2

Management of Nonseminomatous Germ Cell Tumor of the Testis

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1. Introduction

1.1 Management options for clinical stage I non-seminomatous germ cell tumor of the testis

1.1.1 Introduction to clinical stage I disease

About 5-7/100,000 men are diagnosed with testis cancer annually. A large proportion of these are pathologically classified as non-seminomatous germ cell tumor (NSGCT). The majority of NSGCT patients present with clinical stage (CS) I disease, which is characterized by a germ cell tumor confined to the testis, a negative metastatic work-up which includes a chest X-ray (CXR), computed tomography scan of the abdomen and pelvis (CT A&P), and negative serum tumor markers (STM) post-orchiectomy. Patients who present with CS I testis cancer have a 30 percent chance of harboring occult metastatic disease post-orchiectomy, and thus controversy exists as to what represents the best treatment strategy following radical orchiectomy. Currently, there are 3 treatment strategies available for patients with CS I testis cancer, each one associated with a 99% cure rate: surveillance, adjuvant chemotherapy, and primary retroperitoneal lymph node dissection (RPLND).

1.2 Risk stratification for stage I disease

The ability to risk classify CSI patients to "high risk" of harboring micrometastatic disease and "low risk" of having micrometastatic disease would aid in tailoring therapy. Those patients identified as "high risk" could more preferentially be treated with primary RPLND or adjuvant chemotherapy, as they would have a greater risk of relapse on surveillance. Conversely, "low risk" patients may be managed with surveillance as they would have a greater likelihood of being cured with orchiectomy alone and thus overtreated with primary RPLND or adjuvant chemotherapy.

Several key studies have been published identifying pathologic factors predictive of metastatic disease in these patients. In 1987, a retrospective MRC trial identified four important negative prognostic indicators: presence of embryonal carcinoma, absence of yolk sac tumor, vascular invasion of the primary tumor, and lymphatic invasion of the primary tumor. (Freedman et al., 1987) These risk factors were then evaluated prospectively, revealing the presence of 3 or more risk factors as predictive of recurrence in approximately

50% of patients, and the presence of 2 or less risk factors as predictive of micrometastatic disease in about 20% of patients. Notably, vascular invasion of the primary tumor was most predictive. (Read et al., 1992) More recently, Vergouwe et al. reviewed 23 publications assessing predictors of occult metastases. (Vergouwe, Steyerberg, Eijkemans, Albers, & Habbema, 2003) Of the 2,587 total patients involved, 759 (29.3%) patients had occult metastasis. Pooled univariate odds ratios identified that lymphovascular invasion of the primary tumor, embryonal carcinoma component representing >50% of tumor, advanced pathologic stage (T2-4 versus T1), and monoclonal antibody MIB-1 staining greater than 70% of the tumor as the strongest predictors of occult metastases. Though somewhat variable, high risk groups, with the presence of either or both lymphovascular invasion and an embryonal dominant primary, carried a recurrence rate of approximately 50%. In patients without either pathologic variable, a recurrence rate of less than 20% was observed.

At best, with current risk classification, 50% of the "high risk" group harbor micrometastatic disease and 50% are cured by orchiectomy alone. Thus any therapy beyond orchiectomy for the "high risk" group overtreats 50% of patients, who are never destined to relapse. As such, risk classification is less than ideal in determining treatment. Future research aims to improve the prognostic ability of risk classification.

1.3 Surveillance for clinical stage I disease

1.3.1 Clinical outcomes of surveillance

The primary rationale for surveillance as a therapeutic modality is: 1) it avoids any further therapy in the 70% patients who do not harbor micrometastatic disease and who were cured by orchiectomy alone, and 2) those 30% of patients that relapse are curable with chemotherapy and/or surgery. To achieve a high cure rate, all patients on surveillance must be adherent to a strict follow-up schedule to identify those destined to relapse.

While surveillance avoids therapy in the large proportion of patients who are not destined to recur, there remains a burden of therapy for those that do. Some surveillance patients relapsing in the retroperitoneum with normal serum tumor markers may be candidates for primary RPLND. The remainder will require 3 courses of chemotherapy, and approximately a quarter of these will require surgery following chemotherapy. In the single center surveillance series of testis cancer patients from Toronto, at a median follow up of 6.3 years, 104 of 371 (28%) patients relapsed on surveillance. (Kakiashvili, Zuniga, & Jewett, 2009) Of the 104 patients that recurred, the burden of therapy included chemotherapy alone in 31, surgery alone in 31, and a combination of chemotherapy, surgery and radiation in the remaining 42 patients. Similar results were seen in a cohort of 223 patients from British Columbia and Oregon, where 26% relapsed on surveillance. (Kollmannsberger et al., 2010) No deaths were observed among those who recurred, although 20% of those who relapsed (8% of the original cohort) required post-chemotherapy retroperitoneal lymph node dissection (PC RPLND) in addition to chemotherapy.

