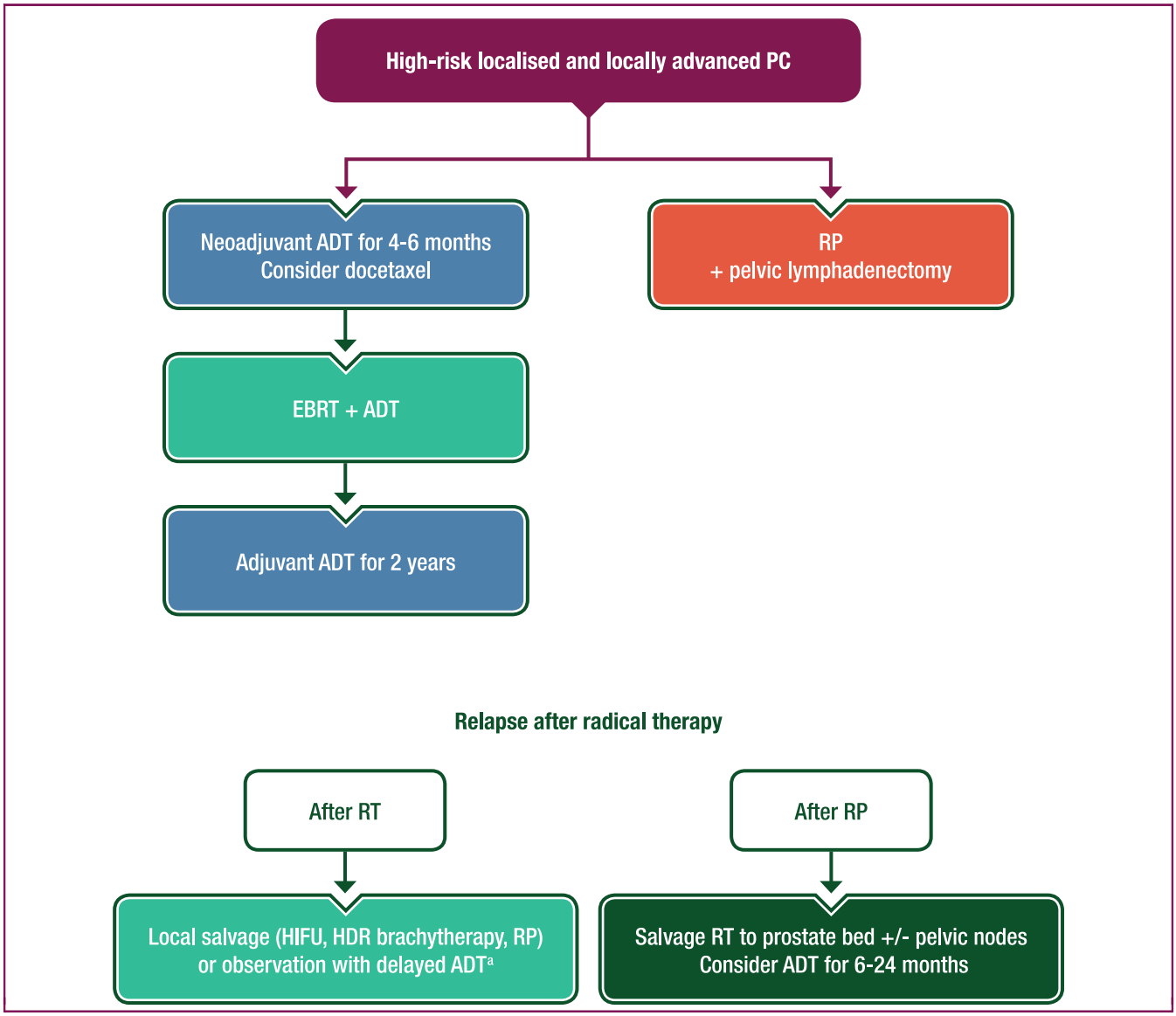

Figure 3. High-risk localised and locally advanced prostate cancer treatment algorithm.
ADT, androgen deprivation therapy; EBRT, electron beam radiotherapy; HDR, high-dose rate; HIFU, high-intensity focused ultrasound; PC, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy.
[a] For men with biochemical relapse and symptomatic local disease, proven metastases or a PSA doubling time of <3 months.

The case for adding radical local treatment for men with high-risk localised and locally advanced disease is based on two RCTs. The SPCG-7 trial included 875 men who received 3 months of combined androgen blockade (CAB) followed by flutamide monotherapy.[18] They were randomised whether to receive radical RT to the prostate. It showed a beneficial impact of radical RT in terms of cause-specific (11.9% versus 23.9%, $P < 0.001$), and overall mortality (29.6% versus 39.4%, $P = 0.004$). The National Cancer Institute of Canada/Medical Research Council (NCIC/MRC) trial randomised high-risk patients to either lifelong androgen deprivation therapy (ADT) alone or to ADT plus RT. The addition of RT improved the 7-year survival from 66% to 74% ($P = 0.003$).[19]

For patients receiving radical prostate RT, dose escalation using intensity-modulated RT or image-guided RT improves biochemical control with acceptable toxicity.[20] Moderate hypofractionation is non-inferior in terms of biochemical control, is more convenient and has acceptable toxicity.[21]

Patients treated with RP for high-risk disease often require postoperative RT ± ADT.

Neoadjuvant and adjuvant hormone treatment

The value of neoadjuvant and concurrent ADT, with RT, in men with high-risk localised and locally advanced disease, has been established by multiple randomised trials. For example, in the Trans Tasman Radiation Oncology Group (TROG) 96-01 trial, 818 men with locally advanced prostate cancer were randomly assigned to RT alone, RT plus 3 months' neo-adjuvant and concurrent CAB or RT plus 6 months' CAB.[22] Compared with RT alone, the use of 6 months' hormone therapy significantly improved overall mortality (HR 0.63; 95% CI 0.48—0.83). Similarly, the Radiation Therapy Oncology Group (RTOG) trial 8610, in 456 men with T2-4 disease, found

an improvement in 10-year prostate cancer-specific mortality (23% versus 36%; $P = 0.01$) for the addition of 4 months' neoadjuvant and concurrent ADT.[23]

Intermediate-risk localised prostate cancer has been subdivided into favourable and unfavourable categories.[24] Unfavourable intermediate-risk disease was defined as any of primary Gleason pattern 4, percentage of positive biopsy cores $\geq$50% or $\geq$2 intermediate-risk factors (cT2b-c, GS 7, PSA 10–20). Patients with unfavourable intermediate-risk disease have a worse outcome than those with favourable intermediate-risk disease, and might be more likely to benefit from neoadjuvant ADT.

Adjuvant ADT, after RT, has been studied in multiple RCTs. The RTOG 92-02 trial randomised 1554 patients to receive either 4 months or 28 months of ADT in addition to RT.[25] In an unplanned subgroup analysis, the addition of adjuvant ADT improved OS in those with a GS of 8–10 (81.0% versus 70.7%, $P = 0.044$). The European Organisation for Research and Treatment of Cancer (EORTC) 22961 trial randomised 970 men with locally advanced disease to receive either 6 months or 36 months of ADT in addition to radical RT.[26] The 5-year overall mortality for short-term and long-term suppression was 19.0% and 15.2%, respectively (HR 1.42; CI 1.09–1.85).

A recent RCT evaluated 18 versus 36 months' adjuvant ADT in 630 men with high-risk prostate cancer.[27] After a median follow-up of 9.4 years, the 5-year OS was 91% for the 36-months arm and 86% for the 18-months arm ($P = 0.07$). While this was a relatively small trial, with a more favourable case mix than EORTC 22961, given the additional toxicity of longer-term ADT, 18 months of treatment may be preferred by some patients.

No large RCTs are available for adjuvant treatment following RP for lymph node-positive disease. Based on the data of a large retrospective series including 2596 patients with pN1 disease, combined adjuvant RT and 2 years of ADT results in an improved 8-year cancer-specific mortality rate for men with two positive lymph nodes associated with pT3b/pT4 and/or positive surgical margins as compared with RT alone.[28] However, the option of PSA-triggered follow-up and initiation of ADT at time of PSA rise was not included.

Neoadjuvant docetaxel for M0 disease

Six RCTs have tested early docetaxel-based chemotherapy (ChT) in high-risk localised disease. GETUG-12 compared standard of care (ADT for 3 years plus RT) with or without 4 cycles of docetaxel-estramustine. The primary end point of relapse-free survival (RFS) was improved (HR 0.71; 95% CI 0.54–0.94, $P = 0.017$).[29] A recent update with a median follow-up of 12 years showed that clinical RFS (cRFS; defined as metastases, local relapse or death) was also improved with docetaxel (median cRFS 13.9 years versus 12.5 years; HR 0.75; 95% CI 0.56–1.00; $P = 0.0491$).[30] RTOG 0521 tested RT plus 2 years ADT with or without 6 cycles of docetaxel and reported a borderline improved RFS [HR 0.76; (95% CI 0.57–1.00); $P = 0.05$]. OS did not reach significance by standard two-sided P value (one-sided $P = 0.03$; HR 0.68; 95% CI 0.44–1.03).[31] A subset of men randomised in the STAMPEDE trial had high-risk localised disease (and/or pelvic enlarged lymph nodes) and RFS was improved in men randomised to receive docetaxel (HR 0.60; 95% CI 0.45–0.80; $P = 0.283 \times 10^{-3}$).[32] A meta-analysis of these three trials supported RFS improvement with docetaxel in men with high-risk localised disease (HR 0.70; 95% CI 0.61–0.81; $P < 0.0001$) but OS data were immature.[33]

Since then, three other trials [SPCG-12, SPCG-13 and VA Cooperative Study Program (CSP) #553] have reported preliminary data in congresses with no significant RFS benefit.[34–36] SPCG-13 may have included patients at insufficient risk of relapse to derive any benefit.[34] SPCG-12 did not use ADT as part of the standard of care,[35] and VA CSP #553 had limited power (only 297 patients participated), although a trend favouring docetaxel was observed.[36]

In men with high-risk localised prostate cancer, very long-term follow-up is needed to show survival differences: assuming cooperative groups are able to collect long-term data, this should be achieved around 2020–2025 for these trials. Based on the available data, offering docetaxel-based ChT may be a reasonable option for younger, fit men with multiple risk factors for recurrence.

Postoperative RT

Postoperative RT following RP may be given as adjuvant RT (ART; undetectable postoperative PSA) or salvage RT (SRT; persistent or rising PSA). Three RCTs investigated ART compared with observation (EORTC 22911, SWOG 8794 and ARO 96-02).[37] All showed improved biochemical control for ART, but no consistent OS benefit was seen. More recent trials, RADICALS-RT, RAVES and GETUG-17, have compared ART with a policy of observation with early SRT given at the time of PSA failure. All three trials have been combined in the ARTISTIC meta-analysis that was presented at ESMO 2019. The results show that ART has some harms (increased bladder and bowel morbidity), but no proven benefit in terms of biochemical progression-free survival (PFS). Thus, observation with SRT in the event of PSA failure is the current standard after RP. SRT should be given early. Outcomes are more favourable if SRT is used when PSA is $<$0.5 ng/ml.[38]

Three trials have compared SRT versus SRT plus 6 months of ADT (GETUG-AFU 16, RTOG 0534) or plus 24 months of bicalutamide (RTOG 9601).[39] RTOG 9601 showed a reduced rate of prostate cancer death (HR 0.77; 95% CI 0.59–0.99; $P = 0.04$) and improved OS (HR 0.49; 95% CI 0.32–0.74; $P < 0.001$).[39] *Post hoc* subgroup analysis indicated that men with a pre-SRT PSA above 0.7 ng/ml, GS 8-10 and positive margins had the largest benefit from the addition of bicalutamide.[39] The GETUG-AFU 16 trial showed an improvement in metastasis-free survival (HR 0.73; 95% CI 0.54–0.98; $P = 0.034$),[40] but not OS.

The SPPORT-trial, presented at the 2018 American Society for Radiation Oncology annual meeting,[41] investigated the potential of pelvic nodal RT with 6 months of ADT as

compared with prostate bed-only RT or prostate bed RT plus 6 months of ADT. The addition of pelvic RT improved freedom from failure, as well as an improvement in freedom from metastases for the comparison with prostate bed-only RT (HR 0.52; 95% CI 0.30—0.92; $P = 0.014$). There were no OS differences observed between arms.

Treatment of relapse after radical local treatment

Re-staging. For patients with biochemically recurrent prostate cancer, PSMA-PET imaging is replacing conventional imaging, based on its superior sensitivity and specificity.[42] Nevertheless, there are no trials indicating that the earlier detection of recurrence and subsequent change in management improves outcomes. The study of modern imaging methods has focused on their diagnostic performance, not their effect on care pathways.[42]

Local salvage therapy. The natural history of PSA recurrence following primary treatment[43] is long, and life expectancy should be taken into account when considering local treatment options. Molecular imaging studies have indicated that up to 50% of men experience a local recurrence in case of a PSA rise.[42] mpMRI is useful in the detection of local recurrence and can guide targeted biopsies. In case of a biopsy-confirmed local recurrence and the absence of metastases, several local treatment options are available, such as salvage RP, high-intensity focused ultrasound, cryoablation or brachytherapy. Taken together, these treatments typically give only temporary biochemical control in most patients with important morbidity.[44] None of these options have been compared head-to-head.

Metastasis-directed therapy. Earlier visualisation of recurrence makes it technically possible to selectively ablate metastases. Hypothetically, this would slow down progression and improve survival.[45] Most evidence in this setting comes from retrospective case series.[46] More recently, two randomised phase II trials have been published.[47,48] The STOMP trial showed an improved biochemical progression and time to palliative ADT with metastasis-directed therapy compared with observation and deferred ADT.[48] In the SABR-COMET trial, different solid tumour types were included, of which 16% were prostate cancer. This trial showed improved OS for additional stereotactic body RT (SBRT) to standard of care.[48] Both trials have paved the way for larger confirmatory phase III trials, but should not be considered as conclusive evidence to offer metastasis-directed therapy.

Systemic therapy. Two randomised trials, TOAD and ELAAT, have compared early versus deferred ADT for men with a PSA failure after local therapy.[49] The reasons to start ADT were development of symptoms or metastases on conventional imaging or PSA doubling time decreasing to $\leq$6 months. Pooled analysis found no survival benefit with early ADT (HR 0.75; 95% CI 0.40—1.41; $P = 0.37$).[50] Early ADT had an adverse effect on quality of life (QoL), specifically in terms of sexual activity and hot flushes.[49]

Intermittent versus continuous ADT was studied in a randomised trial of 1386 patients with a PSA at relapse of >3.0 ng/ml >1 year after radical RT. Intermittent ADT had a more favourable toxicity profile with no difference in OS (HR 1.02; 95% CI 0.86—1.21).[51]

Recommendations

- Watchful waiting with delayed ADT for symptomatic progression is an option for men who are not suitable for, or unwilling to have, radical treatment [I, A].
- Active surveillance is recommended for men with low-risk disease [II, A].
- RP or RT (external beam or brachytherapy) is an option for men with low-risk disease not suitable for active surveillance [III, B].
- RP or RT (external beam or brachytherapy) is recommended for men with intermediate-risk disease [I, B].
- Primary ADT alone is not recommended as standard initial treatment for non-metastatic disease [I, D].
- External beam RT plus ADT is recommended for men with high-risk or locally advanced prostate cancer [I, B].
- RP plus pelvic lymphadenectomy is an option for selected men with high-risk disease [III, B].
- Men receiving radical RT for intermediate-risk disease should have short-course ADT for 4—6 months [I, A].
- Men receiving radical RT for high-risk disease should have long-course ADT (18—36 months) [I, A].
- Neoadjuvant docetaxel ChT may be offered before RT for young, fit men with very high-risk localised prostate cancer [I, C].
- Following RP, patients should have their serum PSA level monitored, with salvage RT recommended in the event of PSA failure [III, B].
- Adjuvant postoperative RT after RP is not routinely recommended [I, B].
- Salvage RT should start early (e.g. PSA <0.5 ng/ml) [III, B]. Concomitant ADT for 6 months or bicalutamide 150 mg daily for 2 years may be offered to men having salvage RT [I, B].
- Men having SRT to the prostate bed may be offered pelvic nodal RT [I, C].
- Men with biochemical relapse after radical RT who may be candidates for local salvage or metastasis-directed treatment should undergo imaging with PET-CT [III, B].
- Early ADT alone is not recommended for men with biochemical relapse unless they have a rapid PSA doubling time, symptomatic local disease or proven metastases [II, D].
- Men starting ADT for biochemical relapse, in the absence of metastatic disease, should be offered intermittent rather than continuous treatment [I, B].

METASTATIC HORMONE-NAIVE PROSTATE CANCER

Treatment recommendations for metastatic hormone-naive prostate cancer (mHNPC) are shown in Figure 4. Addition of abiraterone, apalutamide, enzalutamide or docetaxel to

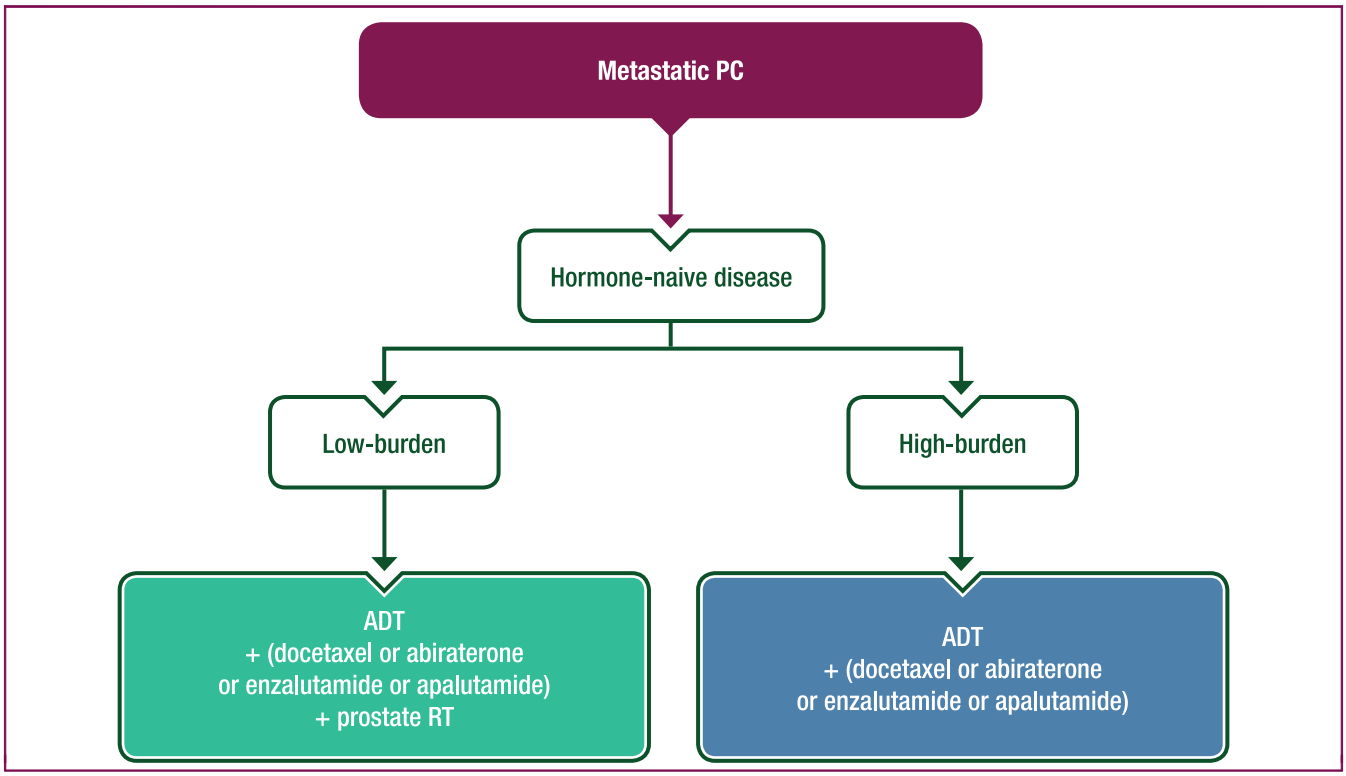

Figure 4. Metastatic prostate cancer treatment algorithm.
ADT, androgen deprivation therapy, PC, prostate cancer; RT, radiotherapy.

ADT improves OS in mHNPC. Most of the relevant trials, discussed below, largely included men with *de novo* metastatic disease, and caution should be used when extrapolating the results to men who relapsed with metastases after previous local treatment.

The benefit of docetaxel for mHNPC was established by two phase III trials, CHAARTED[52] and STAMPEDE.[32] The CHAARTED study randomised 790 patients to receive ADT alone or in combination with docetaxel 75 mg/m^2 every 21 days for 6 cycles. Docetaxel improved OS (HR 0.72; 95% CI 0.59—0.89). The STAMPEDE study is a multi-arm, multi-stage phase III study designed to test whether the addition of various treatments to ADT improves OS. It includes patients with both M0 and M1 disease. Patients were randomised to ADT alone ($n = 1184$) or in combination with docetaxel 75 mg/m^2 every 21 days with prednisone 10 mg daily for 6 cycles ($n = 592$). The addition of docetaxel in M1 patients significantly improved OS compared with ADT alone (HR 0.76; 95% CI 0.62—0.92). The OS benefit for docetaxel was similar when combined with zoledronic acid (HR 0.79; 95% CI 0.66—0.96). A third study, GETUG-AFU 15[53] randomised 385 mHNPC patients to receive ADT or ADT plus docetaxel 75 mg/m^2 every 21 days for 9 cycles. Patients in the ChT arm had improved PSA PFS and radiographic PFS (rPFS), but these did not translate into a benefit in OS (HR 1.01; 95% CI 0.75—1.36). Subgroup analysis of the CHAARTED study showed more pronounced benefit in patients with high-volume disease (HR 0.63; 95% CI 0.50—0.79),[54] defined as the presence of four or more bone metastases with one or more beyond vertebral bodies and pelvis, visceral metastasis or both. However, meta-analysis of CHAARTED, STAMPEDE and GETUG-AFU 15 have confirmed the improvement in OS with the addition of docetaxel to ADT regardless of disease volume (HR 0.77; 95% CI 0.68—0.87).[33,55]

The addition of abiraterone to ADT has demonstrated improved OS compared with ADT alone in two phase III trials, LATITUDE[56] and STAMPEDE.[57] Both studies randomised participants to ADT alone or in combination with abiraterone 1000 mg plus prednisone 5 mg daily until disease progression. LATITUDE randomised 1199 patients with high-risk metastatic prostate cancer, defined as the presence of at least two of the following: GS $\geq$8, three or more bone metastases or visceral metastases. The addition of abiraterone to ADT resulted in a significant improvement in OS (HR 0.62; 95% CI 0.51—0.76).[56] Updated data after crossover and 2-year additional follow-up confirmed this (HR 0.66; 95% CI 0.56—0.78).[58] A similar benefit in survival was observed in the STAMPEDE trial for the M1 subgroup (HR 0.63; 95% CI 0.52—0.76).[57] LATITUDE enrolled only patients with *de novo* metastatic prostate cancer, and only 5% of patients included in STAMPEDE were relapsing M1. Therefore, the benefit of adding abiraterone to ADT in the latter group of patients is uncertain.

The phase III trial TITAN demonstrated that addition of apalutamide to ADT improves OS in mHNPC.[59] The study randomised 1052 participants to ADT alone or in combination with apalutamide 240 mg per day. A total of 16% of patients had received treatment of localised disease and were enrolled at M1 relapse. Only 11% of patients had

received early docetaxel. Most patients had high-volume disease (63%). The addition of apalutamide improved OS (HR 0.67; 95% CI 0.51—0.89; $P = 0.005$) with no significant differences according to disease volume. Given the limited number of patients that received apalutamide after docetaxel, the benefit of this strategy remains unclear.

The benefit of adding enzalutamide to ADT for the treatment of mHNPC patients has been established by two phase III studies, ARCHES[60] and ENZAMET.[61] ARCHES randomised 1150 mHNPC patients to ADT plus enzalutamide 160 mg daily or ADT plus placebo. Participants were stratified by disease volume and prior docetaxel therapy. At the interim analysis, the primary end point was met, as enzalutamide significantly improved rPFS (HR 0.39; 95% CI 0.30—0.50; $P < 0.001$). The rPFS benefit was consistent across all prespecified subgroups, including disease volume and prior docetaxel ChT. At the time of this interim analysis, data on OS were immature. The second phase III study, ENZAMET,[61] randomised 1125 men with mHNPC to either ADT plus other non-steroidal anti-androgens, including bicalutamide, nilutamide or flutamide, versus ADT plus enzalutamide. Enzalutamide resulted in a significant improvement in OS (HR 0.67; 95% CI 0.52—0.86). This is the first study to examine the use of an androgen receptor (AR) signalling inhibitor with or without concurrent docetaxel; 45% of patients were planned to receive docetaxel. The HR for OS was 0.53 (95% CI 0.37—0.75) for those who were not planned to receive docetaxel, and 0.90 (95% CI 0.62—1.31) for those who were planned to receive docetaxel.

Docetaxel plus ADT and abiraterone plus ADT have been compared in an opportunistic randomised analysis from the STAMPEDE trial, suggesting similar outcomes in the M1 subgroup.[62] On the other hand, indirect Bayesian comparisons have suggested that the survival and QoL benefit provided by abiraterone may be greater than that seen with docetaxel.[63] Since no biomarkers have been identified to select one therapy over another, the decision to use abiraterone, apalutamide, enzalutamide or docetaxel should be individualised taking into consideration the cost, access to treatment, toxicity profiles, duration of treatment, comorbidities and patient preferences.

Two randomised trials, HORRAD[64] and STAMPEDE,[65] have compared lifelong ADT alone or in combination with RT to the primary tumour for mHNPC. The HORRAD trial randomised 446 patients to receive ADT alone or in combination with RT to the primary (70 Gy in 35 fractions for 7 weeks or 57.76 Gy in 19 fractions for 6 weeks). RT improved time to PSA progression (HR 0.78; 95% CI 0.63—0.97), but not OS (HR 0.90; 95% CI 0.70—1.14).[64] The STAMPEDE trial allowed docetaxel in both arms in addition to ADT. RT to the primary was then commenced within 3—4 weeks after the last docetaxel dose (55 Gy in 20 fractions over 4 weeks or 36 Gy in six fractions over 6 weeks). RT improved failure-free survival (HR 0.76; 95% CI 0.68—0.84; $P < 0.0001$) but not OS (HR 0.92; 95% CI 0.80—1.06). The prespecified low-volume subgroup, defined according to the CHAARTED criteria, had a significant benefit in both failure-free survival (HR 0.59; 95% CI 0.49—0.72) and OS (HR 0.68; 95% CI 0.52—0.90).

Management of bone health and prevention of cancer treatment-induced bone loss (CTIBL) is an important part of the treatment of men with prostate cancer under hormonal treatment. Prevention of CTIBL is covered by separate ESMO guidelines.[66]

Recommendations

- ADT is recommended as first-line treatment of mHNPC in combination with abiraterone/prednisone [ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4] or apalutamide [ESMO-MCBS v1.1 score: 4] or docetaxel [ESMO-MCBS v1.1 score: 4] or enzalutamide [ESMO-MCBS v1.1 score: 4] [I, A].
- RT to the primary tumour combined with the systemic treatment is recommended for patients with low-volume mHNPC [I, A].
- ADT alone is recommended as first-line systemic treatment of mHNPC in men who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel [III, A].
- For men starting on ADT, management to prevent CTIBL is recommended.[66]

NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Castration-resistant prostate cancer (CRPC) is defined as disease progression during ADT, with serum testosterone at castrate levels.[67] The absence of metastases (M0) on traditional imaging (bone scintigraphy and CT scan) has been used to identify M0 CRPC disease.[67] This disease setting exists because of the use of early, long-term ADT for men with non-metastatic prostate cancer. If ADT is delayed in men with biochemical failure after radical treatment until the site of recurrence is detected, M0 CRPC will be unusual because men will typically only develop castration-resistant disease after the detection of metastases.

Apalutamide significantly increased median metastasis-free survival (40.5 months versus 16.2 months, HR 0.28; 95% CI 0.23—0.35) and time to symptomatic progression (HR 0.45; 95% CI 0.32—0.63) as compared with placebo in a multicentre, randomised, placebo-controlled, phase III trial (SPARTAN) conducted in 1207 men with high-risk M0 CRPC (baseline PSA >2.0 ng/ml and a PSA doubling time of ≤ 10 months). Data on OS are still immature (HR 0.70; 95% CI 0.47—1.04). The most frequent side-effects observed in the experimental arm were rash, hypertension, fracture, hypothyroidism and mental-impairment disorder.[68]

Enzalutamide was evaluated in patients with high-risk M0 CRPC (PROSPER trial). In 1401 patients, enzalutamide was superior to placebo with regard to the primary end point of median metastasis-free survival (36.6 months versus 14.7 months, HR 0.29; 95% CI 0.24—0.35), and the key secondary end points of median time to PSA progression (37.2 versus 3.9 months; HR 0.07; 95% CI 0.05—0.08) and time to subsequent antineoplastic therapy (39.6 versus 17.7 months;

HR 0.21; 95% CI 0.17—0.26). Data on OS are still immature. Side-effects most commonly reported in the enzalutamide group were fatigue, hypertension, adverse cardiovascular events and mental-impairment disorders.[69]

Darolutamide was evaluated in the ARAMIS trial, a multicentre, randomised, double-blind, placebo-controlled, phase III trial involving 1509 men with high-risk M0 CRPC and a PSA doubling time of $\leq$10 months. Darolutamide significantly increased the median metastasis-free survival compared with placebo (median 40.4 months versus 18.4 months; HR 0.41; 95% CI 0.34—0.50). Data on OS are immature. Grade 3 or 4 adverse events were reported in 19.5% versus 24.7% of patients receiving placebo and darolutamide, respectively.[70]

Recommendation

- Apalutamide [ESMO-MCBS v1.1 score: 3], darolutamide [ESMO-MCBS v1.1 score: 3] or enzalutamide [ESMO-MCBS v1.1 score: 3] should be considered as options for men with M0 (on bone scan and CT) CRPC and a high risk of disease progression [I, B].

