Postchemotherapy Surgery for Germ Cell Tumors—What Have We Learned in 35 Years?

STEPHEN B. RIGGS,^{a,b} EARL F. BURGESS,^a KRIS E. GASTON,^{a,b} CAROLINE A. MERWARTH,^a DEREK RAGHAVAN^a

^aLevine Cancer Institute and ^bMcKay Department of Urology, Carolinas Healthcare System, Charlotte, North Carolina, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Retroperitoneal lymph node dissection • Testicular cancer • Postchemotherapy retroperitoneal lymph node dissection • Seminoma • Nonseminoma • Germ cell tumor

ABSTRACT

Postchemotherapy surgery for advanced testicular cancer has evolved over the last couple of decades. Patients with nonseminomatous germ cell tumors and residual retroperitoneal mass ≥ 1 cm should undergo postchemotherapy retroperitoneal lymph node dissection (RPLND). For seminoma, RPLND is considered in those patients with masses ≥ 3 cm that are also positron emission tomography positive. Masses that occur outside of the retroperitoneum should be completely

resected with the possible exception of bilateral lung masses when resection of the first mass shows necrosis. The role of surgery in patients with extragonadal germ cell tumors is most vital in those with primary mediastinal nonseminomatous germ cell tumors. Importantly, patient selection, surgical planning, and consideration of referral to centers with this expertise are important to optimize success. *The Oncologist* 2014;19:498–506

Implications for Practice: Patients with advanced testicular cancer will often be considered for surgical consolidation following chemotherapy. This review article focuses on the evaluation and role of surgery in treatment of these complex patients. It underscores the selection of patients, vital role of surgery, as well as providing guidance in the use of surveillance as opposed to surgical extirpation.

INTRODUCTION

The role of surgery following primary chemotherapy for testicular cancer has evolved over the past 3 to 4 decades. Since the 1970s, there has been exploration of salvage surgery for those who do not achieve complete response to chemotherapy and even to consolidate successful chemotherapy by removing occult residual foci of germ cell malignancy or teratoma. Furthermore, it has become apparent that germ cell tumor can have transformation (either as a side effect of treatment or due to benign evolution) to mature teratoma that is inherently chemotherapy-resistant [1].

Our senior author and colleagues reported from the Royal Prince Alfred Hospital group its experience from 1977 to 1980 involving 21 patients (mix of stage II and III) who failed to achieve a clinical or radiological response (CR), of whom 14 had retroperitoneal node dissections, 5 had biopsy only, and 2 had thoracotomies for residual disease outside the retroperitoneum [2]. Several important observations were evident from this early series: first, the surgery was complex, requiring an average of 7 hours and at times requiring resection of adjacent organs. Second, those patients with tumor markers elevated at diagnosis and after primary chemotherapy either relapsed or had viable carcinoma at the time of surgery. Next, those patients with positive prechemotherapy tumor markers who

subsequently normalized had a low probability of either relapse or viable carcinoma following surgery. In addition, multiple residual sites (e.g., lung, supraclavicular node, and retroperitoneum) did not necessarily have concordant pathology (i.e., one site could have necrosis and the other site viable germ cell tumor or teratoma) [2]. Other early series confirmed the prognostic importance of a good response to chemotherapy, marker status after induction chemotherapy, and tissue type in resected specimen. Finally, those with residual viable disease have the potential for adverse outcomes and should be considered for further chemotherapy [3–5]. It is our intent in this article to update the oncologist regarding the role of surgery after chemotherapy for advanced germ cell tumors.

IMAGING AFTER CHEMOTHERAPY

In nonseminomatous germ cell tumors (NSGCTs), the imaging of choice is usually computed tomography (CT), with fludeoxyglucose (FDG) positron emission tomography (PET) reserved for residual masses in seminomatous patients only. One complicating factor surrounding the use of FDG PET for evaluation in patients with NSGCTs is due to the possibility that any residual mass could contain viable tumor, teratoma, or fibrosis/necrosis/inflammation/fluid. Therefore, a positive PET

Correspondence: Stephen B. Riggs, M.D., McKay Department of Urology, Levine Cancer Institute, Carolinas Healthcare System, 1021 Morehead Medical Drive, Suite 6100, Charlotte, North Carolina 28204, USA. Telephone: 980-442-6410; E-Mail: Stephen.Riggs@carolinashealthcare.org Received October 1, 2013; accepted for publication January 23, 2014; first published online in *The Oncologist Express* on April 9, 2014. ©AlphaMed Press 1083-7159/2014/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2013-0379>

scan in this population could represent viable germ cell or benign inflammation; fibrosis/necrosis and mature teratoma do not have affinity for the radiolabeled tracer unless they contain pockets of tissue fluid that allow passive absorption and retention of tracer. However, after chemotherapy for seminomatous tumors, there is only binary choice for the histology of the remaining mass: viable germ cell cancer or fibrosis, of which the latter appears to be much less “PET-active” [6].

The use of FDG PET in those patients with pure seminoma and especially masses >3 cm appears to have utility. De Santis et al. published a multicenter study involving 51 patients in whom 19 had residual masses >3 cm with a median follow-up of 34 months [7]. The positive predictive value and negative predictive value of FDG PET, irrespective of tumor size, were 100% and 96%, respectively. The two false negatives were seen in tumors ≤ 3 cm in size. Size >3 cm or ≤ 3 cm was confirmed to be a predictor of residual disease, as it has been in other series, with a cancer rate of 37% and 8%, respectively [7–10]. This series was followed up 1 year later and reported an additional false negative (3 of 11) in tumors <3 cm but maintained its perfect positive predictive value for a final sensitivity and specificity of 80% and 100%, respectively [11]. Therefore, all postchemotherapy masses >3 cm in size in patients with primary seminoma do not necessarily need treatment. A positive PET scan strongly suggests tumor (requiring additional therapy); therefore, we recommend the use of PET CT in this setting. Finally, it is worth mentioning that the timing of FDG PET after chemotherapy should be between 4 and 12 weeks, but no earlier because of the potential for inflammation-based false-positive results [7].