Despite those recurrences, the overall survival for patients on surveillance equals that of primary RPLND or adjuvant chemotherapy. In a pooled analysis of 3424 patients on surveillance in series that reported death, a 98.6% disease specific survival was demonstrated. (Groll, Warde, & Jewett, 2007)

1.3.2 Follow up for surveillance

While some patients on surveillance will bear the burden of therapy upon relapse, all patients on surveillance bear the burden of compliance. Studies indicate that up to a third of patients miss at least one clinic visit. (Divrik, Akdogan, Ozen, & Zorlu, 2006; Meinke, Estes, & Ernst, 1979) A recent evaluation of compliance of CS I patients at the University of Calgary showed extremely poor compliance with scheduled follow up. (Hao et al., 1998) In this study, compliance with clinic visits and tumor markers was only 61% during the first year and 35% in year 2. Furthermore, compliance with scheduled CT scans was only 25% in year 1 and 12% in year 2. The only two deaths in 76 total patients were in individuals who were non-compliant with follow up. There is concern that non-compliance may translate into a decrease in disease specific survival. (Colls et al., 1999; Gels et al., 1995; Kakehi, Kamoto, Kawakita, & Ogawa, 2002; Raghavan et al., 1988) Nevertheless, the true impact of non-compliance on survival is unknown. A national surveillance study in New Zealand failed to correlate non-compliance with compromise in cure. (Colls, et al., 1999)

In addition to the risk of poor compliance, some patients on a surveillance protocol will experience anxiety due to the possibility of relapse. Although such anxiety is difficult to quantify, it is understandable that for some patient personalities, active therapy by way of primary RPLND or chemotherapy would be more desirable.

The burden of compliance involves more than anxiety or clinic attendance. Compliance with scheduled imaging studies will result in increased radiation exposure, and this exposure carries a slightly increased risk of secondary malignancy in this young population. (Brenner & Hall, 2007) Given higher relapse rates in the first 2 years of surveillance, (Groll, et al., 2007) more intensive follow-up is required in this time period using a combination of physical exam, CXR, STM, and CT A&P. In an effort to minimize radiation exposure, a randomized trial evaluated CT A&P at 3 and 12 months versus 3, 6, 9, 12, and 24 months and found no detection benefit in more frequent imaging. This study involved 414 patients with a median follow-up of 40 months, though only 10% of the patients were considered high risk based on vascular invasion. (Rustin et al., 2007) A popular follow-up schedule is that of the Toronto group, which is of moderate frequency compared to the aforementioned schedules, and is outlined in Table 1.

	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12
Year 1	STM,CXR	STM,CXR,CT A&P	STM, CXR	STM,CXR,CT A&P	STM, CXR	STM,CXR,CT A&P
Year 2	STM,CXR	STM,CXR,CT A&P	STM, CXR	STM,CXR,CT A&P	STM, CXR	STM,CXR,CT A&P
Year 3		STM,CXR		STM,CXR		STM,CXR
Year 4			STM,CXR			STM,CXR
Year 5						STM,CXR

Table 1. Toronto CS I NSGCT Surveillance Schedule

In addition to compliance issues, surveillance protocols also affect fertility rates, which approach 65% during surveillance, but decreases to 20% for surveillance patients that recur. (Herr, Bar-Chama, O'Sullivan, & Sogani, 1998).

1.3.3 Summary: Surveillance for clinical stage I disease

Surveillance offers an equal cure rate to either primary RPLND or adjuvant chemotherapy, and does so while avoiding further therapy in 70% of patients. Therefore, it is arguably the treatment option of choice in patients without significant pathologic risk factors for occult retroperitoneal metastases, who are willing to undergo serial imaging and intense follow-up. However, patients who choose surveillance must be aware of the importance of adherence to their follow-up schedule, and the fact that 30% of patients will require chemotherapy at relapse. As a result, patients strongly averse to chemotherapy may not wish to choose a surveillance protocol, favoring primary RPLND instead.

1.4 Adjuvant chemotherapy for clinical stage I disease

1.4.1 Clinical outcomes of adjuvant chemotherapy

The rationale for chemotherapy in CS I NSGCT is that it virtually eliminates the risk of recurrence, with an incidence rate much lower than that observed with either primary RPLND or surveillance. Recurrence rates were reported by the Spanish Germ Cell Group involving 231 high risk patients who received two courses of bleomycin, etoposide, and cisplatinum (BEP). (Maroto et al., 2005) Two patients (0.9%) relapsed and both are disease free after salvage therapy. Long-term follow up extending 10 years has confirmed the low relapse rates associated with adjuvant chemotherapy. (Chevreau et al., 2004; Westermann et al., 2008) Similarly low recurrence rates have been reported in other series also using 2 courses of BEP, (Cullen et al., 1996; Oliver, Raja, Ong, & Gallagher, 1992) allowing clinicians to draw the conclusion that there is little doubt on the efficacy of chemotherapy in preventing recurrence and achieving cure rates similar to surveillance or RPLND strategies for CS I NSGCT patients.