METASTATIC CRPC

For men with metastatic CRPC (mCRPC), both bicalutamide and low-dose corticosteroids show a benefit in terms of PSA and symptomatic responses, but no randomised trials have demonstrated a benefit in OS.[71,72]

The combination of abiraterone acetate and prednisone was compared with placebo plus prednisone in the COU-AA-302 trial[73] in >1000 men with ChT-naive, asymptomatic or mildly symptomatic mCRPC. Abiraterone significantly improved OS (HR 0.79; 95% CI 0.66—0.95). The main specific side-effects were hypokalaemia, hypertension, oedema and cardiac events. Low-dose abiraterone taken with food appeared to have similar activity to standard dose abiraterone under fasting conditions[74]; however, this has not been tested in phase III trials.

In the same setting, 1717 patients were treated with enzalutamide or placebo in the PREVAIL trial.[75] Enzalutamide was superior to placebo in terms of OS (HR 0.71; 95% CI 0.60—0.84), with fatigue/asthenia and hypertension as the most common adverse events.

The role of ChT in mCRPC was established in two phase III randomised trials. In the TAX-327 trial, in a population of 1006 patients with mCRPC, docetaxel (75 mg/m^2 3-weekly) combined with prednisone significantly increased OS as compared with mitoxantrone plus prednisone (HR 0.76; 95% CI 0.62—0.94).[76] Similarly, the SWOG-9916 trial showed that the combination of docetaxel (60 mg/m^2 3-weekly), estramustine and prednisone was superior to mitoxantrone plus prednisone in prolonging OS (HR 0.8; 95% CI 0.67—0.97). In both studies, docetaxel increased the risk of myelosuppression, febrile neutropaenia, fatigue, alopecia, diarrhoea, neuropathy and peripheral oedema.[77]

The ALSYMPCA trial showed that the treatment with radium-223 (^{223}Ra), a bone-targeted alpha-emitter, significantly increased OS (HR 0.70; 95% CI 0.55—0.83) and time to first symptomatic skeletal event (HR 0.66; 95% CI 0.52—0.83) compared with placebo in 926 patients with progressive bone-predominant, symptomatic mCRPC.[78] Side-effects of ^{223}Ra include thrombocytopaenia (3% G3) and diarrhoea (2% G3). Based on this trial, ^{223}Ra was rated at the highest level of the ESMO-MCBS [ESMO-MCBS v1.1 score: 5].[79] However, the ERA-223 trial showed an increased incidence of fractures (28.6% versus 11.4%) among patients receiving ^{223}Ra in combination with abiraterone acetate plus prednisone compared with patients receiving placebo in combination with abiraterone acetate plus prednisone.[80] The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency has restricted the use of ^{223}Ra to patients who have received at least two lines of systemic treatment of CRPC (abiraterone/enzalutamide and docetaxel) or who are ineligible to receive these therapies.[81] The administration of ^{223}Ra in association with abiraterone acetate and prednisone/prednisolone is not permitted.

In the post-docetaxel setting, cabazitaxel improved OS (HR 0.70; 95% CI 0.59—0.83) compared with mitoxantrone in 755 patients (TROPIC trial).[82] The treatment was associated with increased myelosuppression, including febrile neutropaenia and diarrhoea. Similarly, abiraterone plus prednisone, tested against placebo plus prednisone in the COU-301 study[83] improved OS (HR 0.74; 95% CI 0.64—0.86). Enzalutamide was tested against placebo in the post-docetaxel setting in the AFFIRM trial, and also improved OS (HR 0.63; 95% CI 0.53—0.75).[84]

The optimal sequence or combination of all these agents is largely unknown. There is strong evidence suggesting cross-resistance between abiraterone and enzalutamide. A second AR inhibitor (abiraterone for those with prior enzalutamide and vice versa) had only modest activity.[85] The CARD trial compared cabazitaxel versus a second AR inhibitor. The median OS was 13.6 months with cabazitaxel and 11.0 months with the second androgen-signalling-targeted inhibitor (HR 0.64; 95% CI, 0.46—0.89; $P = 0.008$). In the control arm, the response rate and the duration of response to a second AR inhibitor were poor.[86]

In daily practice, sequencing decisions will be made in light of the distribution, extent and pace of disease, comorbidities, previous treatments (ChT or new hormone agents), patient preferences and drug availability.

Recommendations

- Abiraterone or enzalutamide [ESMO-MCBS v1.1 scores: 4] is recommended for asymptomatic/mildly symptomatic men with ChT-naive mCRPC [I, A].
- Docetaxel [ESMO-MCBS v1.1 score: 4] is recommended for men with mCRPC [I, A].
- In patients with mCRPC in the post-docetaxel setting, abiraterone [ESMO-MCBS v1.1 score: 4], enzalutamide [ESMO-MCBS v1.1 score: 4] and cabazitaxel [ESMO-MCBS v1.1 score: 3] are recommended options [I, A].
- In patients with bone metastases from CRPC at risk for clinically significant skeletal-related events (SREs), a

bisphosphonate or denosumab is recommended (see section on palliative care) [I, B].
- ^{223}Ra [ESMO-MCBS v1.1 score: 5] is recommended for men with bone-predominant, symptomatic mCRPC without visceral metastases [I, B].
- ^{223}Ra is not recommended in combination with abiraterone and prednisolone [I, E].
- The use of a second AR inhibitor (abiraterone after enzalutamide or vice versa) is not recommended [II, D].

PRECISION MEDICINE

Various tissue-based molecular assays provide prognostic information, additional to conventional clinicopathological parameters, regarding outcomes of conservative management and the likelihood of relapse following treatment of the primary.[87,88] Assessment of their clinical utility would require long-term prospective studies, and cost-effectiveness analyses.

AR splice variant 7 (AR-V7) detected in circulating tumour cells is prognostic in CRPC.[89] AR-V7-positive patients are less likely to respond to abiraterone and enzalutamide than AR-V7-negative patients,[90] while AR-V7 status does not seem to affect the response to taxanes.[84] Prevalence of AR-V7 is low before treatment but increases with subsequent therapy lines.[84] Thus, it would be of little use to investigate AR-V7 status in the treatment-naive setting. Switching from one AR signalling inhibitor to another after disease progression is rarely effective, and a therapy with a different mechanism of action (i.e. taxane) would be preferable. Therefore, AR-V7 is of limited value for therapy selection and cannot be recommended.

Actionable targets are identified in the majority of advanced prostate tumours.[91] Approximately 20% of metastatic prostate cancers harbour aberrations in genes involved in DNA damage and repair (DDR) and *BRCA2* is the most commonly altered.[91] A substantial proportion of these aberrations are also present in the germline.[91] Prostate tumours related to germline *BRCA2* mutations often have GS $\geq$8, nodal and distant metastases at diagnosis, but these genetic variants cannot be excluded in patients without such clinicopathological features.[92] Germline mutations in *BRCA2* have been associated with poor clinical outcomes across different disease states[92] while the prognostic implications of inheritable mutations in other DDR genes are less well established. Importantly, 30% of metastatic prostate cancer patients found to carry a germline DDR mutation did not have a previous family history of cancer.[93] Due to the prevalence of germline DDR in advanced prostate cancer (12%—16%),[92] these patients should be offered germline screening regardless of tumour features at diagnosis or family history of cancer. Men with localised prostate cancer should also be considered for germline testing if at least two close blood relatives on the same side of the family have been diagnosed with tumours linked to hereditary cancer predisposition syndromes (including breast, ovarian, prostate, pancreatic, melanoma, sarcoma, adrenocortical, brain, colorectal, endometrial, gastric, thyroid and kidney cancers).[94] The germline origin of pathogenic mutations affecting cancer-risk genes identified by tumour sequencing should also be investigated.[95] There is limited evidence to guide prostate cancer management based on germline status, but early identification of mutation carriers may contribute to the prevention and early diagnosis of tumours in relatives.

Some germline and somatic mutations in genes involved in the homologous recombination pathway, including *BRCA2*, are potential predictors of response to platinum-based ChT and poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors.[96] Tumours with germline and somatic mismatch repair defects are likely to respond to pembrolizumab.[97,98]

The PROFOUND trial tested olaparib versus a second AR axis inhibitor in patients with mCRPC with alterations in any of 15 genes with a role in DDR whose disease had progressed on prior new hormonal agent therapy. In 245 patients who had at least one alteration in *BRCA1*, *BRCA2* or *ATM*, olaparib improved rPFS [HR 0.34 (0.25—0.47)] and OS [HR 0.64 (0.43—0.97)].[99] In the control arm, the response rate and the duration of response to a second AR axis inhibitor was poor.

Recommendations

- Tissue-based molecular assays may be used in conjunction with clinicopathological factors for treatment decision making in localised prostate cancer [IV, C].
- Germline testing for *BRCA2* and other DDR genes associated with cancer predisposition syndromes is recommended in patients with a family history of cancer and should be considered in all patients with metastatic prostate cancer [III, B].
- Consider tumour testing for homologous recombination genes and mismatch repair defects (or microsatellite instability) in patients with mCRPC [II, B].
- Patients with pathogenic mutations in cancer-risk genes identified through tumour testing should be referred for germline testing and genetic counselling [IV, A].
- Olaparib can be considered after new hormonal agents for patients with mCRPC with alteration in *BRCA1* or *BRCA2* [I, B].

PALLIATIVE CARE

Fractionated versus single-fraction RT for bone pain has been compared in multiple randomised trials. Single-fraction treatment provides similar pain relief.[100] A recent non-inferiority phase II trial indicated that the single-fraction dose of 14—16 Gy using SBRT results in a better pain response than multifraction RT.[101] Multifraction RT is commonly used for bone metastatic disease associated with complications such as nerve root compression from soft tissue extension.

Zoledronic acid, a bisphosphonate, was shown to prolong time to first SREs, namely fracture, spinal cord compression, surgery or RT for bone pain or a change in anticancer treatment of bone pain.[102] However, there was no difference in disease progression, OS or QoL. Adverse effects included anaemia, fever, myalgia and osteonecrosis of the jaw (ONJ). Denosumab, a receptor activator of nuclear

factor kappa-β ligand inhibitor, has been compared with zoledronic acid.[103] Denosumab was superior with respect to time to first SRE (HR 0.82; 95% CI 0.71−0.95, $P = 0.0002$), but was associated with an increased risk of hypocalcaemia (13% versus 6%) and a trend towards higher incidence of ONJ (2.3% versus 1.3%). There was no difference in OS.

The management of mCRPC has changed markedly since the trials of zoledronic acid and denosumab were done. Abiraterone, enzalutamide, corticosteroids and ^{223}Ra all increase the risk of fragility fractures but reduce the risk of other SREs. These changes have heightened awareness of the importance of bone health (see below) in men on ADT. If the bone health recommendations are followed, the added value of zoledronic acid or denosumab for SRE prevention is unclear.

Spinal cord compression is a devastating complication of metastatic prostate cancer and early detection is critical for successful management. A systematic review found that spinal cord compression is a common finding, even in asymptomatic patients with metastatic prostate cancer and spinal metastases.[50]

Beta-emitting, bone-seeking radionuclides such as strontium-89 and samarium-153 hydroxyethylidene diphosphonate (^{89}Sr-HEDP and ^{153}Sm-HEDP) have proven symptomatic benefits in the treatment of mCRPC. However, their use is limited by myelotoxicity and they have largely been superseded by ^{223}Ra.

Recommendations

- A single fraction of external beam RT is recommended for palliation of painful, uncomplicated bone metastasis [I, A].
- In patients with bone metastases from CRPC at risk for clinically significant SREs, a bisphosphonate or denosumab is recommended [I, B].
- MRI of the spine to detect subclinical cord compression is recommended in men with CRPC with vertebral metastases [III, B].
- Urgent MRI of the spine to detect cord compression is very strongly recommended in men with CRPC with vertebral metastases and neurological symptoms [III, A].

FOLLOW-UP AND LONG-TERM IMPLICATIONS

ADT may cause hot flushes, lethargy, mood changes, osteoporosis, insulin resistance and muscle loss. Because survival in mCRPC has improved substantially, men are living longer on ADT. Taken together with the adverse effects on bone health of abiraterone, enzalutamide, steroids and ^{223}Ra, bone health in men with prostate cancer is an increasingly important issue. The FRAX® (Fracture Risk Assessment Tool) score to estimate the risk of fragility fracture is not directly applicable to such men because it does not include a correction specifically for use of ADT. The risk of fragility fracture in men on long-term ADT exceeds accepted intervention thresholds. Even before starting ADT, a large proportion of men diagnosed with prostate cancer have osteopaenia or osteoporosis.[104]

Lifestyle measures (weight-bearing exercise, stopping smoking, two or fewer units of alcohol daily and adequate calcium intake and vitamin D status) help to maintain bone health. Treatment with an oral bisphosphonate, such as alendronic acid, reduces the incidence of fractures.[105] Alendronic acid should be taken after an overnight fast, at least 30 min before food, drink or other medicines. Whole tablets should be swallowed with a glass of water. Patients should remain upright for 30 min. If an oral bisphosphonate is not tolerated, zoledronic acid every 12 months or denosumab every 6 months are appropriate alternatives.

Recommendations

- Lifestyle measures to maintain bone health are recommended for men on ADT: weight-bearing exercise, stopping smoking, two or fewer units alcohol daily, adequate calcium intake and vitamin D status (reach and maintain reference vitamin D levels) [IV, B].
- Men starting long-term ADT should:
  - either be offered an oral bisphosphonate [I, B].
  - or be monitored with DEXA scanning and then treated according to the ESMO guidelines for CTIBL[66] [IV, B].

METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. An ESMO-MCBS table with ESMO-MCBS scores is included in supplementary Table S3, available at *Annals of Oncology* online. ESMO-MCBS v1.1[79] was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016 (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. Levels of evidence and grades of recommendation have been applied using the system shown in supplementary Table S4, available at *Annals of Oncology* online.[106] Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

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DISCLOSURE

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European Association of Urology

Review – Testis Cancer – Editor's Choice

European Association of Urology Guidelines on Testicular Cancer: 2023 Update

Anna Patrikidou [a], *Walter Cazzaniga* [b], *Daniel Berney* [c], *Joost Boormans* [d], *Isabel de Angst* [d], *Domenico Di Nardo* [e], *Christian Fankhauser* [f], *Stefanie Fischer* [g], *Carmen Gravina* [h], *Hendrik Gremmels* [e], *Axel Heidenreich* [i], *Florian Janisch* [j], *Ricardo Leão* [k], *Nicola Nicolai* [l], *Christoph Oing* [m], *Jan Oldenburg* [n], *Robert Shepherd* [d], *Torgrim Tandstad* [o], *David Nicol* [b,p,*]

[a] *Department of Oncology, Institut Gustave Roussy, Villejuif, France;* [b] *Department of Urology, The Royal Marsden NHS Foundation Trust, London, UK;* [c] *Barts Cancer Institute, Queen Mary University of London, London, UK;* [d] *Department of Urology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands;* [e] *Patient Representative, European Association of Urology Guidelines Office, Arnhem, The Netherlands;* [f] *Department of Urology, Luzerner Kantonsspital, Luzern, Switzerland;* [g] *Department of Medical Oncology and Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland;* [h] *Department of Urology, Sant'Andrea Hospital-Sapienza University, Rome, Italy;* [i] *Department of Urology, Uniklinik Koln, Cologne, Germany;* [j] *Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [k] *Department of Urology, Faculty of Medicine, University of Coimbra, Clinical Academic Center of Coimbra, Coimbra, Portugal;* [l] *Department of Surgery, Urology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy;* [m] *Department of Oncology, Freeman Hospital NHS Foundation Trust, London, UK;* [n] *Department of Oncology, Akershus University Hospital, Lorenskog, Norway;* [o] *Department of Oncology, The Cancer Clinic, St. Olav's University Hospital, Trondheim, Norway;* [p] *Institute of Cancer research, London, UK*

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Abstract

Context: Each year the European Association of Urology (EAU) produce a document based on the most recent evidence on the diagnosis, therapy, and follow-up of testicular cancer (TC).
Objective: To represent a summarised version of the EAU guidelines on TC for 2023 with a focus on key changes in the 2023 update.
Evidence acquisition: A multidisciplinary panel of TC experts, comprising urologists, medical and radiation oncologists, and pathologists, reviewed the results from a structured literature search to compile the guidelines document. Each recommendation in the guidelines was assigned a strength rating.
Evidence synthesis: For the 2023 EAU guidelines on TC, a review and restructure were undertaken. The key changes incorporated in the 2023 update include: new supporting text regarding venous thromboembolism prophylaxis in males with metastatic germ cell tumours receiving chemotherapy; quality of life after treatment; an update of the histological classifications and inclusion of the World Health Organization 2022 pathological classification; inclusion of the revalidation of the 1997 International Germ Cell Cancer Collaborative Group prognostic risk factors; and a new section covering oncology treatment protocols.
Conclusions: The 2023 version of the EAU guidelines on TC include the highest available scientific evidence to standardise the management of TC. Better stratification and optimisation of treatment modalities will continue to improve the high survival rates for patients with TC.

* Corresponding author. Department of Urology, The Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK.
E-mail address: david.nicol@rmh.nhs.uk (D. Nicol).

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Patient summary: This article presents a summary of the European Association of Urology guidelines on testicular cancer published in 2023 and includes the latest recommendations for management of this disease. The guidelines are a valuable resource that may help patients in understanding treatment recommendations.

1. Introduction

Testicular cancer (TC) is a rare malignancy representing 1% of adult neoplasms and 5% of urological tumours, with three to ten new cases per 100 000 males annually in Western societies [1]. While the rising incidence over recent decades [2,3] continues, prospects of a cure after treatment remain high, with overall long-term survival of 97%. Current evidence suggests that optimal outcomes are obtained in high-volume reference centres, irrespective of disease stage [4].

Clinical guidelines play a fundamental role in summarising the most recent and highest-quality evidence to guide medical professionals in the treatment of this condition and facilitate the highest standard of care. Here we report a summary of and key changes to the 2023 version of the European Association of Urology (EAU) guidelines on TC.

2. Evidence acquisition

The EAU Guidelines Panel on TC comprises a multidisciplinary group of expert clinicians from urology, medical and radiation oncology, pathology and radiology. This document was produced after obtaining input from the multidisciplinary team.

The 2023 EAU TC guidelines focused on restructuring of the text and addition of an online section covering oncology treatment protocols. The full version of the 2023 guidelines is available on the EAU website (http://uroweb.org/guideline/testicular-cancer/). References were assessed according to the level of scientific evidence, and guideline recommendations were generated [5]. Further online sections will be created and an appraisal of all newly published literature will be performed for the 2024 TC guidelines.

3. Evidence synthesis

3.1. Diagnosis and initial management of TC

3.1.1. Clinical assessment

Patients with TC usually present with a painless testicular mass or an incidental finding on testicular ultrasound (US). Clinical assessment should include examination of both testes, the abdomen, and the supraclavicular fossae, as well as the chest to identify gynaecomastia [4].

3.1.2. Imaging

High-frequency (>10 MHz) testicular US should be used to confirm the presence of a testicular mass. This imaging modality can detect whether a mass is intratesticular or extratesticular, the size of the lesion, multifocal disease, and the characteristics of the contralateral testicle. Staging with contrast-enhanced computed tomography (CECT) should be performed before orchidectomy, but can be deferred until confirmation of malignancy [6].

Patients with either multiple lung metastases or poor-prognosis International Germ Cell Cancer Cooperative Group (IGCCCG) risk group (especially with human chorionic gonadotropin [hCG] >5000 UI/l), or clinical symptoms [7] should also undergo brain imaging.

3.1.3. Serum tumour markers

Serum α-fetoprotein (AFP), hCG [8], and lactate dehydrogenase (LDH) should be determined before orchidectomy as they support the diagnosis of TC and may be indicative of germ cell tumour (GCT) histology. Tumour markers have limitations owing to their low sensitivity, as normal levels do not exclude the presence of disease [9]. Serum tumour marker levels need to be repeated following orchidectomy taking in consideration half-life kinetics, as delayed declines or rising levels provide staging and prognostic information [8,10].

3.1.4. Novel emerging markers

MicroRNAs (miRNAs) are emerging as potential new biomarkers. A number of studies suggest higher discriminatory accuracy for miRNAs (particularly miR-371a-3p) in comparison to conventional GCT serum tumour markers in diagnosis, treatment monitoring, and predicting residual or recurrent viable disease [11]. Several practical issues need to be resolved before incorporation in clinical practice (laboratory standardisation, availability of the test, and prognostic validation) [12].

3.1.5. Radical orchidectomy and testis-sparing surgery

Inguinal orchidectomy with division of the spermatic cord at the internal inguinal ring is the initial intervention for suspected TC. A scrotal approach should be avoided, as this is associated with a higher local recurrence rate [13].

Orchidectomy represents the standard of care for testicular GCTs. Testis-sparing surgery should only be offered to well-informed patients with a single testicle, excellent compliance, a single tumour of <2 cm located at the lower pole of the testicle, and normal preoperative endocrine function [14]. If testis-sparing surgery is considered, at least two additional testicular biopsies from the remaining testicle should be taken to exclude germ cell neoplasia "in situ" (GCNIS) [15]. Testis-sparing surgery may also be offered for small or indeterminate testicular masses, negative tumour markers, and a normal contralateral testis [16,17].

Routine contralateral biopsy in all patients remains controversial. Patients with TC at high risk of contralateral GCNIS (ie, testicular volume <12 ml and/or a history of cryptorchidism) should be fully informed regarding the risk/

benefit ratio for biopsy of the contralateral testis. Contralateral biopsy is not indicated in patients aged >40 yr without risk factors [15,18,19].

3.1.6. Impact on fertility

Treatment for TC, including orchidectomy, may impact on fertility [20], although sperm abnormalities and Leydig cell dysfunction are frequently found in patients with TC before orchidectomy. Where feasible, patients with a suspicion of TC should be offered semen preservation, ideally before orchidectomy, in order to maximize the chances of fertilisation [20,21].

3.2. Staging and prognostic classification

Histopathological results, postorchidectomy tumour markers, and CECT scan results are used to stratify patients according to the TNM classification [22,23] and Union for International Cancer Control staging (Table 1 and Table 2).

Patients presenting with metastatic disease (clinical stage IIC–III) are classified according to the IGCCCG classification. The IGCCCG classification has recently been revalidated in a more contemporary cohort (Table 3). The 5-yr progression-free survival (PFS) for patients with nonseminoma germ cell tumour (NSGCT) is unchanged for good- and intermediate-risk categories, but significantly improved for the poor-risk category (from 41% to 54%). The 5-yr overall survival (OS) is substantially better for all groups, particularly the poor-risk group. For seminoma germ cell tumour (SGCT), the 5-yr PFS has increased to 89% and 79% in the good- and intermediate-risk groups, with corresponding OS rates of 95% and 88% [8].

3.2.1. Prognostic factors for progression and recurrence in clinical stage I

Primary testicular tumour size and stromal invasion of the rete testis have been associated with the risk of relapse in

Table 1 – TNM classification for testicular cancer (adapted from the eighth edition of the Union for International Cancer Control staging system [22])

pT: primary tumour			
pTX	Primary tumour cannot be assessed[a]		
pT0	No evidence of primary tumour (eg, histological scar in testis)		
pTis	Intratubular germ cell neoplasia (carcinoma in situ)[b]		
pT1	Tumour limited to the testis and epididymis without vascular/lymphatic invasion; tumour may invade the tunica albuginea but not the tunica vaginalis[c]		
pT2	Tumour limited to the testis and epididymis with vascular/lymphatic invasion, or tumour extending through the tunica albuginea with involvement of the tunica vaginalis[d]		
pT3	Tumour invades the spermatic cord with or without vascular/lymphatic invasion[d]		
pT4	Tumour invades the scrotum with or without vascular/lymphatic invasion		
N: regional lymph nodes – clinical stage			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension, or multiple lymph nodes, none more than 2 cm in greatest dimension		
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour		
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
pN: regional lymph nodes – pathological stage			
pNX	Regional lymph nodes cannot be assessed		
pN0	No regional lymph node metastasis		
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour		
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M: distant metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis[d]		
M1a	Nonregional lymph node(s) or lung metastasis		
M1b	Distant metastasis other than nonregional lymph nodes and lung		
S: serum tumour markers (prechemotherapy)			
SX: serum marker studies not available or not performed			
S0: serum marker study levels within normal limits			
	LDH (U/l)	**hCG (mIU/ml)**	**AFP (ng/ml)**
S1:	<1.5 × ULN and	<5000 and	<1000
S2:	1.5–10 × ULN or	5000–50 000 or	1000–10 000
S3:	>10 × ULN or	>50 000 or	>10 000

ULN = upper limit of normal; LDH = lactate dehydrogenase; hCG = human chorionic gonadotropin; AFP = α-fetoprotein; AJCC = American Joint Committee on Cancer.

[a] Except for pTis and pT4, for which radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is assessed in the radical orchidectomy specimen; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

[b] The current "carcinoma in situ" nomenclature is replaced by germ cell neoplasia "in situ".

[c] The AJCC eighth edition subdivides T1 pure seminoma into T1a and T1b, depending on size no greater than 3 cm or greater than 3 cm in greatest dimension [23].

[d] The AJCC eighth edition considers hilar soft-tissue invasion and epididymal invasion as pT2, while discontinuous involvement of the spermatic cord is considered as pM1 [23].

Table 2 – Prognostic groups for testicular cancer [22]

Stage group	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1–T4	N0	M0	SX
Stage IA[a]	pT1	N0	M0	S0
Stage IB[b]	pT2–T4	N0	M0	S0
Stage IS[c]	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-N3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1a	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-N3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-N3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

[a] Stage IA: patients have primary tumours limited to the testis and epididymis, with no evidence of microscopic vascular or lymphatic invasion by tumour cells on microscopy, no sign of metastases on clinical examination or imaging, and postorchidectomy serum tumour marker levels within normal limits. Marker decline in patients with clinical stage I disease should be assessed until normalisation occurs on two consecutive measurements.
[b] Stage IB: patients have a more locally invasive primary tumour, but no sign of metastatic disease.
[c] Stage IS: patients have persistently elevated (and usually increasing) serum tumour marker levels after orchidectomy, indicating the presence of subclinical metastatic disease or possibly a second germ cell tumour in the contralateral testis.

clinical stage I SCGT [24]. A systematic review of the prognostic significance of risk factors showed that the level of evidence was too low to justify routine use of either risk factor to guide adjuvant treatment decisions [25].

For clinical stage I NSGCT, lymphovascular invasion (LVI) is strongly associated with the risk of relapse [26]. The risk of relapse at 5 yr is 50% for LVI-positive tumours versus 15% for LVI-negative tumours.

3.3. Management of clinical stage I GCT

3.3.1. Germ cell neoplasia "in situ"

For patients with germ cell neoplasia "in situ" (GCNIS) the risk of developing TC is 50% at 5 yr [27]. Management options include radical orchidectomy and close observation or local radiotherapy (RT; 18–20 Gy in fractions of 2 Gy) in the case of a solitary testis [28–31]. In men who wish to father a child, organ-sparing surgery with regular US observation might represent an option [15].

3.3.2. Clinical stage I SGCT

Up to 20% of patients with clinical stage I SGCT have occult metastatic disease, usually in the retroperitoneum, and will experience relapse after orchidectomy alone [32,33].

3.3.2.1. Surveillance. Surveillance requires a protocol involving regular cross-sectional imaging, measurement of serum tumour markers, and clinical assessment for early identification of patients who might experience relapse (Table 4). The overall risk of relapse in unselected patients with clinical stage I disease ranges from 12% to 20% at 5 yr, with a mean of 17% [34]. The majority of relapses occur in the retroperitoneum within the first 3 yr [33,35,36]. Among patients experiencing relapse on "active surveillance" for clinical stage I SGCT, the cancer-specific survival rate is >99% [34]. This appears to be a cost-effective approach [37,38], although it can represent a psychological burden for the patient.

3.3.2.2. Adjuvant chemotherapy. One randomised controlled trial (RCT) comparing one cycle of carboplatin reaching an area under curve of 7 mg/ml/min (AUC 7) with adjuvant RT showed no difference in relapse-free rates (95% vs 96%), time to recurrence, or survival after median follow-up of 4 yr [39]. Adjuvant carboplatin (AUC 7) is therefore an alternative to RT or surveillance in clinical stage I seminoma.

3.3.2.3. Adjuvant RT. RT with a cumulative dose of 20 Gy should be reserved for a highly selected group of patients who would be unsuitable for systemic combination chemotherapy in the event of relapse. This is related to the potential risk of developing secondary RT-induced non–germ cell malignancies as well as metabolic and cardiovascular events.

3.3.2.4. Risk-adapted treatment. This approach uses testicular tumour size and rete testis invasion to stratify the risk of relapse as high versus low for delivery of different treatment options. A trial of 897 patients offered surveillance to individuals with no or one risk factor, while those with both risk factors were offered one dose of carboplatin (AUC 7) [40]. At median follow-up of 5.6 yr, relapse was experienced by 4% of the surveillance group versus 2% of the adjuvant carboplatin group. Among patients with one or both risk factors, 15.5% of the surveillance cohort experienced relapse versus 9% of the adjuvant carboplatin cohort. Ultimately, the decision on adjuvant treatment remains one of patient choice after discussion of the options outlined [40].

Table 3 – Prognostic-based system for staging of metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group) [8,96][a]

Good-prognosis group	
Nonseminoma	*All of the following criteria:*
5-yr PFS 90% 5-yr survival 96%	• Testis/retroperitoneal primary tumour • No nonpulmonary visceral metastases • AFP <1000 ng/ml • hCG <5000 IU/l (1000 ng/ml) • LDH <1.5 × ULN
Seminoma	*All of the following criteria:*
5-yr PFS 89% 5-yr survival 95%	• Any primary site • No nonpulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate-prognosis group	
Nonseminoma	*Any of the following criteria:*
5-yr PFS 78% 5-yr survival 89%	• Testis/retroperitoneal primary tumour • No nonpulmonary visceral metastases • AFP 1000–10 000 ng/ml or • hCG 5000–50 000 IU/l or • LDH 1.5–10 × ULN
Seminoma	*All of the following criteria:*
5-yr PFS 79% 5-yr survival 88%	• Any primary site • Nonpulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor-prognosis group	
Nonseminoma	*Any of the following criteria:*
5-yr PFS 54% 5-yr survival 67%	• Mediastinal primary tumour • Nonpulmonary visceral metastases • AFP >10 000 ng/ml or • hCG >50 000 IU/L (10 000 ng/ml) or • Lactate dehydrogenase >10 × ULN
Seminoma	No patients classified as having poor prognosis

AFP = alpha-fetoprotein; hCG = human chorionic gonadotropin; LDH = lactate dehydrogenase; PFS = progression-free survival; ULN = upper limit of normal.
[a] Prechemotherapy serum tumour markers should be assessed immediately before administration of chemotherapy (same day).