RETROPERITONEAL LYMPH NODE DISSECTION

Retroperitoneal lymph node dissection (RPLND) (Fig. 1) was first performed in the 1950s using knowledge from lymphatic drainage studies derived many years earlier. The primary landing zones were further elucidated and determined to be predictable in subsequent studies [12–14]. In general, as evidenced from early studies involving RPLND in patients without prior treatment, right-sided tumors metastasize to the interaortocaval lymph nodes first (just below the left renal vein), followed by the precaval and paracaval lymph nodes. Left-sided testicular tumors metastasize to the para- and preaortic areas. Contralateral involvement is more frequent in right-sided tumors as well as in bulky retroperitoneal disease [12, 15]. The involvement of suprahilar zones is infrequent in patients with minimal to moderate retroperitoneal disease (old staging B1; current staging IIA), but this incidence increases with increasing retroperitoneal volume (old staging B1, B2; current staging IIB, IIC). Furthermore, ipsilateral or contralateral disease below the bifurcation of the internal iliac vessels seems to be present only in the setting of more bulky retroperitoneal adenopathy (stage IIB, IIC) [12]. Enthusiasm for a modified template in primary treatment for stages I and IIA was reinforced in subsequent years with reaffirmation of the predictable drainage patterns in testicular cancer. In addition, the hypothesis that the drainage follows that of the testicular veins (on either side) to a so-called “lymphatic epicenter” was refuted [14].

Ultimately, an attempt to achieve sympathetic preservation and antegrade ejaculation has resulted in greater use of

Figure 1. Retroperitoneal lymph node dissection. (A): Aorta. (B): Vena cava. (C): Left renal vein.

either modified templates or nerve-sparing RPLND. The former is accomplished by staying above the inferior mesenteric arteries (based on the distribution of nodal disease referred to above), whereas a prospective nerve-sparing RPLND involves identification and preservation of sympathetic nerves from the T12–L3 thoracolumbar spinal cord in addition to the hypogastric plexus [15]. Nerve-sparing templates may even be applicable to postchemotherapy RPLNDs, whereas modified templates have, historically, been advocated for primary surgery [16], but its use in the postchemotherapy setting is evolving. Long-term follow-up studies that prove the absence of late relapse will be needed before such modified templates can be viewed as standard of care, and it seems unlikely that the hypothesis would ever be tested in a randomized trial.

INDICATIONS FOR POSTCHEMOTHERAPY RPLND IN SEMINOMA GERM CELL TUMORS

Postchemotherapy residual masses in patients with advanced seminoma warrant a different approach to that given to residual masses after chemotherapy in patients with non-seminoma. In general, the chance for malignancy is low if the tumor size is <3 cm and, therefore, observation is warranted. However, it increases to approximately 30% for residual masses ≥ 3 cm [9, 10]. Patients with pure seminoma and residual tumors >3 cm after chemotherapy should be submitted for PET CT as described above. If the PET scan is positive, then biopsy or surgery is indicated. Of importance, seminoma appears to remain sensitive to radiation after chemotherapy and, therefore, this approach, in addition to

Table 1. Postchemotherapy pathology for patients with residual masses ≤ 2 cm and ≤ 1 cm

Study	n (≤ 2 cm [18] or < 2 cm [19])	T and/or GCT	n (≤ 1 cm)	T and/or GCT
Norwegian Radium Hospital [18]	87	29 (33%) (23 T; 6 GCT)	54	16 (29%) (11 T; 5 GCT)
Memorial Sloan-Kettering Cancer Center [19]	237	75 (31.6%) (62 T; 11 GC; 2 mixed)	154	43 (27.9%) (33 T; 8 GCT; 2 mixed)

Abbreviations: GCT, germ cell tumor; T, teratoma.

surgery, should be considered [9]. There appears to be an increased rate of perioperative morbidity after RPLND for seminoma. For reasons that are not clear, the residual masses after advanced seminoma treated with cisplatin-based chemotherapy are associated with much more extensive fibrosis and, thus, constitute a much more complex surgical challenge. Albeit retrospective, one study evaluating outcomes in patients submitted for RPLND with seminoma suggested a higher rate (38%) of additional operative procedures (e.g., nephrectomy, inferior vena cava resection, arterial grafting, or bowel resection) as compared with those undergoing the same procedure for nonseminoma (26.8%). As expected, the rate of postoperative complications was also greater in the seminoma group (24.7% vs. 20.3%) [17].

reported on 141 patients determined to have a CR after chemotherapy, defined as normalization of tumor markers as well as radiographic disease < 1 cm [20]. Median follow-up was 15.5 years, and 12 (9%) patients experienced relapse, with four (3%) deaths attributed to germ cell tumor (GCT). Only six sites of relapse were in the retroperitoneum, suggesting that one half of the patients with relapse had the potential to benefit from PC RPLND. International Germ Cell Consensus Classification (IGCCC) predicted outcome with good-risk disease enjoying a 99% cause-specific survival versus 73% if disease risk was intermediate to poor. However, only 32 (29%) patients of the entire cohort were classified as intermediate to poor risk [20, 21]. Another retrospective study (Table 2) in support of surveillance was reported in 2008, evaluating 276 patients from both the British Columbia Cancer Agency and the Oregon Testis Cancer Program [22]. Like the series from Indiana University, 161 underwent surveillance for CR (same criteria as above); however, the median follow-up was much shorter (only 40 months), lending uncertainty to the potential for further late relapses. Ten patients (6%) relapsed at a median of 52 months, all of whom were salvaged and continuously in remission after a median follow-up of 64 months. Interestingly, all but two of the relapses were considered to have pristine postchemotherapy scans (i.e., no radiographic residual disease), and all but one of the relapses were in the retroperitoneum. Salvage therapy consisted of nine RPLNDs (one after additional chemotherapy) and one received only systemic chemotherapy. These two surveillance studies illustrate that the most likely recurrence site for patients who do not undergo immediate postchemotherapy RPLND is the retroperitoneum [23].