1.4.2 Morbidity of adjuvant chemotherapy

While the recurrence rates following 2 cycles of adjuvant BEP are impressively low, all patients, including the 70% who did not require this additional therapy, are subjected to the burden of systemic chemotherapy. Given the young age of most testis cancer patients, a lifetime remains to accrue complications secondary to this treatment choice. Specifically, the Royal Marsden Hospital reported a 2-fold greater risk of developing cardiovascular disease in testis cancer patients treated with chemotherapy and radiation. (Huddart et al., 2003) Others have reported that cured patients treated with cisplatin-based chemotherapy have a higher prevalence of hypertension and an excessive weight gain compared with patients treated with other modalities, and compared to controls. (Sagstuen et al., 2005) A recent report evaluated the long-term toxicity of cisplatin-based chemotherapy in 1409 men at a median follow-up of 10.7 years. (Brydoy et al., 2009) All chemotherapy groups had statistically higher odds of toxicity than men who did not receive chemotherapy, and that toxicity most commonly included Raynaud-like phenomena in 39%, paresthesias in the hands or feet in 29%, hearing impairment in 21% and tinnitus in 22%. Finally, it is worth noting that fertility rates during chemotherapy will drop substantially, recovering to approximately an 85% conception rate for couples desiring children, with a mean of 3 years of follow up. (Huyghe et al., 2004)

Bearing these concerning morbidity rates in mind, efforts have been made to decrease the toxicity of chemotherapy regimens by decreasing dose rates. Investigators have attempted to decrease the exposure to chemotherapy by treating clinical stage I patients with a single cycle of BEP. The Swiss Group for Clinical Cancer Research reported outcomes of high risk stage I patients receiving a single course of BEP in the adjuvant setting. (Westermann, et al., 2008) Data from 40 of the 44 patients were analyzed. Thirty-five showed no evidence of disease during a median follow up of 99 months. One patient developed pulmonary metastases after 13 months and died of pneumonia. Two patients developed contralateral testis cancer, subsequently received three cycles of BEP, and were relapse free for 4 and 92 months, respectively, thereafter. Two final patients were free of disease at 10 and 31 months when lost to follow-up. Also utilizing one course of BEP, the German Testicular Cancer Study Group has reported a 2-year disease free survival of 99.5% after a median follow up of 4.7 years, with just 2 recurrences observed in the intention-to-treat population. (Albers et al., 2008)

1.4.3 Follow up for adjuvant chemotherapy

During chemotherapy, serum markers are monitored prior to each cycle. Upon completion of 2 cycles of BEP, patient follow-up need be tailored based upon individual patient outcomes, and will include periodic physical examination, serum markers, and imaging of the chest, abdomen, and pelvis. (L. Wood et al., 2010)

1.4.4 Summary: Adjuvant chemotherapy for clinical stage I disease

To summarize chemotherapy as a treatment option, its greatest advantage lies in its recurrence rate of less than 2%. However, it subjects all patients, including the 70% never destined to recur, to the short and long term complications of systemic chemotherapy. While recent data suggest that one cycle of BEP may be adequate to achieve acceptably low recurrence rates, the standard of care continues to be two cycles of BEP, and the attendant morbidities of this therapeutic choice must be borne in mind.

1.5 Primary RPLND for clinical stage I disease

1.5.1 Clinical outcomes of primary RPLND – pathologic stage I disease

Testis cancer is unique among urologic cancers in that surgery (RPLND) can cure patients that have metastatic disease. Of CS I patients choosing primary RPLND, 70% will have no metastatic disease in their retroperitoneum, and are classified as pathologic stage I. Despite negative lymph nodes, 10% will relapse, and thus these patients still require follow-up. The remaining 30% with occult cancer identified in the lymph nodes are classified as pathologic stage II. For patients with pathologic stage II disease, surgery alone is curative in approximately 70%, and those 30% that relapse are cured with chemotherapy. Irrespective of pathologic stage, 99% patients who choose primary RPLND will ultimately be cured of their disease. (Donohue, Thornhill, Foster, Rowland, & Bihrle, 1993b)

1.5.2 Clinical outcomes of primary RPLND – low volume pathologic stage II disease

Management options for pathologic stage II disease include observation or adjuvant chemotherapy, as both have equal survival. This is based on a randomized trial of

pathologic stage II patients which compared adjuvant chemotherapy to close observation (with chemotherapy for recurrence). (Williams, et al., 1987) Analysis revealed no difference in survival (95%) between the two treatment arms at a median follow-up of 4 years.

Outcomes for patients with low volume pathologic stage II disease who choose observation are well described in the literature. Pathologic stage II disease was identified in 112 of 464 patients undergoing primary RPLND at Indiana for what was originally staged as clinical stage I disease, from 1965 to 1989. (Donohue, Thornhill, Foster, Rowland, & Bihrle, 1993c) Sixty-six percent of those patients with pathologic stage II disease were cured by RPLND alone. Memorial Sloan Kettering reported an 81% four-year progression free probability for pathologic stage II patients who did not receive adjuvant chemotherapy following a full, bilateral RPLND with less than a 2cm retroperitoneal mass. (Stephenson et al., 2005) Similar results were obtained in a series from Indiana University which included 118 RPLND patients with pathologic stage II disease, who did not receive adjuvant chemotherapy, and were followed for a minimum of 2 years. The 5 year disease free survival for this cohort was 68%. (S. D. Beck, Foster, Bihrle, Cheng, & Donohue, 2005; S. D. Beck et al., 2005)

