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Retroperitoneal Lymph Node Dissection for the Primary Treatment Recommendation in Clinical Stage I Nonseminomatous Germ Cell Tumors of the Testis: Contrary to European Guidelines

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Abstract

Context: The optimal management strategy for clinical stage I (CS1) nonseminomatous germ cell tumors (NSGCTs) of the testis is controversial.
Objective: Evidence is presented to suggest that retroperitoneal lymph node dissection (RPLND) is among the primary treatment options in the management of CS1 NSGCTs.
Evidence acquisition: A nonsystematic search performed in January 2011 was used to identify relevant literature regarding advantages of RPLND as the primary adjuvant therapy for CS1 NSGCT after orchiectomy.
Evidence synthesis: European guidelines follow a risk-adapted strategy for the primary management of CS1 NSGCTs based on the presence of vascular invasion. Surveillance is recommended as the primary treatment option for the low-risk group, whereas two cycles of platin-based chemotherapy is suggested for high-risk patients. Aside from the benefits of this strategy, there are some drawbacks that surgery may ameliorate. The absence of accurate prognostic markers compels risk adaptation. The difficulties in radiologic staging of retroperitoneum, the high relapse rates in surveillance, the long-term toxicity of chemotherapy, and a teratoma component in retroperitoneal relapses are the main problems that nerve-sparing RPLND (ns-RPLND) can resolve with minimal morbidity. The ns-RPLND provides similar oncologic outcomes with better retroperitoneal staging and facilitation of follow-up for abdominal recurrences.
Conclusions: Surveillance, adjuvant chemotherapy, and ns-RPLND are all accepted treatments for long-term survival. The ns-RPLND has similar merits to surveillance and adjuvant chemotherapy and should be presented to patients as an equal option.

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1. Introduction

Testicular cancer is the most common malignancy of men between ages 20 and 34. Nonseminomatous germ cell tumors (NSGCTs) constitute 40–70% of all germ cell tumors [1]. According to European publications, 61–78% of these tumors present as clinical stage I (CS1) disease [2,3]. In the last 30 yr, we have witnessed dramatic improvement in the management of advanced testicular cancer; however, the optimal management strategy for CS1 NSGCTs is still controversial. Surveillance, primary chemotherapy, and nerve-sparing retroperitoneal lymph node dissection

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(ns-RPLND) are all accepted treatment options with long-term survival. European guidelines follow a risk-adapted treatment protocol, whereas National Comprehensive Cancer Network (NCCN) guidelines do not [4,5]. The risk is defined on the basis of vascular invasion (VI). Two cycles of platin-based chemotherapy is recommended for CS1 NSGCT patients with VI who are regarded as high risk for relapse; surveillance is preferred for patients without VI.

When survival is considered as the indicator of success, none of the three options has been shown to have any superiority over the other. Consequently, patient preferences and morbidity profiles should factor into physicians' treatment plans. Given the young patient population, long-term toxicity of the treatment modalities remains a critical consideration.

The aim of this article is not to convince readers that ns-RPLND is the only option for treating CS1 NSGCT but rather to present an evidence-based view for offering it as an option that is equal with others in the guidelines.

2. Evidence acquisition

A nonsystematic search performed in January 2011 was used to identify relevant literature regarding advantages of retroperitoneal lymph node dissection (RPLND) as the primary adjuvant therapy for CS1 NSGCT after orchiectomy.

3. Evidence synthesis

3.1. Current strategy and guidelines in the management of stage I nonseminomatous germ cell tumors

European Association of Urology (EAU) 2010 guidelines for testicular cancer recommend stratifying patients with CS1 NSGCTs into risk groups for relapse based on the VI risk factor. Patients without VI are classified as low risk, and those with VI are regarded as high risk.

Surveillance is recommended as the first choice for the low-risk group (grade B recommendation). Patients who are not willing to undergo surveillance should be treated with either chemotherapy or ns-RPLND (grade A recommendation).

Primary chemotherapy is considered the standard option for treatment of the high-risk group. This includes two courses of cisplatin, etoposide, and bleomycin (PEB). Surveillance and ns-RPLND are options that are used for conditions against chemotherapy.

In Europe, adjuvant chemotherapy is recommended for CS1 or pathologic stage IIa (PS2a) NSGCT patients. This strategy considers RPLND as a diagnostic procedure only. In the United States, however, the approach is different. The US strategy considers RPLND as a definitive therapeutic measure for PS2a NSGCTs despite relapse rates ranging from 8% to 55% [6].

3.1.1. Rationale for a surveillance strategy

The surveillance regimen for CS1 NSGCT patients was first reported in 1982 [7]. Technological advancement in imaging techniques and reliable surrogate markers ease the follow-up of these patients. Confidence in salvage chemotherapy motivated physicians to defer toxic treatment [8].

Surveillance promises cause-specific survival of 95–100% and pooled cause-specific survival of 98.6% in CS1 NSGCT patients [1]. Several authors have noted that the deaths are often those who dropped out of a surveillance schedule or who refused salvage treatment.

Risk adaptation is used for defining suitable patients for surveillance. The literature presents VI, predominance of embryonal carcinoma histology, absence of yolk sac tumor in the orchiectomy specimen, undifferentiated histology, high proliferation rate (MIB-1 score >70%), T category, and scrotal violation as negative prognostic factors. Guidelines use only VI for risk adaptation. The Spanish Germ Cell Group presented a reduction of the relapse rate to 19% in surveillance by risk-adapted management based on VI or local invasion of adjacent structures [9].

3.1.2. Rationale for adjuvant chemotherapy

Imaging techniques are insufficient for the determination of retroperitoneal micrometastasis in CS1 NSGCTs; therefore, the identification of patients at risk for relapse cannot rely on imaging. Risk stratification according to histology of the primary tumor can help. As presented by several reports, long-term survival after administration of two cycles of adjuvant PEB is excellent [10,11]. EAU guidelines recommend two cycles of adjuvant chemotherapy for CS1 NSGCT patients with VI. This proven modality has a 95–97% relapse-free rate and a 100% overall survival rate.

Adjuvant chemotherapy spares additional surgery; with such a success rate, poor compliance with a follow-up schedule loses importance. To decrease chemotherapy-related adverse effects, a single adjuvant PEB course is suggested by European groups. It has been shown that an excellent outcome with reduced morbidity can be achieved with this approach [12,13].

3.1.3. Rationale for retroperitoneal lymph node dissection

The role of primary RPLND for CS1 NSGCT has been demonstrated in the literature. Because 25% of patients are upstaged with RPLND, it is best as a staging modality with modest therapeutic success. Especially for low-volume nodal disease, RPLND is curative in most patients and reduces potential for late relapse. The retroperitoneum is the initial site of metastatic spread in >80% of patients, and it is also the most frequent spread site for chemoresistant malignant germ cell cancer and teratoma [14].

Stephenson et al investigated the impact of patient-selection criteria on the outcome of patients with NSGCTs in a group of 453 patients who were treated with RPLND between 1989 and 2002. The authors excluded patients with persistent elevation of serum tumor markers after orchiectomy and patients with clinical stage IIb after 1999. These exclusions caused an increase in pathologic stage II (PS2) patients (from 40% to 64%, $p = 0.01$); however, the teratoma rate did not differ (21% vs 22%, $p = 0.89$). Additionally, the detection rate for pathologic stage I