The German Testicular Group analyzed the pathological outcomes of patients undergoing postchemotherapy RPLND for any size tumor [24]. Size correlated with potential findings: those with tumors < 1 cm had a 9.4% and 21% chance of harboring either viable cancer or mature teratoma, respectively. These findings elevated to 21% and 25% for postchemotherapy tumors 1–1.5 cm and, ultimately, to 36% and 42% for those tumors greater > 1.5 cm in size [21, 24]. The usual histologic findings after PC RPLND have been reported as 40%–50% fibrosis/necrosis, 35%–40% teratoma, and approximately 10% viable germ cell tumor; of importance, a higher proportion of viable cancer was noted in the early series, prior to the implementation of predictive algorithms that matched aggression of chemotherapy to anticipated prognosis. Therefore, based on the considerations above, one’s ability to predict (to some degree) the histology of a postchemotherapy mass is based on the size of the mass after primary chemotherapy [21, 23, 24]. Several groups have evaluated predictive models in an attempt to determine retroperitoneal pathology [25–29]; unfortunately, all had variable success.

INDICATIONS FOR POSTCHEMOTHERAPY RPLND IN NONSEMINOMA GERM CELL TUMORS

Debate continues regarding which patients should be submitted for PC RPLND, most specifically around subcentimeter residual masses. Two divergent views are centered on the uncertainty and unpredictability regarding the biologic behavior of residual microscopic teratoma as well as the possibility of viable cancer. Furthermore, there remains variation among institutions as to what constitutes a radiographically normal retroperitoneum. The proponents of RPLND (Table 1) cite several observations, including a Norwegian study demonstrating 33% (29 of 87) of tumors ≤ 2 cm as having viable germ cell or teratoma, of which 55% (16 of 29) were ≤ 1 cm [18]. Furthermore, Carver et al., from Memorial Sloan-Kettering Cancer Institute, reported on 532 patients who underwent RPLND after chemotherapy: 154 patients had residual tumors ≤ 1 cm, of which 28% had either teratoma and/or viable germ cell (the majority were teratoma) [19]. On multivariate analysis, teratoma within the primary specimen as well as relative change in nodal size predicted teratoma within the retroperitoneum [19].

In contrast, the group from Indiana University (Table 2) has advocated surveillance of subcentimeter residual masses based on review of their experience. In 2009, Ehrlich et al.

Table 2. Outcome of surveillance for patients with complete response (≤ 1 retroperitoneal mass; normalized tumor markers) after first-line chemotherapy

Study	Patients, <i>n</i>	Median follow-up (yr)	Relapse	Relapse in retroperitoneum
Oregon/British Columbia Cancer Agency [22]	161	3.3	10 (6%)	9 (5.6%)
Indiana [20]	141	15.5	12 (9%)	6 (4.3%)

It appears that patients who achieve a complete radiographic response (normalization of tumor markers and radiographic disease ≤ 1 cm) after primary chemotherapy usually do not require postchemotherapy surgery [23]. Of course, these patients must be followed carefully as some will require salvage RPLND and consideration of further chemotherapy depending on the histologic results. Of note, we strongly advocate review of images by a highly experienced surgeon, oncologist, and radiologist to make this determination. Any residual tumor ≥ 1 cm in size should be removed because of the increasing probability of either viable tumor or teratoma [18, 21, 23, 24].

Finally, historical data have suggested that the morbidity was as much as twofold greater (20.7%) in patients undergoing postchemotherapy RPLND as compared with primary RPLND [15, 30]. Often this was secondary to pulmonary toxicity (adult respiratory distress syndrome or prolonged ventilation) from bulky retroperitoneal disease and bleomycin-induced pulmonary toxicity. However, current literature suggests that the morbidity after postchemotherapy RPLND is more comparable to that seen after primary RPLND with the exception of greater blood loss and operative time in addition to a reduced chance to maintain antegrade ejaculations [31]. This shift is most likely due to surgical experience, collaboration with other surgical disciplines (i.e., a qualified and experienced vascular surgeon is vital), and improved chemotherapy that has resulted in smaller residual volumes of tumor. All of the above underscores the need to have this surgery performed at centers with considerable expertise as well as appropriate ancillary services.

CHEMOTHERAPY AFTER POSTCHEMOTHERAPY RPLND

Current treatment paradigms predominantly involve second-line chemotherapy after the finding of viable GCT following postchemotherapy surgery (including RPLND and metastasectomy). Fizazi et al., in a retrospective analysis, evaluated the outcomes of 238 patients, all of whom had normal tumor markers before resection and residual viable NSGCT (so-called “surgical complete response”) removed following initial induction chemotherapy [32]. Seventy percent of their cohort received various postsurgery (second-line) chemotherapy regimens. Patients were stratified to one of three groups based on three identified risk factors: complete resection, $<10\%$ of viable malignant cells, and good-risk IGCCC. Those with all three factors were considered good risk, those without one of the risk factors were considered intermediate risk, and those without two or three were considered poor risk. Patients in the favorable group had a 100% overall survival (OS) rate at 5 years irrespective of postoperative chemotherapy. After adjustment for tumor volume, risk status, and status of resection, postoperative chemotherapy was associated with a significantly better progression-free survival (PFS) ($p < .001$) but not

overall survival [32]. A follow-up validation study was performed in 2008 across 12 institutions [33]. Ninety percent of patients underwent first-line chemotherapy with cisplatin. Median follow-up was 65 months and, similar to the first study, 5-year PFS for the entire cohort was 65%, with 5-year OS being 72%. The indices of complete resection, $<10\%$ viable germ cell and IGCCC risk status, were together highly predictive of both PFS ($p = .0008$) and OS ($p = .003$). However, as with the first study, there was no evidence of a survival benefit with postsurgery chemotherapy; thus, the index above does prognosticate but does not predict response to treatment [33].

This does bring into question the need for second-line chemotherapy in all patients with viable GCT after surgery in the postchemotherapy setting, especially for those patients who have undergone complete resection. However, the two studies above were retrospective, analyzing a cohort among multiple institutions and over many years, thus weakening the interpretation of the data. We currently consider observation versus several cycles of adjuvant cisplatin-based chemotherapy for those patients with residual viable GCT who have received induction chemotherapy only [34], with the duration of chemotherapy predicated on apparent response and toxicity; however, we favor the concept that this would be a fertile area for a multicenter collaborative trial to identify a truly optimal approach.

