The Role of Surgery in the Management of Recurrent or Persistent Non-seminomatous Germ Cell Tumors

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Abstract

Objective: To review the management of patients with non-seminomatous germ cell tumors (NSGCTs) with persistent or recurrent disease following primary or secondary therapy, with particular attention devoted to the role of surgery.

Methods: A non-structured review of the literature until January 2007 was performed using the PubMed database.

Results: The management of persistent or recurrent disease among patients with NSGCT depends on stage at presentation and relapse, serum tumor marker levels at relapse, prior therapy, and timing of relapse. Clinical stage I patients who relapse following active surveillance are usually treated with induction chemotherapy. Likewise, patients who relapse following primary retroperitoneal lymph node dissection (RPLND) are treated with induction chemotherapy based on the systemic pattern of recurrence. Advanced cases with residual radiographic disease >1 cm and normal tumor markers following induction chemotherapy are generally recommended for postchemotherapy surgical resection, whereas those with persistently elevated markers undergo salvage chemotherapy. Select patients with resectable disease and elevated serum tumor markers may be appropriate candidates for surgery. Based on intrinsic chemoresistance, the treatment of patients with advanced disease who relapse >2 yr (late relapse) following successful chemotherapy is primarily surgery.

Conclusion: Patients with NSGCTs with persistent disease or recurrence within 2 yr of initial therapy remain highly curable. The prognosis of patients with late relapse is compromised based on tumor chemoresistance. The role of surgery in the management of recurrent disease is primarily limited to the postchemotherapy setting; however, in the context of late relapse it often represents the primary treatment.
1. Introduction

Germ cell cancer of the testis is the most common solid tumor in men aged 20–35 years [1]. Over 8000 new cases are expected in the United States in 2006, of which non-seminomatous germ cell tumors (NSGCTs) will account for more than half. With the introduction of effective cisplatin-based chemotherapy, long-term survival now exceeds 85%. Although the role of chemotherapy cannot be overstated, surgery, particularly retroperitoneal lymph node dissection (RPLND), retains critical importance in the contemporary management of patients with both early and advanced stage disease.

This article reviews the management of NSGCT patients with persistent or recurrent disease following primary or secondary therapy, with particular attention devoted to the role of surgery. Early and late relapse will be discussed as will be role and technique of postchemotherapy RPLND (PC-RPLND).

2. Relapse following active surveillance for clinical stage I NSGCT

2.1. Rationale for active surveillance

Roughly 50% of non-seminoma patients present with clinical stage I (CS I) disease based on negative radiographic evaluation and normalization of serum tumor markers (STMs) after orchiectomy (Table 1) [2,3]. Management options include primary RPLND, two cycles of BEP (bleomycin, etoposide, cisplatin) and active surveillance. Although one third of such patients harbor subclinical metastases at presentation, cure rates approach 100% regardless of initial chosen therapy. This reflects the early detection of recurrence through STM analysis or computed tomography (CT) imaging, coupled with the availability of efficacious salvage treatment.

Seventy percent of CS I non-seminoma patients will never develop a recurrence following orchiectomy if managed by surveillance. Recognizing this fact, a significant proportion of patients choose active surveillance as primary therapy, rather than RPLND or chemotherapy. Thirty percent of patients on surveillance will subsequently relapse, the vast majority of whom are cured with chemotherapy. Whereas the role of primary RPLND at relapse is unknown, PC-RPLND is integral to the management of patients with an incomplete response to chemotherapy. It is estimated that 5–10% of patients on surveillance will eventually require PC-RPLND for residual disease [4].

2.2. Predictors of recurrence on active surveillance

Established predictors of recurrence in CS I non-seminoma patients on surveillance include lymphovascular invasion (LVI) and embryonal carcinoma predominance (EC-pred) in the primary tumor [5–8]. Depending on the number of risk factors present, patients can be stratified into low- (no risk factors) and high-risk (LVI or EC-pred or both) groups with predicted relapse rates of 10% and 50%, respectively [2,4,6]. Risk-adapted management guidelines recommend primary RPLND or two cycles of BEP for patients considered to be at high risk for recurrence, whereas those at low risk are appropriate for active surveillance [9].

2.3. Pattern, timing, and evaluation of recurrence on active surveillance

The pooled relapse rate for CS I non-seminoma patients on active surveillance is 29% (23–36%) based on the accepted diagnostic criteria of a radiographic mass ≥1 cm or larger or an elevation of one or both STMs [2]. The vast majority of recurrences occur within 2 yr of initial diagnosis at a median time of

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical stage (CS)</th>
<th>Regional (retroperitoneal) lymph nodes</th>
<th>Pathologic stage (PS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>cN0</td>
<td>No regional lymph node metastases</td>
<td>pN0</td>
</tr>
<tr>
<td>II A</td>
<td>cN1</td>
<td>Metastases with a lymph node mass ≤2 cm; or multiple lymph nodes, none &gt;2 cm</td>
<td>pN1</td>
</tr>
<tr>
<td>II B</td>
<td>cN2</td>
<td>Metastases with a lymph node mass &gt;2 cm but ≤5 cm; or multiple lymph nodes, any one mass &gt;2 cm but ≤5 cm</td>
<td>pN2</td>
</tr>
<tr>
<td>II C</td>
<td>cN3</td>
<td>Metastases with a lymph node mass &gt;5 cm</td>
<td>pN3</td>
</tr>
<tr>
<td>III</td>
<td>Distant metastases</td>
<td>(including non-regional lymph node metastases)</td>
<td></td>
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6 mo [2,4,6,8,10,11]. Recurrence beyond 2 yr is very uncommon (<3%).