Table 4 – Recommendations for the management of stage I seminoma

Recommendation	Strengthrating
Fully inform the patient about all available management options, including surveillance or adjuvant therapy after orchidectomy, as well as treatment-specific recurrence rates and acute and long-term side effects.	Strong
Offer surveillance as the preferred management option if resources are available and the patient is compliant.	Strong
Offer one dose of carboplatin at an area under curve of 7 if adjuvant chemotherapy is considered.	Strong
Do not administer adjuvant treatment in patients at very low risk of recurrence (no risk factors).	Strong
Do not routinely administer adjuvant radiotherapy.	Strong
Adjuvant radiotherapy should be reserved for highly selected patients not suitable for surveillance and with a contraindication for chemotherapy.	Strong

3.3.3. *Clinical stage I NSGCT*

Up to 30% of patients with clinical stage I NSGCT have occult metastatic disease and will experience relapse after orchidectomy alone [4].

3.3.3.1. Surveillance. The largest reports of surveillance indicate a cumulative relapse risk of approximately 30% among patients with clinical stage I NSGCT (5-yr conditional risk of relapse is 42% for high-risk and 17% for low-risk clinical stage I NSGCT [33,34]), which predominantly occur within 2 yr of orchidectomy.

3.3.3.2. Retroperitoneal lymph node dissection. Data from high-volume and expert centres report relapse rates of 10% in the case of negative nodes (pathological stage I) and <30% in the case of nodal metastases (pathological stage II [41–43]). The presence of LVI, predominant embryonal carcinoma, primary pT stage, and extranodal tumour extension on histology all appear to be associated with a higher risk of recurrence.

The few indications for upfront surgery (retroperitoneal lymph node dissection [RPLND]) in clinical stage I NSGCT include men with teratoma with somatic malignant component and patients unwilling or unsuitable to undergo chemotherapy in cases of recurrence (eg, chemotherapy-unfit patients, musicians who need to avoid neuropathy), in particular in the presence of LVI or macroscopic blood vessel invasion.

Nerve-sparing RPLND and minimally invasive approaches have been developed to reduce the morbidity associated with this procedure, although these should be performed by an experienced surgeon in a specialist centre [44] (Table 5).

3.3.3.3. Adjuvant chemotherapy. Large prospective studies with long follow-up have shown that one cycle of adjuvant cisplatin, etoposide, and bleomycin (BEP) reduces the risk of relapse by 90–95% [45], resulting in relapse rates of 1.5–3% according to LVI status [46], with a significantly better risk/benefit ratio [47].

3.3.3.4. Risk-adapted treatment. LVI is the strongest predictive factor for relapse in CS1 NSCGT and patients with LVI should have their high risk of relapse (up to 50%) highlighted and be guided to consider adjuvant management and chemotherapy with BEP x 1 as the "preferred" option.

Primary RPLND might represent an option in this cohort of patients, although patients need to be aware of the potential additional requirement of adjuvant chemotherapy if nodes contain active disease (pN1), as well as the 10% risk of systemic relapse, even if pN0, requiring subsequent chemotherapy treatment (BEP x 3)

Table 5 – Recommendation for the management of stage I NSGCT

Recommendations	Strengthrating
Inform patients about all management options after orchidectomy: surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection, as well as treatment-specific recurrence rates and acute and long-term side effects.	Strong
Offer surveillance or risk-adapted treatment based on lymphovascular invasion (see below).	Strong
Discuss one course of cisplatin, etoposide, bleomycin as an adjuvant treatment alternative for stage I NSGCT if patients are not willing to undergo or comply with surveillance.	Strong

NSGCT = nonseminomatous germ cell tumour.

3.4. Metastatic GCTs

3.4.1. Clinical stage I GCT with (persistently) elevated serum tumour markers

If AFP or hCG increases or does not normalise after initial treatment, US examination of the contralateral testicle is recommended to exclude a contralateral tumour. In the presence of a contralateral tumour, repeat staging 4 wk after orchidectomy is required [8]. Treatment as for metastatic disease should be commenced if markers rise (Table 6).

3.4.2. Stage IIA/B seminoma

Historically, treatment of stage IIA/B seminoma has been RT (30 Gy in stage IIA and 36 Gy in stage IIB), with relapse rates of 9–24% [48,49] and 5-yr relapse-free survival rates of 92% in stage IIA and 90% in stage IIB.

Chemotherapy is the alternative option for stage II seminoma (Fig. 1). The standard regimen is three cycles of BEP or four cycles of etoposide/cisplatin (EP) if bleomycin is contraindicated [50]. Acute toxicity was almost exclusively reported with chemotherapy, with long-term toxicity more frequent following RT, mainly comprising bowel toxicity and secondary cancers, generally in the irradiated field [51].

Current trials are addressing the role of primary RPLND in comparison to standard options. The data remain immature and insufficient to recommend primary RPLND in stage II seminoma outside clinical trials.

Table 6 – Guidelines on the treatment of metastatic testicular germ cell tumours

Recommendation	Strengthrating
Treat low-volume stage IIA/B NSGCT with elevated markers as for metastatic good- or intermediate-prognosis disease (IGCCCG groups) with three or four cycles of BEP.	Strong
Nerve-sparing retroperitoneal lymph node dissection when performed by an experienced surgeon in a specialised centre is the recommended initial treatment in clinical stage IIA NSGCT disease without elevated tumour markers.	Weak
Repeat staging after 6 wk before making a final decision on further management should be considered in patients with small-volume (clinical stage IIA <2 cm) marker-negative NSGCT.	Weak
Treat metastatic NSGCT (stage >IIC) with intermediate prognosis with four cycles of standard BEP.	Strong
For metastatic NSGCT with poor prognosis, treat with one cycle of BEP (or VIP in cases with pulmonary dysfunction), followed by tumour marker assessment after 3 wk. Continue the same schedule up to a total of four cycles with favourable marker decline. With unfavourable decline, initiate chemotherapy intensification.	Weak
Perform surgical resection of visible (>1 cm) residual masses after chemotherapy for NSGCT when serum tumour markers are normal or normalising.	Strong
Initially offer cisplatin chemotherapy according to IGCCCG prognosis groups, or alternatively radiotherapy to patients with stage IIA/B seminoma, and inform the patient of the potential long-term side effects of both treatment options.	Weak
Treat stage ≥IIC seminoma with primary chemotherapy according to IGCCCG classification (BEP × 3 for good prognosis and BEP × 4 for intermediate prognosis).	Strong

BEP = cisplatin, etoposide, and bleomycin; IGCCCG = International Germ Cell Cancer Collaborative Group; NSGCT = nonseminomatous germ cell tumour; VIP = cisplatin, etoposide, and ifosfamide.

3.4.3. Stage II NSGCT

In clinical stage IIA NSGCT, an initial period of surveillance followed by re-evaluation after 6 wk may be considered for patients with normal markers and equivocal lymph nodes (<2 cm). If the lesion progresses or fails to resolve, it should be treated as clinical stage II. For clinical stage IIA NSGCT with normal tumour markers, nerve-sparing RPLND with at least a modified template, and not just a pick-up lymphadenectomy, performed by an experienced surgeon in a specialised centre is the initial treatment recommended (Fig. 2). In men with histologically confirmed teratoma in the primary RPLND specimen, adjuvant chemotherapy adds no benefit, whereas in men with viable GCT, adjuvant chemotherapy may further decrease the risk of relapse [52].

3.4.4. Metastatic disease

3.4.4.1. Primary chemotherapy. For metastatic seminoma, a cisplatin-based regimen should be used [53]. Cisplatin-based combination chemotherapy has shown superior efficacy to carboplatin-based regimens. The standard regimen in good-risk seminoma is three cycles of BEP. Alternatively, four cycles of EP may be considered, especially when bleomycin is contraindicated [54]. In patients with intermediate-risk seminoma, four cycles of BEP is the standard regimen.

The standard regimen for good-risk NSGCT is three cycles of BEP with a 5-d regime. Chemotherapy should be given without delay or dose reduction at 21-d intervals.

For intermediate-prognosis NSGCT, the standard regimen is four cycles of BEP [55]. Four cycles of ifosfamide, cisplatin, and etoposide (VIP) has similar efficacy but is more myelotoxic [56].

In poor-prognosis NSGCT, four cycles of BEP is the standard regimen. Serum tumour marker decline is the only prospectively confirmed predictor of response to cisplatin-based chemotherapy in poor-prognosis metastatic GCTs. Patients with an inadequate tumour marker decline after the first or second cycle represent a group with unfavourable prognosis [57,58]. An RCT demonstrated better PFS when intensifying treatment with dose-dense chemotherapy in patients with an early unfavourable decline in tumour markers [59]. The trial was not powered to estimate OS differences. On the basis of results from this trial, patients with an unfavourable decline in tumour markers after one cycle of BEP can be switched to a more intensive (dose-dense) chemotherapy regimen.

Primary high-dose chemotherapy (HDCT) with subsequent autologous stem-cell transplantation has not shown an OS benefit in the overall poor-prognosis patient population in RCTs [57,60]. However, selected patients may derive a benefit from primary HDCT with three consecutive cycles of high-dose VIP [61].

3.4.4.2. Prevention of thromboembolism events during chemotherapy. All members of the guideline panel agreed that men with metastatic GCT undergoing chemotherapy

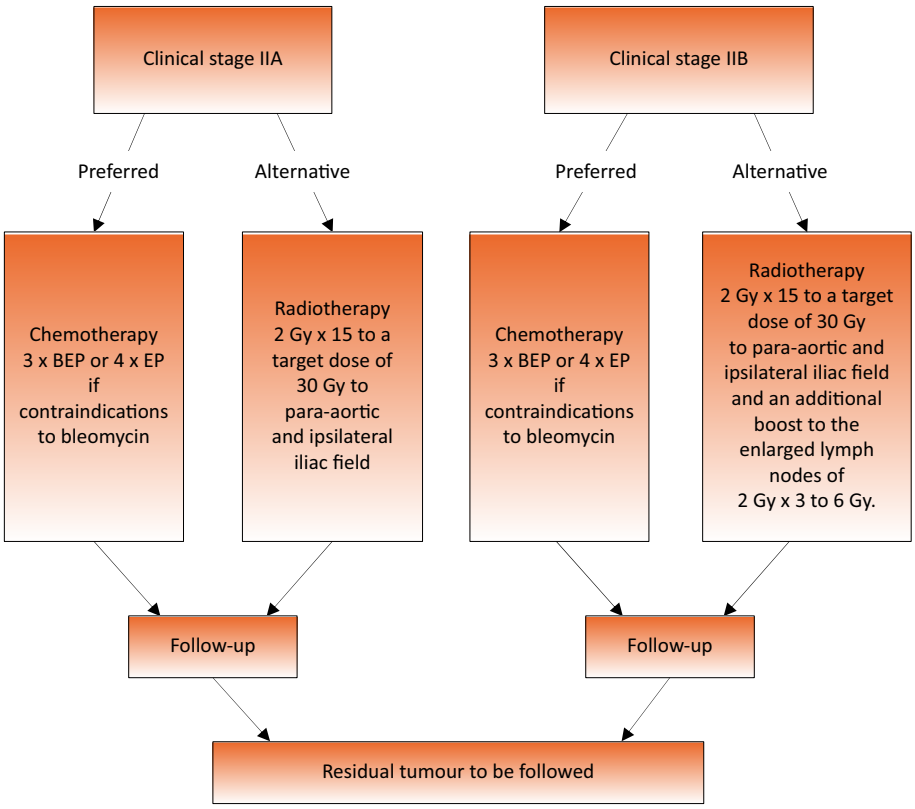

Fig. 1 – Treatment options for patients with clinical stage IIA or IIB seminoma*. BEP = cisplatin, etoposide, and bleomycin; EP = etoposide and cisplatin. *When enlarged retroperitoneal lymph nodes are <2 cm and markers are normal, treatment should not be initiated unless metastatic disease is unequivocal on the basis of biopsy, increasing nodal size/number, or subsequent marker rise.

are at high risk of venous thromboembolism (VTE). Thus, except for men with choriocarcinoma and high-volume extraperitoneal disease, who are at high risk of bleeding, thromboprophylaxis should be considered (Table 7). The majority of the panel agreed that a central venous-access device should be avoided whenever possible as this represents the only modifiable risk factor that remained significantly associated with VTE [62,63].

3.4.5. Restaging and treatment evaluation

Response to treatment should be assessed after the initial induction cycle via repeat imaging and/or re-evaluation of tumour markers. With marker decline and/or radiologically regressing or stable tumour features, the planned chemotherapy should be completed. If markers have normalised and masses with features of postpubertal teratoma progress, early surgical resection should be considered [64]. In patients with a low-level hCG plateau after completion of treatment, observation to determine whether complete normalisation subsequently occurs should be undertaken. Conversely, for patients with a low plateau for serum AFP after chemotherapy, removal of residual masses is advised, followed by subsequent AFP monitoring.

3.4.6. Residual tumour resection

3.4.6.1. Seminoma. A residual mass of seminoma should initially be monitored via imaging and tumour markers [65]. Almost all residual masses of ≤3cm only contain necrosis/fibrosis and just need to undergo routine follow-up assessments [66]. As ^{18}F-fluorodeoxyglucose positron emission tomography (PET) has high negative predictive value in patients with residual masses of >3 cm in largest diameter, PET imaging can provide more information on disease viability [67]. This should be performed only after at least 2 mo following completion of chemotherapy to prevent false-positive results due to inflammation and/or desmoplastic reaction induced by chemotherapy [68]. Patients with persistently high and/or progressing hCG elevation after first-line chemotherapy should proceed to salvage chemotherapy. Patients with progressing disease without hCG progression should undergo histological verification (eg, via percutaneous or surgical biopsy) before salvage chemotherapy is given. When RPLND is indicated, this should be performed in referral centres, as residual seminoma masses may be difficult to remove because of intense fibrosis [69].

3.4.6.2. Nonseminoma. For postchemotherapy nonseminomas, no diagnostic or risk calculator can accurately predict the histology of residual masses. Thus, resection is mandatory in all patients with a residual mass of >1 cm in greatest diameter on cross-sectional CECT imaging [70–73]. Surgery when indicated should be performed within 6–8 wk after the last chemotherapy cycle. The role of surgery for residual retroperitoneal lesions of <1 cm is uncertain [74]; the alternative option is close surveillance, with

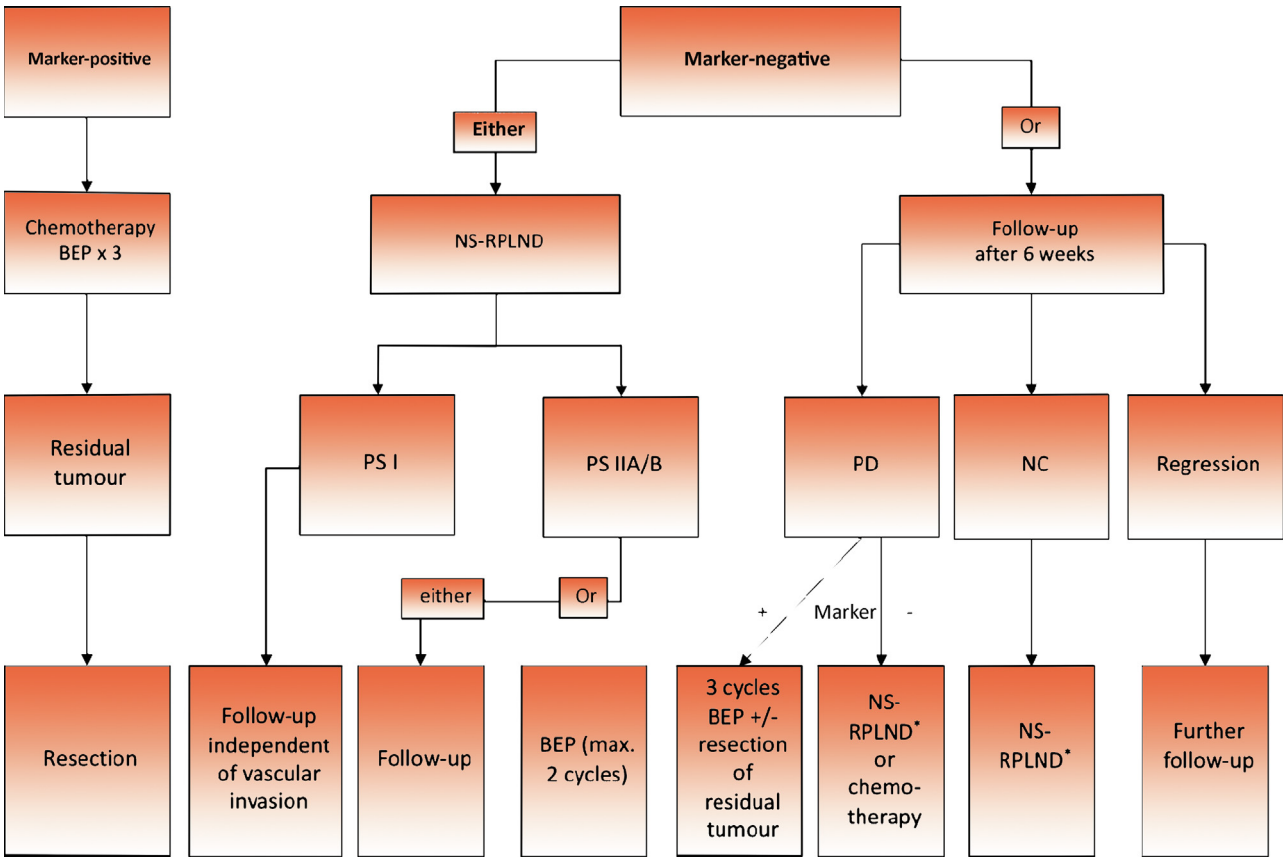

Fig. 2 – Treatment options for patients with clinical stage IIA nonseminoma. BEP = cisplatin, etoposide, and bleomycin; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection; PS = pathological stage; PD = progressive disease; NC = no change. *In cases of pathological stage IIA/B, patients can be followed after receipt of adjuvant chemotherapy (maximum of 2 cycles).

Table 7 – Guidelines on the prevention of thromboembolism events during chemotherapy

Recommendation	Strengthrating
Balance the individual patient's potential benefits and risks of thromboprophylaxis during first-line chemotherapy in men with metastatic germ cell tumours.	Weak
Avoid the use of central venous-access devices during first-line chemotherapy whenever possible.	Weak

a risk of recurrence of 6–9%, depending on the follow-up duration [75,76].

Residual masses after salvage chemotherapy or HDCT in the first line or subsequent salvage settings have a greater risk of harbouring active disease [77]. Surgery is therefore indicated even for residual masses of <1 cm [75,76].

When resection is indicated, bilateral nerve-sparing RPLND is the standard option. Ipsilateral template resection avoids contralateral nerve dissection and may be considered for residual masses with a diameter of <5 cm [78], as well as unilateral lymph-node metastases on prechemotherapy and postchemotherapy CT scans. Laparoscopic or robotic RPLND may yield comparable outcomes to open procedures in selected cases with low-volume residual disease and when undertaken by very experienced surgeons. To date, there are no data verifying long-term comparability with open surgery. This should only be considered in specialist TC centres with expertise in open RPLND and minimally invasive surgery to ensure appropriate case selection and the highest surgical standards.

3.4.6.3. Sequencing of surgery in cases with multiple sites. In general, surgery should commence at the site with the highest volume of residual disease, In cases with residual retroperitoneal and lung masses, the presence of fibronecrotic tissue in the retroperitoneum is associated with probability as high as 90% that lung masses contain the same histology [79]. Whereas some experts recommend resection of any postchemotherapy residual lesions, others suggest that necrosis in previous surgeries may predict the histology of further residual masses and that not all residual masses require immediate surgery [80].

3.4.7. Systemic salvage treatment for relapse or refractory disease

Cisplatin combination salvage chemotherapy will result in long-term remission in approximately 50% of patients with relapse after first-line chemotherapy. The regimens of choice are four cycles of a three-agent regimen including cisplatin and ifosfamide plus a third drug: VIP, paclitaxel (TIP), or potentially gemcitabine (GIP [10,81]). In a large retrospective analysis, histology, primary tumour location, response, progression-free interval after first-line treat-

ment, AFP and hCG levels, and the presence of liver, bone, or brain metastasis at salvage treatment were identified as independent variables prognostic for relapse after initial cisplatin chemotherapy [82]. Using these factors, five risk groups were identified with significant differences in PFS and OS: very low risk = −1 points; low risk = 0 points; intermediate risk = 1–2 points; high risk = 3–4 points; and very high risk = >5 points. A secondary analysis of the International Prognostic Factors Study Group cohort (n = 1600 patients) showed a 10–15% improvement in OS across all prognostic subgroups when treated with high-dose salvage therapy in comparison to standard-dose therapy.

3.5. Late relapse

Late relapse is defined as recurrence more than 2 yr after completion of successful primary treatment of metastatic TC [83]. This occurs in 1.4% seminoma and 3.2% of nonseminoma cases.

All patients with late-relapsing seminoma have viable GCT [84] and thus can be treated with chemotherapy and RT.

By contrast, patients with late-relapsing NSGCT should undergo surgical resection when feasible, alone or in combination with chemotherapy. Some patients, including those with rapidly rising hCG, may benefit from induction salvage chemotherapy with subsequent reconsideration of surgery for resection of persisting residual masses [83]. If the disease is not completely resectable, biopsies should be obtained for histological evaluation to direct salvage chemotherapy according to tumour phenotype. For unresectable but localised refractory disease, stereotactic or conventional RT may be considered. To avoid excess mortality, late relapses should be treated only at centres experienced in managing such patients [85].

3.6. Follow-up after curative therapy

The recommended follow-up schedules are listed Tables 8–10.

3.7. Quality of life and long-term toxicities after TC cure

Patients with TC are usually aged between 18 and 40 yr at diagnosis and their life expectancy after cure extends over several decades [86]. Patients should be informed before treatment of potential long-term toxicities (metabolic syndrome, cardiovascular events, and secondary malignancies, as well as long-term psychological sequalae including anxiety, depression, and fatigue).

Second malignant neoplasms of different histological origin usually occur after the first 10 yr and are considered to be induced by chemotherapy and/or RT [87]. The incidence of second neoplasms increased with time, resulting in a remarkably high and accelerating 35-yr cumulative incidence rate of 20% (95% confidence interval 18.9–21.5%) [88].

Mortality from cardiovascular disease (CVD) is higher among TC survivors than in the general population (odds ratio 5) [89,90]. Furthermore, CVD is more common among chemotherapy-treated TC survivors than among those who underwent surgery only [91]. In a cohort of 1819 patients with GCT, use of BEP chemotherapy increased the risks of hypertension and hypercholesterolaemia and thus CVD within 1 yr of initiation of BEP; at 1 yr after BEP treatment, the risk of CVD decreased to normal levels, but after 10 yr, increasing risks were found for myocardial infarction and cardiovascular death [89].

Metabolic syndrome, a strong risk factor for CVD, and its components (hypertension, obesity, and hypercholesterolaemia) increase with treatment intensity [90].

Subnormal testosterone levels have been reported in TC survivors treated with chemotherapy, and hypogonadism increases the risk of insulin resistance and hence the risk of metabolic syndrome, which in turn might lead to CVD in the long term [92]. Therefore, patients should be screened and treated for known risk factors such as hypertension, hyperlipidaemia, and testosterone deficiency during follow-up.

Quality of life is transiently reduced by chemotherapy, during which patients experience loss of appetite, increased fatigue and dyspnoea, reduced social and physical function, anxiety, depression, fear of cancer recurrence, and distress [93,94].

Furthermore, modifiable risk factors contribute to adverse health outcomes, such as hypertension and noise exposure to hearing impairment, and smoking to Raynaud's phenomenon [95]. Therefore, a healthy lifestyle should be strongly encouraged during follow-up consultations.

Table 11 summarises the changes in the 2023 version of the guidelines.

Author contributions: David Nicol had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cazzaniga, Berney, Boormans, de Angst, Di Nardo, Fankhauser, Fischer, Gravina, Gremmels, Heidenreich, Janisch, Leão, Nicol, Nicolai, Oing, Oldenburg, Patrikidou, Shepherd, Tandstad.

Acquisition of data: Cazzaniga, Berney, Boormans, de Angst, Di Nardo, Fankhauser, Fischer, Gravina, Gremmels, Heidenreich, Janisch, Leão, Nicol, Nicolai, Oing, Oldenburg, Patrikidou, Shepherd, Tandstad.

Analysis and interpretation of data: Cazzaniga, Berney, Boormans, de Angst, Di Nardo, Fankhauser, Fischer, Gravina, Gremmels, Heidenreich,

Table 8 – Recommended minimal follow-up for clinical stage I seminoma on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 yr
Tumour markers ± doctor visit	2 times	2 times	2 times	Once	Further management according to survivorship care plan
Chest X-ray	–	–	–	–	
Abdominopelvic MRI/CT	2 times	2 times	Once at 36 mo	Once at 60 mo	

CT = computed tomography; MRI = magnetic resonance imaging.

Table 9 – Recommended minimal follow-up for clinical stage I nonseminoma on active surveillance

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 yr
Tumour markers ± doctor visit	4 times[a]	4 times	2 times	1–2 times	Further management according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in care plan if LVI$^+$	At 60 mo if LVI$^+$	
Abdominopelvic MRI/CT	2 times	At 24 mo[b]	Once at 36 mo[c]	Once at 60 mo[c]	

CT = computed tomography; LVI = lymphovascular invasion; MRI = magnetic resonance imaging.
[a] For high-risk cases (LVI$^+$) a minority of the consensus group members recommended six times.
[b] For high-risk cases (LVI$^+$) a majority of the consensus group members recommended additional CT at 18 mo.
[c] Recommended by 50% of the consensus group members.

Table 10 – Recommended minimal follow-up after adjuvant treatment or complete remission for advanced disease (excluded: patients with poor prognosis and no remission)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 yr
Tumour markers ± doctor visit	4 times	4 times	2 times	2 times	Further management according to survivorship care plan[b]
Chest X-ray	1–2 times	Once	Once	Once	
Abdominopelvic MRI/CT	1–2 times	At 24 mo	Once at 36 mo	Once at 60 mo	
Thoracic CT	1–2 times[a]	At 24 mo[a]	Once at 60 mo[a]	Once at 60 mo[a]	

CT = computed tomography; MRI = magnetic resonance imaging.
[a] In conjunction with abdominopelvic MRI/CT in cases with pulmonary metastases at diagnosis.
[b] For cases with teratoma in resected residual disease, the patient should remain with the uro-oncologist.

Table 11 – Summary of changes in the 2023 guidelines

Old citations have been refreshed and replaced with newer references.
The recent revalidation of the 1997 International Germ Cell Cancer Collaborative Group prognostic risk factor system for metastatic testicular GCTs in patients treated with cisplatin-etoposide as first-line chemotherapy has been included in the text.
New supporting text regarding venous thromboembolism prophylaxis in males with metastatic GCTs receiving chemotherapy have been summarised in an online appendix.
Update of the histological classifications and inclusion of the World Health Organization 2022 pathological classification.
An online appendix for the reference chemotherapy protocols in GCT management has been created, including the main principles of toxicity and emergency management specific to GCTs.
An online appendix regarding the quality of life of testicular cancer survivors has been added. Specifications regarding type, prevalence, and risk factors for several long-term toxicities can be found in this document.

GCT = germ cell tumour.

Janisch, Leão, Nicol, Nicolai, Oing, Oldenburg, Patrikidou, Shepherd, Tandstad.
Drafting of the manuscript: Cazzaniga, Nicol, Patrikidou.
Critical revision of the manuscript for important intellectual content: Cazzaniga, Berney, Boormans, de Angst, Di Nardo, Fankhauser, Fischer, Gravina, Gremmels, Heidenreich, Janisch, Leão, Nicol, Nicolai, Oing, Oldenburg, Patrikidou, Shepherd, Tandstad.
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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

T. Powles[1], J. Bellmunt[2], E. Comperat[3], M. De Santis[4], R. Huddart[5], Y. Loriot[6], A. Necchi[7], B. P. Valderrama[8], A. Ravaud[9,10], S. F. Shariat[11], B. Szabados[1,12], M. S. van der Heijden[13] & S. Gillessen[14], on behalf of the ESMO Guidelines Committee*

[1]Barts Cancer Centre, Barts Health NHS Trust, Queen Mary University of London, London, UK; [2]Beth Israel Deaconess Medical Centre-IMIM Lab, Harvard Medical School, Boston, USA; [3]L'Assistance Publique-Hôpitaux de Paris, Hôpital Tenon, Paris, France; [4]Department of Urology, Charité Universitätsmedizin, Berlin, Germany; [5]Royal Marsden Hospital, Institute of Cancer Research, London, UK; [6]Département de Médecine Oncologique, Université Paris-Saclay and Gustave Roussy, Villejuif, France; [7]Vita-Salute San Raffaele University, Department of Medical Oncology, IRCCS San Raffaele Hospital, Milan, Italy; [8]University Hospital Virgen del Rocio, Seville, Spain; [9]Hôpital Saint-André CHU, Bordeaux; [10]Department of Medical Oncology, Bordeaux University Hospital, Bordeaux, France; [11]Department of Urology, Medical University of Vienna, Vienna General Hospital, Vienna, Austria; [12]Department of Urology, University College London Hospital, London, UK; [13]Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [14]Oncology Institute of Southern Switzerland (IOSI), EOC, Lugano, Switzerland

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INCIDENCE AND EPIDEMIOLOGY

Urothelial carcinoma (UC), also described as bladder cancer, is the 10th most common cancer type worldwide, with an estimated 549 000 new cases and 200 000 deaths in 2018. The highest incidence rates in Europe are observed in Southern Europe, e.g. Greece (5800 new cases and 1537 deaths in 2018), Spain and Italy, and Western Europe, e.g. Belgium and the Netherlands.[1] The most important risk factor for developing bladder cancer is tobacco smoking, which accounts for ∼50% of cases,[2] followed by occupational exposure to aromatic amines and ionising radiation.[3]

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

Diagnosis

Painless haematuria is the most common presenting symptom in bladder cancer and should be investigated in all cases. Other common symptoms include dysuria, increased frequency and/or urgency (Figure 1). Bladder ultrasonography or cross-sectional imaging can identify an intraluminal mass in the bladder, but the final diagnosis is based on cystoscopic examination of the bladder and histological evaluation of the tissue obtained either with cold-cup biopsy or transurethral resection of the bladder tumour (TURBT). Complete resection of all tumour tissue should be achieved when possible. The presence of lamina propria and detrusor muscle in the resected specimen is essential for accurate staging in most cases. Concurrent carcinoma *in situ* (CIS) is an adverse prognostic factor;[4] hence, bladder biopsies from suspicious urothelium or mapping biopsies from normal-looking mucosa in patients with positive urine cytology, or a history of high-grade (HG) non-muscle-invasive bladder cancer (NMIBC) should be taken.[5] In patients with high-risk NMIBC (described in Table 1), and in particular those with CIS, upper tract imaging should be carried out to screen for synchronous upper urinary tract urothelial carcinoma (UTUC). Computed tomography (CT) urography or magnetic resonance imaging (MRI) urography is used to detect papillary tumours in the urinary tract.[6] The management of bladder cancer is based on the pathological findings of the biopsy, with attention to histology, grade and depth of invasion (Table 1). Muscle-invasive bladder cancer (MIBC) should be staged according to the Union for International Cancer Control (UICC) TNM (tumour—node—metastasis) eighth edition and the American Joint Committee on Cancer (AJCC) TNM staging systems and should be grouped into categories (Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2021.11.012).