POSTCHEMOTHERAPY SURGERY FOR SITES OUTSIDE THE RETROPERITONEUM

The concordance between retroperitoneal masses and masses outside the retroperitoneum is incomplete, with outcomes dictated by the ability to resect all residual masses in addition to tumor marker status and whether viable GCT remains. In fact, the histologic discordance between sites is reported to be between 25% and 47% [35, 36]. Interestingly, the concordance between patients with bilateral residual lung masses who have pure necrosis in the first lung appears very good, with 19 of 20 (95%) also having this finding in the second lung [37]. Therefore, careful consideration to observation regarding a contralateral lung mass after the finding of necrosis in the first can be given; however, this does not hold true for mediastinal masses. Our view is that, in general, all masses should be considered for simultaneous resection if technically feasible.

The use of surgery for either relapse or in the primary setting in patients with metastatic germ cell tumor to the brain remains a topic of debate. Prospective trials are lacking and almost certainly will not be conducted as this constitutes less than 10% of patients with advanced germ cell tumors and less than 1% of all germ cell tumor patients [38]. National Comprehensive Cancer Network guidelines recommend radiation for patients with brain metastasis following chemotherapy, with surgery reserved for consideration in those in

whom it appears feasible (solitary metastasis) [39]. However, the evidence basis for this recommendation is not particularly strong. In the presence of significant elements of choriocarcinoma (predicted by the histology of the primary tumor or of metastases at other sites or very high circulating human chorionic gonadotropin), we believe that initial surgical resection of isolated brain metastases may be safer (if feasible) to avoid life-threatening intracranial hemorrhage after chemotherapy or radiotherapy.

Bone metastasis is also rare, constituting less than 1% of metastasis at the time of primary diagnosis or relapse [40]. However, it has been shown in patients specifically with poor-risk disease to constitute up to 9% [41]. In this study, Oechsle et al. retrospectively reviewed 40 patients with bone metastases from a cohort of 434 patients with poor-risk disease [41]. All patients underwent primary high-dose cisplatin-based chemotherapy with peripheral blood stem cell reinfusion. Four patients (10%) underwent surgical consolidation, all of whom had the finding of necrosis at the time of surgery [41]. As with disease of the brain, the ultimate timing and role of surgery for bone metastasis remain uncertain.

EXTRAGONADAL GERM CELL TUMORS

Extragonadal germ cell tumors represent less than 5% of all adult germ cell malignancies. Most of these are located in the anterior mediastinum followed by the retroperitoneum and very rarely in the pineal gland or presacral area [42]. Those containing seminoma are considered good or intermediate IGCCC risk and are recommended to undergo chemotherapy, usually with very good outcomes irrespective of location. Unfortunately, primary mediastinal nonseminomatous germ cell tumors (PMNSGCTs) are considered IGCCC poor risk and carry only a 40%–50% rate of survival after combination treatment with cisplatin-based chemotherapy and surgery [42, 43]. This is inferior to those occurring in the retroperitoneum, which are considered IGCCC good or intermediate classification depending on tumor marker status. Surgery plays a vital role in the management of PMNSGCTs as there is a high rate of viable tumor at the time of resection after chemotherapy [44, 45]. In general, we advocate that patients with PMNSGCTs are treated initially with VP-16, etoposide or vinblastine plus ifosfamide and cisplatin, or another poor-risk cisplatin-based regimen (to avoid bleomycin and its potential pulmonary toxicity) followed by thoracotomy and resection (residual mass is usually present). It is important that this complex surgery is undertaken by an experienced thoracic surgeon who has done this type of surgery, assuming the disease is deemed potentially resectable [45]. Because of the lack of effective salvage therapy, resection should be considered even in the face of elevated tumor markers as well as at the time of any recurrence [42, 45].

SURGERY AFTER SALVAGE OR SECOND-LINE CHEMOTHERAPY

It should be mentioned that the paradigm for aggressive surgical resection after salvage or second-line chemotherapy is to some degree different. In general, these are patients who progressed after first-line chemotherapy or who remain with unresectable disease. Residual masses after second-line chemotherapy have been associated with a much higher chance of residual GCT [10, 35], and surgery is often considered

even in the face of elevated tumor marker status because of the paucity of effective, alternative options.

However, Eggener et al., in a review of 71 patients after multiple chemotherapy regimens in 2007 (90% received second-line chemotherapy only), suggested that there was declining incidence of viable GCT in the retroperitoneal residual mass (ultimately paralleling that seen after primary chemotherapy) [46]. Overall, the rate of viable GCT was 28%; however, when analyzing the subset of patients who received taxane therapy, this rate dropped from 42% to 14%. Finally, with this reduction came higher rates of fibrosis (63% vs. 39%) with a relatively stable distribution of teratoma (31% vs. 33%). Of note, the rate of viable GCT or teratoma if located outside of the retroperitoneum was 31%. The 10-year disease-specific survival (DSS) was 70%, but was most favorable for those with a finding of only fibrosis (87%), as compared with teratoma (47%) or viable GCT (47%). On multivariate analysis, tumor size ≥ 5 cm as well as the presence of GCT predicted DSS [46]. All of the above supports the vital role of postchemotherapy surgery after second-line chemotherapy while at the same time suggesting that second-line taxane (paclitaxel, ifosfamide, and cisplatin or paclitaxel and ifosfamide followed by carboplatin and etoposide plus peripheral blood stem) therapy has improved the outcome and shifted histopathological distribution similar to that seen after first-line platinum-based therapy.

TEMPLATE

Controversy regarding the anatomical extent of RPLND after chemotherapy continues. Patients in the 1970s and 1980s often had high-volume residual disease necessitating full bilateral retroperitoneal dissection including suprahilar dissection. However, current chemotherapy regimens tend to leave remaining disease burden very low and restricted to the primary landing zones with contralateral crossover currently less likely [21, 47]. Some have advocated use of intraoperative frozen sections to guide extent of surgery. Herr et al. evaluated 62 patients, of whom 37 underwent limited lymph node dissection based on the finding of necrosis on frozen section [48]. The remaining patients underwent bilateral full template dissection of the retroperitoneum after frozen section revealed viable germ cell or teratoma. Fourteen patients had relapse, of whom only 1 had germ cell or teratoma in the retroperitoneum after limited dissection. Interestingly, there were six surgical complications, five of which occurred after bilateral dissection [48]. Others have suggested that a template RPLND is appropriate in those patients presenting with low-volume retroperitoneum disease (< 5 cm, stage IIA or IIB). Beck et al. evaluated 100 patients submitted for modified template RPLND (for postchemotherapy residual disease) after primary chemotherapy, of which there were only four recurrences in the retroperitoneum after 32 months of follow-up [47]. Interestingly, the locations of all recurrences were deemed to also be outside the boundaries of a full bilateral dissection. In this highly select population (98% had good-risk disease and 94% were stage IIA or B), a modified template did not appear to affect outcome [47].