Thus, 70% of patients with pathologic stage II disease are cured with RPLND alone, and those 30% that do relapse remain curable with 3 courses of chemotherapy. An alternative approach in managing pathologic stage II disease is 2 courses of adjuvant chemotherapy. While this approach reduces recurrence rates to less than 2%, (Behnia, Foster, Einhorn, Donohue, & Nichols, 2000; Culine et al., 1996; Gerl, Clemm, Kohl, & al., 1994; Kennedy, Torkelson, & Fraley, 1994; Kondagunta et al., 2004; Vugrin, Whitmore, Herr, Sogani, & Golbey, 1982; Weissbach & Hartlapp, 1991; Williams et al., 1987) it subjects all patients to chemotherapy, including the 70% who were cured by surgery alone. (Donohue, Thornhill, Foster, Rowland, & Bihrle, 1993a, 1995a; Richie & Kantoff, 1991)

Similar to risk stratification in CS I disease, efforts have been made to identify risk factors predictive of relapse for pathologic stage II disease after RPLND. Knowledge of such risk factors would allow “high risk” patients to receive adjuvant chemotherapy, and “low risk” patients to be observed. To date, no pathologic or clinical variable has been identified to predict relapse. (S. D. Beck, et al., 2007) (S. D. Beck, R. S. Foster, R. Bihrle, L. Cheng, & J. P. Donohue, 2005) (S. D. Beck, R. S. Foster, R. Bihrle, L. Cheng, T. M. Ulbright, et al., 2005) (Rabbani et al., 2001) (Richie & Kantoff, 1991)

1.5.3 Primary RPLND technique

The traditional full bilateral suprahilar RPLND involved removal of all lymphatic tissue from the suprahilar areas to the bifurcation of the common iliac arteries, from ureter to contralateral ureter. This was, by intent, a radical procedure, because chemotherapeutic rescue was not available when full bilateral RPLND was initially developed. All sympathetic efferent fibers were sacrificed, and lymphatic tissue was removed en bloc. Therefore, these patients suffered from anejaculation post-operatively.

Since the original extent of dissection was developed, it has been discovered, through the advent of CT scanning, and with the aid of meticulous anatomic mapping studies, that patients with clinical stage I disease may be treated with a much more limited dissection in the retroperitoneum, ipsilateral to the affected testis. Specifically, patients with low-volume retroperitoneal tumor from a left sided primary characteristically had metastases localized

to the upper left periaortic zone, and patients with low-volume disease from a right-sided primary were found to have metastases to the interaortocaval or precaval zones. These facts led investigators to modify the traditional full bilateral RPLND further and limit the dissection to the left- and right-sided templates, as depicted in Figures 1 and 2.