Pathology/molecular biology

Pathological diagnosis should be made according to the World Health Organization (WHO) 2016 classification

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

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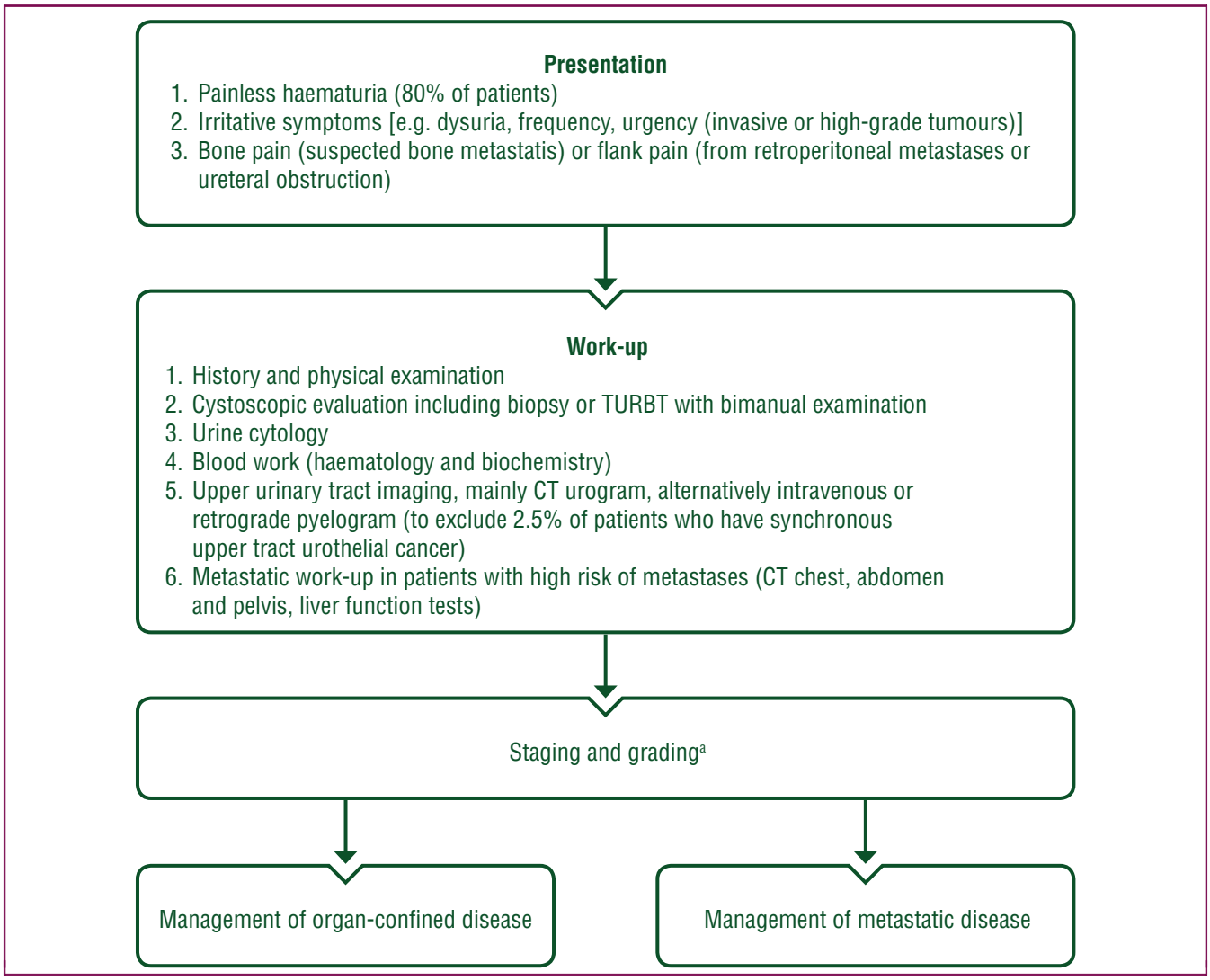

Figure 1. Diagnostic work-up of patient with suspected bladder cancer.
CT, computed tomography; TURBT, transurethral resection of the bladder tumour.
[a] See Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2021.11.012.

(Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.11.012).[7]

Approximately 75% of patients with bladder cancer present with NMIBC pTa-pT1, pTis).[3] The majority of patients with MIBC (pT2a-pT4b) are diagnosed with primary invasive bladder cancer and up to 15% of patients have a previous history of NMIBC, almost exclusively high-risk NMIBC.[3] All MIBCs are considered as HG.

TURBT or bladder biopsy only allow for staging up to T2. Clinical T3 or T4 disease is identified by bimanual exam under anaesthesia and/or cross-sectional imaging. NMIBC is graded as low grade (LG) or HG according to the latest WHO 2016 criteria.

Ninety percent of carcinomas of the upper and lower urothelial tract are UCs, with or without other variants (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.11.012). The percentage of the variant morphology should be given in the pathological report. If the squamous or adenocarcinoma part is >95%, the UC should be considered as a pure squamous/adenocarcinoma. The variant histology group comprises nested carcinoma, large nested, microcystic, micropapillary, lymphoepithelioma-like, plasmacytoid/signet ring cell/diffuse, sarcomatoid, giant cell, poorly differentiated, lipid rich and clear-cell UC, all of which are of urothelial origin.[7] Small-cell/neuroendocrine subtypes should be specified when they are present and the percentage should be noted.

Urine cytology can facilitate the diagnosis of HG UC but should not be used as the primary method of histological diagnosis. It has a high sensitivity in HG tumours including CIS (84%), but low sensitivity in G1/LG tumours (16%).[8]

Further molecular diagnosis is being investigated in the advanced disease setting, but its role has yet to be clearly defined. Oncogenic alterations [e.g. fibroblast growth factor receptor (*FGFR*) DNA alterations] and other forms of immuno-oncology therapy biomarker testing, such as programmed death-ligand 1 (PD-L1) expression, are being used for patient selection. Multiple methodologies exist for biomarker measurement and clinicians should follow European Medicines Agency (EMA) guidance for PD-L1,

Table 1. Risk group stratification of patients with NMIBC and treatment recommendations

Risk group stratification	Characteristics	Treatment recommendations
Low-risk tumours	Primary, solitary, Ta G1 (PUNLMP, LG), <3 cm, no CIS	One immediate instillation of intravesical ChT after TURBT [I, A] followed by cystoscopic surveillance
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk)	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score <5, one immediate instillation of intravesical ChT after TURBT [IV, C] In all patients, either: • instillations of ChT for a maximum of 1 year [I, A] Or • one-year full-dose BCG treatment (induction plus 3-weekly instillations at 3, 6 and 12 months) [I, A]
High-risk tumours	Any of the following: • T1 tumour • G3, HG tumour • CIS • Multiple, recurrent and large (>3 cm) Ta G1-G2/LG tumours (all features must be present)	Full-dose BCG instillations for 1-3 years or radical cystectomy [I, A]
Subgroup of highest-risk tumours	• T1 G3/HG associated with concurrent bladder CIS • Multiple and/or large T1 G3/HG and/or recurrent T1 G3/HG, T1 G3/HG with CIS in the prostatic urethra • Some forms of variant histology of urothelial carcinoma, lymphovascular invasion	Radical cystectomy or BCG induction and 3 years of maintenance if achievable [I, A]

BCG, bacillus Calmette-Guerin; ChT, chemotherapy; CIS, carcinoma *in situ*; EORTC, European Organisation for Research and Treatment of Cancer; G, grade; HG, high grade; LG, low grade; NMIBC, non-muscle-invasive bladder cancer; PUNLMP, papillary urothelial neoplasm of low malignant potential; TURBT, transurethral resection of the bladder tumour.

linking specific biomarkers methods with specific agents. Molecular diagnostics such as molecular subtype classification, FGFR and PD-L1 status are not routinely required [IV, C]. Molecular subtype analysis does not currently have a role in treatment selection. Genomic testing (PCR- or next-generation sequencing-based) should be used for detection of *FGFR2/3* mutations and fusions.[9,10] A personalised medicine synopsis is shown in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.11.012.

Recommendations

- Painless haematuria is the most common presenting symptom in bladder cancer and should in all cases be investigated [IV, A].
- The diagnosis of bladder cancer is based on cystoscopic examination of the bladder and histological evaluation of tissue obtained either with cold-cup biopsy or TURBT. Complete resection of all tumour tissue should be achieved when possible. Muscle tissue should be included in the biopsies, except when a Ta/LG is expected [IV, A].
- Cross-sectional upper tract imaging (CT/MRI urography) is recommended to screen for synchronous UTUC, in cases of HG bladder cancer [IV, B].
- Pathological diagnosis should be made according to latest WHO classification [IV, A].
- In addition to stage and grade, presence and percentage of variant histology, lymphovascular invasion and presence of detrusor muscle should be reported [IV, A].
- Urine cytology can facilitate the diagnosis of HG UC but cannot be used as the primary method of histological diagnosis [IV, B]. The Paris system should be used for reporting.
- Molecular diagnostics such as The Cancer Genome Atlas (TCGA) classification and PD-L1 status are not required for all tumours [IV, C].

STAGING AND RISK ASSESSMENT

Staging of NMIBC

A scoring system and risk assessment table has been developed to predict 1- and 5-year disease recurrence and progression in patients with Ta-T1 disease, using the WHO 1973 grading system.[11] An updated model has been developed for patients with Ta-T1 bladder cancer, treated with 1-3 years of bacillus Calmette-Guerin (BCG) maintenance. Patients with CIS alone were not included. The scoring system takes into account the number and size of tumours resected, depth of invasion, prior recurrences, presence of CIS and grade of the tumours after TURBT. Based on the above, the European Association of Urology classified the patients into four risk categories: low-risk, intermediate-risk, high-risk and very-high-risk tumours (Table 1), which constitutes the basis for treatment and follow-up recommendations in NMIBC [IV, B]. Patients with NMIBC have a heterogeneous prognosis. While patients with high-risk NMIBC suffer from a high recurrence rate (up to 50% at 5 years), they also have a low progression rate (<5% at 5 years). Those with T1/HG (grade 3) do poorly, with 1- and 5-year disease progression rates with 11% and 20%, respectively. Cancer-specific 5-year survival for these patients is >90%.[12,13]

Regional and distant staging of invasive bladder cancer

If muscle invasion has been confirmed, regional and distant staging should be carried out with further imaging

studies such as contrast-enhanced CT of the chest, abdomen and pelvis or MRI of the abdomen and pelvis (with CT of the chest). The risk of lymph node (LN) metastasis increases proportionally with advancing local tumour stage.[14,15] Both tests can be used to assess extravesical invasion but are often unable to reliably differentiate between T stages. Imaging is recommended before TURBT. Both tests are useful to detect enlarged LNs, but have low sensitivity (48%-87%) and specificity for the detection of LN metastasis.[16,17] Overall, pelvic nodes >8 mm and abdominal nodes >10 mm in maximum short-axis diameter, detected by CT or MRI, should be considered as suspicious for LN metastasis.[18,19] MRI generally is more accurate for determining depth of invasion and is recommended when imaging definition of stage of invasion is important. A scoring system for defining muscle invasion has been proposed (VI-Rads) with some accuracy, with a sensitivity and specificity of 0.83 [95% confidence interval (CI) 0.70-0.90] and 0.90 (95% CI 0.83-0.95), respectively.[20,21] A chest-abdomen-pelvis CT should also be carried out for staging of potential distant metastatic disease [III, A]. The authors did not reach a consensus on the role of [^{18}F]2-fluoro-deoxy-D-glucose positron emission tomography (FDG-PET)-CT in MIBC. Despite inconsistencies in sensitivity (23%-89%), FDG-PET-CT seems to have a high specificity (81%-100%) for LN staging.[22]

Recommendations

- Patients with NMIBC are classified into four risk categories based on tumour characteristics (low risk, intermediate risk, high risk and very-high-risk; Table 1), which constitutes the basis for treatment and follow-up recommendations [IV, B].
- In patients with invasive disease (≥T1), regional and distant staging should be carried out with further imaging studies such as contrast-enhanced CT of chest-abdomen-pelvis or MRI of abdomen/pelvis combined with chest CT [IV, B]. FDG-PET-CT may aid in the detection of LN and distant metastases [IV, C], but no clear consensus was reached.

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

Treatment of NMIBC

Optimal treatment of NMIBC is the complete removal of all visible lesions in the bladder, followed by intravesical instillations or early radical cystectomy (RC), according to risk stratification described in the preceding text [I, A] (Figure 2, Table 1, Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2021.11.012). If available, improved tumour visualisation techniques (fluorescence cystoscopy, narrow-band imaging) during TURBT are recommended.

In patients with low-risk NMIBC and those with small papillary recurrences, detected >1 year after the previous tumour, single, immediate, intravesical chemotherapy (ChT) instillation, such as mitomycin C (MMC), is recommended [I, A], in combination with continued cystoscopic surveillance. Immediate, intravesical ChT instillation significantly reduces the 5-year recurrence rate compared with TURBT alone (59% versus 45%).[23] The rate of progression is negligible (<2% at 5 years).[13]

In patients with intermediate-risk NMIBC, additional courses of intravesical therapy are recommended to reduce risk of recurrence [I, A]. This can consist of either:

1. Instillations of ChT for a maximum of 1 year.

Or

2. 12 months of BCG instillation therapy (induction therapy with six BCG instillations at weekly intervals, followed by maintenance therapy with three BCG instillations each at 3, 6 and 12 months after the start of the induction cycle) is recommended [I, A]. In trials with BCG therapy (induction and maintenance therapy) in intermediate- and high-risk NMIBC, there was a 32% reduction in the risk of recurrence ($P < 0.0001$) for BCG compared with MMC. However, no statistically significant difference was observed in progression rate between the two groups.[24]

In patients with high-risk NMIBC, full-dose intravesical BCG for 1-3 years (at least 1 year) is recommended [I, A]. Three-year maintenance is more effective than 1 year to prevent recurrences.[25] Induction consists of weekly instillations for 6 weeks while maintenance consists of weekly instillations for 3 weeks. Instillations at 3, 6, 12, 18, 24, 30 and 36 months are recommended [I, A]. The 3-year maintenance BCG schedule significantly reduces the risk or recurrence compared with 1-year maintenance [hazard ratio (HR) for 1 versus 3 years: 1.61, 95% CI 1.13-2.30, $P = 0.01$] in patients with high-risk tumours. This benefit of 3-year therapy does not occur for patients with intermediate-risk tumours.[25]

In patients with high-risk NMIBC, there is a significant risk of residual disease after initial TURBT.[26] Therefore, a second resection should be carried out 4-6 weeks after the first resection when:

- The initial TURBT was incomplete.
- If there is no detrusor muscle in the specimen on the initial resection, except for Ta LG and CIS.
- In all pT1 tumours and all HG tumours, except for patients with primary CIS [I, A].

The second TURBT should include a resection of the previous tumour site.

Treatment after failure of BCG therapy. The definition of failure after BCG therapy is important to identify patients who are unlikely to respond to further BCG therapy. In patients with very-high-risk NMIBC, these recommendations apply, except in those in whom early RC is planned. Early RC should be considered and discussed with all very-high-risk NMIBC cases. The final choice is made based on a shared decision-making process between patient and physician.

BCG failure is divided into the following four types:[27]

1. BCG-refractory:
   - persistent HG disease at 6 months despite adequate BCG treatment; OR

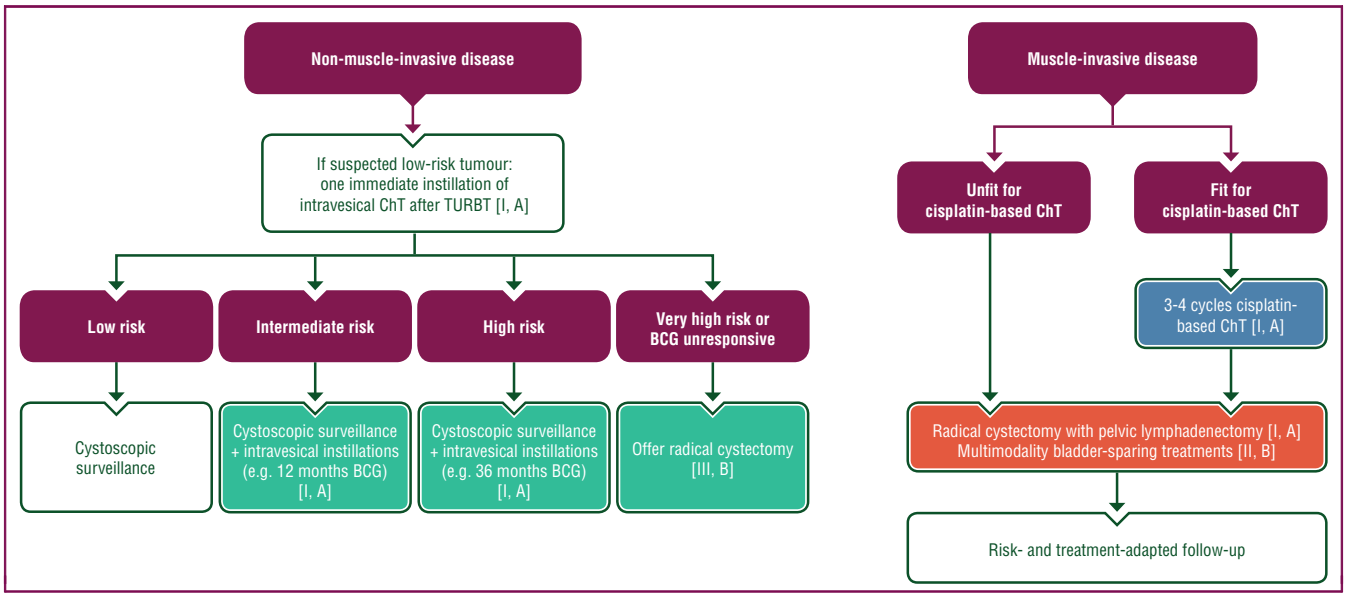

Figure 2. Management of patients with histopathologically confirmed bladder cancer.
Purple: general categories or stratification; red: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
BCG, bacillus Calmette-Guerin; ChT, chemotherapy; TURBT, transurethral resection of the bladder tumour.

- stage progression at 3 months after adequate BCG induction (i.e. HG T1 at 3 months after initial CIS or HG Ta).

2. BCG-relapsing: recurrence of HG disease after achieving a disease-free state at 6 months after adequate BCG.
3. BCG-intolerant: disease persistence as a result of inability to receive adequate BCG because of toxicity.
4. BCG-unresponsive: combination of BCG-refractory and BCG-relapsing within 6 months of last BCG.

RC should be carried out in HG tumours (T1/HG, Ta/HG, CIS) that are unresponsive to BCG due to the high risk of progression [III, B]. Thermo-ChT can be offered as an alternative, only in patients unwilling or unable to have RC and can obtain 2-year disease-free survival (DFS) in 47% of patients.[28] BCG re-induction achieved similar disease control to thermo-ChT in a randomised trial [II, B][29] and can be considered as an alternative.

The immune checkpoint inhibitor (ICI) pembrolizumab given intravenously was evaluated in a single-arm phase II trial (KEYNOTE-057), in patients with BCG-unresponsive NMIBC with CIS who were ineligible for or elected not to undergo RC ($n = 102$).[30] At 3 months, the study showed a complete response (CR) rate of 41% (95% CI 31%-51%) in 96 patients with high-risk NMIBC with CIS with or without papillary tumours, and a median duration of response of 16.2 months (range: 0.0-30.4). Intravenous pembrolizumab can be considered in patients with BCG-unresponsive disease who are not fit for or refuse RC [III, C]. More robust data are required before stronger recommendations can be made.

Intravesical nadofaragene firadenovec therapy [not Food and Drug Administration (FDA) or EMA approved as of November 2021] has also been studied in BCG-refractory NMIBC with CIS ($n = 103$; 53% CR at 3 months; 24% CR at 12 months) [III, C].[31] These data have the same recommendations as pembrolizumab in this population.

Treatment of MIBC

Multidisciplinary care via tumour board discussions and/or directed consultations with a medical oncologist, radiation oncologist and urologist is recommended for the optimal management of bladder cancer [IV, B].

Radical cystectomy. RC with pelvic lymph node dissection (PLND) is the standard treatment of MIBC cT2-T4a, N0 M0 [I, A].[32] RC with PLND is strongly recommended in very-high-risk and BCG-unresponsive NMIBC (Figure 2). A continent orthotopic (neobladder), continent cutaneous (catheterisable pouch) or incontinent cutaneous (conduit) reconstructions are chosen based on patient's general health and wishes.[33] A neobladder can be offered to patients lacking any contraindications and who have no tumour in the urethra or at the level of urethral dissection [IV, C]. Standard PLND is defined as the removal of all lymphatic tissues around the common iliac, external iliac, internal iliac and obturator regions up to the crossing of the ureters over the common iliac vessels at a minimum.[34,35] Extended lymphadenectomy includes lymphatic tissues in the region of the aortic bifurcation and presacral and common iliac vessels above the crossing ureters, in addition to the standard PLND region. The optimal extent of PLND is not established to date. In a recent prospective phase III, randomised trial, extended PLND failed to show a significant advantage in absolute improvement of 5-year recurrence-free survival compared with standard PLND, though the study suffered from many limitations.[36]

Patients with radiological suspicious node-positive disease (cN1) can be considered for surgery[37] (with or without neoadjuvant ChT) [IV, B]. Patients with clinical node positivity benefit from preoperative platinum-based ChT followed by RC plus PLND.[38-40] Overall, the number of positive LNs is significantly associated with increased risk of

cancer-specific death (HR 1.9, 95% CI 1.04-3.46 for N1 disease; HR 4.3, 95% CI 2.25-8.34 for ≥2 LNs).[41]

Organ-preservation therapy. Organ-preservation therapy for MIBC is a reasonable option for patients seeking an alternative to RC and for those who are medically unfit for surgery (Figure 2) [II, B]. Contemporary protocols utilise aggressive TURBT alone, TURBT plus radiotherapy (RT), TURBT plus ChT or a tri-modality combination of TURBT plus RT and ChT, the latter being preferred [II, B]. There are multiple patient- and tumour-related factors which contribute to the selection of trimodal therapy versus RC. The ideal patient for trimodal therapy has a tumour that can undergo a visible complete resection, has no associated hydronephrosis, does not invade the prostatic urethra and is not associated with diffuse CIS throughout the bladder. Select patients who do not meet all these criteria can still be successfully treated with this approach. The initial prospective, randomised comparison of RT alone versus concomitant chemoradiotherapy (CRT) demonstrated improved local control rate when cisplatin was given with RT (HR 0.50, 90% CI 0.29-0.86) [II, B].[42] A second trial showed that hypoxic sensitisation with carbogen and nicotinamide (bladder carbogen nicotinamide) reduced the risk of relapse (54% versus 43% with RT alone) and death [II, B].[43] A third randomised trial (BC2001) demonstrated improved results for CRT using the combination of 5-fluorouracil and MMC in terms of locoregional survival (67%) and DFS (54%) [I, A].[44] A multidisciplinary approach including urologists, medical oncologists and radiation oncologists is necessary. A cystoscopy with bladder biopsy is mandatory for response evaluation either midway through treatment or 2-3 months thereafter. If persistent or recurrent muscle-invasive disease is observed at response evaluation or during follow-up (cystoscopy and urinary cytology every 3 months during the first 2 years, and every 6 months thereafter), prompt RC is recommended when possible [II, A]. NMIBC recurrences can occur in up to one-fourth of patients after completion of trimodal therapy, with many being treated by routine and standard therapy for NMIBC. In this population after trimodal therapy, however, early salvage RC should be considered in those with adverse features, including T1 disease, tumour >3 cm, CIS or lymphovascular invasion. The 5-year cancer-specific survival and overall survival (OS) rates range from 50% to 82% and from 36% to 74%, respectively, with salvage RC rates of ∼20% for studies with a follow-up >5 years.[45,46] The pooled rate of non-response to trimodal therapy and local recurrence after trimodal therapy, the two primary reasons for salvage RC, is approximately 16% and 29%, respectively.[46] Salvage RC can be carried out for local recurrences with acceptable oncological control and no clear evidence of any greater risk of early complications; however, there may be a slightly increased risk for late complications, namely small bowel obstruction, ureteral stricture and parastomal hernia. The pooled rates of 5- and 10-year DFS after salvage RC have been estimated at 54% and 46%, respectively.[46,47] Trimodal therapy with other sensitising agents has been investigated in series from single-centre cooperative groups and meta-analysis [III, B]. There are clinical activity and acceptable outcome data. Patient selection may play a role in these outcomes. Cross-trial comparisons with RC should be avoided due to biases arising from patient selection and follow-up.[45,48-51]

Neoadjuvant and adjuvant therapy. The use of cisplatin-based neoadjuvant ChT for bladder cancer is supported by a meta-analysis of 11 randomised trials of 3005 patients [I, A] (HR 0.86, 95% CI 0.77-0.95), which translated to a 5% absolute increase in 5-year OS and a 9% absolute increase in 5-year DFS compared with cystectomy alone.[52] There is a lack of clarity about the optimal regimen.

Cisplatin—gemcitabine or accelerated methotrexate, vinblastine, adriamycin and cisplatin (MVAC) are the most widely given neoadjuvant ChT regimens and can be recommended [III, B].[53-55] There is also a lack of clarity on the number of cycles to be given. Three cycles were given in the original positive randomised phase III study, although most regimens/physicians currently administer four cycles.[56] Pure squamous cell or adenocarcinoma MIBC should be treated with primary RC [IV, B].[57] MIBC with small-cell neuroendocrine variant should be treated with neoadjuvant ChT followed by consolidating local therapy [IV, B].[57] A recent consensus meeting recommended cystectomy without neoadjuvant ChT for micropapillary disease, while data show no difference in response rates (RRs) compared with pure UC [IV, B].[57,58] Phase II data exist for neoadjuvant ICI therapy and they are not currently recommended in cisplatin-eligible or -ineligible patients [III, B].[59,60] There is no role for adjuvant treatment (ChT or RT) for those who have received neoadjuvant ChT. These patients have been included in the adjuvant immunotherapy trials.

Adjuvant cisplatin-based ChT in patients who did not receive neoadjuvant therapy remains an area of debate. There are no published positive randomised, phase III studies for survival. An updated meta-analysis of nine randomised trials including 945 patients found an OS benefit (HR 0.77, 95% CI 0.59-0.99) and DFS benefit (HR 0.66, 95% CI 0.45-0.91) among those who received cisplatin-based adjuvant ChT versus observation [II, B].[61] Subsequently, a randomised trial [European Organisation for Research and Treatment of Cancer (EORTC) 30994] reported a significant benefit of cisplatin-based ChT for DFS (HR 0.54, 95% CI 0.4-0.73) compared with observation.[62] A statistically significant OS benefit was not shown (adjusted HR 0.78, 95% CI 0.56-1.08) possibly due to insufficient recruitment. Adjuvant ChT in cisplatin-unfit patients is not recommended [I, D].

Adjuvant atezolizumab for 1 year versus observation did not improve DFS or OS in a large ($n = 809$) randomised study for high-risk UC [HR for DFS 0.89 (95% CI 0.74-1.08)[63] and HR for OS 0.85 (95% CI 0.66-1.09)]. There was no enrichment for outcome with the PD-L1 biomarker. Adjuvant atezolizumab is not recommended.

Adjuvant nivolumab for 1 year versus placebo showed improved DFS of 0.70 (95% CI 0.54-0.89; median follow-up

of 20.9 months). There were also positive results in the 26% of patients who were PD-L1-positive [DFS 0.53 (95% CI 0.34-0.84)]. OS (a secondary endpoint) has not yet been presented.[64] 17.9% grade 3 or more treatment-related adverse events occurred in the nivolumab arm. These results are promising, especially in the biomarker-positive population. Due to the inconsistency across trials and uncertainty of the relationship between DFS and OS with immunotherapy, OS results are awaited before this treatment can be recommended [I, D].

Recommendations

Treatment of NMIBC

- Treatment of NMIBC should follow a risk-stratified approach with TURBT and intravesical ChT or BCG in intermediate- and high-risk patients [I, A].
- Subsets of patients with very-high-risk disease should be offered RC. RC should be carried out in CIS or HG T1 that are unresponsive to BCG due to the high risk of progression [III, B].
- In patients who are BCG-unresponsive and -ineligible for or refuse cystectomy, pembrolizumab or nadofaragene firadenovec can be considered; however, more robust data are required before stronger recommendations can be made for these and other bladder-sparing approaches in BCG-unresponsive disease [III, C]. A multidisciplinary approach is required for these patients [IV, C].