Another 152 patients with postchemotherapy residual masses were retrospectively reviewed by Heidenreich et al. from two tertiary referral centers, of whom 98 underwent modified template resection if the mass was located in the

primary landing zone and <5 cm [49]. Mean length of surgery was significantly longer (90 minutes) in the full bilateral group as compared with the modified group. Antegrade ejaculation was preserved in 85% of patients undergoing modified template (average mass size of 4.5 cm) but only 25% in those undergoing full bilateral dissection (average mass size 11 cm). For the entire analyzed cohort, there were nine recurrences (three after modified dissection [3%] and six after full template dissection [12%]), with only one recurrence occurring within the boundary of a modified template dissection and all others occurring outside the boundaries of a full template dissection. Interestingly, all recurrences within the modified group were outside of the retroperitoneum; however, three in the full bilateral group were suprahilar in location [49]. Obviously, there is some selection bias with the average size for patients undergoing modified template being 4.5 cm versus 11 cm for full bilateral dissection. Also, 30% and 15% were IGCCC poor-risk classification for the full and modified groups, respectively [49].

What we take away from this, in contrast to earlier series [50], is that patients with postchemotherapy residual masses need to be carefully considered for a surgical plan. Also, with the advancement of systemic therapy, the current tumor burden of residual disease does not parallel that seen 20 years ago and, thus, the primary landing zones are more likely to be the only site of disease. Therefore, in patients with stage IIB or lower with a postchemotherapy residual mass within the primary known landing site, the surgeon can consider template dissection. High-volume tumors (i.e., stage IIC) and those with either pre- or postchemotherapy masses outside of the predicted lymphatic drainage should be submitted for full bilateral template as well as consideration for suprahilar and iliac dissection. Ultimately, however, there is little substitute for surgeon experience and judgment; therefore, we find this to be paramount in deciding the extent of dissection. It should also be emphasized that this type of surgery should not be undertaken solo by a surgeon who is inexperienced in the nuances of postchemotherapy germ cell cancer surgery.

LAPAROSCOPY

The use of laparoscopy in postchemotherapy RPLND appears technically feasible but uncertain with regards to its long-term outcome [51, 52]. Most of the current experience is in the primary setting as opposed to after chemotherapy. In general, the total lymph nodes removed in series evaluating laparoscopic RPLND have been considerably less than those reported for open series [53–55]. Understanding the utmost importance of “controlling the retroperitoneum,” we have not advocated laparoscopy in the postchemotherapy setting. Currently, the gold standard for postchemotherapy RPLND remains an open surgical approach.

“REDO” RPLND

As mentioned above, it is of utmost importance to achieve complete resection at the time of initial surgery. Hendry et al. reported on 442 patients undergoing RPLND for radiographic masses ≥ 1 cm, of whom 112 received their surgery in a salvage fashion [56]. The salvage group consisted of a referred population who had recurrent disease after observation of a known para-aortic mass. Also, they were submitted for reinduction chemotherapy prior to surgery. Complete resection

was accomplished in 87% of the primary group versus 72% of the salvage group, and lack of complete resection was elucidated on multivariate analysis as a predictor for OS. The need for concurrent nephrectomy was statistically twice as high in the salvage group, with an operative mortality 1.8% as compared with 0.9% in the primary group. Finally, overall survival was improved by an absolute difference of 33% in the primary (89%) as compared with the salvage (56%) group [56]. Incomplete control of the retroperitoneum after primary RPLND has been shown by others to be associated with an increased complication rate as compared with primary RPLND [57]. This at times requires coordination from additional surgical subspecialties (e.g., vascular surgery). McKernion et al. evaluated 34 patients who underwent primary PC RPLND who subsequently were submitted for reoperation [58]. Teratoma was the most common histologic finding at PC RPLND and at the time of reoperation. Notably, at a median follow-up of 29.5 months, the disease-specific survival rate for patients undergoing a second RPLND following PC RPLND was 56% [58]. Sonneveld et al. evaluated 51 patients with residual teratoma after postchemotherapy RPLND, of whom 15.7% (8) were deemed by the surgeon to be “incomplete” resections. Of these 8 patients, 4 relapsed with disease in the retroperitoneum, emphasizing the importance of complete resection [59]. Another more recent study evaluated the outcomes of 18 patients undergoing repeat RPLND, of whom 3 (16.7%) were deemed “out-of-field” recurrence, leaving the remaining 83% as “in-field” recurrences. Most recurrences were located in the interaortocaval, para-aortic, and suprahilar locations, with 10 patients (63%) having residual teratoma or GCT. Adjunctive procedures such as thoracotomy or vessel resection and grafting were required 55% of the time, and the overall postoperative complication rate was 38.8% [57]. This increased rate of perioperative complications as well as location of recurrence have been supported by others [58, 60]. The location of the recurrences may be related to incomplete surgery with respect to the renoaortic junction and the need to control (and dissect) all major tributaries before addressing any retroperitoneal mass. Of note, patients with teratoma after primary or postchemotherapy RPLND often have teratoma on repeat RPLND (as evidenced by 12 of 15 patients in one series [58]).

Our own experience and review of the above literature give us some insight into how to approach those patients presenting with residual masses in the retroperitoneum after primary RPLND who are also marker-negative. First, patients with the appearance of teratoma on imaging (cystic masses) would be best served with upfront repeat surgery. Teratoma only on initial RPLND (whether it be primary or after chemotherapy) often predicts teratoma in the residual retroperitoneum mass, and these patients also should be submitted for repeat surgery. It is reasonable to use percutaneous biopsy to attempt to identify patients who may have only necrosis/fibrosis. This would be most appropriate in those patients with negative tumor markers, no teratomatous elements at the time of initial RPLND, and no radiographic features suggesting teratoma. It is quite evident that salvage chemotherapy cannot salvage inadequate surgical resection, and complete surgical resection of any residual masses is imperative, as this may be the only prognostic factor that we can actually control. Moreover, it is obvious that

these complex surgeries need to be planned and coordinated appropriately to optimize surgical outcomes and success.