Lymphatic spread, common to all GCTs, usually follows a predictable and systematic pattern from the testis to the retroperitoneum and subsequently to distant sites, most notably the lungs and mediastinum. Indeed, recurrence among CS I patients on active surveillance is most common in the retroperitoneum (65–80%) followed by the chest (15–30%) [2,4,6]. STM levels are elevated in 65–85% of patients and constitute the only sign of recurrence in 10–15%. Because surveillance strategies involve frequent clinical evaluation, most patients are asymptomatic at relapse and disease burden is typically smaller in comparison to patients who initially present with CS II/III disease. Retroperitoneal tumor volume usually does not exceed 5 cm in greatest dimension (50–94%) and very few patients are categorized as poor risk by International Germ Cell Cancer Collaborative Group (IGCCCG) criteria [6,12–14]. The complete evaluation for confirmed or suspected relapse is outlined in table format (Table 2). In addition to routine staging of the chest and abdomen it is important to rule out the presence of a second primary GCT in the contralateral testis, which may develop in 1–2% of patients on surveillance [12,13]. Likewise, patients with only biochemical recurrence must be evaluated for other conditions known to elevate α-fetoprotein (AFP; liver disease) or β-human chorionic gonadotropin (β-HCG; hypogonadism, marijuana use) levels.

Surveillance strategies vary among institutions and no one schedule appears to be superior to another with regard to overall survival (97–100%) [2]. Based on the predictable pattern of GCT recurrence, all protocols concentrate follow-up during the first 2 yr after which evaluation is less frequent.

### Management of recurrence on active surveillance

The standard treatment for recurrent GCT following active surveillance is cisplatin-based chemotherapy. RPLND is an option for patients with low-volume retroperitoneal recurrence (CS II); however, it does not retain the same diagnostic and therapeutic value as demonstrated in CS I/II patients who undergo RPLND at diagnosis. Whereas 23–40% of patients who present with CS II NSGCT have no active disease identified at RPLND, the vast majority of patients with an enlarging retroperitoneal mass on surveillance harbor teratoma or viable GCT [15,16]. Up to 26% of CS II patients with pathologic stage IIA (PS IIA) disease and 55% with PS IIB disease will relapse following RPLND monotherapy versus only 2% with the addition of adjuvant chemotherapy [16,17]. As a result, two cycles of adjuvant BEP is sometimes recommended in patients who undergo primary RPLND for isolated retroperitoneal recurrence. Rather than commit patients to dual-modality therapy, induction chemotherapy is recommended as first-line treatment in the vast majority who relapse on surveillance, including those with isolated retroperitoneal recurrence and normal STM levels. Patients with teratoma in the orchietomy specimen may represent one caveat to this recommendation because 27% with CS IIA and 57% with CS IIB disease are also found to have retroperitoneal teratoma [18]. RPLND may be more appropriate in these patients because teratoma is not sensitive to chemotherapy.

Surgery in non-seminoma patients who recur on surveillance is limited primarily to the postchemotherapy setting. Approximately one third of patients with advanced NSGCT will not achieve a complete response to induction chemotherapy as indicated by residual radiographic disease (>1 cm) [19–21]. Response rates are slightly better among surveillance patients because recurrence is typically diagnosed at an early stage in this cohort. Postchemotherapy surgery is recommended in all patients with normal STM levels and residual radiographic disease >1 cm because >50% of such masses harbor persistent active disease (teratoma or viable GCT) [20,22,23]. Unfortunately, there exist no sufficiently accurate criteria by which to predict the presence of benign histology (necrosis) and avoid PC-RPLND in this setting. The management of patients with little or no radiographic abnormality (≤1 cm) is a matter of some controversy. Most centers, including ours, consider this to represent a radiographic complete response and recommend observation in lieu of surgery [24]. A low rate of relapse (5%) with long-term follow-up provides justification for such an approach [25]. Still, other centers continue to perform PC-RPLND in patients with normal STMs and minimal or no radiographic lesions, particularly in those with bulky (>3 cm).

### Table 2 – Evaluation of relapse

<table>
<thead>
<tr>
<th>Modality</th>
<th>Indication</th>
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<tr>
<td>History</td>
<td>Routine</td>
</tr>
<tr>
<td>Physical examination (including contralateral testis)</td>
<td></td>
</tr>
<tr>
<td>AFP, β-HCG</td>
<td></td>
</tr>
<tr>
<td>CT chest, abdomen, pelvis</td>
<td></td>
</tr>
<tr>
<td>CT brain</td>
<td>If clinically indicated</td>
</tr>
<tr>
<td>Bone scan</td>
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APF = α-fetoprotein; β-HCG = β-human chorionic gonadotropin; CT = computed tomography.
retroperitoneal disease at original diagnosis [26,27]. Motivation for this comes from series that demonstrate a 20–30% incidence of active disease (teratoma or viable GCT) in residual masses \( \leq 1 \text{ cm} \) [26–28]. Interestingly, the rate of relapse among series with an aggressive surgical policy is 6%, similar to series in which residual masses \( \leq 1 \text{ cm} \) are observed (5%) [25,26,29]. The indications, rationale, technique, and results of PC-RPLND are discussed at a later point in this article.

