



Surgical salvage in patients with advanced testicular cancer: indications, risks and outcomes

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Abstract: The purpose of this review is to present a comprehensive and updated review of the literature and summary of the indications, risks and outcomes related to salvage, desperation and late relapse surgery for advanced testicular cancer. After completing a thorough review of the current literature, this review has attempted to provide an overview of the indications for salvage, desperation and late relapse retroperitoneal lymph node dissection (RPLND) followed by a summary of the histopathologic and clinical outcomes regarding each. Recent literature, combined with a significant contribution from historical studies suggest that while testicular cancer is a relatively uncommon malignancy overall, it represents the most common solid organ malignancy for young men. Although a significant number of men are cured with a combination of first-line treatments, the remaining men are a diverse and often challenging cohort who require the benefit of expertise to improve their outcomes. The role of surgical strategies in the salvage, desperation and late relapse settings is unquestionable, although the most important question remains who will benefit. This often requires a multi-disciplinary approach at centers specializing in this disease process in order to recognize who should get surgery, what surgery to do and how to minimize the potential morbidity associated with the operation.

Keywords: Testicular neoplasms; salvage retroperitoneal lymph node dissection (salvage RPLND); desperation retroperitoneal lymph node dissection (desperation RPLND); late relapse retroperitoneal neoplasms; retroperitoneal lymphadenectomy

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Introduction

Germ cell tumors (GCTs), comprising 1% of male cancers overall and 5% of male genitourinary malignancies, are the most common tumors in young men (1). While 70% of patients with advanced GCTs who undergo induction chemotherapy with cisplatin-based chemotherapy will be cured based on serologic and radiographic response, the remaining 30% represent a heterogeneous and challenging group of patients (2,3). For those patients with a residual mass and normal serum tumor markers (STM), a post-chemotherapy retroperitoneal lymph node dissection

(PC-RPLND) is the standard treatment approach. After 3 cycles of bleomycin, etoposide and cisplatin (BEP), the expected histologic breakdown of the PC-RPLND specimen is active cancer in 2–9%, teratoma in 64–67% and necrosis in 27–31% (4).

Patients who have persistently elevated STM following induction chemotherapy are presumed to have residual GCT and salvage chemotherapy is the usual option, with PC-RPLND being utilized in select cases. Salvage chemotherapy results in STM normalization and further tumor regression in 25–70% of cases (5). Following salvage

chemotherapy, patients who normalize their STM have a higher rate of malignancy in the specimen compared with the post-induction specimens (Table 1). As such, a post-salvage chemotherapy retroperitoneal lymph node dissection (RPLND) is recommended for all patients with a residual mass immediately following second-line therapy, even if tumor markers completely normalize. Even with this approach, the overall long-term results remain poor with 5-year survival rates of 15–40% in patients who have failed induction chemotherapy (6).

The surgical management of patients with rising or persistently elevated STM after second line chemotherapy has evolved. Several studies have shown benefit as a result of desperation and late relapse (LR) surgical resections (7–10). Elevated STM after salvage 2nd or 3rd line chemotherapy indicates the presence of chemo-refractory disease and long-term survival rates with desperation RPLND have ranged from 33–75% (11). As such, these patients may benefit from surgical resection in selected cases. Based on these results, many investigators questioned whether or not surgery could be applied earlier in the course of disease, potentially obviating the need for salvage chemotherapy altogether.

In this review of the literature, we discuss the indications for and outcomes related to the surgical management of GCTs in the salvage, desperation, and LR settings.

Definitions

When addressing the management of advanced GCT through salvage, desperation, or LR surgery, it is worthwhile to define certain disease specific parameters as well as the surgical categories. The diagnosis of relapsed testicular GCT occurs when there is either a rise in the human chorionic gonadotropin (hCG) or serum alpha fetoprotein (AFP) or radiographic progression following a complete response (CR) or surgical cure (12). Confirming the diagnosis of relapse is crucially important. Early relapse, constituting a majority of relapse occurrences, is defined as relapses which occur within 2 years of initial treatment (13–15). Patients who fail to achieve a CR to induction chemotherapy or who relapse within 6 months have a more unfavorable prognosis (16). While a rising STM should raise concerns for relapsed GCT, there are other widely known causes for mild STM elevations in this setting, and caution should be taken prior to deciding on aggressive intervention. Serum hCG has shown to be elevated in mononucleosis, chronic marijuana use, as well as luteinizing

hormone (LH) elevation, due to the cross-reactivity. Additionally, AFP is found to be elevated in benign liver disease and can be mildly elevated due to certain hereditary conditions. According to Rashdan and Einhorn (2016) an AFP of 8–25 ng/mL should never be the only indication for salvage therapy unless it represents a clear and sustained rise. As a separate word of caution, for patients presenting with hCG >50,000 mIU/mL, they may have a rapid decline during the first 2 cycles of chemotherapy but may plateau and may take several months to normalize. As such, in these circumstances, an element of patience is prudent.