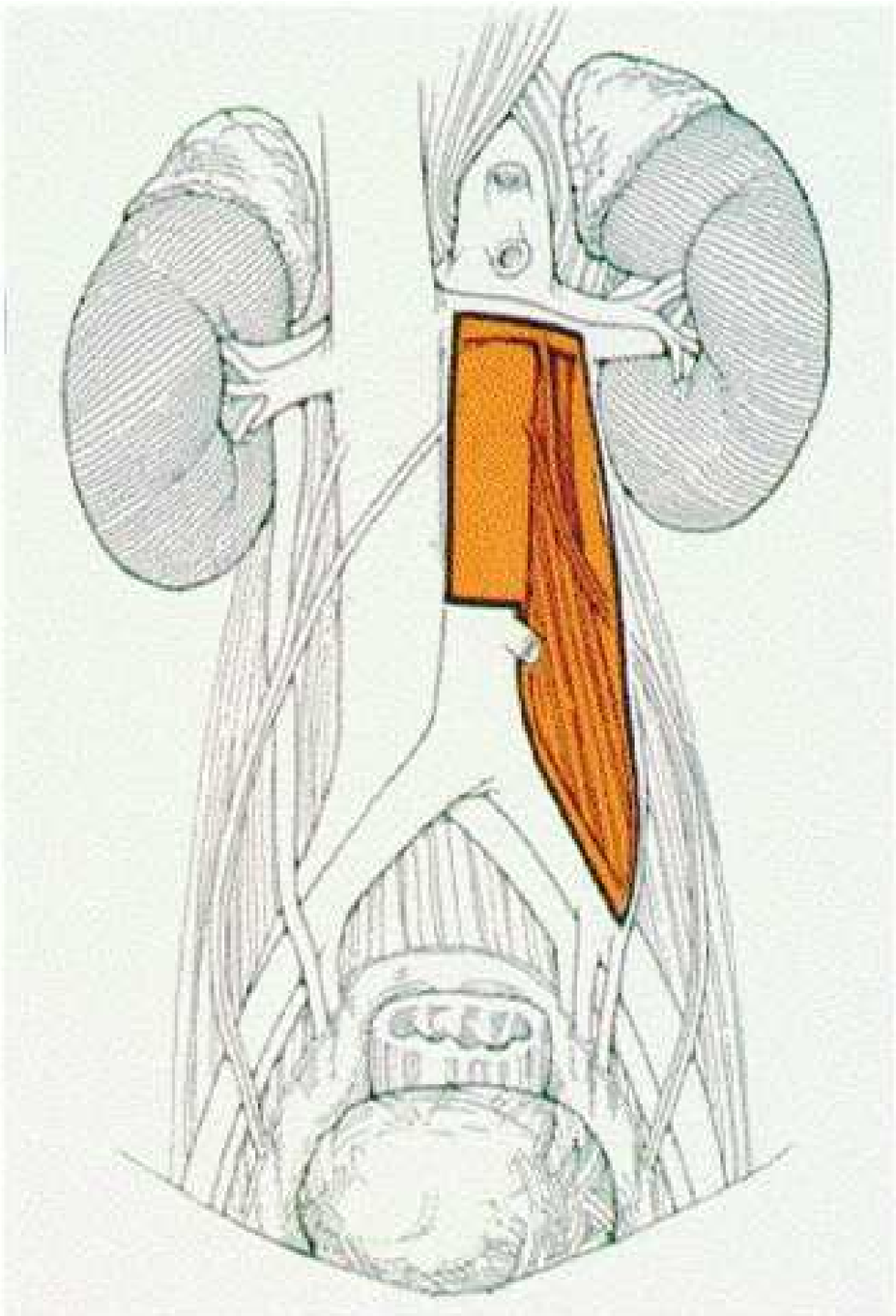

Fig. 1. Left-sided RPLND Template. Artist's rendering of the retroperitoneum. Orange area depicts area of surgical dissection.

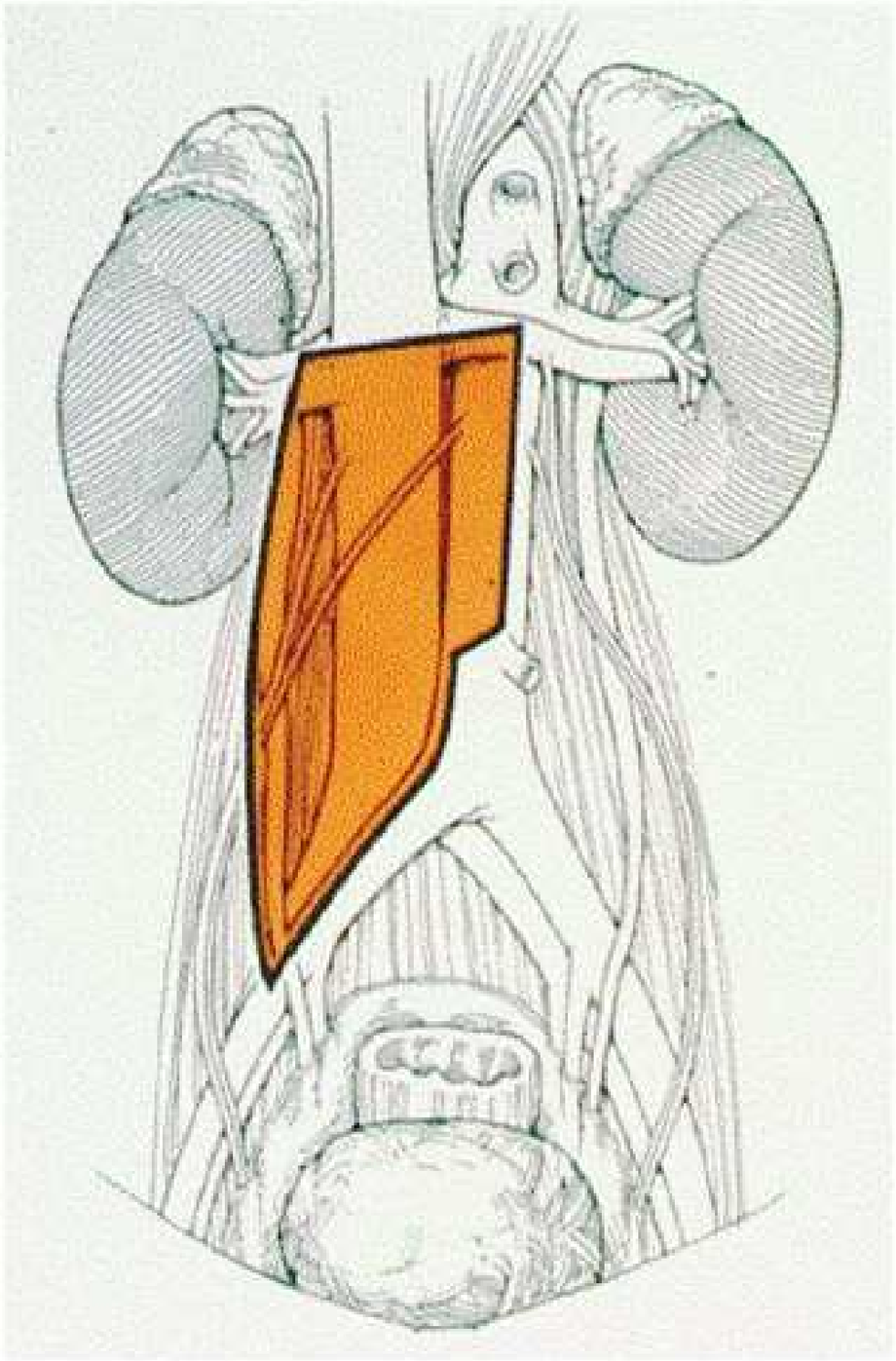

Fig. 2. Right-sided RPLND Template. Artist's rendering of the retroperitoneum. Orange area depicts area of surgical dissection.