3. Relapse following primary RPLND for clinical stage I and II NSGCT

3.1. Rationale for primary RPLND for clinical stage I and II NSGCT

RPLND is an important diagnostic and therapeutic modality for patients with early stage testis cancer including those with normal STM levels and evidence of low-volume retroperitoneal disease (< CS IIB). Despite technological improvements, 20–37% of CS I patients remain under-staged by modern CT imaging [6,7,16,30–32]. Conversely, 23–40% of CS IIA/IIB patients are found to have no evidence of retroperitoneal disease at the time of surgery [15,16]. In this regard, RPLND directs appropriate stage-specific treatment and follow-up strategies. Patients with proven lymph node metastases may be selected for adjuvant chemotherapy on a risk-adjusted basis, whereas those with negative lymph nodes are spared the potential long-term toxicity associated with primary chemotherapy and are subjected to less intensive follow-up than is otherwise required by active surveillance protocols.

The therapeutic value of primary RPLND derives from the orderly spread of GCT from the testis first to the retroperitoneum. The majority of CS I patients (70%) have no evidence of retroperitoneal metastases (PS I) at RPLND [15,32]. Although retroperitoneal recurrence is exceedingly rare in these cases, 7–10% will recur at a distant location [7,33]. Thirty percent of CS I patients have active retroperitoneal disease, three fourths of which are low volume (pN1). Surgery alone is curative in 66–92% of CS I patients with pN1 disease and 50% with larger volume disease (pN2, pN3) [16,17,33,34].

Although patients who present with low-volume retroperitoneal disease (CS IIA, IIB) are more commonly treated with induction chemotherapy, they can also derive therapeutic benefit from primary RPLND. Surgery alone provides cure in approximately two thirds of CS II patients with confirmed retroperitoneal metastases (PS II), whereas the remaining one third will relapse if adjuvant chemotherapy is withheld [16]. The individual risk of relapse depends on the volume of retroperitoneal disease (pN1 26%, \( \geq \) pN2 55%). Two cycles of adjuvant chemotherapy reduce the risk of relapse below 2% and is sometimes chosen for patients with pN2 or pN3 disease (>2 cm) [16,17,35]. By excluding patients with CS IIB disease or elevated STMs from RPLND (ie, only CS I or IIA and normal STM levels), investigators at Memorial Sloan-Kettering Cancer Center (New York, NY, USA) have reduced the rate of subsequent relapse (4% vs. 17%) as well as the need for adjuvant chemotherapy [15]. Even among high-risk patients with EC-pred or LVI (or both), 5-yr progression-free survival rates of 90% can be expected following RPLND for CS I or IIA NSGCT [36].

3.2. Pattern, timing, and management of recurrence following primary RPLND

The risk of recurrence following primary RPLND ranges from 10% to 50%, depending on the volume of retroperitoneal disease [16,17,33,34]. In the absence of adjuvant chemotherapy, the pattern and timing of recurrence is similar regardless of pathologic stage. The vast majority of failures occur within 2 yr of surgery and are most commonly diagnosed in the chest (lungs, mediastinum) or serologically. Based on this systemic pattern, induction chemotherapy represents the standard treatment for postsurgical relapse. The combination of surgery and chemotherapy in this manner provides long-term survival in >96% of patients who undergo RPLND for CS I and II disease [16,33].

Retroperitoneal recurrence, particularly within the template of dissection, is distinctly uncommon (<2%) after RPLND and reflects inadequate surgical technique [37]. Most patients are treated initially with systemic chemotherapy followed by PC-RPLND for residual radiographic disease. If retroperitoneal teratoma is suspected on the basis of negative STM, imaging characteristics (cystic), and presence of teratoma in the orchiectomy specimen, repeat RPLND is sometimes performed in lieu of chemotherapy. Reoperative surgery in the primary and postchemotherapy settings is a formidable task. Adjunctive procedures such as thoracotomy, nephrectomy, and vascular reconstruction are often required (59–71%) and major morbidity is common (21–27%) [37–39]. Following reoperation after primary RPLND, the overall 5-yr disease-specific survival rate is 86% [38].

Recurrence following RPLND and adjuvant chemotherapy is very uncommon (<2%) and typically develops outside the retroperitoneum [16,17,33].
Unless the suspicion for teratoma is high, standard treatment is systemic chemotherapy. Second-line (ifosfamide and cisplatin plus etoposide [VIP] or vinblastine [VeIP] or paclitaxel [TIP]) or third-line (high-dose chemotherapy) salvage regimens are commonly used in this circumstance [40–42].