There is a diverse classification scheme for RPLNDs in the literature. In general, a primary RPLND refers to surgery after orchiectomy for clinical stage I (CSI) or low volume clinical stage II (CSII) non-seminoma germ cell tumour (NSGCT) with normal post-orchiectomy STMs. PC-RPLND refers to a surgery after completion of chemotherapy. Classically, this includes patients who have a residual mass but negative STMs. Residual or growing masses after chemotherapy are the result of either teratoma or viable GCT. While it is impossible to predict the pathology with 100% certainty based on the clinical and serologic history, there are certain hints that can help predict the histology of resected masses. Growing masses that are associated with rising STM typically indicate relapsed or persistent GCT while radiographic progression without a corresponding rise in STM should raise suspicion for growing teratoma. In the absence of radiographic progression in the setting of rising markers, sanctuary sites must be considered to include the brain and contralateral testis, and appropriate investigation of these sites should be undertaken.

Under this “PC-RPLND” heading falls the terms salvage and desperation RPLND. While used interchangeably at some institutions, at Indiana University we define salvage RPLND as an operation performed in the setting of an enlarged or growing mass following salvage chemotherapy. Patients who normalize their tumor marks following salvage chemotherapy and have residual radiographic disease are recommended to undergo a salvage RPLND. Justification for this management strategy was originally supported by Fox *et al.*, who showed that 55% of salvage RPLND specimens harbored active cancer (17). In the era of taxane-based salvage chemotherapy, this rate decreased. The group from Memorial Sloan Kettering Cancer Center showed that 14% of their patients who received taxane based salvage chemotherapy harbored active cancer compared to 42% who received other salvage therapies (18). In spite of the

improved rates of active cancer in the specimens, RPLND is still uniformly recommended as the rates of active cancer remain unacceptably high.

The term desperation RPLND, as described by Donohue, refers to a PC-RPLND (either induction or salvage chemotherapy) performed in the setting of elevated or rising STM (3). Patients who experience progressive disease either during or within 4 weeks after completion of cisplatin-based chemotherapy are deemed to have platinum refractory GCT. Historically, patients who relapsed after previously receiving first-line chemotherapy were not considered surgical candidates and were given additional chemotherapy. However, a surgical cure is possible even in the setting of elevated markers after both induction and salvage chemotherapy so long as appropriate patient selection is undertaken.

LR is defined as the experience of relapse >2 years after initial chemotherapy. While it does occur in 1–3% of patients, it is more frequent in those patients who present with disseminated disease. A pooled analysis of 5,900 patients revealed LR in 119/3,700 (3.2%) of NSGCT and 31/2,200 (1.4%) of seminoma patients (19). Most commonly occurring within 10 years of diagnosis, the retroperitoneum is the most common site of relapse. Because a significant fraction of LR occurs in the RP only, with or without elevated AFP, and somatic malignant transformation is common, LR should be managed surgically if achievable. This is often referred to as resection of LR and is defined as a PC-RPLND performed for RP recurrence 24 months or later after CR to primary therapy (which may or may not have included RPLND).

Indications for salvage, desperation and LR RPLND

Assuming normalization of STM's after salvage chemotherapy, thorough surgical resection of residual disease with curative intent should be considered given the possibility of residual teratoma or viable GCT (18). Up to 50% of patients undergoing salvage resection have viable GCT in the resected specimen. When multiple metastatic sites are present, all residual disease should be resected as there exists histologic discordance between sites in 30% of cases (20). That being said, necrosis found in the RPLND specimen correlates to necrosis found in lung lesions 90% of the time. Some have thus advocated for expectant management of lung lesions if the findings of the RPLND indicate necrosis to minimize the surgical

burden and morbidity (21). PC-RPLND following salvage chemotherapy may, in certain cases, obviate the need for further chemotherapy. Donohue *et al.* evaluated 91 patients who underwent PC-RPLND at Indiana University following salvage chemotherapy. Fifty-three patients were deemed a complete resection, of whom 25 underwent repeat salvage chemo and 28 did not. Overall, 12 patients in each group died of disease and there was no difference in survival between the two groups (22). As such, in the setting of a presumed complete resection, adjuvant salvage chemotherapy is currently not recommended. While there is a higher likelihood of complications and incomplete resection in the salvage setting, this should not deter experienced surgeons from proceeding with surgical extirpation and reconstruction when indicated. These cases more frequently involve concomitant procedures such as vascular resection, bowel resection and the removal of associated visceral, pulmonary and mediastinal disease.