Treatment of MIBC

- Multidisciplinary care via tumour board discussions and/or directed consultations with a medical oncologist, radiation oncologist and urologist is recommended for the optimal management of bladder cancer [IV, B].
- RC with standard PLND is the standard treatment of MIBC T2-T4a, N0 M0 [I, A].
- Patients with radiological suspicious node-positive disease (cN1) can be considered for surgery but should be considered for preoperative platinum-based ChT [IV, B].
- Organ-preservation therapy with RT, as part of multimodal schema for MIBC, is a reasonable option for patients seeking an alternative to RC and an option for those who are medically unfit for surgery [II, B].
- Contemporary organ-preservation protocols should utilise tri-modality combination of TURBT, RT and ChT [II, B].
- Palliative RT can be offered for palliation (bleeding, pain) [III, C].
- Adjuvant RT (with or without radiosensitising ChT) is not standard treatment of patients with MIBC [III, C].
- Three to four cycles of cisplatin-based neoadjuvant ChT should be given for MIBC [I, A]. Cross-sectional imaging should occur after ChT before RC [IV, B].
- There is weak evidence to support the use of adjuvant cisplatin-based ChT in patients who did not receive neoadjuvant therapy [II, B]. Neoadjuvant ChT is preferred.
- Inconsistent results exist for adjuvant ICIs in UC [I, A]. An OS advantage is needed before it can be recommended as standard therapy [I, D].

MANAGEMENT OF ADVANCED/METASTATIC DISEASE

Advanced or metastatic UC in patients fit enough to tolerate cisplatin-based combination ChT

Cisplatin-containing combination ChT is standard in advanced or metastatic patients fit enough to tolerate cisplatin (Figure 3). A number of cisplatin-containing ChT regimens are acceptable although gemcitabine—cisplatin [I, A] is the most widely used.[65] Dose-dense MVAC [I, B], MVAC with granulocyte colony-stimulating factor [I, B] and gemcitabine, cisplatin and paclitaxel [I, C] have been tested against gemcitabine and cisplatin.[66-68] Although these alternative regimens may lack proven advantages over gemcitabine and cisplatin, similar results are reported and either can be considered as an option in selected patients. New treatments which build on the gemcitabine—platinum backbone will require clinically meaningful progression-free survival (PFS) advantages, significant OS or non-inferiority with better tolerability to be recommended. For these reasons, gemcitabine, cisplatin and bevacizumab regimen is not recommended.[69,70] The combination of platinum-based ChT with ICIs has not resulted in positive significant survival advantages and is not currently recommended.[71] Potential benefits in other endpoints such as PFS are modest. Final results for atezolizumab with ChT are awaited.[72] There is currently no role for ICI therapy alone in this population.[73]

Advanced or metastatic UC in patients not eligible for cisplatin-based combination ChT

Carboplatin-based ChT is recommended in patients unfit for cisplatin [I, A]. Criteria for these have been defined.[74] Carboplatin with gemcitabine is the preferred regimen [II, B].[75] Gemcitabine and cisplatin can be considered for patients otherwise fit without comorbidities, a good performance status (0-1) and a creatine clearance between 50 and 60 ml/min [III, B].[76,77] This alternative has been established over time as a standard treatment and can, therefore, be supported despite a lack of robust data. A recent randomised trial evaluated the safety of split-dose cisplatin due to renal toxicity;[78] the authors did not reach consensus on its role. Six cycles of ChT are considered the standard of care, although fewer cycles are acceptable, with cumulative toxicity.[79]

Pembrolizumab or atezolizumab are alternative choices for patients who are PD-L1-positive and not eligible for cisplatin-based ChT, although randomised trials, which have reported, failed to show significant superiority compared with ChT [III, B] (final results are awaited for atezolizumab) (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2021.11.012).[73,80] In exploratory analyses, the OS HR for pembrolizumab and atezolizumab versus gemcitabine and carboplatin in this subset of biomarker positives was 0.82 (95% CI 0.57-1.17) and 0.53 (95% CI 0.30-0.94), respectively. Final OS results for the atezolizumab study are awaited. Biomarkers (SP142 for atezolizumab; 22C3 for pembrolizumab) should be used to match the drug, as recommended by the EMA.[72,81]

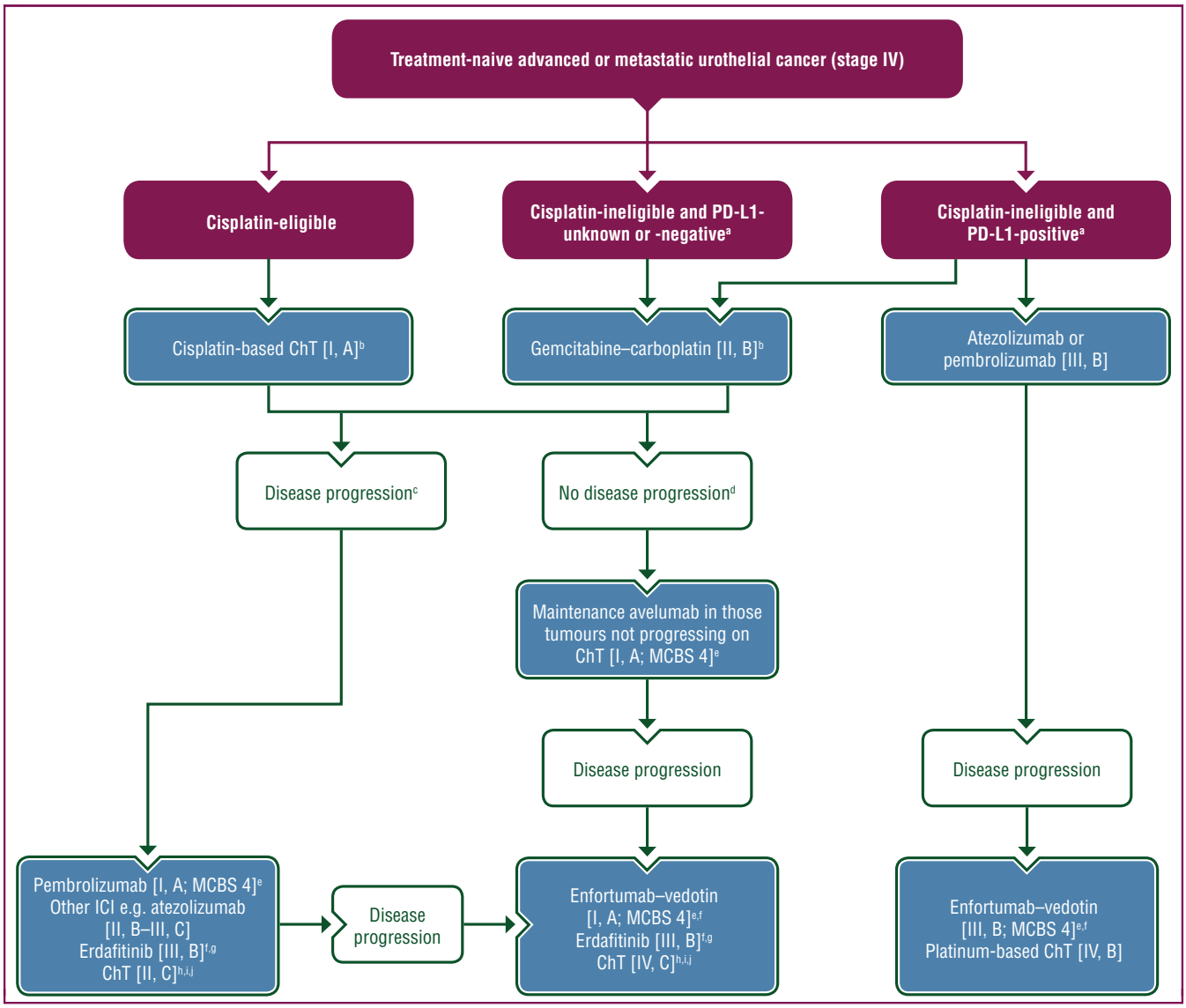

Figure 3. Management of patients with metastatic bladder cancer.
Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.
ChT, chemotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; MCBS, ESMO-Magnitude of Clinical Benefit Scale.
[a] Creatinine clearance <60 ml/min or World Health Organization (WHO) performance status 2 or comorbidity [neuropathy/hearing loss >grade 2 and New York Heart Association (NYHA) class III heart failure].
[b] Re-challenge with platinum-based ChT may be considered if progression occurred ≥12 months after the end of previous platinum-based ChT or ≥12 months after the end of previous platinum-based ChT and maintenance avelumab.
[c] For progressive disease on ChT or after the completion of ChT where maintenance avelumab was not given.
[d] This should be assessed within 10 weeks of completion of ChT.
[e] ESMO-MCBS v1.1[120] was used to calculate scores for new therapies/indications approved by the EMA or the FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).
[f] FDA approved; not currently EMA approved.
[g] With selected *FGFR* DNA fusions and mutations.
[h] Platinum doublets should be recommended if the treatment-free interval from the last platinum ChT is >1 year.
[i] To be considered when other therapies are not available.
[j] Paclitaxel, docetaxel or vinflunine should be used.

Well-tolerated durable responses were observed with both immunotherapy drugs; however, in randomised trials, ChT had higher RRs and longer PFS while immunotherapy had longer duration of response.[82,83] Median OS (mOS) was not better with the use of ICIs. The PD-L1 biomarker for pembrolizumab (22C3) was not associated with improved outcomes compared with the biomarker negatives; the authors question this approach. Final data from randomised trials with durvalumab are similar with no OS benefit.[73]

Treatment should continue for 2 years for pembrolizumab and until progression for atezolizumab. Treatment post-progression is not recommended.

Platinum-based ChT followed by maintenance avelumab is preferential compared with upfront ICIs in PD-L1

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biomarker-positive patients. No consensus could be reached for ICIs in PD-L1 biomarker-negative patients not eligible for any ChT.

Data for enfortumab—vedotin (EV) with pembrolizumab in first-line cisplatin-ineligible population are encouraging but no recommendations can be proposed due to the small size of the study ($n = 43$).[84]

Maintenance avelumab, started within 10 weeks of completion of first-line platinum-based ChT, is associated with an OS advantage compared with best supportive care in patients who did not have disease progression after four to six cycles of gemcitabine plus cisplatin or carboplatin, and is recommended (HR 0.69, 95% CI 0.56-0.86) [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4] (Figure 3).[85,86] An increase in mOS from 14 to 21 months was observed with avelumab. Treatment was given until progression.

Treatment of relapsed advanced/metastatic UC

Pembrolizumab has a significant survival advantage compared with ChT in patients with tumours which have relapsed after platinum-based therapy and did not receive previous immunotherapy [mOS: 10.3 for pembrolizumab and 7.4 months for ChT (HR 0.73, 95% CI 0.59-0.91)] [I, A; ESMO-MCBS v1.1 score: 4] (Figure 3). Responses were more frequent and durable for pembrolizumab compared with ChT (21% versus 11%, respectively).[87] An update with a minimum follow-up of 5 years showed 3-year response duration of 44% for pembrolizumab compared with 28.3% for ChT [I, A].[87,88] The IMVigor211 trial explored atezolizumab in PD-L1 biomarker-positive tumours in this population and failed to show a significant OS advantage. Results in the intention-to-treat population favoured atezolizumab, but statistical significance could not be drawn due to the study design (HR 0.85, 95% CI 0.73-0.99). The drug was associated with an RR of 13%.[89] In a recent updated analysis, atezolizumab showed a 30-month OS of 18% compared with 10% for ChT.[90] Phase I-IV trials for atezolizumab exist in this population and the results are consistent.[91-93] For these reasons, the authors support the use of atezolizumab in this setting [II, B] with a weaker recommendation than for pembrolizumab.

Three other drugs (nivolumab [III, B], durvalumab [III, C] and avelumab [III, C]) have data from single-arm trials.[94-96] Durable responses occurred in ~15%-20% of patients. It is premature to assume that all these drugs have the same activity in this setting.

Treatment with further ChT for platinum-refractory disease is an alternative for patients in whom anti-programmed cell death protein 1/PD-L1 therapy is not possible. This approach is, however, not clearly associated with a survival benefit. Vinflunine [II, C], docetaxel [III, C] and paclitaxel [III, C] can be considered,[97,98] although vinflunine is the only EMA-approved agent. Combinations with taxanes may be considered as an option in selected patients.[99] Retreatment with platinum-based ChT for those tumours that relapse >1 year after previous ChT is a reasonable option, particularly where ICI therapy is not available [IV, B].

Erdafitinib is a pan-FGFR tyrosine kinase inhibitor of FGFR1-4 that has been tested in a phase II trial in 99 patients with locally advanced or metastatic previously treated UC and *FGFR* DNA genomic alterations (*FGFR2* or *3* fusions, or *FGFR3* mutations). In this trial, 45% of patients had previously received only first-line platinum-based ChT.[9] In a recent update with a median follow-up of 24 months, confirmed RR in all populations was 39% in ChT-relapsed/-refractory patients. Median PFS (mPFS) and mOS were 5.5 months (95% CI 4.0-5.7) and 10.6 months (95% CI 9.0-14.7), respectively, in ChT-relapsed/-refractory patients.[9,100] mPFS and mOS were 5.5 months (95% CI 4.0-5.7) and 10.6 months (95% CI 9.0-14.7), respectively, in ChT-relapsed/-refractory patients.[9,100] Erdafitinib is recommended in platinum-refractory tumours with *FGFR* alterations [III, B]. No consensus could be reached on whether second-line ICI therapy or erdafitinib should be used in preference in these patients.

Treatment of tumours that have relapsed after first-line immunotherapy

There are no prospective randomised data regarding treatment of patients with progression of disease after ICIs in advanced UC. Retrospective data support the use of standard first-line platinum-based therapy [IV, B].[101] RRs and PFS are in line with those seen for first-line platinum-based ChT. Recommendations are similar to those for front-line ChT. Gemcitabine with cisplatin or carboplatin are the preferred regimens.

EV is an antibody drug conjugate targeting nectin-4. Monomethyl auristatin E is the payload drug within this molecule (microtubule-disrupting agent). A single-arm phase II trial for EV in this population shows RRs of 52%, PFS of 5.8 months (95% CI 5.0-8.3) and OS of 14.7 months (95% CI 10.5-18.2).[102] This agent can, therefore, be recommended as an alternative to ChT in this population irrespective of nectin-4 expression [III, B].

Treatment of ChT and immunotherapy-relapsed disease

This population included third-line therapy after the sequence of platinum-based ChT and ICIs. It also included second-line therapy after first-line ChT and maintenance avelumab. EV has been tested in phase II and phase III trials in advanced disease UC after progression with ChT and ICIs. Confirmed RRs were 44% (95% CI 35% to 53%) in the phase II study.[103] The phase III trial showed superior RRs (41% versus 17%), PFS (HR 0.62, 95% CI 0.51-0.75) and OS (HR 0.70, 95% CI 0.56-0.89; 12.8 versus 9.0 months) for EV versus ChT (vinflunine or taxanes).[104] Grade 3 or more adverse events of special interest associated with the new class of drug were rash (15%), peripheral neuropathy (5%) and hyperglycaemia (4%). EV should be considered the standard of care in this population, which includes patients with progression of disease after first-line ChT and maintenance avelumab [I, A].

The erdafitinib phase II trial described previously included 22 patients whose tumours had progressed after immunotherapy and ChT. The RR to erdafitinib was 59% in this population. mPFS and mOS were 5.7 months (95% CI 4.9-8.3) and 10.9 months (95% CI 8.0-21.1), respectively.[100] Therefore, erdafitinib is also recommended, with less robust evidence, in this FGFR-selected population [III, B].

ChT (taxanes or vinflunine) is a less attractive alternative to EV or erdafitinib in patients who have had progressive disease on platinum-based ChT and ICIs (RR of 21%) [IV, C].[105]

UTUC

UTUCs account for only 5%-10% of UCs.[106,107] Multifocal tumours are found in 10%-20% of UTUC cases.[108] The presence of concomitant CIS of the upper tract is between 11% and 36%.[107]

At first diagnosis, 60% of UTUCs are invasive compared with 15%-25% of bladder tumours.[109] The most common histological type is UC; variants are present in up to 25% of the cases.[110] The most common symptom is haematuria (70%-80%) or flank pain (10%-20%).[111,112]

The key investigations for UTUC are CT urography and diagnostic ureteroscopy. During the ureteroscopy, an *in situ* cytology sample of the upper tract should be collected, despite the fact that cytology is less sensitive for UTUC than UC of the bladder.[113]

UTUCs invading the muscle wall usually have a poor prognosis. The 5-year cancer-specific survival is $<$50% for patients with pT2-pT3 tumours and $<$10% for those with pT4.[114-116]

UTUCs are stratified into two risk categories, low- and high-risk tumours. Low-risk tumours include unifocal tumours of $<$1 cm, LG disease at cytology/biopsy and no invasive features on CT urography. High-risk tumours are $>$2 cm, with possible hydronephrosis, HG disease at cytology/biopsy, multifocal disease, variant histology or previous RC for bladder cancer.[116]

Kidney-sparing management, such as endoscopic laser ablation, should be offered as primary treatment option to patients with low-risk UTUC. High-risk UTUC patients should undergo open or laparoscopic radical nephroureterectomy with bladder cuff excision regardless of tumour location [II, B].[109]

There are limited studies in UTUC evaluating systemic therapy in patients with locally advanced or metastatic disease. Most of the clinical decision making is extrapolated from evidence of the bladder literature and small, single-centre UTUC studies ($<$50 patients). Systemic therapy for advanced disease should follow the recommendations for urothelial bladder cancer [IV, B]. This included adjuvant cisplatin-based ChT. A randomised, phase III adjuvant ChT study [the Peri-Operative chemotherapy versus sUrveillance in upper Tract urothelial cancer trial (POUT): gemcitabine—cisplatin/carboplatin versus observation] showed improved DFS (HR 0.45, 95% CI 0.30-0.68) in patients with locally advanced UTUC (pT2-T4 pN0-N3 M0 or pT any N1-3 M0).[117] The study was not powered for OS (HR 0.7, 95% CI 0.46-1.06). There is evidence to support the use of adjuvant cisplatin-based ChT, based on the POUT data and the OS meta-analysis for cisplatin-based treatment of urothelial bladder cancer [II, C]. The role of adjuvant carboplatin-based treatment is not fully elucidated due to power limitations on the analyses for the subgroup of patients included in the POUT trial. Therefore, adjuvant carboplatin-based ChT should not be recommended at the present time in this setting [II, D]. The role for adjuvant ICIs in this population is controversial. Patients with UTUC who were included in CheckMate 274 study seemed to benefit less from adjuvant nivolumab compared with the bladder tumour counterpart and OS data are unavailable. Therefore, at the present time, ICIs cannot be recommended in this setting.[64]

Recommendations

Treatment of advanced or metastatic UC in patients fit enough to tolerate cisplatin-based combination ChT

- Cisplatin-based ChT [I, A] followed by maintenance avelumab in those tumours not progressing on ChT is the standard of care [I, A; ESMO-MCBS v1.1 score: 4].

Treatment of advanced or metastatic UC in patients not eligible for cisplatin-based combination ChT

- Gemcitabine/carboplatin [II, B] followed by maintenance avelumab (in those tumours not progressing on ChT) for those not eligible for cisplatin-based therapy is the standard of care [I, A].
- Atezolizumab or pembrolizumab are alternatives for patients with PD-L1 biomarker-positive tumours who are not eligible for cisplatin-based combination ChT. The level of evidence, however, is weaker than for ChT followed by maintenance avelumab and this approach requires careful consideration [III, B].

Treatment of relapsed advanced/metastatic UC

- Pembrolizumab has the most robust data for treatment in the setting of progression of disease after platinum-based ChT [I, A; ESMO-MCBS v1.1 score: 4]. Other ICIs such as atezolizumab can be given with less robust evidence [II, B-III, C].
- Erdafitinib is an alternative to ICIs in tumours with FGFR alterations. This has weaker levels of evidence than pembrolizumab [III, B].
- ChT can be considered instead of best supportive care when other options are not available (vinflunine [II, C]; taxanes [III, C]).

Treatment of tumours that relapse after first-line single-agent immunotherapy

- Randomised data are lacking in immunotherapy-refractory disease. EV [III, B; ESMO-MCBS v1.1 score: 4] or platinum-based ChT [IV, B] should be given.

Treatment of ChT and immunotherapy-relapsed disease

- EV is recommended as standard treatment in this population [I, A; ESMO-MCBS v1.1 score: 4].
- Erdafitinib is an alternative in patients with FGFR alterations with a weaker level of evidence [III, B].

- ChT can be considered instead of best supportive care [IV, B], if clinically appropriate.
- Retreatment with ChT for those patients that relapse after all other treatment options can be considered. Single-agent taxane therapy or vinflunine can be considered [IV, C].

Treatment of UTUC

- Kidney-sparing management should be offered to low-risk UTUC and radical nephroureterectomy with bladder cuff excision for high-risk UTUC [II, B].
- Systemic therapy recommendations for advanced UTUC should follow those for advanced bladder cancer [IV, B].
- There is evidence to support the use of adjuvant cisplatin-based ChT based on the POUT data and the OS meta-analysis for cisplatin-based treatment of UC [II, C].

FOLLOW-UP AND LONG-TERM IMPLICATIONS

NMIBC

There is no generally accepted follow-up protocol as recommendations are mainly based on retrospective data. Therefore, the frequency and duration of cystoscopy and subsequent imaging should reflect the individual patient's degree of risk of recurrence and progression [IV, B].[11,118] In all patients with a new diagnosis of Ta-T1 tumours and/or CIS, the first cystoscopy should be carried out at 3-month intervals [IV, B].[119] Regular cystoscopy and cytology is subsequently recommended every 3-6 months during the first 2 years of follow-up, and every 6-12 months thereafter. Regular upper tract imaging (CT intravenous urography) is recommended for high-risk tumours.

MIBC

There is no generally accepted follow-up protocol for muscle-invasive UC [IV, B]. Current surveillance protocols are based on patterns of recurrence drawn from retrospective series. Imaging of the chest, upper tract, abdomen and pelvis should be carried out to detect relapse after potentially curative therapy every 3-4 months for 2 years, and then every 6-12 months up to 5 years [IV, B].[57] The benefits of follow-up beyond 5 years are unclear and it is reasonable to discharge patients. UTUC occurs in 4%-10% of cases after RC;[32] hence, regular upper tract imaging is recommended [IV, B].

After bladder-sparing procedures with curative intent, such as trimodal therapy, follow-up must investigate for local as well as systemic relapses. Cystoscopic examination should be carried out every 3-6 months for the first 5 years. CT of the thorax and abdomen is recommended as the imaging method for follow-up every 3-4 months for the first 2 years, and then every 6 months up to 5 years [IV, B].[57] The role of surveillance beyond 5 years is uncertain.

Advanced/metastatic disease

Response evaluation every 2-3 months should occur for those patients on systemic therapy for advanced disease. Regular (3-4 months) cross-sectional imaging should occur for 2 years upon completion of systemic therapy. Bone scans/MRI may be required if CT cannot address these adequately [IV, B].

Recommendations

- Follow-up for NMIBC requires regular cystoscopic examination according to the patient's risk category [IV, A].
- Follow-up after curative therapy for MIBC requires cross-sectional imaging for 5 years. This should include 3-4 monthly imaging for the first 2 years. Bladder-sparing approaches also require regular cystoscopy [IV, B].
- Follow-up during and after systemic therapy for advanced UC should focus on regular cross-sectional imaging of the chest, abdomen and pelvis and other target lesions [IV, B].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the European Society for Medical Oncology (ESMO) standard operating procedures for Clinical Practice Guideline development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. An ESMO-MCBS table with MCBS scores is included in Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2021.11.012. ESMO-MCBS v1.1[120] was used to calculate scores for new therapies/indications approved by the EMA and/or the FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. The FDA/EMA approval status of new therapies/indications is correct at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2021.11.012.[121] Statements without grading were considered justified standard clinical practice by the authors.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

T. Powles[1], L. Albiges[2], A. Bex[3,4,5], E. Comperat[6], V. Grünwald[7], R. Kanesvaran[8], H. Kitamura[9], R. McKay[10], C. Porta[11,12], G. Procopio[13], M. Schmidinger[14], C. Suarez[15], J. Teoh[16], G. de Velasco[17], M. Young[1,18] & S. Gillessen[19,20], on behalf of the ESMO Guidelines Committee*

[1]Barts Cancer Institute, Department of Medical Oncology, Queen Mary University of London and Royal Free London NHS Foundation Trust, London, UK; [2]Université Paris Saclay, Institut Gustave Roussy, Villejuif, France; [3]Specialist Centre for Kidney Cancer, Royal Free London NHS Foundation Trust, London; [4]Division of Surgery and Interventional Science, University College London, London, UK; [5]Department of Urology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [6]Department of Pathology, Medical University of Vienna, General Hospital of Vienna, Vienna, Austria; [7]Interdisciplinary Genitourinary Oncology, West German Cancer Center Clinic for Internal Medicine and Clinic for Urology, University Hospital Essen, Essen, Germany; [8]Division of Medical Oncology, National Cancer Centre, Singapore, Singapore; [9]Department of Urology, Faculty of Medicine, University of Toyama, Toyama, Japan; [10]Department of Medicine and Urology, University of California San Diego, La Jolla, USA; [11]Interdisciplinary Department of Medicine, University of Bari 'A. Moro', Bari; [12]Division of Medical Oncology, A.O.U. Consorziale Policlinico di Bari, Bari; [13]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; [14]Department of Urology, Medical University of Vienna, Vienna, Austria; [15]Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [16]S. H. Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong SAR, China; [17]Instituto de Investigación i+12 and Departamento de Oncología Médica, Hospital University 12 de Octubre, Madrid, Spain; [18]Barts Cancer Institute, Department of Experimental Cancer Medicine, Queen Mary University of London, London, UK; [19]Oncology Institute of Southern Switzerland (IOSI), Ente Ospedaliero Cantonale (EOC), Bellinzona; [20]Università della Svizzera Italiana, Lugano, Switzerland

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INCIDENCE AND EPIDEMIOLOGY

Renal cancer is the 14th most common malignancy worldwide, with >430 000 new cases diagnosed in 2020.[1] The incidence varies geographically, with higher incidence in Europe and North America. Renal cell carcinoma (RCC) accounts for ∼90% of all renal cancers.[1-3]

While incidence rates of renal cancer have been steadily increasing, including a slow rise over the past decade, mortality rates have slowly declined.[1,2] This can be explained in part by increased rates of incidental diagnoses on abdominal imaging.[1] Improvements in treatments are also contributing to the declining mortality rates.

There are several established risk factors for RCC such as smoking, obesity, hypertension and chemical exposures, which have been described previously.[3] An estimated 6%-9% of renal cancers have germline mutations in genes associated with cancer predisposition.[1] Several autosomal dominant syndromes have been described, including von Hippel—Lindau syndrome (VHL), hereditary leiomyomatosis and RCC (HLRCC) or fumarate hydratase (FH)-deficient RCC, hereditary papillary RCC, tuberous sclerosis complex, Birt—Hogg—Dubé syndrome and succinate dehydrogenase (SDH)-deficient RCC.[1]

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

The initial presentation of RCC, based on the classic triad of flank pain, gross haematuria and palpable abdominal mass, has been largely replaced by incidental detection.[1] The recommended diagnostic investigations are summarised in Figure 1. Contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis is required for accurate staging of RCC for tumours of all stages. For advanced disease, neuroimaging [CT or magnetic resonance imaging (MRI)] and bone scan are desirable before starting systemic therapy. Positron emission tomography is not recommended for routine staging or assessment of RCC.