It is quite evident that salvage chemotherapy cannot salvage inadequate surgical resection, and complete surgical resection of any residual masses is imperative, as this may be the only prognostic factor that we can actually control. Moreover, it is obvious that these complex surgeries need to be planned and coordinated appropriately to optimize surgical outcomes and success.

“DESPERATION” POSTCHEMOTHERAPY RPLND

The use of “desperation” PC RPLND has been coined to refer to the use of surgery in patients with increased serum tumor markers after chemotherapy [21, 61]. At the time of desperation surgery, the incidence of viable GCT ranges from 40% to 81%, considerably higher than that seen after first-line chemotherapy and normalized tumor markers [61]. Beck et al. reported on 114 patients with metastatic germ cell tumor and elevated tumor markers after first- or second-line chemotherapy [62]. Retroperitoneal pathology was GCT in 53.5% (28% after first-line chemotherapy; 75.8% after second-line chemotherapy), teratoma in 34.2%, and fibrosis in 12.3%. There was a 54% 5-year overall survival for the entire cohort. Predictors of adverse outcomes in the induction group were retroperitoneal histology (finding of cancer was least favorable), whereas increasing beta-human chorionic gonadotropin, elevated alpha-feto protein (continuous variable), redo RPLND, and GCT histology predicted adverse outcome in the salvage chemotherapy group [62]. Literature review on the concept of desperation RPLND suggests that results are more favorable among those with stable or declining tumor markers as opposed to elevated ones. Also, in general, 50% of patients with elevated tumor markers at the time of surgery will have mature teratoma or fibrosis/necrosis, with a long-term disease-free interval in one third of patients with viable GCT [61–63]. It should be underscored that the use of RPLND in the face of rising tumor markers and the appearance of resectable disease constitutes an infrequent clinical condition. General guidelines for considering surgery include declining or plateau

serum tumor markers after chemotherapy, slowly increasing tumor markers after an initial complete response to chemotherapy (primary or secondary), resectable disease (one to two sites), increasing markers, and apparently resectable disease after all systemic options have been used [62].

CONCLUSION

Improvement in systemic therapy has, to a large degree, now relegated surgery for advanced GCTs to the postchemotherapy setting. Its use within the armamentarium for treatment of advanced GCTs remains vital. We have learned much over the past several decades. Masses outside the retroperitoneum should be completely resected with the possible exception of bilateral residual lung masses when resection of the first mass shows necrosis. For seminoma, postchemotherapy RPLND or biopsy and radiation should be considered for masses >3 cm that are also PET-positive. For NSCGT, postchemotherapy RPLND should be performed for tumors ≥ 1 cm and normal markers, those with plateauing tumor markers, and those with residual in-field masses and negative markers after prior RPLND. Additional indications include normal markers or plateauing markers after salvage chemotherapy, and in the desperation setting if the tumor appears resectable. It remains vitally important to “control the retroperitoneum” by resection of all disease the first time, thus avoiding the potential disturbing consequences associated with redo RPLND. Although our understanding regarding its use has evolved, it remains a complex procedure with the potential for significant complications; therefore, it is paramount to consider referral to facilities with this expertise.

AUTHOR CONTRIBUTIONS

Conception/design: Stephen B. Riggs, Earl F. Burgess, Kris E. Gaston, Derek Raghavan

Provision of study material or patients: Stephen B. Riggs

Collection and/or assembly of data: Stephen B. Riggs, Caroline A. Merwarth

Manuscript writing: Stephen B. Riggs, Derek Raghavan

Final approval of manuscript: Stephen B. Riggs, Earl F. Burgess, Kris E. Gaston, Caroline A. Merwarth, Derek Raghavan

DISCLOSURES

Derek Raghavan: Sanofi Aventis (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES

- Hong WK, Wittes RE, Hajdu ST et al. The evolution of mature teratoma from malignant testicular tumors. *Cancer* 1977;40:2987–2992.
- Reddel RR, Thompson JF, Raghavan D et al. Surgery in patients with advanced germ cell malignancy following a clinical partial response to chemotherapy. *J Surg Oncol* 1983;23:223–227.
- Donohue JP, Einhorn LH, Williams SD. Cytoreductive surgery for metastatic testis cancer: Considerations of timing and extent. *J Urol* 1980;123:876–880.
- Hendry WF, Goldstraw P, Husband JE et al. Elective delayed excision of bulky para-aortic lymph node metastases in advanced non-seminoma germ cell tumours of testis. *Br J Urol* 1981;53:648–653.
- Vugrin D, Whitmore WF Jr., Sogani PC et al. Combined chemotherapy and surgery in treatment of advanced germ-cell tumors. *Cancer* 1981;47:2228–2231.
- Becherer A. PET in testicular cancer. *Methods Mol Biol* 2011;727:225–241.
- De Santis M, Becherer A, Bokemeyer C et al. 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: An update of the prospective multicentric SEMPET trial. *J Clin Oncol* 2004;22:1034–1039.
- Motzer R, Bosl G, Heelan R et al. Residual mass: An indication for further therapy in patients with advanced seminoma following systemic chemotherapy. *J Clin Oncol* 1987;5:1064–1070.
- Puc HS, Heelan R, Mazumdar M et al. Management of residual mass in advanced seminoma: Results and recommendations from the Memorial Sloan-Kettering Cancer Center. *J Clin Oncol* 1996;14:454–460.
- Herr HW, Sheinfeld J, Puc HS et al. Surgery for a post-chemotherapy residual mass in seminoma. *J Urol* 1997;157:860–862.
- Becherer A, De Santis M, Karanikas G et al. FDG PET is superior to CT in the prediction of viable tumour in post-chemotherapy seminoma residuals. *Eur J Radiol* 2005;54:284–288.
- Donohue JP, Zachary JM, Maynard BR. Distribution of nodal metastases in nonseminomatous testis cancer. *J Urol* 1982;128:315–320.

