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European Association of Urology

Guidelines

Guidelines on Testicular Cancer: 2015 Update

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Abstract

Context: This is an update of the previous European Association of Urology testis cancer guidelines published in 2011, which included major changes in the diagnosis and treatment of germ cell tumours.
Objective: To summarise latest developments in the treatment of this rare disease. Recommendations have been agreed within a multidisciplinary working group consisting of urologists, medical oncologists, and radiation oncologists.
Evidence acquisition: A semi-structured literature search up to February 2015 was performed to update the recommendations. In addition, this document was subjected to double-blind peer review before publication.
Evidence synthesis: This publication focuses on the most important changes in treatment recommendations for clinical stage I disease and the updated recommendations for follow-up.
Conclusions: Most changes in the recommendations will lead to an overall reduction in treatment burden for patients with germ cell tumours. In advanced stages, treatment intensification is clearly defined to further improve overall survival rates.
Patient summary: This is an update of a previously published version of the European Association of Urology guidelines for testis cancer, and includes new recommendations for clinical stage I disease and revision of the follow-up recommendations. Patients should be fully informed of all the treatment options available to them.
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1. Introduction

Testicular cancer is a rare disease, with an incidence of up to 10 in 100 000 men. In Europe, cure rates of up to 97% for all stages have been achieved [1]. However, cure is dependent on excellent diagnosis, treatment facilities, and specialised expertise for patients with advanced disease. In the overwhelming group of patients with low-stage disease, the main goal of treatment is to reduce treatment-related long-term toxicities, including secondary cancers. Thus, regular updates of current treatment guidelines are necessary to achieve the best possible treatment outcome.

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Current evidence suggests that the best results are obtained in high-volume reference centres, not only for patients with advanced disease but also for patients with early-stage disease. Although early stages can be successfully treated in a nonreference centre, the relapse rate is higher [2]. In poor-prognosis nonseminomatous germ-cell tumours, overall survival (OS) within a clinical trial depends on the number of patients treated at the participating centre (poorer if fewer than five patients are enrolled) [3]. In the same context, the frequency of postchemotherapy residual tumour resection is associated with perioperative mortality and OS [4,5].

First analyses of a recently introduced internet-based second-opinion portal suggest that up to 40% of primary diagnoses were incorrect and treatment was changed in a considerably high number of patients after a second opinion [6].

2. Evidence acquisition

A multidisciplinary team of urologists, medical oncologists, radiation oncologists, and a pathologist were involved in producing this document, which is based on a semi-structured review of the literature up to February 2015. This publication focuses on the most important changes and relevant clinical recommendations. For unchanged recommendations, the reader is referred to the previous publication of the guidelines in *European Urology* [7]. The full version of the 2015 guidelines is available on the European Association of Urology (EAU) website (http://uroweb.org/guideline/testicular-cancer/). References were assessed according to their level of scientific evidence, and guideline recommendations were graded according to a system modified from the Oxford Centre for Evidence-based Medicine levels of evidence [8].

Table 1 – Recommended tests for staging at diagnosis

Test	Recommendation	GR
Serum tumour markers	α-Fetoprotein hCG Lactate dehydrogenase	A
Abdominopelvic CT	All patients	A
Chest CT	All patients	A
Testis ultrasound (bilateral)	All patients	A
Bone scan or spinal MRI	In the case of symptoms	
Brain scan (CT/MRI)	In the case of symptoms and patients with metastatic disease with multiple lung metastases and/or high β-hCG levels	
Further investigations		
Fertility investigations: Total testosterone Luteinising hormone Follicle-stimulating hormone Semen analysis		B
Sperm banking	Should be offered	A

GR = grade of recommendation; hCG = human chorionic gonadotrophin; CT = computed tomography; MRI = magnetic resonance imaging.

3. Evidence synthesis

3.1. Diagnosis of testicular cancer

It is very important to correctly classify a patient with a newly diagnosed germ-cell cancer. Ultrasound (US) of both testis remains the cornerstone of primary imaging in patients with testicular tumours followed by computed tomography (CT) of the abdomen and chest as subsequent staging tools (Table 1). Correct interpretation of tumour markers before and after orchiectomy in conjunction with CT findings allows correct patient classification according to TNM and Union for International Cancer Control staging (Tables 2 and 3) [9]. Patients with metastatic disease should be classified according to the International Germ Cell Cancer Collaborative Group (IGCCCG) [10] to tailor further treatment (Table 4).

3.2. Diagnosis and treatment of testicular intraepithelial neoplasia (TIN)

Contralateral biopsy has been advocated to rule out the presence of TIN [11]. Although systematic contralateral biopsy is routine policy in some countries, the low incidence of TIN (up to 9%) and contralateral metachronous testicular tumours (~2.5%) [12,13], the morbidity associated with TIN treatment, and the low stage of most metachronous tumours at presentation mean that biopsy recommendation for all patients is controversial.

It is still difficult to reach a consensus on whether the existence of contralateral TIN must be identified in all cases. However, biopsy of the contralateral testis should be offered to patients at high risk of contralateral TIN (testicular volume <12 ml, history of cryptorchidism, or poor spermatogenesis with Johnson score 1–3). A contralateral biopsy is not necessary in patients older than 40 yr without risk factors [14,15]. A double biopsy increases sensitivity [14]. Patients should be informed that a testicular tumour may arise in spite of a negative biopsy.

When TIN is diagnosed, local radiotherapy (16–20 Gy in fractions of 2 Gy) is the treatment of choice in the case of a solitary testis. Testicular radiotherapy in a solitary testis will result in infertility and a higher long-term risk of Leydig cell insufficiency [16,17]. Fertile patients who wish to father children may delay radiation therapy and can be followed with regular testicular US [14].

If TIN is diagnosed and the contralateral testis is healthy, the options for management are orchiectomy or close observation (with a 5-yr risk of developing testicular cancer of 50%).

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

In stage I seminoma, tumour size (>4 cm) and invasion of the rete testis have been identified as predictors of relapse in a pooled analysis. However, these risk factors have not been validated in a prospective setting, although the

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