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European Association of Urology

Guidelines

EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer

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Abstract

Objective: To present a summary of the 2016 version of the European Association of Urology (EAU) – European Society for Radiotherapy & Oncology (ESTRO) – International Society of Geriatric Oncology (SIOG) Guidelines on the treatment of relapsing, metastatic, and castration-resistant prostate cancer (CRPC).
Evidence acquisition: The working panel performed a literature review of the new data (2013–2015). The guidelines were updated, and the levels of evidence and/or grades of recommendation were added based on a systematic review of the literature.
Evidence synthesis: Relapse after local therapy is defined by a rising prostate-specific antigen (PSA) level >0.2 ng/ml following radical prostatectomy (RP) and >2 ng/ml above the nadir after radiation therapy (RT). ^{11}C-choline positron emission tomography/computed tomography is of limited importance if PSA is <1.0 ng/ml; bone scans and computed tomography can be omitted unless PSA is >10 ng/ml. Multiparametric magnetic resonance imaging and biopsy are important to assess biochemical failure following RT. Therapy for PSA relapse after RP includes salvage RT at PSA levels <0.5 ng/ml and salvage RP, high-intensity focused ultrasound, cryosurgical ablation or salvage brachytherapy of the prostate in radiation failures. Androgen deprivation therapy (ADT) remains the basis for treatment of men with metastatic prostate cancer (PCa). However, docetaxel combined with ADT should be considered the standard of care for men with metastases at first presentation, provided they are fit enough to receive the drug. Follow-up of ADT should include analysis of PSA, testosterone levels, and screening for cardiovascular disease and metabolic syndrome. Level 1 evidence for the treatment of metastatic CRPC (mCRPC) includes, abiraterone acetate plus prednisone (AA/P), enzalutamide, radium 223 (Ra 223), docetaxel at 75 mg/m^2 every 3 wk and sipuleucel-T. Cabazitaxel, AA/P, enzalutamide, and radium are approved for second-line

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treatment of CRPC following docetaxel. Zoledronic acid and denosumab can be used in men with mCRPC and osseous metastases to prevent skeletal-related complications.
Conclusions: The knowledge in the field of advanced and metastatic PCa and CRPC is changing rapidly. The 2016 EAU-ESTRO-SIOG Guidelines on PCa summarise the most recent findings and advice for use in clinical practice. These PCa guidelines are the first endorsed by the European Society for Therapeutic Radiology and Oncology and the International Society of Geriatric Oncology and reflect the multidisciplinary nature of PCa management. A full version is available from the EAU office or online (http://uroweb.org/guideline/prostate-cancer/).
Patient summary: In men with a rise in their PSA levels after prior local treatment for prostate cancer only, it is important to balance overtreatment against further progression of the disease since survival and quality of life may never be affected in many of these patients. For patients diagnosed with metastatic castrate-resistant prostate cancer, several new drugs have become available which may provide a clear survival benefit but the optimal choice will have to be made on an individual basis.

1. Introduction

A prior summary of the European Association of Urology (EAU) Guidelines on prostate cancer (PCa) was published in 2013 [1]. This paper summarises the many changes that have occurred in the treatment of metastatic, relapsing, and castration-resistant PCa (CRPC) over the past 3 yr. The Guidelines on screening, diagnosis, and treatment of clinically localised and locally advanced PCa were published in a separate paper [2]. To facilitate evaluation of the quality of the information provided, levels of evidence (LEs) and grades of recommendation (GRs) have been inserted according to the general principles of evidence-based medicine [3].

2. Diagnosis and treatment of relapse after curative therapies

Physicians treating patients with prostate-specific antigen (PSA)–only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding overtreatment of patients whose disease may never affect their overall survival (OS) or quality of life (QoL). It has to be emphasised that treatment recommendations for these patients should be given after discussion with a multidisciplinary team.

2.1. Definitions

Following radical prostatectomy (RP), biochemical recurrence (BCR) is defined by two consecutive rising PSA values >0.2 ng/ml [4]. After primary radiation therapy (RT), the Radiation Therapy Oncology Group (RTOG) and American Society for Radiation Oncology Phoenix Consensus Conference definition of PSA failure is any PSA increase ≥2 ng/ml higher than the PSA nadir value, regardless of the serum concentration of the nadir [5]. Importantly, patients with PSA recurrence after RP or primary RT have different risks of subsequent PCa-specific mortality. For both groups, however, men with a PSA doubling time (PSA DT) of <3 mo, stage T3b or higher, Gleason score 8–10, and time to BCR of <3 yr represent a subgroup with a high risk of developing metastases and dying from PCa [6–9].

2.2. Staging

Because biochemical recurrence (BCR) after RP or RT precedes clinical metastases by 7–8 yr on average, the diagnostic yield of common imaging techniques is poor in asymptomatic patients [10].

In men with PSA-only relapse after RP, the probability of a positive bone scan is <5% if the PSA level is <7 ng/ml [11]. Consequently, bone scan and abdominopelvic computed tomography (CT) should be considered only for patients with BCR after RP who have a high baseline PSA (>10 ng/ml) or high PSA kinetics (PSA DT <6 mo) or in patients with symptoms of bone disease [11]. Although its sensitivity is low when the PSA level is <1 ng/ml, choline positron emission tomography (PET)/CT may be helpful in selecting patients for salvage therapy after RP [12], especially if PSA DT is <6 mo [13]. Salvage RT (SRT) after RP is usually decided on the basis of BCR, without imaging.

In patients with BCR after RT, the biopsy status is a major predictor of outcome, provided the biopsies are obtained 18–24 mo after treatment. Given the morbidity of local salvage options, it is necessary to obtain histologic proof of the local recurrence before treating the patient [10]. Multiparametric magnetic resonance imaging (MRI) has yielded excellent results in detecting local recurrences [10,14] and can be used for biopsy targeting and guidance of local salvage treatment. Detection of local recurrence is also feasible with choline and acetate PET/CT, but PET/CT has poorer spatial resolution than MRI [15,16].

2.3. Management of prostate-specific antigen relapse following radical prostatectomy

Early SRT provides a possibility of cure for patients with an increasing PSA after RP. More than 60% of patients who are treated before the PSA level rises to >0.5 ng/ml will achieve an undetectable PSA level [17], providing patients with an 80% chance of being progression-free 5 yr later [18]. The addition of androgen deprivation therapy (ADT) to salvage

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