4. Persistent or recurrent disease following chemotherapy for advanced NSGCT

The standard treatment for patients with advanced NSGCT (CS IIC/III) is cisplatin-based chemotherapy. Approximately 70% will achieve a complete response as demonstrated by a normalization of STMs and a complete resolution of radiographic disease (<1 cm) [19–21]. The policy at Indiana University is to observe these patients because the risk of subsequent relapse is 5% [25]. Patients in whom STMs remain elevated following induction chemotherapy usually receive salvage chemotherapy, although surgery for isolated retroperitoneal disease may be curative. In contrast, surgical resection is recommended in patients with residual postchemotherapy masses >1 cm, provided that STM levels are normal, since 50–60% of such masses harbor persistent active disease (teratoma or cancer) [20,22,23]. Select patients with resectable disease and elevated STM levels who demonstrate chemoresistance may be appropriate candidates for “desperation” surgery rather than second- or third-line chemotherapy. The rationale and results of desperation PC-RPLND are discussed elsewhere in this article.

5. PC-RPLND

5.1. Indications and rationale for PC-RPLND

Thirty percent of patients with advanced NSGCT will fail to achieve a complete response to induction chemotherapy as indicated by a persistent elevation of STM or persistent radiographic tumor [21,43]. Most centers, including Indiana University, recommend postchemotherapy surgery in all patients with normal STMs and residual radiographic disease >1 cm because >50% of residual masses harbor teratoma (40–50%) or viable cancer (10–20%) or both [20,22,23]. Resection of residual teratoma or viable GCT is rational and well accepted. Unfortunately, there exist no clinical criteria by which to accurately predict the presence of necrosis (45%) and obviate the need for surgery in such patients [44,45]. Teratoma warrants surgical resection by reason of chemoresistance, disposition for progressive local growth, risk of malignant transformation, and risk of late relapse, whereas persistent viable GCT reflects some element of intrinsic chemoresistance and will progress if left untreated [46–48]. Patients in whom necrosis or teratoma is resected require no further therapy because the risk of relapse is low (necrosis <5%, teratoma 7–14%) [48–50]. In contrast, 48–100% of patients with viable GCT will relapse after surgery, indicating that the provision of two cycles of adjuvant chemotherapy may be appropriate [51,52]. Adverse predictors of progression-free and overall survival in patients with persistent GCT at PC-RPLND include incomplete resection, proportion of viable malignant cells >10%, and intermediate or poor risk disease by IGCCCG criteria [52]. Risk stratification by such parameters may guide the provision of adjuvant chemotherapy (Table 3). The integration of surgery and chemotherapy in patients with advanced NSGCT is well established and provides long-term survival in 70–80% [14,42,53].

Some centers also perform PC-RPLND in patients with minimal or no radiographic disease (<1 cm) provided that retroperitoneal disease was present at diagnosis and STMs have normalized following chemotherapy. The basis for this practice comes from reports of a 20–30% incidence of active disease (teratoma or viable GCT) in residual masses ≤1 cm [26–28]. Although such an observation would appear to support routine postchemotherapy surgery in all patients with retroperitoneal disease at diagnosis, a lack of benefit in terms of disease-free survival argues against such a policy. Indeed, the recurrence rate among patients with little or no radiographic disease (<1 cm) is 6% following PC-RPLND and 5% with long-term (5 yr) observation [25,26,29]. This disconnect in clinical and pathologic outcome suggests that the biologic behavior of residual tumor may, in fact, be variable. Although persistent viable GCT will almost certainly progress, microscopic mature teratoma may represent biologically inert disease with a low risk of growth and late relapse. Such a hypothesis remains purely speculative, however. Alternate explanations include pathologic misdiagnosis of tumor viability, staging error, and differences in chemotherapeutic efficacy among others.

Regardless of size criteria, a substantial proportion of patients (>45%) harbor necrotic tissue only and gain no therapeutic benefit from postchemotherapy surgery. Absence of teratoma in the primary tumor, normal prechemotherapy STM (AFP, β-HCG, lactate dehydrogenase), residual mass size <2 cm, and >90% volume reduction after chemotherapy have all been shown to be predictive of residual necrosis; however, no single criterion, or
Combination thereof, is sufficiently accurate to obviate the need for surgery [44]. It was previously suggested that postchemotherapy surgery could be avoided in patients with teratoma-negative primary tumors, normal STM levels, and a ≥90% reduction in the volume of retroperitoneal disease. This was based on the results of an early series in which 15 of 15 patients who met such criteria were found to have necrosis only at PC-RPLND [54]. A follow-up study, however, found that only 74% of a similar cohort of patients remained continuously free of disease without the addition of surgery [25]. Although the presence of teratoma in the primary tumor is indeed predictive of similar retroperitoneal histology, 33–58% of patients without teratoma in the primary tumor are found to have teratoma in the PC-RPLND specimen. This underscores the limitations of primary histology as a predictive tool [27,55].