With these templates, right and left sided dissection would remove lymphatic tissue at high risk of harboring metastatic disease, but preserve other retroperitoneal lymphatic tissue at low risk of containing metastasis. The advantages of limiting the dissection in patients with low

volume disease were shorter operative times, and shorter postoperative ileus. Additionally, and most importantly, these templates saved contralateral retroperitoneal efferent sympathetic fibers, thereby preserving emission and ejaculation in roughly 50% to 70% of patients.

The most recent modification in technique for RPLND for low-stage disease is the nerve-sparing dissection, in which efferent sympathetic fibers are prospectively identified and dissected, and modified lymphadenectomy is then performed. This advancement in technique preserves the staging and therapeutic aspect of RPLND, while additionally improving upon ejaculation preservation rates. In Figure 3, the right-sided post-synaptic sympathetic nerves are enveloped by vessel loops, and are seen exiting the sympathetic chain from underneath an anteriorly retracted inferior vena cava (IVC).

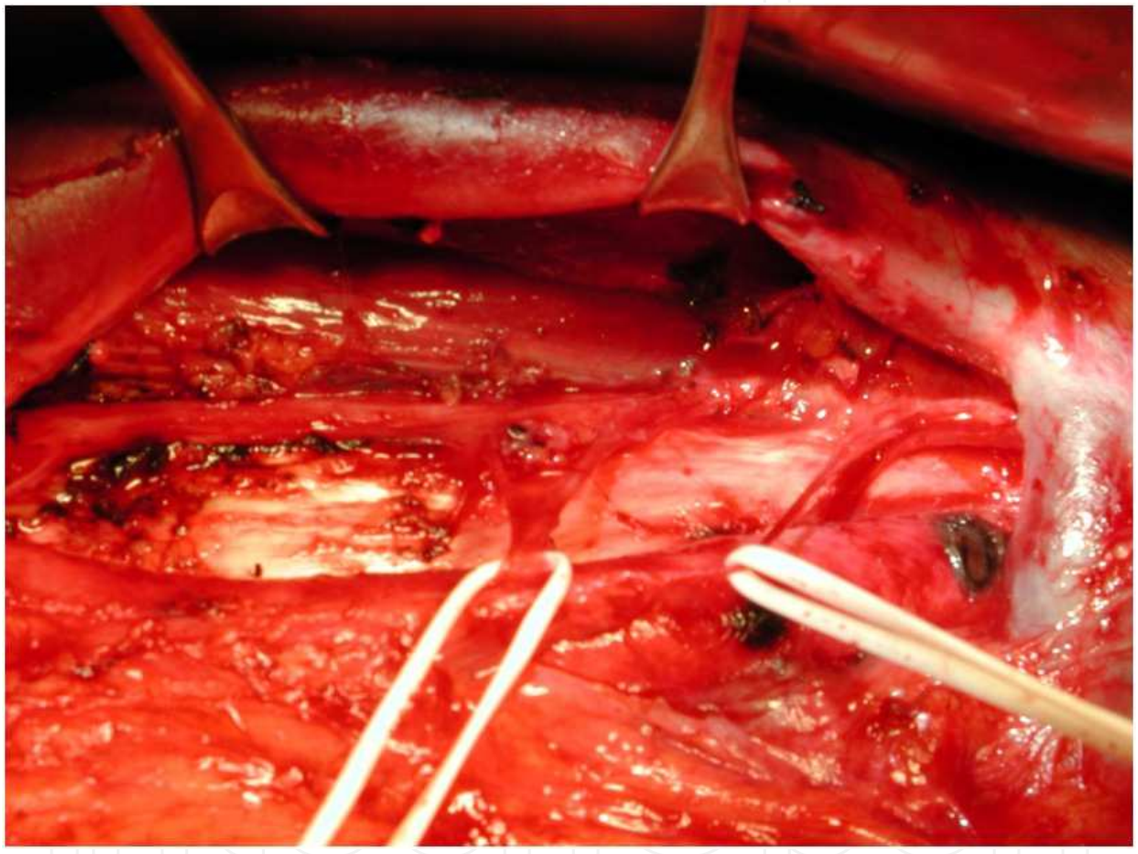

Fig. 3. Nerve-Sparing RPLND Technique. A photograph of the retroperitoneum during RPLND. The post-synaptic sympathetic nerves are encircled by white vessel loops for better visualization. Following the course of these nerves proximally, they can be seen joining the right sympathetic chain, which travels parallel and posterior to the inferior vena cava. The inferior vena cava is retracted anteriorly with vein retractors, to allow better visualization of the sympathetic chain.

