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EAU and NICE guidelines for the diagnosis and management of prostate cancer. How wide is the channel?

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Abstract

Background: Prostate cancer is the most common cancer in men in Europe. Both the European Association of Urologists (EAU) and the National Institute of Clinical Excellence (NICE) provide evidence-based guidelines for the diagnosis and management of prostate cancer. NICE is a national body involved in the production of efficacious guidelines for a wide spectrum of diseases across many specialities, whereas EAU is a specialist body of urologists and members of the urology multidisciplinary team across Europe. This paper describes the areas of agreement and explains the variations between these two often-quoted documents.

Objectives: The objective of this paper is to review the guidelines of prostate cancer and to offer a comparison of prostate cancer guidance management for urologists and associated healthcare professionals.

Conclusion: Both guidelines agree on areas of established consensus, especially in the diagnosis and staging of prostate cancer. There are however differences in the treatment algorithms, especially in advanced and metastatic disease. The differences in general seem to be due to the different functions and make-ups of the two bodies rather than disagreement on current evidence.

Keywords

Prostate cancer, guidelines, EAU, NICE, review

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Introduction

Prostate cancer (PCa) is the most common cancer in men both in the United Kingdom (UK) and Europe, accounting for 26% of all male cancer diagnoses in the UK.[1–3] Both the National Institute of Clinical Excellence (NICE) and the European Association of Urologists (EAU) have produced evidence-based guidelines outlining the diagnosis and management of the disease.[4] It is important to note the NICE guidelines outline the most efficacious and cost-effective method of delivering a service in the UK. Individual advances are reviewed separately and review of PCa services happens infrequently. This differs from the EAU guidelines, which are constantly under revision with new publications each year but don't include a cost assessment in part because healthcare cost varies so widely across the many countries using the guidelines.

Diagnosis and screening

In PCa much of the controversy lies in early detection and screening of the disease. The EAU guidelines and NICE guidance both advise against population screening. However, neither group have gone as far as the United States Preventive Services Task Force (USPSTF), which advise against all prostate-specific antigen (PSA) screening.[5] Current National Health Service (NHS) guidance suggest men over the age of 50 years and those at increased

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Table 1. Risk stratification for localised prostate cancer.[4]

Risk level	PSA		Gleason score		Clinical stage
Low	**<10 ng/ml**	**And**	**<7**	**And**	**T1–T2a**
Intermediate	**10–20 ng/ml**	**Or**	**7**	**Or**	**T2b**
High	**>20 ng/ml**	**Or**	**8–10**	**Or**	**T2c**

PSA: prostate-specific antigen.

Table 2. Table for guidelines for staging prostate cancer (EAU).[4]

Low-risk localised PCa
No additional imaging is recommended for staging purposes.
Intermediate-risk PCa
In predominantly Gleason pattern 4, bone scan and cross-sectional imaging is required.
High-risk localised PCa/High-risk locally advanced PCa
Prostate mpMRI should be used for local staging.
CT or MRI and bone-scan should be used in staging.
For up-front staging, PET-scanning should not be used.

CT: computed tomography; EAU: European Association of Urologists; GR: grade of recommendation; LE: level of evidence; mpMRI: multiparametric magnetic resonance imaging; PCa: prostate cancer; PET: positron-emission tomography.

risk should have access to PSA testing after appropriate counselling.[6] The EAU guidelines suggest the use of individualised, risk-adapted screening strategies, with PSA testing in patients with high-risk factors, to increase the diagnosis of early disease. Both groups recognise the risk of over-diagnosis and the need to ensure that this does not result in over-treatment.

Biopsy is considered if the PSA is above the age-adjusted normal or in the presence of an abnormal digital rectal examination (DRE). Although common practice the use of pre-biopsy magnetic resonance imaging (MRI) is not supported by either the EAU or NICE guidelines. Staging is based on PSA, clinical stage and Gleason score. In addition, the EAU guidelines incorporated the International Society of Urological Pathology (ISUP) Grade groups described since the NICE guidelines were last updated.[7] The guidelines agree on the risk stratification as shown in Table 1.

Staging

The staging of PCa involves radiological imaging to determine if the cancer is local or advanced PCa. The two guidelines differ slightly in how they recommend this to be undertaken. Although both offer blanket guidelines to all risk groups, stating that further staging imaging should be undertaken only if it affects the management plan, EAU gives a more detailed imaging structure for different risk groups as shown in Table 2. Interestingly, both groups thought the supporting evidence that pre-treatment multiparametric MRI improved outcomes was of low quality. Neither group supported a role for positron-emission tomography (PET)-scanning.