In an attempt to improve on the predictive accuracy of individual clinicopathologic factors, statistical models have been developed that incorporate several recognized histologic predictors, as listed above. Even the most accurate predictive model, however, maintains a false-negative rate of 20% [28]. Furthermore, contemporary predictive models suffer from a lack of clinical relevance. This point was highlighted by a recent external validation study of the residual histology in testicular cancer (ReHiT) prediction rule, which found that only 4% of residual masses were classified as benign and could be offered surveillance in lieu of surgery [45].

Table 3 – Results of adjuvant chemotherapy in patients with viable cancer at PC-RPLND according to risk stratification

<table>
<thead>
<tr>
<th>Risk group</th>
<th>No. RF</th>
<th>5-yr PFS (%)</th>
<th>p</th>
<th>5-yr OS (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adj CTx</td>
<td>Observe</td>
<td>Adj CTx</td>
<td>Observe</td>
</tr>
<tr>
<td>Favorable</td>
<td>0</td>
<td>94</td>
<td>84</td>
<td>0.41</td>
<td>100</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1</td>
<td>84</td>
<td>42</td>
<td>0.0005</td>
<td>88</td>
</tr>
<tr>
<td>Poor</td>
<td>≥2</td>
<td>45</td>
<td>45</td>
<td>0.43</td>
<td>55</td>
</tr>
</tbody>
</table>

Risk factors include incomplete resection of tumor, proportion of viable malignant cells >10% and intermediate- or poor-risk disease by International Germ Cell Cancer Collaborative Group criteria.
RF = risk factors; PFS = progression-free survival; OS = overall survival; Adj CTx = adjuvant chemotherapy.

Based on a composite of the aforementioned data, it is the policy of Indiana University to observe patients with normal STM levels and residual masses ≤1 cm after chemotherapy, regardless of primary tumor histology, IGCCCG risk stratification, and volume of retroperitoneal disease at diagnosis. In turn, PC-RPLND is recommended for those patients with normal STMs and residual radiographic disease >1 cm. This management strategy maintains a low rate of relapse (5%) among patients entered into surveillance while at the same time minimizes the number of patients with necrosis who undergo postchemotherapy surgery unnecessarily.

5.2. Surgical considerations

RPLND is an advanced surgical procedure that requires a detailed knowledge of retroperitoneal anatomy, familiarity with vascular surgery techniques, and a full understanding of the natural history of testis cancer. Only then can surgery be performed in a safe, efficient, and efficacious manner. This becomes even more apparent during PC-RPLND on account of a larger tumor volume, the inevitable desmoplastic reaction associated with chemotherapy as well as its adverse effects on renal, hematologic, and pulmonary function. Although the morbidity of PC-RPLND exceeds that of primary RPLND, modifications in surgical technique combined with improvements in chemotherapeutic delivery and perioperative care have reduced the incidence of severe or long-term complications to an acceptable level without compromising cure [56]. To this end, postchemotherapy surgery should be performed in tertiary referral centers specializing in the management of testis cancer.

5.3. Preoperative preparation

PC-RPLND is usually performed 4–6 wk after the completion of chemotherapy to allow for physical and hematologic recuperation. A complete metastatic evaluation, including CT chest/abdomen/pelvis and STM analysis should be performed in the month before RPLND and STM analysis repeated 1–2 d prior. Bleomycin-related pulmonary toxicity is rare in good-risk patients who receive three cycles (9 wk) of BEP; therefore, pulmonary function testing is not routinely performed. Indications for pulmonary evaluation include prolonged administration of bleomycin (≥10 wk or >300 U), age >40 yr, history of smoking, advanced disease, renal insufficiency, and signs or symptoms of pulmonary compromise [57,58].
5.4. Evolution of the surgical technique and template of RPLND

Over the past three decades, considerable modifications in the technique and template of RPLND have occurred. Most notably, these include the modified unilateral template and nerve-sparing RPLND. Founded on improvements made in clinical staging, chemotherapeutic efficacy and our understanding of lymphatic drainage patterns and the neuroanatomy of antegrade ejaculation, these modifications were originally intended to minimize the morbidity of primary RPLND. In fact, such techniques have since found application in select patients undergoing PC-RPLND as well.

Surgical and anatomic mapping studies have detailed the most common sites of retroperitoneal metastases and form the basis for surgical templates in contemporary use. Lymphatic spread follows a predictable and systematic pattern that corresponds to the site of testicular origin and path of embryologic descent. The primary drainage zone for rightsided testicular tumors is the infrahilar precaval and interaortocaval lymph nodes, whereas that for the left is the lateral para-aortic lymph nodes [59–61]. Although not common in the absence of bulky retroperitoneal disease, the potential for contralateral spread does exist, particularly from right to left [62]. For this reason, full bilateral RPLND represents the standard surgical template used in the postchemotherapy setting. The limits of dissection include the crura of the diaphragm (superior), the bifurcation of the common iliac arteries (inferior), and the ureters (lateral). Within these boundaries lie the primary and secondary lymphatic drainage zones of both the right (interaortocaval, paracaval lymph nodes) and left testes (periaortic, preaortic lymph nodes; Fig. 1).

