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Seminar article

Role of surgical resection for refractory germ cell tumors

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Abstract

Purpose: This article aims to critically review the current recommendations with regard to the role of surgery following salvage chemotherapy, growing teratoma syndrome, late relapse, as well as malignant transformation.

Methods: All the literature published in English and available on Pubmed pertaining to refractory germ cell tumors was reviewed and the relevant articles, as well as our own institutional experience were included in this review.

Results: There is universal agreement that patients with non-seminoma who have residual tumor measuring greater than one centimeter should undergo post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) for resection of potential teratoma or viable germ cell tumor. The role of surgical resection is less clear in patients who are deemed to have germ cell tumors refractory to chemotherapy. Patients with residual masses following second line therapy, those with growing teratoma, late relapse, and malignant transformation should all be considered for upfront surgical resection. Compared with the typical PC-RPLND, these operations are generally more complex, with a higher proportion requiring adjunctive procedures; and should be performed in experienced, tertiary referral centers.

Conclusion: Patients who have complete resection of disease are sill curable and patients with chemorefractory disease should have evaluation by an expert surgeon.

Keywords: Refractory; Germ cell tumor; Late relapse; Growing teratoma syndrome; Malignant transformation; Salvage chemotherapy; Testis cancer

Introduction

Postchemotherapy surgical resection remains a critical component in the multimodal management of patients with advanced germ cell tumors (GCTs). Approximately two-thirds of patients who present with disseminated disease and undergo standard first-line cisplatin-based chemotherapy achieve a complete marker response and normalization of radiographic disease. Of the remaining one-third of patients, approximately 10% to 15% have elevated marker levels following chemotherapy [1,2]. The patients with "poor prognosis" according to the International Germ Cell Cancer Collaborative Group (IGCCCG) who have very elevated human chorionic gonadotropin (HCG) levels (>50,000 IU/l) at presentation may not have complete normalization of their marker levels following chemotherapy. Unless there is a subsequent rise in the tumor marker levels, those who have declining or plateaued tumor marker levels with a significant residual retroperitoneal mass should undergo postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) [3]. In addition, it is important to note that cystic teratomas may contain elevated levels of alpha-fetoprotein or HCG that can leach into the bloodstream, accounting for elevated yet stable serum tumor marker levels [4]. Patients with inappropriate tumor marker response or rising levels of markers shortly following appropriate, risk-adapted, first-line chemotherapy may have cisplatin-resistant disease. It is important to ascertain the absence of disease in sanctuary sites (i.e., brain and contralateral testicle) before considering further therapy. Options include complete surgical resection of all radiographically visible disease, if technically feasible, or salvage chemotherapy [4]. Surgery in this setting may be curative and obviates the risk of further systemic therapy. In addition, chemoresistant tumors may progress through salvage therapy and potentially compromise the chance of complete surgical resection. An exception may be patients

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with rapidly rising HCG levels, which is considered to be an adverse prognostic factor, and for whom high-dose chemotherapy (HDCT) with stem cell rescue may be more appropriate [2,4].

Most guidelines recommend PC-RPLND in patients with residual tumor masses measuring 1 cm or more [5,6]. However, there is a relative paucity of literature to support recommendations for surgical resection in patients who may be refractory to chemotherapy. Surgical resection is generally recommended in patients who have resectable masses following salvage chemotherapy, those with late recurrent tumors, malignant transformation (MT), or growing teratoma syndrome (GTS). Surgery in these settings is usually a technically demanding procedure and requires exquisite knowledge and experience with retroperitoneal anatomy and vascular techniques. This article reviews the current role of surgical resection for GCTs that are refractory to systemic therapy.

