The Role of Postchemotherapy Surgery in Germ Cell Tumors

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KEYWORDS

• Germ cell tumors • Chemotherapy • Lymph node dissection • Testicular cancer

KEY POINTS

- Retroperitoneal lymph node dissection (RPLND) after chemotherapy has a proved role in the staging and treatment of metastatic testicular cancer.
- Complete removal of all postchemotherapy residual masses in nonseminomatous germ cell tumor (NSGCT) should be performed.
- Complete removal of positron emission tomography (PET)-avid masses greater than 3 cm in pure seminoma should be performed.
- Outcomes depend on patient selection and extent of surgery.

The first retroperitoneal lymph node dissection (RPLND) was performed in Paris in 1905.[1] Its use did not become popularized until the 1940s, when the results of young men treated at Walter Reed Army Medical Center were published. Since then, the use of RPLND in the treatment of testis cancer has evolved. RPLND was once associated with substantial complications, but the technique has since been refined, with improvement in patient outcomes. Additionally, older chemotherapy treatments for metastatic testicular cancer had significant toxicity. The introduction of cisplatin-based chemotherapy in the treatment of metastatic testicular cancer resulted in improved patient survival. Recent data have demonstrated that a stage migration has occurred, with more patients presenting with clinical stage I disease.[2,3] Additionally, active surveillance has become the standard treatment of clinical stage I disease, resulting in fewer therapies aimed at regional treatment, such as primary RPLND, performed for NSGCT or adjuvant radiotherapy for seminoma.[4]

A substantial number of men with metastatic testicular cancer, however, have residual disease after the administration of chemotherapy. The majority of this residual disease is located in the retroperitoneum. Another subset of men are those with clinical stage I disease on surveillance who relapse and are treated with induction chemotherapy and possibly require subsequent resection. As such, a majority of RPLNDs performed today are in the postchemotherapy setting. This article focuses on the rationale, approach, outcome, morbidity, and follow-up of postchemotherapy RPLND (PC-RPLND).

CLASSIFYING POSTCHEMOTHERAPY RETROPERITONEAL LYMPH NODE DISSECTION

The Indiana University provided definitions of categories of PC-RPLND that are clinically useful and allow meaningful comparisons of outcome.[5] Standard RPLND is performed in patients presenting

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with disseminated disease that after chemotherapy have normal serum tumor markers (STMs) and only retroperitoneal residual disease on imaging. Other situations are more complex. Salvage RPLND refers to cases of patients having received second-line chemotherapy, either with other cisplatin-based chemotherapy regimen or high-dose chemotherapy with bone marrow support, and having normal STMs. Desperation RPLND refers to cases of, despite second-line chemotherapy, RPLND performed in a setting of persistently elevated STMs. Redo RPLND is resection performed after previous surgery for an in-field recurrence. Lastly, unresectable RPLND is the setting where disease found at time of surgery itself is determined as unresectable.

RATIONALE FOR SURGERY AFTER CHEMOTHERAPY

The rationale for PC-RPLND is based on 4 principles. PC-RPLND (1) is diagnostic of the histology of the residual mass, (2) has therapeutic benefit, (3) is the preferred management of teratoma, and (4) has decreasing morbidity.

PC-RPLND establishes if the residual mass contains (1) necrosis/fibrosis, (2) teratoma, (3) viable germ cell carcinoma, or (4) non–germ cell carcinoma. The frequency of the histology varies, as depicted in **Table 1**, but in general necrosis/fibrosis is found in 40% to 50%, teratoma in 35% to 40%, viable germ cell carcinoma in 10% to 15% and non–germ cell carcinoma in less than 1%. Currently, there are no clinical tools that can reliably predict the histology of a postchemotherapy mass in the preoperative setting. Because further treatment and follow-up regimens depend on the histology of residual masses, PC-RPLND is necessary.

Recent studies have examined if the choice of induction chemotherapy has an effect on residual tumor at time of PC-RPLND. Cary and colleagues[6] from Indiana examined the difference in final pathology for patients receiving 4 cycles of etoposide and cisplatin (EP) (47 patients) versus 3 cycles of bleomycin, etoposide, and cisplatin (BEP) (179 patients). They found a higher rate of active tumor in the EP group (22.9%) than in the BEP group (7.8%). Kundu and colleagues[7] from Memorial Sloan Kettering (MSK) reported on 505 patients who received EP $\times$ 4 and compared them with 74 patients who received BEP $\times$ 3. The BEP group was found to have teratoma more often (53% vs 32%) than the EP group. There was no difference in the frequency of active tumor between the groups (BEP 5%, EP 6%).

The results of these 2 retrospective analyses may be attributable to differences other than the choice of chemotherapy regimen.[8] In the study by Cary and colleagues, the majority of patients who received chemotherapy at Indiana University received 3 cycles of BEP (48 patients) rather than 4 cycles of EP (1 patient). The differences in active tumor at PC-RPLND may be a reflection of a higher dose intensity of chemotherapy given at Indiana University than at community chemotherapy centers who then referred patients to Indiana for surgery. In the study by Kundu and colleagues, the differences in teratoma at PC-RPLND may be due to differences in the size of residual masses in the 2 groups. The majority of the EP group received chemotherapy at MSK and had smaller residual masses at time of surgery. The majority of the BEP group received chemotherapy outside of MSK and had larger residual masses at time of surgery. Therefore, factors, such as possible differences in chemotherapy intensity at community versus tertiary centers and referral patterns to tertiary centers for surgery may at least partially explain these apparently conflicting results.

A complete resection of all residual masses during PC-RPLND can be therapeutic. Patients in the International Germ Cell Consensus Classification Group (IGCCCG) good prognosis group with complete resection of residual masses and less than 10% viable tumor cells in the resected specimen can be observed without further chemotherapy, but postoperative chemotherapy should be directed to those with less favorable characteristics.[9] Fox and colleagues[10] from Indiana University reported on 580 men who underwent PC-RPLND; 417 (72%) were after primary chemotherapy and 163 (28%) were after salvage chemotherapy; 43 (10%) of the primary chemotherapy patients and 90 (55%) of the salvage chemotherapy patients had viable germ cell carcinoma. This study demonstrated a survival advantage for those patients with viable germ cell tumor who had a complete resection, even if they did not receive further chemotherapy.

The role of RPLND in the management of teratoma is well established. Teratoma, by definition, is resistant to chemotherapy and radiotherapy. First described by Logothetis and colleagues,[11] growing teratoma syndrome can result in local morbidity and may compromise adjacent structures. Although teratoma itself is benign, a somatic teratoma component of a germ cell tumor may undergo malignant transformation, referred to as teratoma with malignant transformation. This transformation, usually to sarcoma or adenocarcinoma, like teratoma is resistant to chemotherapy.[12–14]

RPLND has developed from a procedure with limited long-term survival in the early 1900s[1] to the current state of limited mortality.[15] This