A laparoscopic technique has been developed in an effort to further diminish primary RPLND's already favorable morbidity profile. It remains unknown as to whether or not the laparoscopic technique offers a morbidity benefit compared to the open technique. (Abdel-Aziz et al., 2006; Albqami & Janetschek, 2005; Janetschek, Hobisch, Holtl, & Bartsch, 1996;

Kenney & Tuerk, 2008) Furthermore, the vast majority of laparoscopic primary RPLND patients receive adjuvant chemotherapy following surgery, thus the therapeutic benefit of laparoscopic RPLND alone also remains unknown. (Rassweiler, Scheitlin, Heidenreich, Laguna, & Janetschek, 2008)

1.5.4 Morbidity of primary RPLND

Although primary RPLND as a treatment strategy offers excellent cure rates, it nonetheless subjects 70% of patients to unnecessary surgery. Fortunately, the morbidity of a primary RPLND is essentially that of a laparotomy. (Foster et al., 1994; Heidenreich et al., 2003; Jewett, 1990) A review of the experience at Indiana University showed that the only significant long-term morbidity is an approximate 1% chance of postoperative small bowel obstruction due to adhesions. (Baniel, Foster, Rowland, Bihrle, & Donohue, 1994) The same institution recently reviewed 75 consecutive primary retroperitoneal lymph node dissections. (S.D.W. Beck, Peterson, Foster, Bihrle, & Donohue, 2006) In this population the mean operative time was 132 minutes, mean blood loss was 207 cc. Nasogastric tubes are not routinely used in either primary or post chemotherapy surgery, and in this series only 2 patients had NG tubes. The mean hospital stay was 2.8 days (range: 2-4). With nerve-sparing technique, 99% maintain antegrade ejaculation, and a 75% fertility rate is observed. (S. D. Beck, Bey, Bihrle, & Foster, 2010; Foster et al., 1994) (S. D. Beck, Bey, Bihrle, & Foster, 2010; Foster, et al., 1994) This compares favorably to fertility rates for surveillance, and is roughly equivalent to fertility rates seen with chemotherapy.

1.5.5 Follow up for primary RPLND

Irrespective of pathologic stage at primary RPLND, the risk of relapse in the retroperitoneum is exceedingly low, with most relapses identified by chest X-ray and/or serum tumor markers. As such abdominal imaging with CT scan is not routinely used and follow-up consists of periodic chest X-ray, serum tumor markers, and physical examination. Given the rarity of relapse more than 2 years after remission, especially in the RPLND population, (Baniel et al., 1995) further follow-up accordingly becomes less rigorous in subsequent years.

1.5.6 Summary: Primary RPLND for clinical stage I disease

Though RPLND subjects all patients to a laparotomy (including the 70% that were pathologic stage I and did not require surgery), with nerve-sparing technique antegrade emission is preserved, and long term morbidity includes an abdominal scar and a 1% chance of latent small bowel obstruction. RPLND offers unique advantages over observation or adjuvant chemotherapy, including immediate pathologic staging, a simplified and less anxiety-prone follow-up involving less radiation exposure, and the potential for cure and the avoidance of chemotherapy for pathologic stage II patients.

1.6 Special considerations in stage I disease

1.6.1 Clinical stage I s patients

A small percentage of patients have elevated serum tumor markers which do not normalize appropriately following radical orchiectomy, despite an otherwise normal metastatic work-up, and are defined as clinical Stage I s disease. By virtue of the increased markers, these

patients continue to harbor disease. While some have advocated RPLND in such situations, confinement of disease to the retroperitoneum is not assured, thus additional chemotherapy may be necessary should RPLND not affect cure. As a result, chemotherapy is recommended for Stage Is patients.

1.6.2 Chemoresistant pathology

A small subset of patients have adenocarcinoma, teratoma with malignant transformation (such as primitive neuroectodermal tumour (PNET)), or a sex chord stromal tumor in their orchiectomy specimen. These histologies are chemoresistant, and a subsequent relapse is unlikely to be responsive to chemotherapy. Thus, first line treatment should be RPLND.

1.7 Summary: Management options for clinical stage I non-seminomatous germ cell tumor of the testis

Appropriate treatment of Stage I NSGCT requires knowledge of the risk factors associated with recurrence, foresight regarding the likely outcomes and percentages associated with the three treatment strategies, the morbidities unique to each modality, and most importantly a keen understanding of a patient's desired approach to this complicated problem. Given that all three treatment modalities offer equivalent cure rates, a treatment strategy which focuses on minimizing overall morbidity, and approaches the problem in a manner which is synergistic with a patient's wishes, is most likely to be successful.

2. Management options for clinical stage II and III non-seminomatous germ cell tumor of the testis

Patients with clinical stage II disease have evidence of disease confined to their retroperitoneum following radical orchiectomy. Clinical stage III patients have disease outside of the retroperitoneum following orchiectomy. Patients with small volume (<5cm) stage II disease and normal serum tumor markers post-orchiectomy may be treated with either primary RPLND or induction chemotherapy. Patients with "bulky" stage II disease, those with persistently elevated serum tumor markers, and all patients with clinical stage III disease, require cisplatinum-based chemotherapy.