Indications for surgery following second-line chemotherapy

Aggressive surgical resection of residual masses following salvage chemotherapy should always be considered to maximize chances of cure. Survival outcomes following salvage chemotherapy and of those who have undergone prior PC-RPLND are generally worse, and patients are at risk for postoperative complications. It is critical that concern for surgical complications does not deter treating oncologists or surgeons from proceeding with aggressive resection. Similarly, masses deemed "unresectable" should be evaluated carefully by experienced surgeons at tertiary referral centers, as most residual masses may be removed with adjunctive procedures including vascular resection, bowel resection, and even resection of involved vertebral lesions [7]. Residual masses following salvage therapy are associated with a higher frequency of finding viable GCT, a higher chance of incomplete surgical resection, and a higher risk of recurrence as compared with the patients undergoing PC-RPLND following induction chemotherapy [8].

Up to 50% of patients undergoing PC-RPLND following salvage chemotherapy have viable GCT in the resected specimen, although this proportion has recently decreased [9–12]. The choice of salvage therapy has an effect on the pathologic findings at resection. Investigators at Memorial Sloan Kettering showed that patients who received taxane-based salvage chemotherapy were at a lower risk of having viable germ cell elements at the time of PC-RPLND. In a series of 71 patients who had undergone multiple regimens of chemotherapy, 35 underwent taxane-containing regimens (paclitaxel, ifosfamide, carboplatin, and etoposide [TICE, a high-dose chemotherapy regimen with stem cell rescue] [n = 25]; paclitaxel, ifosfamide, and cisplatin [TIP] [n = 10]), whereas 36 underwent other regimens. Only 5 patients (14%) had viable GCT in the resected specimen in those undergoing paclitaxel, ifosfamide, carboplatin, and etoposide or TIP vs. 15 (42%) in those who had other regimens with a similar rate of teratoma (31% vs. 33%) as expected. The 10-year disease-specific survival following complete resection of residual disease was 70%, although the finding of viable GCT was a significant predictor of worse outcomes [12].

If the surgery is deemed a complete resection, no further chemotherapy is warranted. Donohue et al. reported on 91 patients from Indiana University who underwent surgery following salvage chemotherapy, of whom 53 were considered completely resected. Of these patients, 25 underwent repeat salvage chemotherapy and 28 did not receive any further therapy. There was no significant difference in survival between the 2 groups, with 12 patients dying of disease in each group [13].

Rarely, patients who undergo PC-RPLND have in-field retroperitoneal relapse secondary to incomplete initial resection [14–16]. Patients who have normal tumor marker levels should proceed with repeat RPLND, as most patients harbor teratoma, although the rates of finding viable GCT are higher at 22% to 24% upon repeat resection [14,16]. Those with elevated marker levels and a residual mass should undergo salvage chemotherapy followed by repeat PC-RPLND regardless of the size of the residual mass. The need for repeat PC-RPLND is associated with a significantly lower 5-year disease-specific survival. Although the finding of fibrosis or teratoma at repeat resection is associated with favorable outcomes, the finding of viable GCT is associated with an overall survival rate of only 40% to 50% [14,15]. Repeat PC-RPLND is a challenging operation, with increased need for adjunctive surgery including vascular resection. Although the complication rates tend to be higher in this setting, the morbidity is acceptable, and surgical resection often represents the ultimate chance for cure, given the significant number of patients with chemoresistant teratoma or MT.

The surgical approach should take into account the location of the residual disease, as well as the need for adjunctive procedures. Most operations can be approached through a midline incision, though bulkier tumors and those in the suprahilar region may be better approached through a thoracoabdominal incision [17]. The thoracoabdominal approach also has the advantage of accessing the lower posterior mediastinum, allowing concomitant resection of disease in this area. However, this incision is associated with significantly higher morbidity, including pain and chest complications [18].

A significant proportion of patients undergoing PC-RPLND require additional surgical procedures to ensure complete resection of residual masses [7,19,20]. The most common additional procedure at PC-RPLND is adjunctive nephrectomy, performed in up to 20% of cases, with more than half of these being in the high-risk setting. Patients who receive salvage chemotherapy, have large masses, are undergoing reoperative surgery, or undergo "desperation" PC-RPLND are at a higher risk of requiring nephrectomy, with a substantial portion of them harboring viable GCT. In