13. Ehrlich Y, Yossepowitch O, Kedar D et al. Distribution of nodal metastases after chemotherapy in nonseminomatous testis cancer: A possible indication for limited dissection. *BJU Int* 2006;97: 1221–1224.
14. Weissbach L, Boedefeld EA. Localization of solitary and multiple metastases in stage II non-seminomatous testis tumor as basis for a modified staging lymph node dissection in stage I. *J Urol* 1987; 138:77–82.
15. Tarin T, Carver B, Sheinfeld J. The role of lymphadenectomy for testicular cancer: Indications, controversies, and complications. *Urol Clin North Am* 2011;38:439–449, vi [vi].
16. Pettus JA, Carver BS, Masterson T et al. Preservation of ejaculation in patients undergoing nerve-sparing postchemotherapy retroperitoneal lymph node dissection for metastatic testicular cancer. *Urology* 2009;73:328–331; discussion 331–322.
17. Mosharafa AA, Foster RS, Leibovich BC et al. Is post-chemotherapy resection of seminomatous elements associated with higher acute morbidity? *J Urol* 2003;169:2126–2128.
18. Oldenburg J, Alfsen GC, Lien HH et al. Post-chemotherapy retroperitoneal surgery remains necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses. *J Clin Oncol* 2003;21:3310–3317.
19. Carver BS, Bianco FJ Jr., Shayegan B et al. Predicting teratoma in the retroperitoneum in men undergoing post-chemotherapy retroperitoneal lymph node dissection. *J Urol* 2006;176:100–103; discussion 103–104.
20. Ehrlich Y, Brames MJ, Beck SD et al. Long-term follow-up of cisplatin combination chemotherapy in patients with disseminated nonseminomatous germ cell tumors: Is a postchemotherapy retroperitoneal lymph node dissection needed after complete remission? *J Clin Oncol* 2010;28: 531–536.
21. Heidenreich A, Pfister D. Retroperitoneal lymphadenectomy and resection for testicular cancer: An update on best practice. *Ther Adv Urol* 2012;4:187–205.
22. Kollmannsberger C, Daneshmand S, So A et al. Management of disseminated nonseminomatous germ cell tumors with risk-based chemotherapy followed by response-guided postchemotherapy surgery. *J Clin Oncol* 2010;28:537–542.
23. Osanto S, Richie J. Testicular cancer. In: *International Consultation on Testicular Cancer*. Shanghai, China: Société Internationale d'Urologie. 2011:112–117.
24. Pfister D, Busch J, Winter C et al. Pathohistological findings in patients with nonseminomatous germ cell tumors (NSGCT) who undergo postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) for small tumours. *J Clin Oncol* 2011;29 (suppl 7):244a.
25. Debono DJ, Heilman DK, Einhorn LH et al. Decision analysis for avoiding postchemotherapy surgery in patients with disseminated nonseminomatous germ cell tumors. *J Clin Oncol* 1997;15: 1455–1464.
26. Donohue JP, Rowland RG, Kopecky K et al. Correlation of computerized tomographic changes and histological findings in 80 patients having radical retroperitoneal lymph node dissection after chemotherapy for testis cancer. *J Urol* 1987;137: 1176–1179.
27. Vergouwe Y, Steyerberg EW, Foster RS et al. Validation of a prediction model and its predictors for the histology of residual masses in nonseminomatous testicular cancer. *J Urol* 2001;165:84–88; discussion 88.
28. Albers P, Weissbach L, Krega S et al. Prediction of necrosis after chemotherapy of advanced germ cell tumors: Results of a prospective multicenter trial of the German Testicular Cancer Study Group. *J Urol* 2004;171:1835–1838.
29. Steyerberg EW, Keizer HJ, Fosså SD et al. Prediction of residual retroperitoneal mass histology after chemotherapy for metastatic nonseminomatous germ cell tumor: Multivariate analysis of individual patient data from six study groups. *J Clin Oncol* 1995;13:1177–1187.
30. Baniel J, Foster RS, Rowland RG et al. Complications of post-chemotherapy retroperitoneal lymph node dissection. *J Urol* 1995;153:976–980.
31. Subramanian VS, Nguyen CT, Stephenson AJ et al. Complications of open primary and post-chemotherapy retroperitoneal lymph node dissection for testicular cancer. *Urol Oncol* 2010;28: 504–509.
32. Fizazi K, Tjulandin S, Salvioni R et al. Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: Prognostic factors and role of postsurgery chemotherapy—Results from an international study group. *J Clin Oncol* 2001;19:2647–2657.
33. Fizazi K, Oldenburg J, Dunant A et al. Assessing prognosis and optimizing treatment in patients with postchemotherapy viable nonseminomatous germ-cell tumors (NSGCT): Results of the sCR2 international study. *Ann Oncol* 2008;19: 259–264.
34. Fox EP, Weathers TD, Williams SD et al. Outcome analysis for patients with persistent non-teratomatous germ cell tumor in postchemotherapy retroperitoneal lymph node dissections. *J Clin Oncol* 1993;11:1294–1299.
35. Hartmann JT, Schmoll HJ, Kuczyk MA et al. Postchemotherapy resections of residual masses from metastatic non-seminomatous testicular germ cell tumors. *Ann Oncol* 1997;8:531–538.
36. Brenner PC, Herr HW, Morse MJ et al. Simultaneous retroperitoneal, thoracic, and cervical resection of postchemotherapy residual masses in patients with metastatic nonseminomatous germ cell tumors of the testis. *J Clin Oncol* 1996;14: 1765–1769.
37. Besse B, Grunewald D, Fléchon A et al. Nonseminomatous germ cell tumors: Assessing the need for postchemotherapy contralateral pulmonary resection in patients with ipsilateral complete necrosis. *J Thorac Cardiovasc Surg* 2009;137: 448–452.
38. Oechsle K, Bokemeyer C. Treatment of brain metastases from germ cell tumors. *Hematol Oncol Clin North Am* 2011;25:605–613, ix [ix.].
39. NCCN Clinical Practice Guidelines in Oncology. Testicular Cancer. Version 1, 2011. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed January 4, 2014.
40. Jamal-Hanjani M, Karpathakis A, Kwan A et al. Bone metastases in germ cell tumours: Lessons learnt from a large retrospective study. *BJU Int* 2013; 112:176–181.
41. Oechsle K, Bokemeyer C, Kollmannsberger C et al. Bone metastases in germ cell tumor patients. *J Cancer Res Clin Oncol* 2012;138:947–952.
42. Albany C, Einhorn LH. Extragenital germ cell tumors: Clinical presentation and management. *Curr Opin Oncol* 2013;25:261–265.
43. Bokemeyer C, Nichols CR, Droz JP et al. Extragenital germ cell tumors of the mediastinum and retroperitoneum: Results from an international analysis. *J Clin Oncol* 2002;20:1864–1873.
44. Vuky J, Bains M, Bacik J et al. Role of postchemotherapy adjunctive surgery in the management of patients with nonseminoma arising from the mediastinum. *J Clin Oncol* 2001;19: 682–688.
45. Kesler KA, Rieger KM, Hammoud ZT et al. A 25-year single institution experience with surgery for primary mediastinal nonseminomatous germ cell tumors. *Ann Thorac Surg* 2008;85: 371–378.
46. Eggener SE, Carver BS, Loeb S et al. Pathologic findings and clinical outcome of patients undergoing retroperitoneal lymph node dissection after multiple chemotherapy regimens for metastatic testicular germ cell tumors. *Cancer* 2007;109: 528–535.
47. Beck SD, Foster RS, Bihlre R et al. Is full bilateral retroperitoneal lymph node dissection always necessary for postchemotherapy residual tumor? *Cancer* 2007;110:1235–1240.
48. Herr HW. Does necrosis on frozen-section analysis of a mass after chemotherapy justify a limited retroperitoneal resection in patients with advanced testis cancer? *Br J Urol* 1997;80: 653–657.
49. Heidenreich A, Pfister D, Witthuhn R et al. Postchemotherapy retroperitoneal lymph node dissection in advanced testicular cancer: Radical or modified template resection. *Eur Urol* 2009;55: 217–224.
50. Wood DP Jr., Herr HW, Heller G et al. Distribution of retroperitoneal metastases after chemotherapy in patients with nonseminomatous germ cell tumors. *J Urol* 1992;148:1812–1815; discussion 1815–1816.
51. Steiner H, Zangerl F, Stohr B et al. Results of bilateral nerve sparing laparoscopic retroperitoneal lymph node dissection for testicular cancer. *J Urol* 2008;180:1348–1352; discussion 1352–1343.
52. Kimura Y, Nakamura T, Kawauchi A et al. Post-chemotherapy nerve-sparing laparoscopic retroperitoneal lymph node dissection in stage IIB testicular cancer. *Int J Urol* 2013;20:837–841.
53. Thompson RH, Carver BS, Bosl GJ et al. Contemporary lymph node counts during primary retroperitoneal lymph node dissection. *Urology* 2011;77:368–372.
54. Thompson RH, Carver BS, Bosl GJ et al. Evaluation of lymph node counts in primary retroperitoneal lymph node dissection. *Cancer* 2010;116:5243–5250.
55. Rassweiler JJ, Scheitlin W, Heidenreich A et al. Laparoscopic retroperitoneal lymph node dissection: Does it still have a role in the management of clinical stage I nonseminomatous testis cancer? A European perspective. *Eur Urol* 2008;54:1004–1015.
56. Hendry WF, Norman AR, Dearnaley DP et al. Metastatic nonseminomatous germ cell tumors of the testis: Results of elective and salvage surgery for patients with residual retroperitoneal masses. *Cancer* 2002;94:1668–1676.
57. Heidenreich A, Ohlmann C, Hegele A et al. Repeat retroperitoneal lymphadenectomy in