Patients who have persistently elevated or rising STM with surgically resectable disease after chemotherapy should be considered for desperation RPLND. Although the STM are elevated at the time of surgery, 50% of patients have necrosis or teratoma in the final specimen. Chemo-refractory patients who have resectable disease may achieve cure through surgery. In fact, at Indiana University, surgery is the preferred approach for patients with initial localized disease and who experienced relapse in the same location. Murphy *et al.* (1993) evaluated 48 chemo-refractory patients who underwent desperation surgery between 1977–1990 at Indiana University. In this report, 38/48 patients (79%) were rendered grossly free of disease at the time of surgery and 29/48 (60%) achieved a serologic remission; 10/48 (21%) remained continuously free of disease without the need for additional treatment at a median of 46 months follow-up. Of the 19 patients who relapsed following serologic remission, 6 were ultimately without evidence of disease with further therapy, 4 of which had additional surgery and 2 had high dose chemotherapy (HDCT) with autologous bone marrow transplant (BMT) (23). Therefore, when systemic options either fail or are not available due to patient factors, desperation surgery may be curative in selected patients with presumably resectable, low volume disease (24).

LR should be managed utilizing a multimodal treatment strategy including surgery when complete resection is achievable. Salvage chemotherapy is rarely curative and CRs are often only achieved with the use of a combined approach with surgical resection. Some studies have shown that

Table 1 Postchemotherapy RPLND in high-risk populations

Study	No. patients	Teratoma (%)	Fibrosis (%)	Viable malignancy (%)	Follow-up (years)	CSS or OS (%)
Salvage						
Donohue <i>et al.</i> , 1998	166	NR	NR	NR	9.7	61.4
Egger <i>et al.</i> , 2007	71	21	51	28	5	74
HDCT						
Rick <i>et al.</i> , 2004	57	16	38	46	7.3	65
Cary <i>et al.</i> , 2011	77	33.8	27.3	39	4.2	71
Desperation						
Donohue <i>et al.</i> , 1998	150	NR	NR	NR	9.7	66
Ravi <i>et al.</i> , 1998	30	26.7	27.6	46.7	4.8	57
Albers <i>et al.</i> , 2000	30	11	25	64	11	57
Beck <i>et al.</i> , 2005	114	34.2	12.3	53.5	6	53.9
Ong <i>et al.</i> , 2008	48	25	17	58	4.3	69
Late relapse						
Baniel <i>et al.</i> , 1995	81	19	0	81	4.8	56.8
George <i>et al.</i> , 2003	83	17	0	78	2.4	74.7
Dieckmann <i>et al.</i> , 2005	72	NR	NR	NR	NR	58.3
Sharp <i>et al.</i> , 2008	75	19	3	78	4.5	61

Reprinted from Campbell-Walsh Urology, 35/11th edition, Rice KR, Cary KC, Masterson TA, Foster RS, Surgery of Testicular Tumors, 815-837.e4, Copyright (2016), with permission from Elsevier. RPLND, relapse retroperitoneal lymph node dissection.

combining salvage chemotherapy with surgery improves the cure rates (25-28). However, at Indiana University we advocate for upfront surgery with no chemotherapy if the LR appears completely resectable. Even when a complete clinical response is achieved after chemotherapy, investigators from Memorial Sloan Kettering Cancer Center still advocate for consolidative surgery as either teratoma or active cancer is still identified frequently (18).

Pathologic findings at and outcomes following salvage, desperation and LR RPLND

Salvage

At the present time, there is still an absence of completed prospective randomized trials comparing outcomes between conventional dose salvage chemotherapy and HDCT with autologous stem cell transplant. While many Urologists and Oncologists eagerly await the phase III "TIGER" trial comparing conventional-dose chemotherapy (CDCT) and HDCT in the initial salvage setting, the management of the

patients after salvage chemotherapy is unlikely to change.