Histopathological confirmation of RCC is mandatory for all patients before starting systemic treatment. Core biopsy of the renal tumour or metastatic site, or examination of the nephrectomy sample at surgery, provides histopathological confirmation with high sensitivity and specificity, and negligible risk of tumour seeding.[4,5] Histopathology

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

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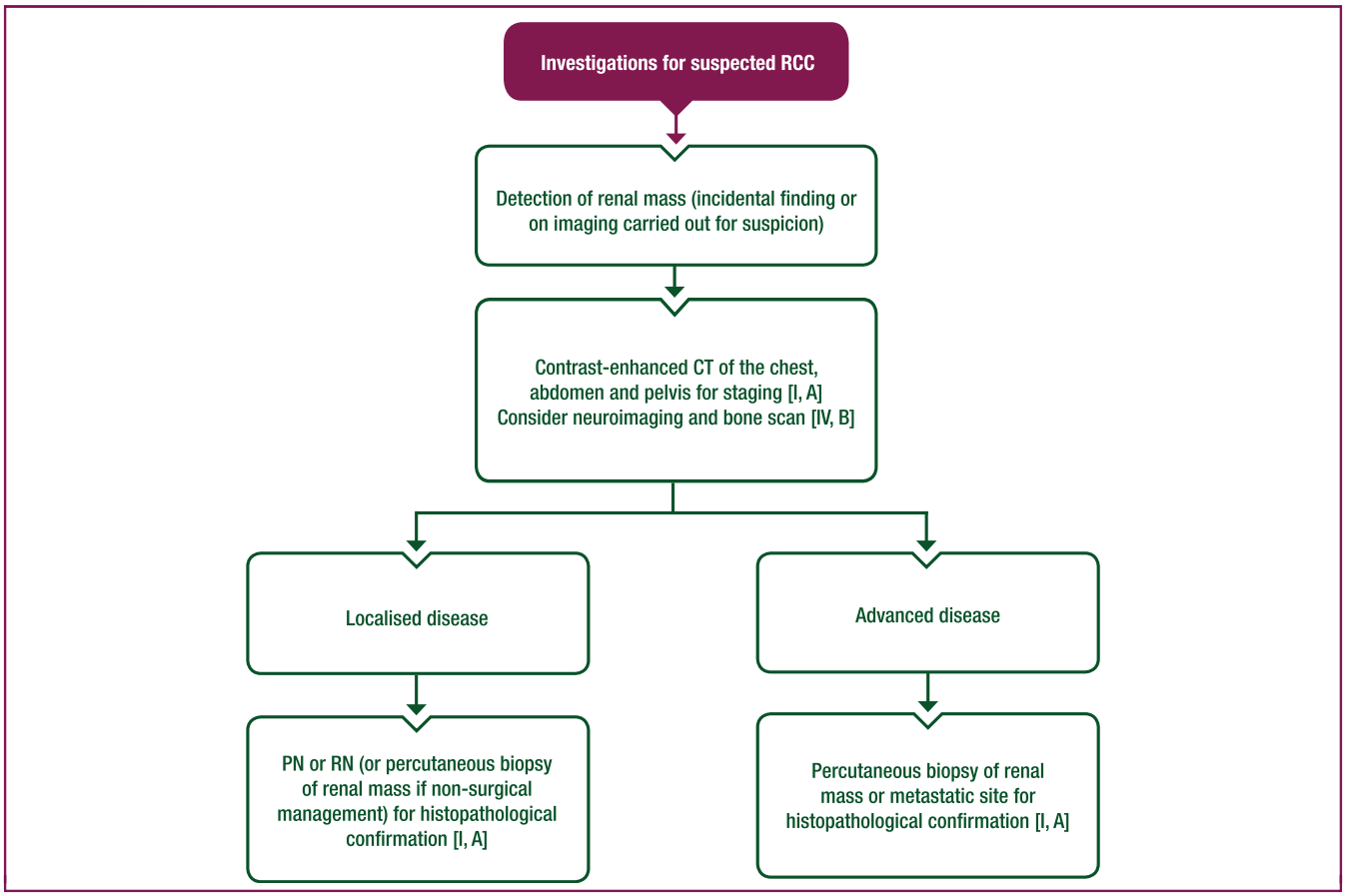

Figure 1. Algorithm for the diagnosis of RCC.
Purple: algorithm title; white: other aspects of management.
CT, computed tomography; PN, partial nephrectomy; RCC, renal cell carcinoma; RN, radical nephrectomy.

assessment to establish the underlying subtype (clear-cell versus variant histology) and presence of sarcomatoid or rhabdoid differentiation using established criteria is strongly recommended due to prognostic and therapeutic implications.[6] More recent classification based on molecular analysis techniques that are not currently widely available, while recommended, is not yet mandated. Patients with suspected metastatic relapse after nephrectomy for renal cancer do not necessarily need a repeat biopsy of the metastatic site, but the decision should be made on an individual basis, especially in the case of late relapse, which is common in RCC. The risk of relapse of the primary tumour and the interval between primary surgery and relapse are relevant in this decision.

Laboratory assessment of serum creatinine, haemoglobin, leukocyte and platelet counts, lymphocyte-to-neutrophil ratio and serum-corrected calcium should be carried out. These tests are used in prognostic scoring systems and treatment selection for advanced disease, including the International Metastatic RCC Database Consortium (IMDC) score (see Staging and risk assessment section).[7]

Pathology

Clear-cell RCCs (ccRCCs) represent ∼80% of malignant renal tumours in adults. The remaining 20% consist of several subtypes with different histological, molecular and cytogenetic profiles. Papillary RCC (pRCC) is the most common of these.[8]

The fifth edition of the World Health Organization (WHO) classification of urogenital tumours, published in 2022, contains significant revisions.[6] With increasing use of massive parallel sequencing to identify molecular alterations in renal tumours, the WHO has introduced a molecular-driven renal tumour classification with 11 subgroups.[6] Molecular-defined renal tumours are those which show very heterogeneous morphological aspects and can therefore not be diagnosed by morphology alone. Such tumours include previously described molecular subtypes (such as microphthalmia transcription factor family translocation carcinomas and SDH-deficient RCC), as well as new entities including *SMARCB1*-deficient medullary RCC, *TFEB*-altered RCC, *ALK*-rearranged RCC and *ELOC*-mutated RCC (Table 1).[6]

The incorporation of molecular-driven classification highlights a shift to using genome sequencing to identify actionable mutations for more personalised treatments. Testing for germline mutations is recommended for younger patients, those with multiple or bilateral lesions, those with first- or second-degree relatives who have had RCC, those with related disorders associated with known predisposing conditions and those who have exhausted standard therapeutic options. While molecular techniques

Table 1. New molecular-defined RCC entities defined by the WHO[6]

RCC subtype (WHO)	Genetic alteration	Comments
Eosinophilic solid and cystic RCC	*TSC* mutation and activation of mTOR pathway	Typically clinically indolent Responses with use of mTOR inhibitors have been reported
ELOC-mutated RCC	*ELOC* (*TCEB1*) mutation	Clear cells with abundant cytoplasm and presence of fibromuscular bands Based on limited data, seem to behave indolently and are associated with good prognosis
ALK-rearranged RCC	*ALK* rearrangements	Typically morphologically very heterogeneous Responses with use of ALK inhibitors have been reported
SMARCB1-deficient medullary RCC	*SMARCB1* loss	Highly aggressive subtype Frequently occurs in young patients with sickle cell trait (although not required for diagnosis)
TFEB-altered RCC	*TFEB* translocation and *TFEB* amplification	*TFEB*-translocated RCC is typically clinically indolent *TFEB*-amplified RCC is typically highly aggressive, tends to occur in older patients
FH-deficient RCC	*FH* loss or mutation	May be associated with HLRCC

ALK, anaplastic lymphoma kinase; FH, fumarate hydratase; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; mTOR, mammalian target of rapamycin; RCC, renal cell carcinoma; WHO, World Health Organization.

are becoming more widely available, many laboratories still lack access to them, and most of the identified targets are not currently actionable. When genome sequencing is not available, pathologists should include comments regarding the possible molecular alterations in their diagnoses, along with a detailed morphological description.[6] Currently, the identification of ccRCC as opposed to pRCC or another established subtype (e.g. chromophobe, collecting duct, etc.) remains the priority. The identification of sarcomatoid features, which may be observed in any RCC subtype and are characterised by the presence of spindle or mesenchymal-like cells, has become increasingly important for the consideration of systemic therapy. The latest WHO classification no longer differentiates between type 1 and type 2 pRCC, reducing its importance. The clinical relevance of the new WHO subtypes remains uncertain.

Recommendations

- Patients with suspected renal cancer should have appropriate investigations with cross-sectional imaging, histopathology analysis and laboratory tests [I, A].
- Neuroimaging (CT or MRI) and a bone scan are desirable before starting systemic therapy for advanced disease [IV, B].
- Histopathology analysis should be carried out to determine tumour subtype and results should be available before starting systemic treatment [I, A].
- The recent WHO classification is not routinely required; instead, attention should be given to established subtypes with well-defined treatment algorithms, such as ccRCC and pRCC [IV, B].
- Genetic assessment is recommended for younger patients, those with multiple or bilateral lesions, those with first- or second-degree relatives who have had RCC, those with related disorders associated with known predisposing conditions and those who have exhausted standard therapeutic options [IV, A].

STAGING AND RISK ASSESSMENT

Staging

Staging should follow the eighth edition of the Union for International Cancer Control (UICC) TNM (tumour—node—metastasis) system (Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2024.05.537).[9]

Risk assessment

Given the variable clinical course of RCC, the use of prognostic models is recommended in both localised and metastatic disease for the assessment of individualised risk.

Localised disease. The approval of adjuvant pembrolizumab for high-risk RCC makes the TNM prognostic classification used in KEYNOTE-564 clinically relevant; this is now the preferred risk classification for operable disease. As per the trial protocol, intermediate-high risk is defined as pathological (p)T2, grade 4 or sarcomatoid, N0, M0, or pT3, any grade, N0, M0.[10] High-risk disease is defined as pT4, any grade, N0, M0, or any pT, any grade, lymph node positive, M0. Other risk models testing pre- and post-operative scores can be used for prognostic purposes.[11,12]

Advanced disease. The IMDC score, developed in the vascular endothelial growth factor receptor (VEGFR)-targeted therapy era, is a useful tool for predicting the prognosis of patients with advanced RCC. This scoring system uses six clinical and laboratory risk factors to produce three risk categories: favourable, intermediate and poor.[7] The risk category can be used to estimate prognosis and guide treatment decisions in first-line therapy and beyond.[13] It should be noted, however, that this scoring system was validated in the era of VEGFR tyrosine kinase inhibitor (TKI) therapy and its predictive value with immune checkpoint inhibitor (ICI) therapy is less certain.

Molecular prognostication and biomarkers. The introduction of the molecular-driven classification for RCC by the

WHO highlights the prognostic implications of certain gene mutations, as discussed above. Gene expression panels can identify high-risk disease in operable cases and can potentially identify angiogenic versus immunogenic tumours in advanced disease;[14] however, these are not applicable for routine use. Programmed death-ligand 1 (PD-L1) has been unreliable as a biomarker in renal cancer, and serum and urine biomarkers are experimental.

Recommendations

- Staging should follow the eighth edition of the UICC TNM system [IV, B].
- Prognostic scoring systems should be used to assess risk in operable disease (KEYNOTE-564 classification) and advanced disease (IMDC classification) [I, A].

MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE

Role of surgery and local therapy

T1 tumours (≤7 cm). Partial nephrectomy (PN) is the preferred option in organ-confined tumours measuring ≤7 cm (elective indication). This recommendation is based on a systematic review of multiple retrospective studies and a prospective, randomised controlled trial comparing radical nephrectomy (RN) with PN in solitary T1a-b N0 M0 renal tumours (<5 cm) with normal contralateral kidney function, which showed that PN was associated with significantly better preservation of renal function.[15]

PN can be carried out via open, laparoscopic or robot-assisted laparoscopic approaches. Conventional or robot-assisted laparoscopic RN is recommended if PN is not technically feasible. A nephron-sparing strategy, including PN, is the standard of care (SoC) in patients with compromised renal function, solitary kidney or bilateral tumours, with no tumour size limitation (imperative indication). Renal mass biopsy before surgery for clinical T1a tumours is recommended, as up to 30% are benign and may not need an intervention; however, a clear consensus has not been reached.[16]

Radiofrequency ablation (RFA), stereotactic body radiotherapy (SBRT), microwave ablation and cryoablation (CA) are non-surgical options, particularly in patients with small cortical tumours. These may be especially appropriate for patients who are frail, present a high surgical risk, have a solitary kidney, compromised renal function, hereditary RCC or multiple bilateral tumours, or decline surgery. Pre-intervention biopsy is recommended to confirm malignancy and subtype in this setting.[17] Systematic reviews suggest a long-term cause-specific survival with RFA that is equal to PN, with a low metastasis rate but slightly higher local recurrence rate compared with PN and CA.[15] The quality of the available evidence prevents definitive conclusions regarding morbidity and oncological outcomes for RFA and CA. Data from meta-analyses as well as prospective and retrospective studies support the efficacy and safety of SBRT, including favourable long-term outcomes.[18] Further randomised trials are needed to define its efficacy; SBRT cannot be strongly recommended without these data.

Active surveillance is an option for those with a short life expectancy and for patients with small renal masses (≤4 cm); indeed, the growth rate of renal tumours is low in most cases (mean 3 mm/year) and progression to metastatic disease is reported in 1%-2% of patients.[17,19] In all cases, a risk—benefit discussion should occur with the patient.

T2 tumours (>7 cm). Minimally invasive RN is the preferred option. Other approaches are likely to have similar oncological outcomes.

Locally advanced RCC (T3 and T4). Open RN remains the SoC for complex T3 and T4 tumours, although robotic and laparoscopic approaches can be considered. Routine adrenalectomy or lymph node dissection is not recommended when abdominal CT and intraoperative exploration show no evidence of adrenal or lymph node invasion.[20]

The evidence regarding management of venous tumour thrombus is based on retrospective studies.[21] Resection of venous thrombi is challenging and associated with a high risk of complications. Surgical intervention should be considered, but the most effective approach remains uncertain and outcomes depend on tumour thrombus level.

There is no established role for neoadjuvant therapies.

Unique considerations for VHL-associated RCC. VHL is a rare, autosomal dominant, hereditary disorder caused by germline pathogenic variants in the *VHL* gene. Approximately 70% of patients with VHL will develop RCC during their lifetime.[22] Historic approaches to the management of RCC in this population have mostly relied on surgical or ablative approaches; however, given the propensity of patients with VHL to develop multiple RCCs, this often requires multiple procedures.

Belzutifan is a novel hypoxia-inducible factor 2α transcription factor inhibitor. A recent phase II, open-label, single-group trial of 61 patients investigated belzutifan in VHL-associated RCC.[23] The overall response rate (ORR) was 64% and there was a reduction in the need for subsequent intervention. Belzutifan appears to be well tolerated and should be recommended for patients who do not require immediate surgery.

Adjuvant therapy in ccRCC

The phase III KEYNOTE-564 trial evaluated pembrolizumab (17 cycles of 200 mg three times weekly) versus placebo as adjuvant therapy in 994 patients with ccRCC with intermediate-high- or high-risk disease (as defined by the trial protocol), or M1 and no evidence of disease (NED).[10] After a median follow-up of 57.2 months, pembrolizumab was associated with improved overall survival (OS) [hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.44-0.87, $P = 0.005$] and disease-free survival (DFS) (HR 0.72, 95% CI 0.59-0.87) versus placebo.[24] This is the first adjuvant therapy with proven survival benefit in operable RCC and is

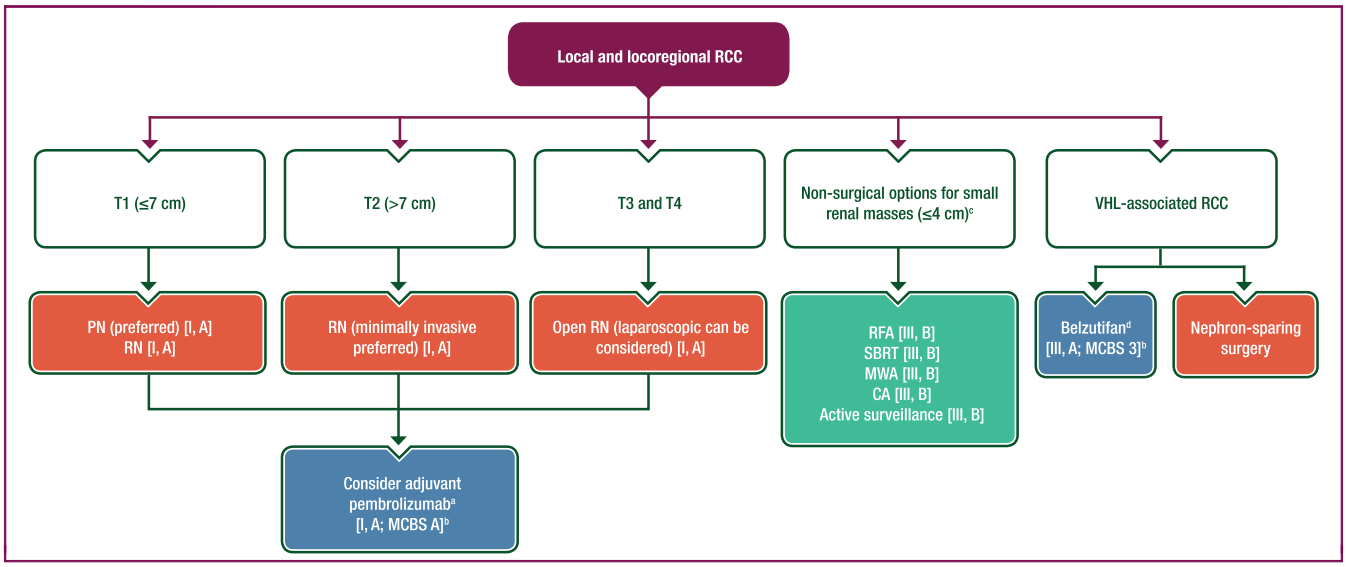

Figure 2. Management of local and locoregional RCC.
Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments or treatment modalities; white: other aspects of management.
CA, cryoablation; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Score; MWA, microwave ablation; PN, partial nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation; RN, radical nephrectomy; SBRT, stereotactic body radiotherapy; T, tumour; VHL, von Hippel—Lindau syndrome.
[a]If appropriate at final histology (e.g. T2 with nuclear grade 4 or sarcomatoid differentiation, ≥T3 or regional lymph node metastasis).
[b]ESMO-MCBS v1.1[75] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[c]For example, in cases of high surgical risk, patient frailty, solitary kidney, compromised renal function, hereditary RCC or bilateral tumours.
[d]FDA approved, not EMA approved.

recommended in patients with intermediate-high- and high-risk (KEYNOTE-564 criteria) ccRCC, after careful patient selection and counselling regarding potential acute and long-term adverse events (AEs). If used, treatment should start within 12 weeks of surgery and continue for up to 1 year.

The DFS and reported OS benefits observed in KEYNOTE-564 contrast with other trials of immunotherapy in the adjuvant setting (e.g. atezolizumab[25] and ipilimumab—nivolumab[26]). Differences in trial design, duration of treatment, ICI activity or increased toxicity associated with the use of ipilimumab may offer explanations for the contrasting results. Biomarker data from these trials are also required.

Adjuvant VEGFR-targeted therapies have demonstrated inconsistent benefit in phase III randomised trials.[27,28]

An algorithm for the treatment of local and locoregional RCC is shown in Figure 2.

Recommendations

- Surgical resection remains the SoC for localised renal cancer [I, A] with either minimally invasive or open approaches preferred depending on tumour size and complexity.
- Several nephron-sparing options, ranging from surveillance to PN, are recommended for small renal masses (T1 ≤4 cm) [III, B].
- Belzutifan may avoid surgeries and can be considered for patients with germline *VHL* variants and localised renal cancer [III, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 3; Food and Drug Administration (FDA) approved, not European Medicines Agency (EMA) approved].
- Adjuvant pembrolizumab should be considered for patients with intermediate-high- or high-risk operable ccRCC (as defined by the KEYNOTE-564 criteria) after careful patient counselling regarding potential long-term AEs [I, A; ESMO-MCBS v1.1 score: A]. Treatment should start within 12 weeks of surgery and continue for up to 1 year.
- Adjuvant VEGFR-targeted therapies are not recommended [I, D].

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

Role of surgery and local therapy in advanced and metastatic ccRCC

Upfront cytoreductive nephrectomy (CN) is no longer considered the SoC in unselected patients with intermediate-risk asymptomatic primary ccRCC and all patients with poor-risk asymptomatic primary ccRCC in the advanced and metastatic setting.[29] Due to the inclusion criteria and subset analysis from the CARMENA trial, CN may still be considered for patients with low-volume single-organ metastatic disease with a large primary tumour, or for patients who have had a near complete response (CR) to upfront systemic therapy.[29] These patients may be candidates for observation rather than systemic therapy after CN, although data are limited regarding long-term outcomes in this setting.

Metastasectomy, thermal ablation, stereotactic radiosurgery, SBRT, CyberKnife radiotherapy (RT) and hypofractionated RT can be considered for selected patients with low metastatic burden after multidisciplinary team (MDT) review, although randomised or robust prospective data to support their use are lacking.[30] Typically, these treatments focus on a single site of disease.

A DFS and OS advantage was demonstrated with pembrolizumab in patients with M1 and NED after metastasectomy in the KEYNOTE-564 study.[24] Systemic therapy rather than surgery is the optimal approach for early relapse (<1 year) after nephrectomy, making surgery in this population controversial. A multidisciplinary approach is required for these patients and surgery is usually avoided. Surveillance is also an option for patients who relapse after nephrectomy with indolent, low-burden, IMDC favourable-risk disease.[31]

Systemic treatment for advanced and metastatic ccRCC

An algorithm for the systemic treatment of advanced and metastatic ccRCC is shown in Figure 3.

First-line treatment. First-line treatment with programmed cell death protein 1 (PD-1) inhibitors in combination with either VEGFR-targeted therapy or cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibition has improved OS for patients

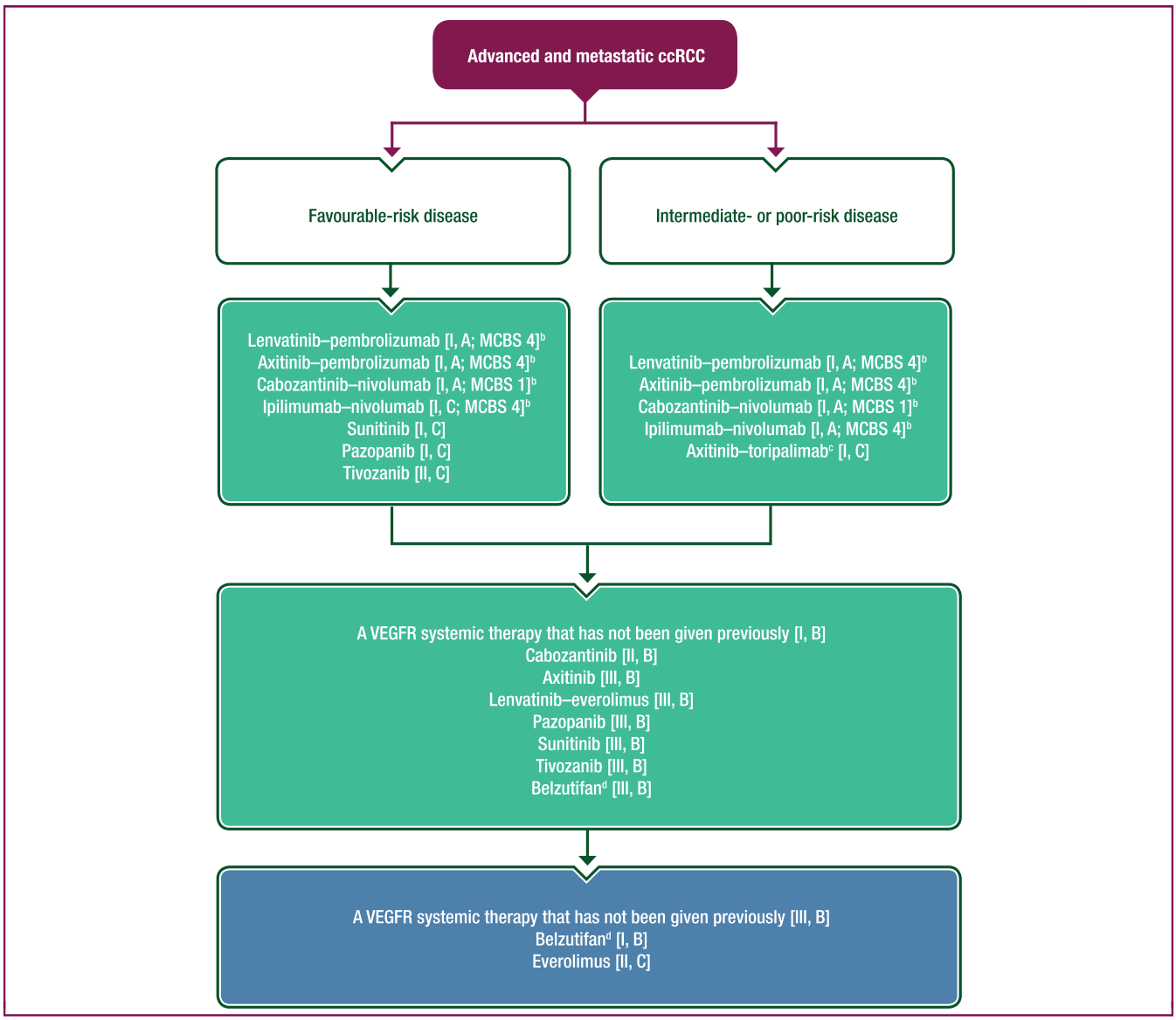

Figure 3. Systemic treatment for advanced and metastatic ccRCC.[a]
Purple: algorithm title; blue: systemic anticancer therapy; turquoise: combination of treatments or treatment modalities; white: other aspects of management.
ccRCC, clear-cell renal cell carcinoma; EMA, European Medicines Agency; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MCBS, Magnitude of Clinical Benefit Scale; VEGFR, vascular endothelial growth factor receptor.
[a]See Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.05.537, for treatment options when ICIs are contraindicated or not available.
[b]ESMO-MCBS v1.1[75] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[c]Not EMA or FDA approved.
[d]FDA approved, not EMA approved.

with advanced ccRCC.[32-35] Median OS for unselected patients receiving PD-1-targeted combinations is >4 years. Lenvatinib—pembrolizumab, axitinib—pembrolizumab or cabozantinib—nivolumab is recommended for first-line treatment of advanced ccRCC, irrespective of IMDC risk group. Recent data also support the use of axitinib—toripalimab in intermediate- and poor-risk disease, although OS data are immature.[36] There is no preferred combination and indirect cross-trial comparisons are not recommended. The combination of axitinib—avelumab was not associated with an OS benefit compared with sunitinib.[37]

Ipilimumab—nivolumab is also recommended as an equal therapeutic option for first-line treatment of IMDC intermediate- and poor-risk disease and can be considered with a weaker recommendation in favourable-risk disease. The justification for now including the favourable-risk indication is based on improved efficacy observed in more recent data cuts and an existing statistical justification for the inclusion. The statistical justification is that primary endpoints of the phase III CheckMate 214 trial included analysis of IMDC intermediate- and poor-risk disease, but also the intention-to-treat (ITT) population (including favourable-risk disease). Improved OS was observed in the ITT population (HR 0.72, 95% CI 0.62-0.85).[38] Subset analysis of the favourable-risk group was not a primary endpoint; however, initial results were not favourable for this population, resulting in recommendations restricted to intermediate- and poor-risk disease.[39] Updated results are more promising, with the reported OS for ipilimumab—nivolumab in favourable-risk disease within the range observed with the VEGFR—PD-1-targeted combinations. After a median follow-up of 67.7 months, ipilimumab—nivolumab was associated with an OS HR of 0.94 (95% CI 0.65-1.37).[38] While ORR (30% versus 52%) and progression-free survival (PFS) favoured sunitinib (HR 1.60, 95% CI 1.13-2.26), improved CR rates (13% versus 6%) and durability of response (59% versus 52% with ongoing response at 5 years) were observed with ipilimumab—nivolumab.[38] Longer-term results are awaited to see if this improving trend continues.

The authors discussed the recommendation of ipilimumab—nivolumab in favourable-risk disease extensively but were unable to reach a unanimous position. The recommendation reflects a majority (70%) of authors in favour of ipilimumab—nivolumab as an option in favourable-risk disease. Those in favour of this recommendation felt that the improved OS in the ITT population of CheckMate 214, which included favourable-risk disease, justified this recommendation. The potential for durable CRs with ipilimumab—nivolumab, which are infrequently observed with sunitinib, was also discussed in favour of this recommendation. Those against the inclusion of this recommendation felt that the lack of a clear OS benefit in this subgroup, worse PFS and ORR compared with sunitinib, and the current inability to select patients with favourable-risk disease who are more likely to derive benefit from the combination, did not justify use in this population. Toxicity was also discussed, and there was consensus that the potential for life-threatening acute toxicity, as well as the potential for lifelong toxicity, must be carefully discussed with patients if ipilimumab—nivolumab is considered. Across authors both in favour of and against the inclusion of the recommendation, it was felt that IMDC risk categories may not be reflective of the biology of this disease, nor responses to ICI-based therapy, and reliable biomarkers are needed for treatment selection.

A summary of the trials establishing OS benefit with PD-1—VEGFR-, PD-1—CTLA-4- and PD-1—CTLA-4—VEGFR-targeted therapy is shown in Table 2.

In patients with a contraindication to ICIs, or where ICIs are not available, sunitinib, pazopanib or tivozanib may be used.[40-42] An algorithm for the systemic treatment of advanced and metastatic ccRCC when ICIs are unsuitable is shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.05.537. Cabozantinib is an alternative in IMDC intermediate- and poor-risk disease for those patients who cannot receive first-line PD-1-targeted therapy.[43] Surveillance may be appropriate for selected patients with IMDC favourable-risk disease with low tumour burden.[31]

OS data for patients with IMDC favourable-risk disease treated with VEGFR—PD-1-targeted combinations remain immature, but these regimens do not appear clearly superior to sunitinib. Nevertheless, better response and PFS data support the use of combinations in this exploratory and

Table 2. Summary of clinical trials evaluating first-line ICI- and VEGFR-based therapy in advanced and metastatic ccRCC

Study	Comparator	OS HR	PFS HR	ORR, %	CR rate, %	Median follow-up, months
CheckMate 214[35] Ipilimumab—nivolumab	Sunitinib	ITT: 0.72 I/P risk: 0.68	ITT: 0.86 I/P risk: 0.73	ITT: 39 I/P risk: 42	ITT: 12 I/P risk: 11	67.7
KEYNOTE-426[77] Axitinib—pembrolizumab	Sunitinib	0.73	0.68	60	10	42.8
CheckMate 9ER[78] Cabozantinib—nivolumab	Sunitinib	0.70	0.56	56	12	32.9
CLEAR[79] Lenvatinib—pembrolizumab	Sunitinib	0.72	0.42	69	17	33.7
RENOTORCH[36] Axitinib—toripalimab (I/P risk)	Sunitinib	0.61 (immature)	0.65	57	5	14.6
COSMIC-313[47] Ipilimumab—nivolumab—cabozantinib	Ipilimumab—nivolumab	NR	0.73	43	3	20.2

ccRCC, clear-cell renal cell carcinoma; CR, complete response; HR, hazard ratio; ICI, immune checkpoint inhibitor; I/P, intermediate or poor; ITT, intention to treat; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; VEGFR, vascular endothelial growth factor receptor.

underpowered subset.[34-36] Sunitinib, pazopanib and tivozanib should be considered as alternatives to VEGFR—PD-1-targeted combinations in IMDC favourable-risk disease, with weaker levels of evidence.

PD-1-targeted combination therapy appears particularly active in tumours with sarcomatoid features and is strongly recommended.[44-46]

Evaluation of ipilimumab—nivolumab—cabozantinib versus ipilimumab—nivolumab in treatment-naive metastatic intermediate- or poor-risk RCC demonstrated a significant PFS benefit with the triplet combination, but with increased toxicity.[47] This combination is not currently recommended as OS data are awaited.

The optimal duration of therapy in the first-line setting remains uncertain. In CheckMate 214, nivolumab was continued to progression, whereas in ICI plus VEGFR TKI combination therapy, PD-1 inhibitors were stopped after 2 years. Treatment breaks for VEGFR-targeted monotherapy do not appear to have any detrimental effect on efficacy.[48] The benefit of continuing PD-1-targeted therapy beyond 2 years is uncertain.