In times past, RPLND was routinely performed using the extended bilateral template, which also includes resection of the suprarebral lymphatic region. Although this procedure was historically morbid, the rationale for its wide extent came from the inaccuracy of clinical staging and the suboptimal efficacy of chemotherapy available at the time. Studies have since demonstrated that suprarebral lymphatic metastases are rare in the absence of bulky retroperitoneal disease (CS IIB, IIC) and, when present, are most commonly found in the retrocrural space [59,61,63]. In conjunction with improvements in imaging and chemotherapy, it became difficult to justify such radical surgery and, as such, suprarenal resection was omitted from routine use. Without evidence of retrocrural disease, the template of resection used at Indiana University does not extend above the origin of the diaphragmatic crura.

Loss of antegrade ejaculation, the most consistent long-term complication of RPLND, is almost inevitable with full bilateral RPLND and represents the impetus for two important modifications [64,65]. Previous series had demonstrated that retroperitoneal metastases in the setting of low-volume PS II disease is almost always unilateral and confined to the infrarenaal zone of primary spread [59,60,63]. Recognizing that the postganglionic sympathetic nerves critical to antegrade ejaculation join the hypogastric plexus in the para-aortic tissue just below the inferior mesenteric artery (IMA), it was proposed to omit contralateral dissection (Fig. 2) [66]. Dubbed the modified unilateral RPLND, this procedure has since been shown to preserve ejaculation in up to 90% of patients undergoing primary RPLND without compromising cure [67]. Although it is considered the standard template for primary RPLND at most centers, intraoperative evidence of high-volume or contralateral retroperitoneal disease remains an indication for full bilateral dissection.
Application of the modified unilateral template to PC-RPLND remains controversial. Many centers routinely perform bilateral dissection based on a 3–8% reported incidence of active disease (teratoma/cancer) in the contralateral landing zone [68,69]. It is important to note, however, that such reports come from studies involving a large proportion of patients with bulky disease at presentation. The risk of contralateral disease in the patient with small-volume disease clinically limited to the ipsilateral landing zone (CS IIA, IIB) is likely much less. Because most patients who completely respond to chemotherapy are observed based on a low risk of subsequent relapse (5%), the necessity of contralateral resection in patients with low-volume ipsilateral disease comes into question [25]. This issue becomes even more relevant as the number of patients with small volume disease treated with primary chemotherapy continues to rise, a scenario that accurately describes most patients with retroperitoneal relapse while on surveillance. Investigators at Indiana University recently reported the outcome of 100 patients who underwent modified unilateral template PC-RPLND [70]. Selection criteria included low-volume retroperitoneal disease (<5 cm), both before and after chemotherapy, confined to the ipsilateral primary landing zone. Updated results at a median 32-mo follow-up found that only four patients had a relapse (median, 8 mo), all outside the confines of a full bilateral template (unpubl. data, S.D.W. Beck, Indianapolis, Indiana, USA). The 2- and 5-yr disease-free survival was 95%. Based on these data it appears that modified unilateral resection is appropriate in select patients after chemotherapy. We currently perform modified unilateral PC-RPLND in patients with low-volume residual disease who meet the aforementioned criteria.

Up to 40% of patients who undergo modified unilateral template RPLND will develop retrograde ejaculation secondary to sympathetic denervation. The sympathetic nerves that mediate seminal emission and antegrade ejaculation arise from the T12 to L3 nerve roots. Postganglionic fibers from the paravertebral sympathetic chains converge toward the midline forming the hypogastric plexus below the IMA and travel thereafter to the pelvis where they innervate the seminal vesicles and bladder.
The prospective identification and preservation of these postganglionic nerves was described and popularized by both Jewett and Donohue [71,72]. Although the nerve-sparing technique is used more commonly in the primary setting, it may be appropriate in select patients undergoing PC-RPLND for low-volume residual disease. Of 472 PC-RPLND procedures performed at Indiana University between 1988 and 1995, 93 patients (20%) were deemed appropriate candidates for nerve-sparing procedures. Antegrade ejaculation was preserved in 77% of patients (62 of 81) with adequate follow-up, none of whom developed a retroperitoneal recurrence [67]. It must be remembered, however, that fertility issues should never take precedence over cancer control. Evidence of viable tumor warrants full bilateral RPLND with resection of nerves en bloc if preservation proves difficult.

6. Complicated postchemotherapy surgery

Certain groups of patients undergoing PC-RPLND are severely disadvantaged in terms of relapse-free and overall survival. These include patients who have received salvage chemotherapy, have undergone prior RPLND (reoperative RPLND), or have demonstrated disease progression prior to surgery (desperation RPLND). Review of the Indiana University PC-RPLND experience has shown that the presence of any one high-risk feature portends a 45% risk of relapse versus only 12% in patients without any complicating risk factors [22]. A fourth group of patients with especially poor prognosis are those judged to have unresectable disease. In this setting the relapse rate following surgery is 90% and overall survival is only 21% [22].

Residual radiographic disease after second-line or salvage chemotherapy is associated with a higher incidence of viable GCT (50% vs. 10%) and higher rate of incomplete surgical resection (39% vs. 16%), defined as gross residual disease, persistent postoperative STM elevation, or relapse within 1 mo of surgery, relative to patients who have only received induction chemotherapy [51]. Long-term survival after PC-RPLND is also lower in salvage chemotherapy patients (50–60%) and, unlike their induction chemotherapy counterparts, adjuvant chemotherapy appears to provide no survival benefit.