Treatment

Low-risk localised PCa. In patients with low-risk disease who would be considered fit for radical treatment at a later stage, active surveillance (AS) is an appropriate management plan for both the EAU and NICE. The objective is to avoid unnecessary treatment of men with indolent disease. Although there is a lack of consensus internationally about AS, NICE has published clear guidelines (Table 3) as to how men should be managed based on a survey of current UK practice and a Delphi consensus involving healthcare professionals and patients. In addition, the NICE guidance suggests all men with low-risk disease should be offered AS and be considered for active treatment only if they progress or are unable to contemplate this treatment plan. The EAU guidance suggests all the treatment options should be discussed including the significant risk of over-treatment.

Intermediate-risk localised PCa. Both bodies agree that men with intermediate-risk prostate cancer and a life expectancy of > 10 years should be offered radical prostatectomy (RP) or radical radiotherapy (RT). NICE also states AS should be offered to those who do not wish to undergo immediate treatment based upon the data from Selvadurai et al.[8] and concerns about upward migration in Gleason scores following the ISUP 2005 consensus meeting resulting in a proportion of men previously classified as low risk now being classified as intermediate risk.[7]

Both the EAU and NICE guidelines state that all approaches to RP (open vs laparoscopic (lap) vs robotic (robot)) are acceptable as no one technique has shown superior oncological outcomes.[9,10] However, the EAU cautiously highlights the growing importance of robot-assisted radical prostatectomy (RARP), stating that in Europe it is fast becoming the gold standard, although it does mention

Table 3. NICE Protocol for active surveillance.

Timing	Tests
At enrolment in active surveillance	Multiparametric MRI if not previously performed[a]
Throughout active surveillance	Monitor PSA kinetics[b]
Year 1 of active surveillance	Every 3–4 months: measure PSA[c] Every 6–12 months: DRE[d] At 12 months: prostate rebiopsy[a]
Years 2–4 of active surveillance	Every 3–6 months: measure PSA[c] Every 6–12 months: DRE[d]
Year 5 and every year thereafter until active surveillance ends	Every 6 months: measure PSA[c] Every 12 months: DRE[d]

[a]If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or rebiopsy.
[b]May include PSA doubling time and velocity.
[c]May be carried out in primary care if there are agreed shared-care protocols and recall systems.
[d]Should be performed by a healthcare professional with expertise and confidence in performing DRE.
NICE: National Institute of Clinical Excellence; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; DRE: digital rectal examination.

the lack of high-quality evidence. NICE encourages the commissioning of RARP, on the basis of a decreased hospital stay and blood transfusion (open vs lap/robot) plus a decrease in the number of men with positive surgical margins (lap vs robot), and in centres which can perform at least 150 RARPs per year on the basis of cost.[11]

NICE and EAU also recommend the use of external beam radiotherapy (EBRT) and androgen-deprivation therapy (ADT) for men with intermittent disease. They agree there is no strong evidence for the benefit of one treatment over the other. NICE and EAU recommend 74 Gy and 76 Gy respectively to the prostate combined with short-course ADT (four to six months). EAU also say that patients who are unable or unwilling to receive ADT should have an increased dose of radiation (76–80 Gy).

High-risk localised and locally advanced PCa. The guidelines for high-risk cancer remain the same as for intermediate cancer as long as there is a good chance of disease control. RP is an option but there are differences over the role of adjuvant radiotherapy. NICE advise against immediate postoperative radiotherapy even to men with margin-positive disease, because of a lack of data to confirm an improvement in overall survival. The EAU advise that adjuvant EBRT should be discussed with such patients because it improves biochemical-free survival with the option to delay until the PSA rises (salvage EBRT).

In men with high-risk PCa both guidelines advise the use of long-course ADT for men undergoing EBRT treatment (two to three years rather than short course (six months)). NICE suggest that in addition to treating the prostate, pelvic radiotherapy would be appropriate in patients with a >15% risk of lymph node involvement whereas the EAU guidelines conclude there is no level 1 evidence for prophylactic whole-pelvic irradiation.[12] NICE also advocate the combination of EBRT and high-dose rate brachytherapy (HDR-BT) as a treatment option for men with both localised and locally advanced PCa.[13] Both NICE and EAU guidelines recommend that in patients with high risk, brachytherapy should not be used as a treatment on its own.

Alternative treatments. NICE and the EAU offer guidelines for the use of experimental therapies such as cryotherapy (CSAP) and high-intensity focused ultrasound (HIFU). The EAU suggest men should be warned about the lack of long-term outcome evidence regarding HIFU. CSAP can be offered as an alternate therapy for patients who aren't fit for radical RP or RT. Focal therapy is not recommended as it is still in early development. NICE specifically states not to use these experimental treatments outside clinical trials or data registries.