Second-line treatment. Prospective data in the second-line setting after first-line PD-1-targeted therapy exist for a number of agents (axitinib, pazopanib, cabozantinib, sunitinib) but these results are often contaminated by trial heterogeneity.[49-52] Retrospective and exploratory subset analyses have also been reported from studies of cabozantinib, tivozanib, lenvatinib—everolimus and lenvatinib—pembrolizumab.[53-56] Response rates of ∼20%-40% were reported across all of these studies and outcomes were in line with the expectations for sequencing therapy. These agents are all cautiously recommended due to the imperfections of the datasets. Nevertheless, despite the shortcomings of retrospective, indirect comparisons, these agents appear to be as effective as second-line VEGFR-targeted therapy in the pre-immunotherapy era. Therefore, sequencing VEGFR-targeted therapy is still strongly recommended.

Further ICI therapy after first-line PD-1-targeted combination therapy is not recommended and is potentially harmful. The phase III CONTACT-03 study evaluated atezolizumab (1200 mg intravenously every 3 weeks) plus cabozantinib (60 mg orally once daily) versus cabozantinib alone in patients who had disease progression with ICI therapy.[57] With a median follow-up of 15.2 months, the study failed to demonstrate improvements in either OS (HR 0.94, 95% CI 0.70-1.27, $P = 0.69$) or PFS (HR 1.03, 95% CI 0.83-1.28, $P = 0.78$) with ICI rechallenge. Increased toxicity was reported with second-line ICI therapy, with serious AEs occurring in 48% of patients receiving atezolizumab—cabozantinib and 33% of patients receiving cabozantinib alone. Notably, however, the usefulness of sequencing two ICIs in the case of a long disease-free interval remains unexplored. Other trials exploring these issues are ongoing.

The impressive ORR (40.9%) and median PFS (10.8 months) observed in the control arm of CONTACT-03 make second-line cabozantinib monotherapy an attractive approach.[57] Similarly impressive ORR (28%) and median PFS (9.3 months) were observed in the cabozantinib control arm of CANTATA, a phase III study investigating telaglenastat—cabozantinib versus cabozantinib alone.[58] It is worth noting that 100% of patients in CONTACT-03 and 62% of patients in CANTATA had received prior ICI therapy. These results make cabozantinib the preferred second-line VEGFR TKI therapy, if not received in the first-line setting.

The phase III LITESPARK-005 study of belzutifan versus everolimus in previously treated ccRCC included patients who had received one previous line of therapy (13% of the study population).[59] Based on its observed PFS advantage over everolimus in the overall study population, belzutifan is an option for second-line therapy after progression on VEGFR—PD-1-targeted combination therapy, but with a weaker level of recommendation than in third-line treatment, and with the consideration that alternatives such as cabozantinib may be preferable.

Third-line treatment. Belzutifan has a PFS advantage over everolimus in heavily pretreated (with ICI and VEGFR-targeted therapy) ccRCC (HR 0.75, 95% CI 0.63-0.90).[59] A higher ORR was also observed with belzutifan (23% versus 4%), while interim OS analysis showed no benefit (HR 0.88, 95% CI 0.73-1.07). Toxicity and quality-of-life data also favoured belzutifan. Belzutifan should therefore be used instead of everolimus in this setting. Sequencing VEGFR-targeted therapy is an alternative to belzutifan.

It is likely that sequencing different targeted therapies approved in advanced RCC is beneficial, as in the pre-ICI era. Rechallenge with ICIs is unproven and should not be regarded as a standard option.

Treatment for advanced and metastatic pRCC

Surgery. The role of CN and other surgical techniques is not clearly defined in metastatic pRCC. While surgery may be appropriate for intermediate-risk disease, patients with poor-risk disease are unlikely to derive benefit and surgery should be avoided in this setting. There is no consensus on the definition of patients who should be considered for surgery.

First-line treatment. Despite advances in the treatment of ccRCC, there are limited high-quality studies to guide the management of non-clear-cell histologies. An algorithm for the systemic treatment of advanced and metastatic pRCC is shown in Figure 4.

Cabozantinib is the preferred first-line monotherapy for advanced pRCC, having demonstrated a PFS (but not OS) advantage compared with sunitinib.[60] Other monotherapy options include sunitinib[61,62] and pembrolizumab.[63] Data from small, randomised studies suggest that savolitinib (a MET inhibitor) is also active in the first-line treatment of *MET*-altered pRCC.[64]

Prospective single-arm trials of lenvatinib—pembrolizumab ($n = 147$) and cabozantinib—nivolumab ($n = 47$) have reported ORRs of 49% and 48%, respectively.[65,66] The toxicity profiles of these combinations were in line with expectations.

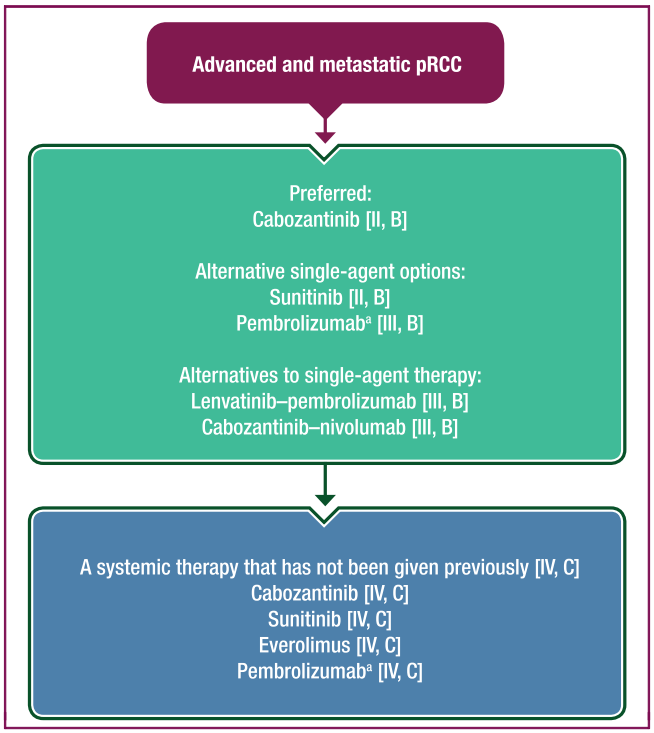

Figure 4. Systemic treatment of advanced and metastatic pRCC.
Purple: algorithm title; blue: systemic anticancer therapy; turquoise: combination of treatments or treatment modalities.
EMA, European Medicines Agency; FDA, Food and Drug Administration; pRCC, papillary renal cell carcinoma.
[a]Not EMA or FDA approved.

Further-line treatment. Robust data are also lacking for second-line treatment of pRCC. Any targeted therapy or immunotherapy recommended in the first-line setting that has not previously been given is cautiously recommended. An OS advantage for any second-line therapy and the principle of sequencing therapy have not been proven in randomised trials. Best supportive care (BSC) alone may be considered in selected individuals.

Treatment for advanced and metastatic non-clear-cell and non-papillary histologies

There is a paucity of robust data to guide management of non-clear-cell, non-papillary RCC histologies; therefore, enrolment into clinical trials is strongly recommended. The available data are largely derived from small prospective studies and subgroup analyses from larger trials.

Surgery is used in patients with intermediate-risk advanced disease; however, there is no available evidence to support this approach as a recommendation.

An algorithm for the systemic treatment of advanced and metastatic non-clear-cell, non-papillary RCC is shown in Figure 5. Sunitinib has been shown to have activity in non-clear histologies (improved PFS compared with everolimus), supporting the use of TKI-based therapy in these rare subtypes.[61] PD-1-targeted combinations are the SoC in patients with sarcomatoid differentiation.[44-46,67] Some patients with chromophobe RCC may benefit from mammalian target of rapamycin (mTOR) inhibitors since mutation on chromosome 17 has been shown to lead to loss of the *FLCN* gene and up-regulation of mTOR.[68]

Collecting duct carcinomas and *SMARCB1*-deficient RCC are treated with platinum-based chemotherapy (ChT). Cabozantinib monotherapy is an alternative treatment for collecting duct carcinomas, having demonstrated efficacy as first-line therapy in a trial of 25 patients with advanced disease.[69] The prognosis of this rare tumour, however, remains generally poor.[70]

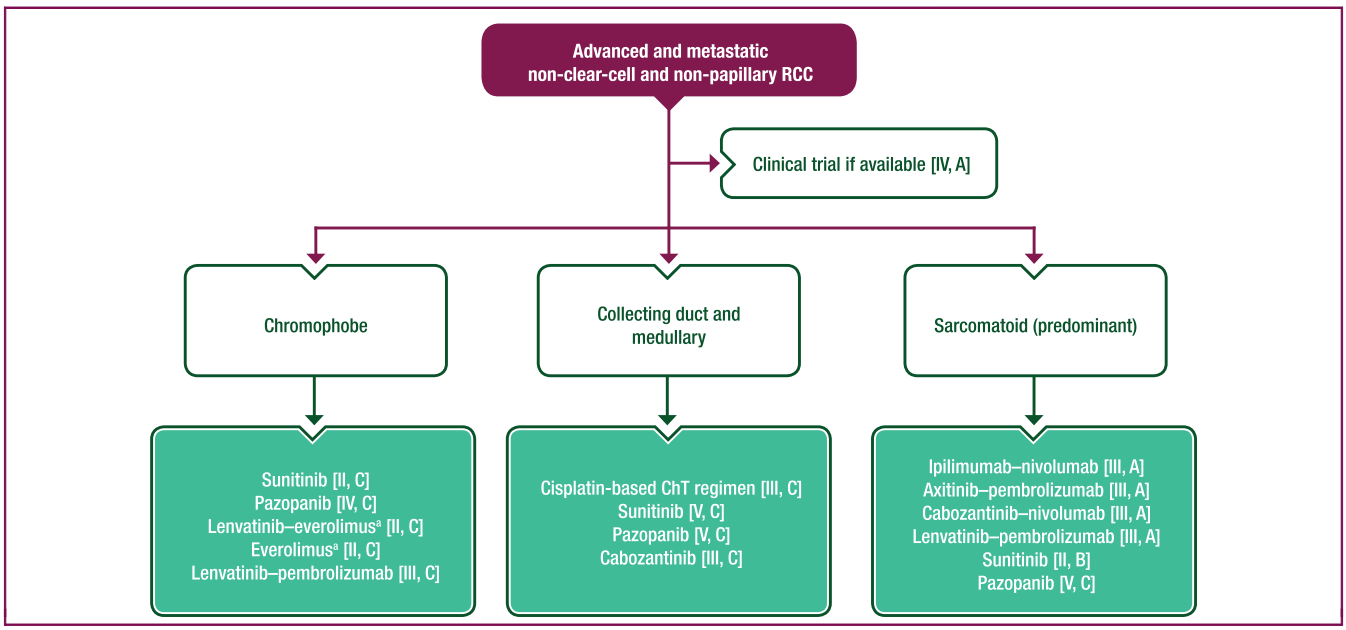

Figure 5. Systemic treatment of advanced and metastatic non-clear-cell and non-papillary RCC.
Purple: algorithm title; turquoise: combination of treatments or treatment modalities.
ChT, chemotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; RCC, renal cell carcinoma.
[a]Not EMA or FDA approved for first-line treatment.

FH-deficient RCC is rare, aggressive and may be associated with HLRCC. Data from a phase II study investigating bevacizumab—erlotinib in HLRCC-associated RCC support the use of this combination in advanced FH-deficient disease.[71] Bevacizumab—erlotinib may be considered in this population without an accepted SoC.

After first-line therapy, no recommendations are possible for subsequent lines of therapy based on available data.

Role of RT and bisphosphonates

RT may provide symptom palliation and local control of disease, including in cases of oligometastatic disease or mixed response to ICIs and/or targeted therapies. RT is also an effective treatment for palliation and prevention of disease progression in critical sites such as the bones or brain. In malignant spinal cord compression, initial surgery followed by post-operative RT has been shown to improve survival and maintenance of ambulation compared with RT alone.[72] Low burden of metastatic disease and good ambulatory status at diagnosis are favourable prognostic factors in patients who are able to undergo neurosurgery. In the management of brain metastasis, stereotactic RT is recommended instead of whole-brain RT (WBRT). WBRT is associated with cognitive dysfunction and should be avoided. The benefits of these approaches on survival are uncertain.

Bisphosphonate therapy with zoledronic acid, as well as the receptor activator of nuclear factor kappa B ligand inhibitor denosumab, has been shown to reduce skeletal-related events (SREs) and increase time to the first SRE in patients with widespread bone metastases across a broad spectrum of cancers, but not specifically in renal cancer.[73,74] Denosumab was non-inferior to zoledronic acid in a randomised trial[73] and has the convenience of subcutaneous administration with no requirement for renal monitoring or dose adjustment, although the risk of hypocalcaemia is greater in patients with renal dysfunction. Therefore, either zoledronic acid or denosumab should be considered in patients with widespread bone metastases and reasonable life expectancy, taking into account the individualised risk, including the possibility of osteonecrosis of the jaw. It is important to note that these studies were not carried out in the era of contemporary treatments for RCC, and as such, the true benefit is uncertain.

Recommendations

Role of surgery and local therapy.

- CN should usually be avoided in advanced RCC. It should only be considered for selected patients with favourable- or intermediate-risk disease after MDT review [I, B].
- Deferred CN is an option for patients with durable and near CR at metastatic sites following systemic therapy after MDT review [II, B].
- Patient selection for local therapies or surveillance in the metastatic setting should be discussed by an MDT [III, B]. While no data exist to describe an exact population, both strategies should be avoided in patients with a high burden of metastases, short interval to recurrence or aggressive disease.
- Metastasectomy is not routinely recommended within 1 year of nephrectomy [I, D]; however, in patients with oligometastatic disease who have undergone complete resection (M1 and NED), adjuvant pembrolizumab can be offered [II, B; ESMO-MCBS v1.1 score: A].

First-line treatment for advanced and metastatic ccRCC.

- Lenvatinib—pembrolizumab [I, A; ESMO-MCBS v1.1 score: 4], axitinib—pembrolizumab [I, A; ESMO-MCBS v1.1 score: 4] or cabozantinib—nivolumab [I, A; ESMO-MCBS v1.1 score: 1] is recommended for first-line treatment of advanced ccRCC, irrespective of IMDC risk group. There is no preferred PD-1 inhibitor—VEGFR TKI combination and indirect comparisons across trials are not recommended.
- Ipilimumab—nivolumab is recommended as first-line treatment for IMDC intermediate- and poor-risk disease [I, A; ESMO-MCBS v1.1 score: 4] and is an option for favourable-risk disease [I, C].
- Axitinib—toripalimab is an option for patients with intermediate- or poor-risk disease [I, C; not EMA or FDA approved].
- Sunitinib [I, C], pazopanib [I, C] and tivozanib [II, C] are potential alternatives to PD-1-targeted combination therapy in IMDC favourable-risk disease due to a lack of clear superiority for PD-1-targeted combinations over sunitinib.
- Sunitinib [I, A], pazopanib [I, A] and tivozanib [II, B] are alternatives to first-line PD-1-targeted combinations when ICI therapy is contraindicated or not available. Cabozantinib is also an alternative in IMDC intermediate- and poor-risk disease for those patients who cannot receive first-line PD-1-targeted therapy [II, A].
- Axitinib—avelumab is not associated with OS benefit compared with sunitinib and is therefore not recommended over single-agent VEGFR TKI therapy [I, D; ESMO-MCBS v1.1 score: 3].
- Surveillance is an alternative approach in a small, undefined subset of patients with favourable-risk disease [III, C]. This approach requires careful consideration.
- Cessation of ICIs should be considered after 2 years [IV, B]. Treatment breaks from VEGFR TKI therapy do not appear to have any detrimental effect on efficacy [I, C].

Second-line treatment for advanced and metastatic ccRCC.

- Sequencing VEGFR TKI therapy after PD-1-targeted first-line therapy is the SoC [I, B]. VEGFR-targeted agents that have not been previously used should be considered [I, B]. Cabozantinib is the preferred agent for second-line treatment [II, B]. Axitinib [III, B], lenvatinib—everolimus [III, B], pazopanib [III, B], sunitinib [III, B] and tivozanib [III, B] are also options.
- For patients who received first-line VEGFR TKI therapy, nivolumab (if available and not contraindicated) [I, A; ESMO-MCBS v1.1 score: 5] and cabozantinib [I, A] are

both associated with an OS benefit. Axitinib [II, B], everolimus [II, B] and lenvatinib—everolimus [II, B] are also options.
- Belzutifan is an alternative option for patients who have progressed on VEGFR—PD-1-targeted combination therapy [III, B; FDA approved, not EMA approved].

Further-line treatment for advanced and metastatic ccRCC.
- Sequencing VEGFR TKI therapy [III, B] or belzutifan [I, B; FDA approved, not EMA approved] can be recommended.
- Belzutifan should be considered instead of everolimus in heavily pretreated patients (after PD-1- and VEGFR-targeted therapy) [I, B; FDA approved, not EMA approved].
- Everolimus remains an option for patients who have received PD-1- and VEGFR-targeted therapy [II, C], but other approaches are preferable. Everolimus should be considered when other approaches (belzutifan, other VEGFR TKIs) are not available.
- The use of further PD-(L)1-targeted therapy after progression on first-line PD-1-targeted therapy is not recommended [I, D].

Systemic treatment for advanced and metastatic pRCC.
- Cabozantinib is the preferred first-line monotherapy for advanced pRCC without additional molecular testing [II, B].
- Lenvatinib—pembrolizumab and cabozantinib—nivolumab have impressive response rates but are not proven to be superior to single-agent therapy. They may be considered as alternatives to single-agent therapy [III, B].
- Alternative single-agent options include sunitinib [II, B] and pembrolizumab [III, B; not EMA or FDA approved]. Savolitinib cannot currently be recommended in *MET*-altered tumours [II, D; not EMA or FDA approved]; randomised data are needed.
- Second-line therapy may focus on agents that have not been used previously [IV, C]. Options include cabozantinib [IV, C], sunitinib [IV, C], everolimus [IV, C] and pembrolizumab [IV, C; not EMA or FDA approved]. BSC can be considered in selected patients due to the lack of data on systemic therapy [IV, C].

Systemic treatment of advanced and metastatic non-clear-cell, non-papillary RCC.
- Enrolment into clinical trials is recommended [IV, A].
- Sunitinib [II, C], pazopanib [IV, C], lenvatinib—everolimus [II, C; not EMA or FDA approved for first-line treatment], everolimus [II, C; not EMA or FDA approved for first-line treatment] and lenvatinib—pembrolizumab [III, C] may be used for advanced chromophobe RCC.
- Cisplatin-based ChT is recommended for collecting duct carcinomas and *SMARCB1*-deficient RCC [III, C]. Sunitinib [V, C], pazopanib [V, C] and cabozantinib [III, C] are alternative options.
- ICI-based therapies including ipilimumab—nivolumab [III, A], axitinib—pembrolizumab [III, A], cabozantinib—nivolumab [III, A] and lenvatinib—pembrolizumab [III, A] are preferred for advanced RCC with sarcomatoid (predominant) histology. Sunitinib [II, B] and pazopanib [V, C] are alternative options for patients with contraindications to ICI-based therapy.
- Bevacizumab—erlotinib may be used in advanced FH-deficient RCC [III, B; not EMA or FDA approved].

Role of RT and bisphosphonates.
- Stereotactic RT is recommended for patients with brain metastases [III, B]. WBRT is associated with cognitive dysfunction and should be avoided [III, D].
- Zoledronic acid or denosumab can be considered in patients with bone metastases after consideration of individualised risk [IV, C].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

There is no robust evidence to guide recommendations regarding the frequency of follow-up imaging in early- or advanced-stage RCC.

Resectable disease

It is reasonable to use follow-up imaging based on the risk factors for recurrence and available treatment options upon diagnosis of recurrence. For patients with high-risk disease, CT scans of the thorax and abdomen should be carried out every 3-6 months for the first 2 years, regardless of whether adjuvant pembrolizumab is used. For patients with low-risk disease, annual CT scans are likely sufficient. Radiological examination after 2 years is less strongly recommended, although continuation for up to 5 years after surgery can be considered. The possibility of long-term relapses should be taken into account when planning follow-up.

Advanced and metastatic disease

During systemic therapy for advanced disease, CT scans should be carried out every ∼2-4 months to assess response to therapy. Response Evaluation Criteria in Solid Tumours (RECIST) remains the most frequently used method to assess drug efficacy; however, there is no evidence that RECIST-defined disease progression is a clinically valid endpoint that should dictate treatment interruption or modification. Therefore, clinical judgement continues to be required in addition to radiological assessment.

Recommendations

- A risk-based follow-up approach should be considered, with imaging for ≥2 years after nephrectomy [IV, B]. Continuation for up to 5 years can be considered, although the benefits of imaging after 2 years are unclear [IV, C].

- In advanced disease, CT scans should be considered every 2-4 months to assess response to therapy [IV, B]. Radiological response may be evaluated in conjunction with clinical assessment [IV, B].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. A table of ESMO-MCBS scores is included in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.05.537. ESMO-MCBS v1.1[75] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated and verified by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.05.537.[76] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-genitourinary-cancers/renal-cell-carcinoma.

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DISCLOSURE

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Article

Uro-Oncology Multidisciplinary Team Meetings at an Australian Tertiary Centre: A Detailed Analysis of Cases, Decision Outcomes, Impacts on Patient Treatment, Documentation, and Clinician Attendance

Ramesh Shanmugasundaram, Alex Buckby *, John Miller and Arman Kahokehr

Urology Department, Lyell McEwin Hospital, Adelaide, SA 5112, Australia
* Correspondence: alexander.buckby@sa.gov.au

Abstract: Objectives: There is currently limited local and international literature on the characteristics of uro-oncology multi-disciplinary team meetings (MDTMs) and their impact on clinical decision making. The aims of this study were to provide a comprehensive descriptive analysis of MDTMs at an Australian tertiary hospital over a 12-month period and their impacts on patient management, and to evaluate adherence to MDTM plans. **Methods:** We conducted a review of a prospectively maintained database of all uro-oncology MDTMs held within the Northern Adelaide Local Health Network (NALHN) over a 12-month period in 2020–2021. **Results:** During this 12-month period, 24 MDT meetings were conducted, in which 280 patients were discussed. Overall, MDTMs resulted in modifications to the management of 25.7% of patients, which was consistent across all three major tumour streams (24% for prostate cancer, 29% for renal cell carcinoma, and 22% for urothelial carcinoma). MDTMs also facilitated cross referrals between specialties for 105 patients (37.5%), including 5 patients who were considered for entry into clinical trials. There was a high acceptance rate, with adherence to MDT recommendations for 270 of the 278 patients discussed (96.4%). MDTM plans were fully implemented within a 6-month period. **Conclusions:** We provided a detailed analysis of uro-oncology MDTMs at an Australian tertiary referral centre, demonstrating that MDTMs facilitate optimal cancer management for patients with urological cancers.

Keywords: multidisciplinary team meetings; urology; oncology

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1. Introduction

The multidisciplinary team meeting (MDTM) model in cancer care has expanded from being utilised for only specific tumour streams to include all cancers. The aims of MDTMs are to review patients' diagnoses and results, and to help establish the best treatment plans according evidence-based medicine. MDTMs have been demonstrated to improve various clinical outcomes in cancer care, including adherence to clinical guidelines, survival, quality of life, and patient satisfaction [1–3]. Various cancer frameworks in Australian states and territories emphasise the importance of multidisciplinary cancer care and have instituted measures to increase their uptake [4]. Despite this, there is currently limited local and international literature regarding the characteristics of urology-specific oncology MDTMs and whether they make meaningful changes in patient care and clinical outcomes, which would be the ultimate indicator of their utility. With this in mind, the urologists of our unit sought to review the practices of our MDTMs.

The aim of this study was to provide a descriptive analysis of uro-oncology MDTMs meetings convened at our Australian tertiary hospital over a 12-month period to gain an understanding of characteristics of the patients and tumour streams discussed. In addition, this study aimed to assess the impact of our institution's uro-oncology MDTMs on patient management decisions and to evaluate adherence to MDTM plans to ensure their effective implementation.

2. Methods

A database of all patients discussed at our uro-oncology MDTMs is maintained as part of our unit's standard audit practice. This database consists of information on patient demographics, key imaging findings, histopathology results, clinical questions being posed to the multidisciplinary team, MDTM recommendations, and consultant attendance. Meetings are held every fortnight, and attended by consultant urologists, radiation oncologists, oncologists, radiologists, a uropathologist, urology nurse practitioners, and junior medical officers. There are no set criteria for patient inclusion; however, all new prostate cancer diagnoses and all new testicular cancer diagnoses were discussed as part of the practice of the unit. MDTM cases were put forward for discussion either directly from triage by the Urology Head of Unit, by other consultant urologists from within the unit, following histopathology clinics performed by registrars, or from other specialties (e.g., medical oncology or radiation oncology). The unit's accredited urology trainee reviewed patient cases awaiting discussion and collated a list of patients prior to distribution via secure internal email to everyone involved in the meeting. Patients were notified by the clinic or on the ward that their care would be discussed in this setting; patients added from triage were not directly notified.

Recommendations were documented by the chair of the meeting (the unit's urology registrars) into a document on a secure internal drive. The unit's resident medical officers then prepared formal documents within our health system's electronic medical records, which upon being published were automatically distributed to each patient's general practitioner. After each meeting, patients, or in some cases representative family members, were contacted by telephone to discuss recommendations within 1 week by the urology registrar who chaired the meeting.

Implementation of recommendations was confirmed by reviewing patients' medical records at up to 6 months post-discussion, confirming commencement of recommended treatments. A few cases did not adopt the recommended treatment; brief clinical vignettes explaining these deviations follow below.

From our prospectively maintained database, we analysed 24 consecutive MDTMs between July 2020 and June 2021. Data obtained from the database included demographic details, tumour streams, cancer stages/grades, times from diagnosis (pathological/imaging) to discussion, instances of treatment before MDTM discussion, and post MDTM correspondence to GPs. Additional data were extracted from patients' electronic records when required. To assess the impact on management decisions, we identified cases in which a preferred treatment strategy was documented, either in a patient's records or within the clinical question submitted to the MDTM chair as part of our MDTM template. When there was no documented preferred treatment option specified, patients were excluded from this analysis. In many cases this was because a formal discussion had not yet taken place regarding a preferred treatment strategy (e.g., cases were added for MDTM discussion by registrars reviewing results in a pathology results clinic) or because documentation in pre-MDTM clinic notes was either unclear as to a preferred treatment strategy or there was no treatment strategy documented. Significant impact was defined as a change in treatment modality (i.e., active surveillance vs. active treatment), treatment intent (i.e., palliative vs. active), or when further investigations were requested to guide treatment (e.g., biopsy, imaging, or genetic testing).

Data were managed via an Excel spreadsheet. Numerical data are presented as medians (ranges), means, or percentages.

3. Results

In total, there were 24 MDTMs conducted during this 12-month period, in which 280 patients were discussed. The median (range) age was 65 (20–93) years, and most patients discussed were male 245 (87.5%). Most cases were submitted for discussion by urologists (273, 97.5%), with the remaining from radiation oncologists and medical oncologists.

The breakdown of cases by tumour stream is shown in Table 1. Prostate cancer (99 cases, 35.4%) and renal tumours (87 cases, 31.1%) were most frequently discussed. Other tumours, in order of frequency, were urothelial cancer (19.3%), testicular cancer (6.4%), and 'dual' tumours (5.7%—examples included patients with concurrent urological tumours (e.g., a renal mass and prostate cancer); lymphadenopathy in the setting of urological cancers and haematological malignancies; new lung lesions in the setting of urological malignancy and concern for concurrent primary lung malignancy; and concurrent urological and non-urological malignancies (e.g., colorectal cancer), for which a decision regarding priority of treatment was required). Apart from testicular cancer, cases from all other tumours had predominantly localised disease (Table 1).

Table 1. Proportion of urological cancers discussed (total, (%)), time from diagnosis to MDTM discussion (median, (range)), extent of disease by tumour stream (total, (%)), impact on management (number modified, (%)), and adherence to MDTM consensus by tumour stream (proportion, (%)).

Tumour Stream	Number of Patients	Time to Discussion	Extent of Disease			Impact on Management	Adherence to MDTM Conensus
			Local	Metastatic	Equivocal		
Prostate	99 (35.4%)	4 weeks (1–12)	72 (72.7%)	9 (9.1%)	18 (18.2%)	Endorsed = 46 (76%) Modified = 15 (24%)	93/99 (95.9%)
Renal	87 (31.1%)	4 weeks (1–24)	68 (78.2%)	6 (6.9%)	13 (14.9%)	Endorsed = 44 (71%) Modifed = 18 (29%)	85/87 (97.7%)
Urothelial cancer	54 (19.3%)	4 weeks (1–12)	45 (83.3%)	4 (9.3%)	5 (7.4%)	Endorsed = 28 (78%) Modified = 8 (22%)	53/54 (98.1%)
Testicular	18 (6.4%)	3 weeks (1–4)	8 (44.4%)	10 (55.6%)	0 (0%)	-	17/18 (94.4%)
Dual	16 (5.7%)	-	-	-	-	-	-
Adrenal	2 (0.7%)	-	-	-	-	-	-

The median time from diagnosis (imaging or histopathology) to MDTM discussion was 4 weeks across all tumour streams (Table 1). There were between 6 and 16 cases discussed at each MDTM. Renal tumours had a wider range of waiting times for MDTM discussion, with a preponderance of elderly patients with low-risk small renal masses on imaging, triaged by the MDTM chair as non-urgent. The average attendances by specialist clinicians was 9 (range 7–12). Every meeting had at least one representative from Urology, Pathology, Medical Oncology, and Radiology. Respective attendances by specialty are summarised in Table 2.

Table 2. Attendance by specialty (mean, range).

Overall	9.26 (7–12)
Urology	3.35 (3–4)
Oncology	2.09 (1–3)
Radiation Oncology	1.61 (1–2)
Pathology	1 (1–1)

In total, 33 patients were discussed more than once (27 twice, and 6 patients three times). This was either due to further investigations being required, further specialty opinions being required on the suitability of different treatment options (e.g., a high-risk anaesthetics clinic), response to a treatment being reviewed, or patients discussed in both pre- and post-operative settings.