Patients undergoing PC-RPLND after salvage chemotherapy demonstrated higher rates of persistent viable malignancy and worsened survival outcomes compared with patients who received first-line chemotherapy only (see *Table 1*, obtained from Campbell-Walsh Urology, 35, 815-837.e4, Table 35-6). While overall (OS) and cancer specific (CSS) survival ranged from 60% to 75% in this group, Fox *et al.* found that patients having received only induction chemotherapy had a CSS of 58.5% compared to those receiving salvage chemotherapy (36.7%) (17,18,29). Regarding surgery after HDCT, Rick *et al.* observed a 59% recurrence free survival (RFS) and 65% CSS at a median follow-up of 7.3 years in a cohort of 57 patients (30). Supporting this data, Cary *et al.* reported a 71% OS at a median follow-up of 4.2 years in their cohort of 77 patients (31).

Several authors have evaluated predictive factors at time of salvage RPLND for the presence of active cancer in the resected specimen. Marker trends prior to RPLND appear to have prognostic relevance. Rising STM are

associated with both a lower OS as well as a higher risk for finding active cancer (9). The absolute value of the markers additionally has been evaluated.

Lakes *et al.* evaluated 149 men who underwent RPLND in the setting of elevated STM. Of them, 64% had elevated AFP alone, 25% elevated hCG alone and the remaining 11% with elevation of both STMs. Forty-three percent underwent RPLND after induction chemotherapy while 54% after salvage chemotherapy, of whom 59% had received HDCT. Overall active cancer was seen in 36.9%, teratoma in 35.6% and necrosis in 26.8%. In patients who had AFP rise only, active cancer was seen in 42%, compared to 18.4% in hCG alone. In patients with elevation in both hCG and AFP, 50% had active cancer (32). Support for the prognostic value of the STM elevation came from 2 other studies in this space. Habuchi *et al.* suggested that high hCG levels is a predictor for disease-related death (33), while Wood *et al.* showed that all patients with elevated hCG levels relapsed after RPLND while only 30% of patients with isolated AFP elevation relapsed (24).

Arguably, the completeness of resection is regarded as the most important prognostic factor relating to patient outcome. While studies have evaluated the effect on mass location (retroperitoneal/mediastinal *vs.* visceral), ultimately, it was the ability to achieve complete resection than proved more important. In this regard, the ability to achieve a complete resection may be influenced by the residual mass location. Habuchi *et al.* reported complete resection in 82% of patients with retroperitoneal/mediastinal disease *vs.* only 57% of patients with visceral disease (33). While the patients with visceral disease do appear to have worse overall outcomes, attempts for resection in selected patients should not be avoided.

The normalization of tumor markers also has long-term prognostic value in regard to outcome. Ong *et al.* showed that patients with persistently elevated STM after resection had a 5-year survival of 8% compared to 93% for those patients who normalized their markers (34). In combination with the findings of necrosis in the resected specimen, elevated STM after surgery is particularly worrisome as this clearly indicates residual GCT remaining outside the attempted region of resection.

Desperation

Desperation RPLND can have a significant role in the successful management of patients with advanced GCT. Data from multiple case series report long-term survival

rates from 33–75%. (11,34). In 2005, Beck *et al.* reported data from 114 patients who underwent RPLND in the desperation setting. Active cancer was identified in 53.5% of the resected specimens, while 34% revealed teratoma and 12.3% revealed necrosis. The median 5-year OS was 53.9%. Significantly lower OS rates were seen for patients with active cancer in the resected tissue (31%), compared to teratoma (77%) or fibrosis (85%). Additionally, they showed that marker trends prior to RPLND have prognostic relevance. Rising STM are associated with both a lower OS as well as a higher risk for finding active cancer. In the setting of declining STMs, the 5-year OS was 93.3% compared to increasing (22.7%) or stable (60%) markers. As such, when selecting appropriate patients for desperation RPLND with the highest likelihood of oncologic benefit, the authors recommended use of the following criteria: declining or stable markers after chemotherapy, slowly rising markers after prior CR, and resectable disease at <3 sites. Additionally, in patients who have exhausted all chemotherapy options, or are unable to receive additional chemotherapy, it may be offered as a last resort, so long as it is believed the disease is completely resectable (7).

In 2008, Ong *et al.* evaluated 48 patients who underwent desperation RPLND and broke the patients down by the presence of rising STM *vs.* stable/downtrending STM. Overall 58% of patients had active cancer, 25% had teratoma and 17% had necrosis. The 5-year OS was 69%. Favorable prognostic factors in their study were elevation of AFP alone, complete resection, histologic finding of differentiated teratoma and a normalization of STM after RPLND. In fact, the normalization of STM was the only prognostic factor that remained robust on multivariable analysis (34).