advanced testicular cancer. *Eur Urol* 2005;47:64–71.

58. McKiernan JM, Motzer RJ, Bajorin DF et al. Reoperative retroperitoneal surgery for nonseminomatous germ cell tumor: Clinical presentation, patterns of recurrence, and outcome. *Urology* 2003;62:732–736.

59. Sonneveld DJ, Sleijfer DT, Koops HS et al. Mature teratoma identified after postchemotherapy surgery in patients with disseminated

nonseminomatous testicular germ cell tumors: A plea for an aggressive surgical approach. *Cancer* 1998;82:1343–1351.

60. Sexton WJ, Wood CG, Kim R et al. Repeat retroperitoneal lymph node dissection for metastatic testis cancer. *J Urol* 2003;169:1353–1356.

61. Beck SD, Foster RS, Bihrlé R et al. Pathologic findings and therapeutic outcome of desperation post-chemotherapy retroperitoneal lymph node

dissection in advanced germ cell cancer. *Urol Oncol* 2005;23:423–430.

62. Beck SD, Foster RS, Bihrlé R et al. Outcome analysis for patients with elevated serum tumor markers at postchemotherapy retroperitoneal lymph node dissection. *J Clin Oncol* 2005;23:6149–6156.

63. Daneshmand S, Albers P, Fosså SD et al. Contemporary management of postchemotherapy testis cancer. *Eur Urol* 2012;62:867–876.

CME

This article is available for continuing medical education credit at CME.TheOncologist.com.

EDITOR'S NOTE: For further reading on germ cell tumors, watch for the forthcoming commentary by Sara J. Stoneham et al., "Adolescents and Young Adults with a "Rare" Cancer: Getting Past Semantics to Optimal Care for Patients with Germ Cell Tumors."

Germ cell tumors are the third most common cancer diagnosis in adolescent and young adult (AYA) patients aged 15–24. Many cancers that arise in AYA patients, including germ cell tumors, are defined as "rare" because they are relatively infrequent during early childhood and older adulthood. Consequently, the clinical care, clinical trials, and biological study of these cancers have not progressed synchronously with common childhood or adult cancers and gains in overall survival for this age group are only half those in either younger or older patients. The authors reflect on how to address this lack of progress, using as their lens, their own experience in creating an international, cross-discipline remodeling of the clinical trial development of GCT to overcome the barriers created by the structure of conventional medical practice.

Forthcoming in the July 2014 issue.