To assess the impact of the MDTM process on patient management, we analysed data from 159 of 280 patients who had a clearly documented management plan in either their patient notes or in MDTM correspondence to the chair, as per our template. Reasons for non-inclusion included being added directly to an MDTM discussion from triage, resulting in discussion at an MDTM prior to the formulation of a treatment plan from a referring surgeon; being added to an MDTM discussion from a registrar results clinic without a

formal discussion about preferred management; or lack of documentation regarding a preferred treatment plan in the clinic or from the ward prior to MDTM discussion. Overall, MDTMs resulted in a modification to management in greater than 20% of patients across all three major tumour streams. This was most apparent in patients with renal tumours (29%) (Table 1). MDTMs also facilitated cross referrals between specialties for 105 patients (37.5%). This process resulted in five patients being considered for clinical trials, as well as six patients (4.3%) being referred to palliative care. There was a significant difference in rates of referrals across tumour streams, with prostate cancer having the highest rate of cross referral (59.1%). A complete breakdown by tumour stream is shown in Table 3. Notable impacts of the MDTM process included two patients who had their pathology upgraded after specimen re-review by an experienced uropathologist.

Table 3. Cross referrals from MDTMs.

Tumour Stream	Radiation Oncology	Medical Oncology	Intervention Radiology	Palliative Care	Total (Percentage)
Prostate n = 99	43	12	0	0	55 (59.1%)
Renal n = 87	7	7	8	1	23 (26.4%)
Urothelial Cancer n = 54	6	5	1	5	17 (31.5%)
Testicular cancer n = 18	0	7	0	0	7 (38.9%)
Total n = 258	56	32	11	6	105 (40.7%)

There was a high adherence to MDTM recommendations, with 270 of 278 patients (96.4%) having their MDTM plans fully implemented within a 6-month period. This was consistent across all major tumour streams, as shown in Table 1. Most patients who did not have plans implemented as per the MDTM process had prostate cancer (6/10). The reasons for this are summarised in Supplementary Table S1. Seven patients' cases required re-discussion due to incomplete information—four of these patients' cases did not have adequate staging studies, and three had inadequate clinical information. An "MDTM summary" was published in the electronic patients' record system and sent to general practitioners for 276 of 280 patients (98.6%).

4. Discussion

In this study, we provided a comprehensive analysis of uro-oncology MDTMs at an Australian tertiary referral centre. We analysed all MDTMs over a 12-month period consisting of 24 MDT meetings and discussion of 280 cases. Most cases (97.5%) were submitted for MDT discussion by urologists, and prostate cancer represented the highest proportion of cases discussed (35.4%). The median time to discussion was 4 weeks for all major uro-oncological tumour streams, and there were no outliers who waited a clinically inappropriate time. A majority (87.5%) of cases discussed were male patients, which was appropriate for the number of male-only cancers and the known disparity in incidences of urothelial cancer and renal cell carcinoma. With the exception of testicular cancer, the other tumour streams discussed at our MDTMs were localised at the time of review, when traditionally, cases discussed were often more advanced. This could reflect changing practices to ensure all patients receive multidisciplinary input that allows the best available evidence; however, these types of data were not measured in this study.

A recent review found that MDTM discussion generally has an impact on management decisions in patients with cancers [5]. In our study, we found that 25.8% of patients had their management modified at an MDTM. Greater than 20% of patients in all three major tumour

streams had a modification to their original management plan. Management changes in our study were similar to those of previous reports from the US (32%) [6], UK (12.6%) [7], and Australasia (8.9% [8] and 26.7% [9]). When interpreting these results, it must be noted that there is a significant heterogeneity in the inclusion criteria for various MDTMs around the globe, which affects the interpretation of these percentages (for example, seeking clarification for a radiological or pathological finding that affects a patient's management plan could be performed outside an MDTM setting; however, this was routinely performed in an MDTM setting in our cohort). In contrast to the UK, our institution does not mandate MDTM discussion for all patients with cancer, and discussion of a case at an MDTM is at the treating clinician's discretion. In addition, we were only able to provide analyses of treatment impact for 159 of the 280 patients discussed at our MDTMs, which is a significant proportion and needs to be considered when interpreting our results. Nevertheless, this proportion of changes highlights the value of the MDTM process in altering management through a collaborative decision-making process. Whether changes in management plans led to positive, clinically meaningful improvements in cancer outcomes was not measured by this study; however, as has been demonstrated in previous studies, cases discussed at MDTMs are more likely to have more complete staging, neo-adjuvant or adjuvant treatment, and treatment in line with evidenced-based guidelines [10,11], which should translate into improved cancer treatment outcomes.

Attendance at our MDTMs was high overall, and well represented by our units' four urologists (at least three attended every meeting); however, oncologists and radiation oncologists were at times only represented by one clinician. Most patients for discussion were put forward by urologists; however, for the few patients put forward for discussion by other specialties, there was a small risk of an MDTM opinion being provided by both the sole treating clinician and representative of their specialty, which was unlikely to result in a change in patient treatment or the MDTM opinion that the treating clinician sought. Mandating that multiple clinicians attend from each representative specialty may navigate this problem.

The uptake of MDTM recommendations is a key performance indicator. Our study confirmed that 270 of 280 patients (96.4%) had their MDTM plans fully implemented within a 6-month period. A key strength of our MDTMs was the high rate of publishing and distributing MDTM summaries to general practitioners, which is a key recommendation set by Cancer Australia and in the Australian national optimal care pathways [12,13]. Studies have shown that when an MDTM recommendation is formally documented, treatment concordance increases from 76% to 95% [14]. At our centre, 276 of 280 cases (98.6%) discussed were published on our electronic system and distributed to general practitioners. This was significantly higher than percentages noted in other similar reports, which found that only one third of MDTM recommendations were communicated to the patient's general practitioner [15]. We believe a key reason for this at our centre was the allocation of an 'MDTM clinic' to the chair within 2 days of the meeting to (i) document and publish the MDTM discussion, (ii) communicate results to patients, and (iii) organise further investigations where indicated. In addition to this, our use of an electronic MDTM database, which serves as a template and includes a post MDTM checklist, ensures all tasks are carried out for each meeting. We believe that having the urology registrar chair MDTMs and carry out the post meeting 'MDTM clinic' reduces ambiguities in plans/recommendations, as they are the best equipped to accurately summarise the complex discussions that took place. Although having these complex discussions via the telephone is not ideal (particularly if the news is quite serious), it was the fastest way to communicate outcomes to patients, which, anecdotally, we found reduced their anxiety. In most cases, it allowed patients to prepare questions prior to meeting in a consultant clinic to formalize their management plan.

Our MDTMs also promoted cross referrals between specialties for 105 patients (37.5%), which for 5 patients resulted in enrolment in clinical trials. The value of having clinicians with a sub-specialty interest in genitourinary tumours was highlighted by the re-staging of pathology specimens and re-grading of imaging reports. For example, a 68-year-old

man with organ-confined prostate cancer had his biopsy report modified from a highest grade of Gleason 3 + 4 = 7 to Gleason 4 + 4 = 8 on review. Similarly, a multiparametric MRI prostate report from an external radiology centre had an upgraded PIRADS score after secondary review.

Limitations of our study include its retrospective nature and single-institution focus. Furthermore, the assessment of 'impact of MDTMs on management' focused on a subset of patients who had clearly documented management plans; this was largely due to triaging practices in our unit, which help streamline patient care through our service and justify costs of performing robotics cases (required by our finance department) for which our unit currently needs to 'rent' time on another hospital's robotics system, which comes at a significant cost. A metric we did not capture was whether, when following our MDTM assessments, patients' management plans were in line with international guidelines (e.g., EAU), which could be performed as part of an audit in the future.

Although we provided numerous significant objective findings, the impact of having nurse practitioners and specialist cancer nurses was not captured by our data. We also did not assess important qualitative measures of MDTMs' functions, such as communication and each team member's input and involvement in the decision-making process. Strengths of our study include a long 12-month period with a 6-month lag time afterward, enabling assessment of adherence to and implementation of MDTM recommendations. Although our study data were analysed retrospectively, maintaining an electronic database of MDTM discussions with a pre-set template that included "question to MDTM/management options" enabled our data to be collected in a prospective manner with clinicians 'blinded' to the study.

There is potential for further interrogation of the performance of the unit's MDTMs by utilising various MDTM quality assessment tools, including the first, developed in 2010, Multidisciplinary Tumor Board Metric for the Observation of Decision-Making (MDT-MODe) [16]. Several other assessment tools have been produced, and were summarised in a recent systematic review [17]. A question for further research could investigate whether patients whose information performed better, according to these quality assessment tools, experienced a greater number of changes in their treatment plans.

5. Conclusions

This study provided a detailed analysis of the uro-oncology MDTMs process at our institution, highlighting its key role in the management of urological cancers. Collaborative multi-specialty input resulted in changes to management plans at the diagnostic, staging, and treatment stages of patient care.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/siuj5040040/s1, Table S1: Brief clinical vignettes describing patient deviations from MDT recommended plans.

Author Contributions: R.S. contributed to the conception of this project, the literature review, protocol development, data acquisition, data analysis, and interpretation of data. R.S. drafted the first manuscript and approved the final draft. A.B. assisted with data acquisition, the first draft of this manuscript, and edited and approved the final version of this manuscript. J.M. and A.K. contributed to analysis of data, editing this manuscript, and approved the final version of this manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Due to the retrograde audit nature of this study, formal ethics approval was not deemed necessary. The investigators of this study conducted this study in full conformance with the ethical principles of the Declaration of Helsinki.

Informed Consent Statement: Informed consent was not sought for this study because it would have been impractical to obtain informed consent for all patients discussed at our MDTMs. This study was

a negligible risk study, and due to its retrospective nature, there was no change in the clinical care of patients involved, and they were not exposed to additional risk by being included in this study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

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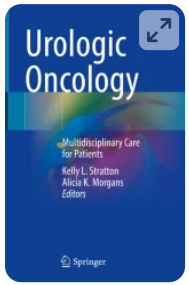

Urologic Oncology

Multidisciplinary Care for Patients

| Book | © 2022

Overview

Editors: Kelly L. Stratton, Alicia K. Morgans

Illuminates the benefits of multidisciplinary co-management

Emphasizes the upcoming expansion of new therapeutics for urologic malignancies

Written by leading experts in the practice of team-based urological care

About this book

Urologists and medical oncologists have witnessed a rapid growth in systemic therapeutic options for treating genitourinary malignancies that increasingly integrates radiation therapy to primary cancers, nodal beds, and even metastatic sites. The culmination of these advances has been the creation of multidisciplinary teams that expertly provide comprehensive care to patients with urologic cancers. This book provides the framework to create such a multidisciplinary clinical team focused on the treatment of urologic malignancies with representation from urologists, medical oncologists, and additional specialists who work together to provide optimal team-based care. The book integrates advanced systemic therapeutics including immune-based and targeted therapies. Readers gain a better understanding of the benefit of multidisciplinary co-management through specific examples such as hormone sensitive metastatic prostate cancer, neoadjuvant chemotherapy for muscle invasive bladdercancer, and immunotherapy approaches to advanced bladder and kidney cancer. The book also discusses the integration of

genomic tumor characterization and personalized medicine into surgical planning, tumor biopsies, and chemo-immunotherapy selection, emphasizing the expansion of new therapeutics for urologic malignancies and the changing definitions of disease progression.

Urologic Oncology: Multidisciplinary Care for Patients is a comprehensive resource for urologists, medical oncologists, radiation oncologists, genetic counselors, fellows in urologic oncology and medical oncology, residents in urology and radiation oncology, advanced practice providers, practice managers, and pharmaceutical representatives.

Keywords

genitourinary malignancy team-based care prostate cancer bladder cancer kidney cancer

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Editors and Affiliations

Urology, University of Oklahoma Health Science Center, Oklahoma City, USA
Kelly L. Stratton

Medical Oncology, Dana-Farber Cancer Institute, Boston, USA

Alicia K. Morgans

About the editors

Kelly L. Stratton

Associate Professor
Department of Urology
University of Oklahoma Health Science Center
Oklahoma City, OK
USA

Alicia K. Morgans
Genitourinary Medical Oncologist
Medical Director, Survivorship Program
Dana-Farber Cancer Institute
Boston, MA
USA

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The Uro-Oncology Multi-disciplinary team (MDT) Clinic – Clinical and Patient-Reported Outcomes From Implementing a New Model of Care

Alvin Yuanming Lee[1]*, Raj Tiwari[1]*, Shuhui Neo[1], Daanesh Huned[1], Arjunan Kumaran[1], Chloe Li Wen Lim[1], Melvin Lee Kiang Chua[2,3], Ravindran Kanesvaran[4], and Lui Shiong Lee[1]

Abstract

Introduction: A multi-disciplinary approach has often been advocated to improve the delivery of oncological care, as compared to a mono-disciplinary and linear approach. Our study elucidates the clinical and patient-reported outcomes from a urologic-oncology multi-disciplinary team (MDT) clinic in a regional general hospital.

Materials and Methods: Patients who attended a uro-oncology MDT clinic which was started in January 2019 were identified. This service was specifically catered to patients who were histologically diagnosed with urological cancers. The MDT service comprised a multi-disciplinary tumour board followed by outpatient clinical consults with representatives from urology, medical and radiation oncology. Demographic variables, disease characteristics and treatment rendered were analysed. A survey was administered to assess patient satisfaction.

Results: Fifty patients with a median age of 70 years with complete case records were identified. The cancer types included prostate cancers (46%), urothelial cancers (26%) and renal cell carcinoma (12%) as the most frequent urological cancers. The median time from MDT to therapy initiation was 8 days. Among those with prostate, urothelial, renal and testicular malignancies, 71% (32/45) of our patients received treatment that were in accordance to guideline recommendations. A post-clinic survey showed that patients were satisfied with the information provided during the clinic and this also facilitated decision and time to initiation of therapy.

Conclusion: A multi-disciplinary service comprising a tumour board followed by a one-stop clinic provides patients with multi-disciplinary care, improved access to subsequent therapy, better time efficiency and high patient satisfaction scores. More studies are warranted to demonstrate its oncological outcomes.

Keywords

Bladder cancer, kidney cancer, multi-disciplinary team clinic, prostate cancer, uro-oncology

Introduction

A multi-disciplinary and patient-centric approach has often been advocated to improve the delivery of oncological care, as compared to a mono-disciplinary and linear approach.[1] Traditionally, multi-disciplinary approaches have been largely defined by paper discussions alone without actual patient involvement.

The idea of multi-disciplinary involvement in patient care was conceptualised several decades ago and its rapid uptake has often been cited to improve patient-outcomes across the

[1]Department of Urology, Sengkang General Hospital, Singapore
[2]Divisions of Radiation Oncology and Medical Sciences, National Cancer Centre, Singapore
[3]Duke-NUS Medical School
[4]Division of Medical Oncology, National Cancer Centre, Singapore

*These authors contributed equally as first authors.

Corresponding Author:
Lui Shiong Lee, Department of Urology, Sengkang General Hospital, 110 Sengkang East Way, Singapore 544886, Singapore.
Email: lee.lui.shiong@singhealth.com.sg

various medical fields.[2-3] Key to this strategy would be the provision of comprehensive evaluation and treatment recommendations from multiple perspectives, which potentially improves the level of care in complex clinical scenarios. For instance, Pawlik and colleagues studied the impact of a single-day multi-disciplinary clinic on the management of pancreatic cancer and found that multi-disciplinary case review resulted in an overall 23% change in therapeutic plan of patients with presumed pancreatic cancer.[4] Similarly, in the urological oncology space, multi-disciplinary clinics for prostate cancer have generally been well-received and played an important role in altering management decisions.[4-5] There is sparse literature about the provision of a urologic-oncology multi-disciplinary team (MDT) clinic in a regional hospital, and there is limited data on patients' perceptions related to such services.[6-7]

This study elucidates the clinical and patient-reported outcomes from a urologic-oncology multi-disciplinary clinic in a regional general hospital over a duration of 1 year since its conception.

Materials and Methods

In our traditional paradigm of patient care, patients diagnosed with a genitourinary malignancy would have management plans discussed at a regular genitourinary tumour board. This platform allowed clinical decision regarding treatment to be made amongst specialities, but did not have the benefit of in-person patient assessment. This would inevitably lead to multiple visits by the patient across all three oncology specialities, and pose a challenge to a holistic care plan when there was an ipsilateral change in management plan required.

A dedicated urologic-oncology MDT clinic was started in January 2019 in a regional acute care hospital with 1000 inpatient beds. This outpatient clinic was specifically catered to patients who were histologically diagnosed with urological malignancies including prostate, urothelial, renal, penile, testicular and adrenal cancers, in particular those with conditions where the management may require two or more specialities' input. In this one-stop service, there is specialist representation from urology, medical oncology and radiation oncology, and was intended to facilitate clinical decision making between specialties and with the patient, as opposed to unilateral decisions between specialities at different visits in the traditional model. All relevant specialists were simultaneously present in the same consultation room during the MDT clinic visit. Each consultation episode was allocated 20 min for resource scheduling purposes. This clinic was held regularly before COVID-19 (coronavirus disease 2019) led to a temporary change in the clinical practice landscape in Singapore. Each MDT session was preceded by a genitourinary tumour board for a paper-based case discussion, together with mandated central pathological and radiological review.

With IRB approval, patient information was obtained from electronic case records. The patients' treatment plans were reviewed and assessed if they had adhered to recommended first-line therapies based on current guidelines.[8-9] The time savings to the patient from the MDT service were also approximated, assuming that a reduction of one clinic visit was equivalent to timing savings of 75 min (comprising 15 min of clinic consult time and 60 min of travel time). Within a month of each MDT clinic visit, a patient survey was administered by phone interview comprising three standardized questions. The responses were scored on a Likert scale ranging from 1 (very unsatisfied) to 5 (very satisfied). The three questions specifically enquired if patients found the MDT clinic session informative and reassuring, if there was travel time saved, and whether the MDT session facilitated the decision making and shortened the time needed to commencement of treatment (Supplementary Table 1).

Results

Fifty patients who attended our MDT clinic were included in our analysis. Their median age was 70 years (range 35–88 years) and 86% were male (43/50). Thirty-three (66%) lived within 5 km of our hospital. The distribution of cases included prostate cancers (46%), urothelial cancers (26%) and renal cell carcinoma (12%) as the most frequent tumour types (Table 1). 20 patients (40%) had metastatic (stage 4)

Table 1. Baseline Characteristics of Patients Attending our Multi-Disciplinary Clinic.

Median age, years (range)	70 (35–88)
Gender, n (%)	
Male	43 (86)
Female	7 (12)
Ethnicity, n (%)	
Chinese	40 (80)
Malay	7 (14)
Indian	3 (6)
Type of urological malignancy, n (%)	
Prostate	23 (46)
Urothelial	13 (26)
Bladder	9 (18)
Upper tract	4 (8)
Renal	6 (12)
Testis	3 (6)
Penis	1 (2)
Others	4 (8)
Median number of days from clinic visit to initiation of treatment, n (range)	8 (0–30)

disease. The median time from MDT to therapy initiation was 8 days (range 0–30 days). Figure 1 depicts the various treatment modalities that were recommended and actualised by patients who attended our MDT clinic. Among those with prostate, urothelial, renal and testicular malignancies, 71% (32/45) of our patients received treatment that were in accordance to guideline recommendations, with a median of one clinic visit after MDT, prior to formal initiation of appropriate therapy. The remaining 29% (13/45) of patients chose to decline or defer therapies offered to them. Four patients were enrolled into clinical trials incorporating immuno-oncology agents as systematic therapy for metastatic bladder cancer (n = 2) and adjuvant therapy for high-risk clear cell renal cell carcinoma (n = 2) after curative resection. A total of 437 min of clinic time and 1860 min of travel time were saved (16 min and 64 min per patient respectively). Of the telephone survey, the mean score of all three questions was 4 (Table 2), representing a response equivalent to 'satisfactory'.

Discussion

Our current model of care in patients with urological malignancies relates to an academic paper discussion at a multidisciplinary genitourinary tumour board with necessary pathological and radiological review. In this traditional model, the patients' case details are discussed at a separate meeting and the key decision-making treatment process often occurs without physical consultation of the patient. The multi-disciplinary team approach has been shown to affect diagnostic and management decisions in urological malignancies where there is a benefit for multi-disciplinary input and collaboration.[10] Jang et al. previously analysed the Surveillance, Epidemiology and End Results-Medicare linked database and found a strong correlation between the type of specialist that was visited, and the type of prostate cancer treatment subsequently received for organ confined disease.[11] Hence, patient preferences for treatment were very much influenced by specialist type at the initial consult, and that a significant proportion of men did not have the benefit of a multi-speciality consult prior to treatment initiation. These findings underscore the importance of providing a balanced viewpoint of the treatment options to the patient, especially in disease types where there is a lack of clinical superiority of one treatment modality over another.[12]

Our current study describes the outcomes of the MDT process in our unit where the process of multi-disciplinary clinical collaboration is multi-faceted. Firstly, the initial multi-disciplinary discussion and central review of pathology and radiology provides the platform for accuracy and consistency in diagnosis and staging, while serving as an educational opportunity to residents in training. Secondly, it provides an opportunity for each relevant speciality to pursue meaningful discussions in person with the patient. For example, in muscle-invasive bladder cancer where staged treatment protocols are indicated (e.g. neoadjuvant therapy prior to radical cystectomy), there is facilitation of patient and physician(s) communication in this setting. In addition, there is also facilitation of inter-speciality scheduling and resourcing which would, otherwise, require more coordination in a historical linear model. The other specific benefits to the patient include a short time interval to initiation of treatment and indicates an attempt towards more expeditious cancer treatment in a public healthcare system which is consistently challenged with resourcing and wait time.[13] The timing savings that are approximated have positive implications on patients who are still in employment and require time off work. For care-givers accompanying the patients at these MDT sessions, the time

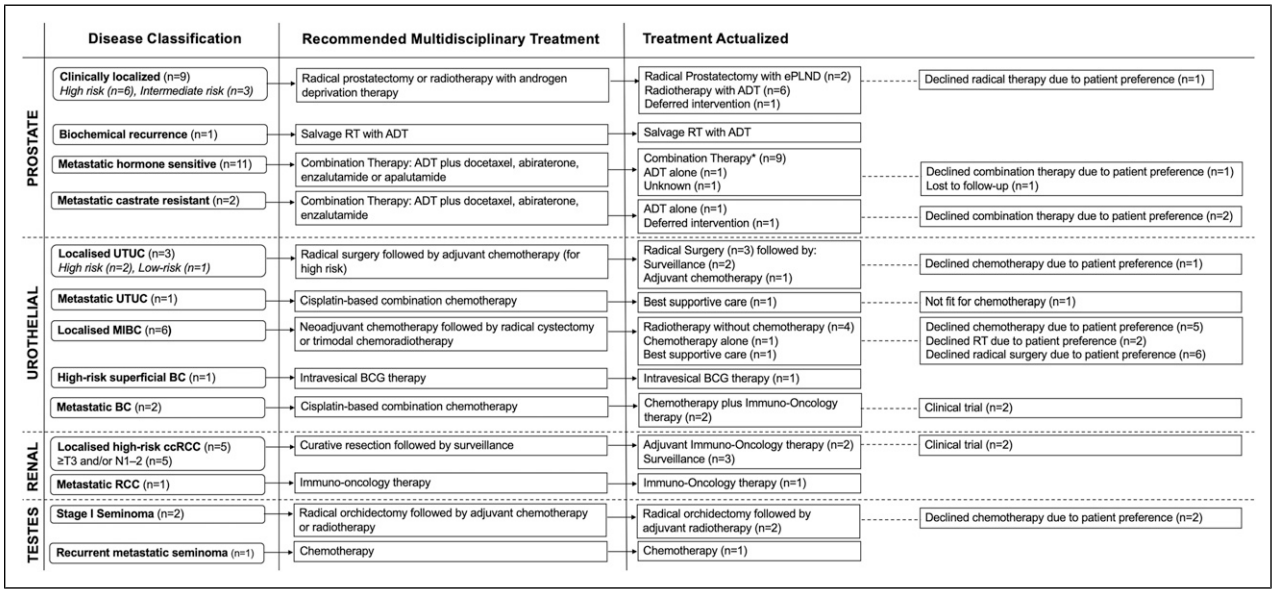

Figure 1. Schematic depicting the distribution and recommended treatment modalities of the most common urological cancers. *Combination therapy refers to androgen-deprivation therapy plus docetaxel, abiraterone, enzalutamide or apalutamide. ADT: androgen-deprivation therapy, BC: bladder cancer, BCG: bacillus calmette guerin, ccRCC; clear cell renal cell carcinoma, ePLND: extended pelvic lymph node dissection, MIBC: muscle-invasive bladder cancer, RT: radiotherapy, UTUC: upper tract urothelial carcinoma.

Table 2. Results from Patient Satisfaction Survey.

The multi-disciplinary clinic was informative and I found it reassuring for me and my family	N (%)
Very unsatisfied	0
Unsatisfied	0
Neutral	1 (6)
Satisfied	10 (59)
Very satisfied	6 (35)
I felt the multi-disciplinary clinic helped save time that was required to travel to another institution	
Very unsatisfied	0
Unsatisfied	1 (6)
Neutral	1 (6)
Satisfied	5 (29)
Very satisfied	10 (59)
I felt that the multi-disciplinary helped to speed up time to receiving treatment	
Very unsatisfied	1 (6)
Unsatisfied	0
Neutral	1 (6)
Satisfied	10 (59)
Very satisfied	5 (29)

savings to these individuals also apply, and the totality of effect is magnified as a system. Hence, the cost savings of this new initiative is difficult to quantify exactly, as the quantum extends beyond the calculable expenditure reductions in trip and consult savings.

Our patient-reported survey also suggests that the MDT clinic is well-received and affords convenience to the patient and care-giver. We postulate that the multi-disciplinary platform that affords in-person consult promote trust between the various parties and also allows the oncology team to execute best practices to foster connection and trust with patients.[14] Patient involvement in the decision-making process also helps in establishment of trust in the physician-patient relationship.[15] Only one patient reported feeling very unsatisfied with regard to the MDT reducing time to treatment. It is possible that the patient expected a recommendation to be made on his behalf during the clinic visit. However, the team maintained the need for the individual decision making by the patient. Hence, this led to a discrepancy in expectations.

However, the MDT approach does not ensure that all evidence-based recommendations are adopted, and treatment 'deviation' occurred in about 29% of cases, largely reflecting the decisions made by the individual patients. While there is evidence of alignment in priorities between patient and physician in prostate cancer treatment, other social and cultural factors may also be contributory especially in a multi-racial practice.[16] Hence, the MDT approach ensures ease of access to information and also treatment resources in our practice. The incremental benefit of the MDT clinic over the traditional linear approach is difficult to quantify precisely as it is not possible to conduct a randomised comparison between the two, in light that MDT board meetings are already highly prevalent in practice.

Several tertiary institutions around the world have already employed multi-disciplinary approaches towards providing holistic care for oncological patients. A group from Thomas Jefferson University had previously reported their 15- year experience in establishing a multi-disciplinary cancer clinic and demonstrated that their 10-year survival data for high-risk, locally advanced prostate cancer had exceeded that of the SEER cohort.[5] Arguably, there is likely selection bias and confounding factors which cast doubt on the true impact of the MDT clinic on their reported oncological outcomes. Men diagnosed with low-risk prostate cancer who attended the multi-disciplinary clinic at academic centres affiliated with Harvard Medical School were also more likely to choose active surveillance compared to those who were treated by individual practitioners in separate settings, thereby suggesting that multi-disciplinary clinics may reduce physician bias.[6] Kulkarni and colleagues also reported that bladder-sparing trimodal therapy yielded comparable survival outcomes to those of matched patients who underwent radical cystectomy, in setting of a multi-disciplinary bladder cancer clinic where patients were evaluated by urologic, radiation and medical oncologists.[17]

Several limitations have to be addressed. Follow-up on oncological outcomes and further comparative studies using historical or parallel cohorts are warranted. While a matched analysis will allow for more robust and scientific comparison, confounding factors due to the heterogeneous profile of the patients seen in the MDT clinic may unfairly influence the comparative analysis. Moreover, it is important to distinguish the benefit of multi-disciplinary discussion from multi-disciplinary consultation. The former ensures that the patient's disease is appropriately diagnosed and staged, while the latter ensures that the patient is given a fair representation of the available treatment options. In our study, time-savings calculations were merely estimations for consultation and travel time between each institution. While our sample size is small, this pilot initiative serves as a stepping stone for further expansion of this multi-disciplinary service locally. Importantly, multi-disciplinary clinics require dedicated resources and commitments from various speciality physicians and is seen as inefficient given that only a limited number of patients can be seen.[4] It is also recognised that significant administrative and logistical coordination is required to sustain the MDT clinic between three different specialities.

Our MDT clinic was held monthly and were able to cope comfortably with 10 cases per session due to a stringent inclusion criterion. For holistic oncology care, our centre is working towards the future involvement of specialist cancer nurses, social workers and other allied healthcare workers.

Lastly, the oncological benefit of the MDT clinic is difficult to ascertain as there is significant evolution of treatment modality with time, and patient prognosis is also largely dependent on disease characteristics and response to treatment.

Conclusion

In conclusion, a one-stop MDT clinic provides patients with multi-disciplinary care, improved access to subsequent therapy, better time efficiency and high patient satisfaction scores. More studies are warranted to demonstrate its clinical significance on oncological outcomes.

Author Contributions

Alvin Lee: formal analysis, writing – original draft. R Tiwari: formal analysis, writing – original draft. SH Neo: Writing – review and editing. D Huned: Writing – review and editing. A Kumaran: Writing – review and editing. CLW Lim: Writing – review and editing. Melvin LK Chua: conceptualisation, writing – review and editing. R Kanesvaran: conceptualisation, writing – review and editing. Lee LS: conceptualisation, writing – review and editing. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Informed Consent

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Data Availability

The datasets generated and/or analysed during the current study are not available.

ORCID iDs

Alvin Y Lee https://orcid.org/0000-0003-3585-5431
Lui Shiong Lee https://orcid.org/0000-0002-8208-0635

Supplemental Material

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