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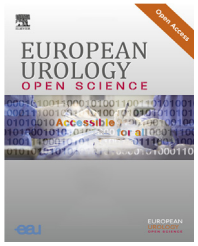

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Open to Debate: For

Retroperitoneal Lymph Node Dissection Should Be a Standard-of-Care Treatment Option For Stage II Seminoma

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The trifecta for contemporary management of germ cell tumor (GCT) includes oncologic efficacy, mitigation of treatment-related morbidity, and improvement of long-term survivorship. The current standard management options for seminomatous GCTs with radiographically enlarged retroperitoneal lymph nodes (stage IIA/B) include multicycle chemotherapy and regional radiation therapy. Robust long-term data support the oncologic efficacy of both modalities in managing early disseminated seminoma, with upwards of 90% of patients experiencing a cure [1]. However, mounting evidence proves that such therapies impose an undue treatment-related burden on patients, with their toxic effects especially relevant because of the long life expectancy of a uniquely young cancer population. Such morbidities, including cardiovascular disease, metabolic syndrome, pulmonary toxicity, nephropathy, ototoxicity, lower fertility, and the risk of secondary malignancies, are a detriment to quality of life and cancer survivorship [2].

In an effort to achieve oncologic cure while minimizing morbidity, retroperitoneal lymph node dissection (RPLND) has been proposed as a stand-alone treatment option for clinical stage II seminoma with limited retroperitoneal lymphadenopathy. The notion of offering surgery in the primary setting for stage II seminoma stems from the proven efficacy of RPLND for nonseminoma in equivalent disease stages. In these patients, surgery results in disease-free survival rates approaching 80% [3]. These data support the notion of offering RPLND to cure the majority of patients with stage IIA/B seminoma, which is a histology with a predictable pattern of lymphatic spread, resulting in a significant proportion of patients with regional disease confined within the retroperitoneum.

It is worth contextualizing the contemporary outcomes of RPLND when discussing this operation as a treatment to supersede systemic therapy. Advances in surgical techniques and a better understanding of the retroperitoneal anatomy have both resulted in a significant reduction in the morbidity of this procedure. This includes template-based approaches and an emphasis on nerve preservation, which have minimized ejaculatory dysfunction rates, especially in the primary setting [4]. Moreover, novel surgical approaches such as the midline extraperitoneal technique have minimized hospital stays, eliminated the risk of bowel complications (ileus and bowel obstruction), and minimized postoperative complication rates [5]. Thus, in the modern surgical era, RPLND is safe and is associated with short hospitalizations and few long-term complications. Such excellent outcomes strongly argue that RPLND could serve as an excellent chemotherapy- or radiotherapy-sparing modality for stage IIA/B seminoma.

To evaluate these outcomes, several clinical studies have investigated and ultimately supported the role of RPLND in early metastatic seminoma. Warszawski and Schmucking [6] evaluated 63 patients who underwent RPLND for stage

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I and II seminoma. At 79-mo follow-up, only 5.7% had developed recurrence, with no patient developing an in-field recurrence. In this study, despite the lower efficacy of RPLND with larger nodal disease (>2 cm), ~50% of the patients remained disease free and thus avoided chemotherapy [6]. Similar results were reported by Mezvrishvili and Managadze [7], who described the outcomes for ten patients with high-risk stage I seminoma and four patients with stage IIA disease who underwent primary RPLND. All patients in this cohort remained disease-free at a median of 56-mo follow-up [7]. Hu et al [8] also demonstrated excellent oncologic efficacy of primary RPLND in four patients with stage IIA/B seminoma, with no disease recurrence noted at 25-mo follow-up and all patients maintaining antegrade ejaculation.

Ultimately, changes in practice paradigms require high-level evidence, and this has been provided by early results from three clinical trials examining the role of surgery in early metastatic seminoma. SEMS (Surgery in Early Metastatic Seminoma), a multi-institutional phase 2 clinical trial, enrolled patients with testicular seminoma and small-volume retroperitoneal disease (<3 cm) with normal tumor markers to undergo primary RPLND [9]. The primary endpoint was 2-yr recurrence-free survival. The study accrued 55 patients from 12 institutions and demonstrated 2-yr recurrence-free survival of 81% and overall survival of 100%. Patients who developed recurrence were successfully treated with chemotherapy (10/55) or additional surgery (2/55), suggesting that cure can still be achieved even in patients who experience recurrence after RPLND. In addition, only 7% of patients experienced long-term complications, which were limited to anejaculation and incisional hernias [9]. PRIMETEST is another ongoing phase 2 clinical trial evaluating the role of unilateral template (open or robotic) RPLND for lymph node–positive seminoma cases for which adjuvant treatment was not planned [10]. The trial included patients with <5 cm retroperitoneal disease and patients with recurrence after single-dose carboplatin. The interim analysis reported by the investigators demonstrated promising results, with a 2-yr recurrence-free survival rate of 71%. In addition, all disease recurrences were successfully managed with systemic therapy. For the COTRIMS trial, Heidenreich et al [11] reported a relapse rate of 9.5% (two of 21) at mean follow-up of 20 mo in a cohort undergoing RPLND for stage IIA/B Seminoma. Taken together, these studies demonstrate that RPLND has significant disease-free survival rates and eliminates the need for chemotherapy in the majority of patients.

It is also worth highlighting the potential of the promising miRNA-371 biomarker to improve GCT management and patient selection for RPLND, including in stage II seminoma. In early studies, this GCT-specific biomarker had superior accuracy to conventional modalities in identifying active germ cell disease. If the accuracy of this biomarker is confirmed in clinical trials, microRNA-371 would aid in identifying seminoma patients with low-volume retroperitoneal disease currently missed on conventional imaging (occult retroperitoneal disease). These patients could potentially be offered earlier RPLND with high confidence of achieving a cure and avoiding chemotherapy.

In conclusion, the tides are changing and the goals of therapy for GCTs have shifted to emphasize the lowest accumulation of toxic modalities while retaining near-perfect long-term cure rates. We can no longer consider the long-term toxicities of chemotherapy or radiation therapy as acceptable collateral damage in the treatment of limited regional disseminated seminoma. Mounting evidence demonstrates that RPLND is the ideal first-line treatment modality for stage IIA/B seminoma with minimal long-term morbidity.

Conflicts of interest: Siamak Daneshmand is the principal investigator for the SEMS trial. The authors have no other relevant conflicts of interest to disclose.

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