Treatment of side effects. All radical treatments for PCa have significant adverse effects, and both guidelines discuss them. NICE give set guidelines as for what to offer in patients with these side effects. For sexual dysfunction, it states that as well as early access to erectile dysfunction clinics, men should also be offered phosphodiesterase inhibitors.[14] If these then fail, then physical devices such as vacuum/intraurethral inserts should be offered. EAU accept that there are adverse functional outcomes to radical treatment but guidelines for intervention following treatment are covered in the relevant chapters of the guideline book.

Managing relapse after radical treatment. Both the EAU guidelines and NICE suggest decisions on further treatment after RP are not helped by MRI or biopsy of the prostatic bed. Instead men with biochemical relapse should be offered EBRT to the prostatic bed. After EBRT salvage local therapies include RP, CSAP and HIFU, but little evidence exists

to support their use, and there may be a higher risk of incontinence, impotence and rectal damage than when used as primary treatment. In addition, both groups are clear in saying to not routinely offer hormonal therapy to men with PCa who have a biochemical relapse, unless they have either symptomatic local disease progression, proven metastases, or a PSA doubling time of < 3 months.

Metastatic cancer. Although metastatic cancer is not curable, the median survival is 42 months.[15] NICE and EAU guidelines recognise the need for a multi-specialty approach including involving support care services early, so that they can be involved in care of the patient from diagnosis rather than just at the end of life. Hormonal therapy has been the standard treatment of symptoms and progression of metastatic PCa for over 50 years, and both guidelines offer bilateral orchidectomy as an option for hormonal control. EAU divide metastatic disease into symptomatic and asymptomatic patients, but state both should be offered castration in order to either palliate symptoms or to prevent progression to symptomatic disease. NICE give recommendations about the use of intermittent therapy for patients on long-term androgen-suppression therapy (rather than adjunct therapy). They state that there is limited evidence for the idea that intermittent therapy reduces side effects and advise that patients should have their PSA monitored every three months. If this rises above 10 ng/ml or symptoms progress, then they should be restarted on androgen therapy. EAU points to evidence that bilateral orchidectomy is the most cost-effective method of androgen suppression, producing the highest quality-adjusted survival, and that complete androgen blockade (a combination of both anti-androgens and androgen suppressors) is the most expensive.[16] Therefore, it is not surprising that NICE recommend that all patients with metastatic disease should be offered bilateral orchidectomy, and that combined therapy should not be offered as a first-line treatment.

Bone agents

The intravenous bisphosphonate zoledronic acid and the RANK ligand inhibitor have been marketed to reduce the number of skeletal-related events. Neither product is thought to be cost effective by NICE. The EAU guidelines confirm there is no cancer specific survival or overall survival benefit when using these drugs and also emphasise the risk of toxicity, especially jaw necrosis.[17,18]

Metastatic castration-resistant PCa (mCRPC)

The NICE PCa guidance mentions only docetaxel, but more recent advice has been given on both abiraterone[19] and enzalutamide.[20] Spicuale T is discussed in the EAU guidelines but it is not available in Europe and as a consequence has not been assessed by NICE. Both NICE and EAU recognise that docetaxel, enzalutamide and abiraterone with prednisolone are effective first-line treatments for men with mCRPC. The second-line options available will be impacted by the treatment chosen as first-line treatment for mCRPC. Generally, because of concerns about cross-resistance between hormone-manipulating agents if either abiraterone or enzalutamide were used as first-line treatment and the patient remains clinically suitable, docetaxel would be offered next. Abiraterone plus prednisolone, enzalutamide and cabazitaxel are all recognised as effective treatments for men with mCRPC after progression despite docetaxel.

Conclusion

The EAU guidelines are written by a group of clinicians reflecting all aspects of the multi-disciplinary team with patient representative support, all of whom are actively involved in treating men with PCa. The NICE guidelines are the product of a wider cohort of professionals with a minority of clinically engaged individuals. However, as both sets of guidelines are evidence based, they come to similar conclusions about the best care for men with PCa. Indeed, NICE quote the EAU guidelines on more than one occasion. They differ slightly on the use of more experimental treatments where evidence is not so robust. NICE are also less likely to recommend the use of treatments, especially when the costs are high and the benefit marginal. This is hardly surprising due to the nature of NICE as they must assess the cost to the UK healthcare system as well as the efficacy of the treatment for individuals. Both groups state that guidelines do not replace the judgement of the clinician but in the UK NICE's view drives commissioning which creates barriers to alternative practice. It must also be noted however that EAU update their guidelines every year and NICE have been updating every 6–10 years, so practitioners looking only at NICE must be advised to review individual technology appraisal assessments along with recent developments in the treatment of PCa.

Conflicting interests

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