Cary *et al.* evaluated 92 patients who had a residual mass after HDCT, describing their histologic findings and the impact on OS. Overall, 76% received HDCT as 1st line salvage while 23% received HDCT as 2nd line or 3rd line, with 24% of patients being platinum refractory. Forty-two percent of the 92 patients underwent PC-RPLND in the desperation setting. Overall, the histologic breakdown was 38% active cancer, 34% teratoma and 26% necrosis. In the subset of patients in the non-desperation setting, the histologic breakdown was 20% active cancer, 41% teratoma and 39% necrosis. Overall, more active cancer was found in patients who received HDCT as $\geq 2^{\text{nd}}$ line (60%), compared to patients who received HDCT as 1st line salvage (33%). The 5-year OS of the entire cohort was 70%. The most

significant predictor of death was PC-RPLND performed in the desperation setting (31).

The approach to patients with combined retroperitoneal and mediastinal disease following induction chemotherapy is not standardized. While some advocate for staged procedures based on the extent of extra-retroperitoneal disease based on data from Memorial Sloan-Kettering Cancer Center (MSKCC) and widely accepted at high volume centers, combination RPLND and mediastinal surgery is safe and effective (35). Fadel *et al.* reported a series of 18 patients who underwent a single stage combined retroperitoneal and posterior mediastinal resection. Of these 18 patients, 4 were in the setting of elevated tumor markers. The 5-year OS rate was 92% with a 5-year disease-free survival rate of 87%. Of the 4 patients with elevated STM, 1 was unable to be completely resected, underwent adjuvant chemotherapy and ultimately died of disease. Another patient relapsed to the liver but was able to be further salvaged with chemotherapy and remained NED. The other two had complete serologic responses to surgery and remained NED at last follow-up (36).

Outcomes reported in several retrospective desperation series are listed in *Table 1* (8,29,37).

LR

Among patients presenting with LR, 80% contain viable GCT, with yolk sac tumor being the predominant tumor subtype (25). When multiple sites of disease are present, all residual disease should be resected when possible as histologic discordance between sites exists. The appropriate management of LR patients should be individualized, as there exists a wide variety of presentations. In general, marker-negative relapse is consistent with teratoma and should be surgically resected. Typically, a cure can be achieved with complete resection. If, however, the patient presents with marker-positive relapse, this typically indicates viable GCT. These cases have traditionally been managed using either a surgery-first strategy or chemotherapy followed by surgery. Supporting the critical utility of surgery in the LR setting, Baniel *et al.* evaluated 81 patients treated for LR at Indiana University. A majority of the patients (47/81) presented >5 years after curative treatment of the initial disease. Eighty point four percent of patients were treated with chemotherapy for the LR and only 26% had a CR, with only 3% remaining NED without surgery. Nineteen patients had complete surgical resection of active cancer or teratoma as part of a multimodal treatment

strategy and all remained disease free (28). Based on these results, the investigators suggested that LR patients have a very underwhelming response rate to chemotherapy and surgery was the preferred approach.

The patients receiving chemotherapy upfront usually receive this in order to decrease the burden of disease and make surgery more feasible. Ronnen *et al.* evaluated 29 patients who received salvage chemotherapy in this setting. Their population consisted of patients not considered surgical candidates because of extensive disease or disease in multiple sites. Treatment with paclitaxel, ifosfamide and cisplatin (TIP) followed by surgical resection resulted in CR in 7/14 (50%) while no other salvage regimen resulted in a favorable clinical response, except for one partial response to combine paclitaxel plus ifosfamide followed by high-dose carboplatin plus etoposide (TI-CE) with stem cell rescue. The median survival of the 29 patients was 23.9 months with a median follow-up of 50.6 months (38).

Conclusions

Overall, the management of patients who are not cured by induction chemotherapy alone presents a challenge to even the most meticulous surgeon. Many authors have advocated for the consolidation of surgical care of patients requiring salvage or desperation surgery to centers with significant experience and the availability of an experienced multi-disciplinary surgical team to include hepatobiliary, thoracic and vascular surgeons. While aggressive surgical resection can offer curative treatment in patients in the salvage, desperation and LR setting, the single most important decision is who to operate on. These surgeries are often challenging; however, they can offer long-term survival in a significant percentage of these patients when complete resection can be achieved and thus the benefit is worth the endeavor.

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Footnote

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