Reoperative surgery is an independent risk factor for poor outcome among patients with testis cancer and likely represents the only prognostic variable not absolutely dictated by the disease process itself [22,37,38,73]. The mean overall survival among patients who undergo repeat PC-RPLND is 56–63% versus 86% of primary PC-RPLND patients, and varies according to tumor histology and type of initial surgery. The prognosis with residual teratoma is intermediate between that of necrosis and viable cancer, whereas the prognosis following reoperation after primary RPLND is superior to that following reoperation after PC-RPLND [22,37,38]. Teratoma is the most commonly identified histologic subtype at secondary surgery and most patients have received chemotherapy between the surgical procedures. Repeat PC-RPLND is a formidable task that should be performed only at centers with extensive experience in the surgical management of testis cancer. Adjunctive procedures including thoracotomy, nephrectomy, and vascular reconstruction are often necessary (59–71%) and major morbidity is common (21–27%) [37–39]. Taken together, these data highlight the importance of complete surgical resection, for which adjuvant chemotherapy is no substitute.

The final high-risk PC-RPLND patient group includes those with rising STM levels ascribed to chemotherapy-resistant disease (desperation PC-RPLND). Although all such patients were traditionally considered to be poor surgical candidates, a recent review from Indiana University has shown that a select group of patients with elevated STMs...
after chemotherapy may benefit from surgery [74]. Of 114 desperation PC-RPLND procedures performed between 1977 and 2000, the mean 5-yr overall survival was 54%. Survival was superior in patients with teratoma or necrosis only; however, one third of the 54% of patients with resected viable cancer also achieved long-term survival. Poor prognostic factors included a rising β-HCG concentration, serum AFP level (continuous variable), repeat RPLND, and viable cancer in the resected specimen. Patient selection guidelines provided by this review include declining or plateau STMs after chemotherapy, rising STMs after initial complete response to chemotherapy, resectable radiographic disease in one or two locations, and increasing STMs with resectable disease after exhausting all chemotherapeutic options. It has become our policy to proceed with postchemotherapy surgery in patients with elevated STM levels and resectable chemoresistant disease rather than proceed with second- or third-line chemotherapy.

Among high-risk patients, adjuvant or concomitant procedures such as nephrectomy, aortic resection, and vena cava resection are not uncommon. Although such procedures potentially add to morbidity, en bloc resection of adjacent organs is often necessary to ensure complete resection of residual tumor. An aggressive surgical approach is justified because many high-risk cases involve chemotherapy-resistant disease.

7. Late relapse

Late relapse is defined as the recurrence of tumor following a disease-free interval of ≥2 yr from the time of initial treatment. The diagnosis rests on biopsy-proven GCT, STM elevation, or the growth of radiographic disease in the absence of a second primary tumor. Although only a small percentage of testis cancer patients will experience late relapse (2–4%), the incidence appears to be rising [75]. This may reflect the extended disease-free survival brought on through improvements in systemic chemotherapy [46,76]. The behavior, treatment, and prognosis of late relapse GCT differs from that of typical or early relapse and deserves individual consideration.

The median time to late relapse is 5–7 yr with a reported range of 2–32 yr [75–77]. The latest relapse observed at Indiana University is 35 yr, which certainly points to the importance of lifelong follow-up in the testis cancer population. Most cases of late relapse are diagnosed through STM elevation, predominantly AFP, which is elevated in 50–76%. Up to two thirds of patients are symptomatic with back or abdominal pain representing the most frequent complaints [75,76]. Consistent with the systematic pattern of metastatic spread, the most common site for late relapse is the retroperitoneum (47–80%) followed by the lungs (7–25%). A single site of radiographic disease is identified in 57% of patients and 8–10% present with elevated STM levels only. Those with marker-only relapse manifest radiographic disease within a median of 19 mo following initial STM elevation.

Although late relapse has been reported in patients of all clinical stages, it develops more commonly in those with advanced disease at initial diagnosis. Likewise, late relapse is more commonly described among NSGCT patients. Established risk factors include early relapse (<2 yr), poor-risk disease by IGCCCG criteria, postchemotherapy teratoma, and an inadequately controlled retroperitoneum at initial or postchemotherapy treatment [75–77]. Among 35 CS I patients with late relapse referred to Indiana University from 1979 to 1992, 31 (89%) had undergone prior RPLND, 19 (61%) of whom recurred within the retroperitoneum [78]. Interestingly, 10 of these 19 patients with retroperitoneal recurrence received immediate adjuvant chemotherapy following RPLND. Conversely, a review of all primary RPLNDs performed at our institution for CS I disease between 1965 and 1989 found that no patients with PS I disease developed late recurrence and only three patients with PS II disease did so, all outside the retroperitoneum. Taken together, this would indicate that incomplete resection may be a major predisposing factor for late relapse and adjuvant chemotherapy is no substitute for proper surgical technique.

Teratoma (60%) and yolk sac tumor (47%) are the most common histologic subtypes identified [76,79,80]. Most tumors consist of mixed histology but when categorized according to most aggressive component, viable GCT is most frequent (54–71%) followed by teratoma (19–28%). In contrast to primary and postchemotherapy RPLND series, teratoma with malignant transformation (sarcoma or adenocarcinoma) is not uncommon in cases of late relapse (10–18%) [76].

Whereas the standard treatment for early relapse is chemotherapy, that for late relapse is surgery. Most cases of late relapse demonstrate inherent chemoresistance such that cure with standard or even high-dose chemotherapy is rare [76]. The high prevalence of teratoma reported in available series echoes this point. In the largest single-institutional series of late relapse to date, a complete response was observed in only 6 (19%) of 32 patients treated
with primary chemotherapy, 4 of whom were chemotherapy naïve [76]. In contrast, 45 (92%) of 49 patients who underwent primary surgery were rendered disease-free and 21 (43%) remained continuously disease-free. The addition of postchemotherapy surgery to patients who failed initial treatment with chemotherapy rendered an additional 18 or 25 patients (72%) disease-free, 12 (48%) of whom were long-term. On the basis of this study and similar reports, primary surgical resection is the preferred treatment for late relapse at our institution [77]. Primary chemotherapy is usually reserved for patients with “unresectable” disease but may also be considered in chemotherapy-naïve patients wherein chemosensitivity is often maintained. Likewise, late relapse among seminoma patients typically responds to chemotherapy. Patients with marker-only relapse and a history of prior chemotherapy are typically observed until radiographic disease is manifest at which time surgical resection is recommended. En bloc resection of adjacent organs or vascular structures (kidney, inferior vena cava, aorta) may be required to ensure surgical cure. Likewise, distant sites of late relapse warrant resection if technically feasible.

The prognosis of late relapse is poor in comparison to that of early relapse. Continuous disease-free survival at 2 and 4 yr is reported in only 47% and 26% of patients, respectively [76]. Factors associated with improved prognosis include pure teratoma histology, single site of radiographic recurrence, serum AFP <100 U/L and chemotherapy-naïve status [75–77]. Although treatment is generally delivered in a multidisciplinary fashion, most patients cannot expect long-term survival without surgical resection.

8. Conclusion

The management of persistent or recurrent disease among patients with NSGCT depends on stage at presentation and relapse, STM levels at relapse, prior therapy, and timing of relapse. Patients with persistent disease or recurrence within 2 yr of initial therapy remain highly curable. Most patients with early-stage disease who relapse following active surveillance or primary RPLND are treated with induction chemotherapy. In this context, surgery for recurrent disease is primarily limited to the postchemotherapy setting. Similarly, postchemotherapy surgery is commonly recommended in patients with advanced disease at presentation who demonstrate residual radiographic disease and normal tumor markers following induction chemotherapy. In contrast, most advanced cases with persistently elevated markers after chemotherapy receive salvage chemotherapy. However, select patients with resectable disease and elevated STMs who are deemed refractory to chemotherapy may be appropriate candidates for “desperation” surgery. In the setting of late relapse, surgery often represents the primary treatment modality based on relative tumor chemoresistance.

Over the past three decades, considerable modifications in the technique and template of RPLND have occurred, most notably, the modified unilateral template and nerve-sparing RPLND. Originally intended to minimize the morbidity of primary RPLND, such techniques have since found application in select patients undergoing PC-RPLND as well. Although the morbidity of PC-RPLND continues to exceed that of primary RPLND, modifications in surgical technique combined with improvements in chemotherapeutic delivery and perioperative care have reduced the incidence of severe or long-term complications to an acceptable level without compromising cure.

Conflicts of interest

The authors have nothing to disclose.

References


CME questions

Please visit www.eu-acme.org/europeanurology to answer these CME questions on-line. The CME credits will then be attributed automatically.

1. The median time to recurrence in patients with clinical stage I non-seminomatous germ cell tumors on active surveillance is?
   A. 3 mo
   B. 6 mo
   C. 12 mo
   D. 18 mo

2. The primary treatment for marker-negative isolated retroperitoneal recurrence in patients with clinical stage I non-seminomatous germ cell tumors on active surveillance is?
   A. Induction chemotherapy (3 cycles BEP or 4 cycles EP)
   B. Second-line salvage chemotherapy
   C. Primary retroperitoneal lymph node dissection
   D. Radiotherapy

3. What percentage of pathologic stage I NSGCT patients will relapse following primary RPLND?
   A. <10%
   B. 20–30%
   C. 40–50%
   D. 60–70%

4. Following induction chemotherapy, what percentage of residual retroperitoneal masses harbor teratoma or viable germ cell cancer?
   A. 10–20%
   B. 30–40%
   C. 50–60%
   D. 80–90%

5. The standard surgical template for postchemotherapy RPLND is:
   A. Bilateral suprahilar RPLND
   B. Bilateral infrahilar RPLND
   C. Modified unilateral RPLND
   D. None of the above

6. The single most effective treatment for late relapse in non-seminoma patients is:
   A. Induction chemotherapy
   B. Second-line salvage chemotherapy
   C. Surgery
   D. None of the above