2.1 Primary RPLND for low volume clinical stage II disease

2.1.1 Clinical outcomes of primary RPLND

As with clinical stage I disease, primary RPLND in low volume clinical stage II disease is both a staging and a therapeutic procedure. Following RPLND, further treatment decisions are based upon the pathologic stage of disease, regardless of the initial *clinical* stage at presentation. Donohue reported on 174 clinical stage II patients undergoing full, bilateral primary RPLND from 1965 to 1989. (Donohue, Thornhill, Foster, Rowland, & Bihrle, 1995b) Interestingly, 23% of patients originally staged as CS II disease were shown to be pathologic stage I disease following primary RPLND. 65% of those patients who were pathologic stage II with a nodal mass of less than 5 cm were cured by RPLND alone – that is, did not receive adjuvant chemotherapy. Thus patients with clinical stage II disease who are proven to be pathologic stage II are cured at roughly the 70% level with surgery alone.

2.2 Induction chemotherapy for clinical stage II and III disease

2.2.1 Clinical outcomes of induction chemotherapy

All patients with persistently elevated tumor markers post orchiectomy and CS III patients should initially be treated with induction chemotherapy. Chemotherapy for germ cell tumors is cisplatinum-based, and the specific regimen is dictated by risk classification, using the International Germ Cell Cancer Consensus (IGCCC) classification system, which assigns risk based on the site of the primary tumor, post-orchiectomy serum tumor markers, and the site(s) of metastatic disease (Table 2). ("International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group," 1997) Good risk patients are treated with 3 courses of bleomycin, etoposide, and cisplatinum (BEP). (Culine et al., 2007; Einhorn et al., 1989) In good risk patients over age 50 or with a strong smoking history, bleomycin may be omitted and 4 cycles of EP may be given instead. (Bosl et al., 1988; Culine, et al., 2007; Xiao et al., 1997) Standard therapy for intermediate and poor risk patients is 4 courses of BEP. Randomized trials evaluating high dose chemotherapy (HDCT) versus 4 cycles of BEP in poor risk patients as initial therapy failed to show an improved outcome in the HDCT arm. (Motzer et al., 2007) Overall, depending upon the patient population selected, roughly 70% of patients treated with induction chemotherapy for CS II or III disease will obtain a complete clinical response (CR) with normalization of serum tumor markers and complete radiographic resolution of all metastatic disease.

	Good Prognosis	Intermediate Prognosis	Poor Prognosis
Primary Site	Testis or Retroperitoneal	Testis or Retroperitoneal	Mediastinal
Metastases Site	No nonpulmonary visceral	No nonpulmonary visceral	Nonpulmonary visceral
Post Orchiectomy Serum Tumor Markers	AFP<1000 ng/mL βhCG<5000 IU/L LDH<1.5 x Normal upper limit	AFP 1-10,000 ng/mL βhcG 5-50,000IU/L LDH 1.5-10 x Normal upper limit	AFP>10,000 ng/mL βhCG>50,000 IU/L LDH>10 x Normal upper limit

Table 2. International Germ Cell Consensus Classification of Non Seminoma

2.3.1 Post-chemotherapy RPLND following complete response to induction chemotherapy

Following induction chemotherapy for CS II or III disease, patients achieving a CR are observed, as the risk of relapse is approximately 5%. (Ehrlich, Brames, Beck, Foster, & Einhorn, 2010) Recently, it has been shown that 20-25% of CR patients undergoing PC RPLND harbour microscopic teratoma in their retroperitoneum. (Karellas et al., 2007; Oldenburg et al., 2003) Thus there has emerged a controversy due to the disconnect between the pathologic finding of microscopic teratoma (20-25%) and clinically observed relapse rates (5%). The concern for physicians advocating immediate PC RPLND in this population is that with longer follow-up, the relapse rate will approach 20-25%. However, at 15 year follow-up, the relapse rate remains roughly 5%, thus the data continues to support surveillance as an appropriate strategy for CR patients.

2.3.2 PC RPLND for residual mass following induction chemotherapy

It is accepted worldwide that patients with normalization of serum tumor markers and persistent retroperitoneal mass following chemotherapy undergo PC RPLND. In this population, pathology reveals necrosis in 45%, teratoma in 45%, and active cancer in 10% (Toner et al., 1990).

For patients with necrosis at PC RPLND, surgery is a staging procedure only, and offers no therapeutic benefit. Relapse rates are approximately 5%, and no additional chemotherapy is required.

For patients with teratoma at PC RPLND, adjuvant chemotherapy is not given, as teratoma is chemotherapy insensitive. Nonetheless, teratoma at PC RPLND requires careful follow-up, as recurrence rates are not insignificant, and range from 5-20% with increasing size of mass. With a median post chemotherapy mass size of 3.0 cm, Memorial Sloan Kettering reported disease free survival of 83% at 5-years for resected teratoma. (Carver et al., 2007) In this study, patients with residual mass size less than 2 cm, 2 to 5 cm and > 5 cm had 5-year probabilities of freedom from recurrence of 94%, 91% and 59%, respectively ($p < 0.0005$). Other authors have had similar results. (Carver, et al., 2007; Loehrer et al., 1986; Svatek et al., 2009) Investigators from Indiana University recently reported recurrence rates after resection of large volume (> 10 cm) teratoma. (S. D.W. Beck, Foster, Bihrle, Donohue, & Einhorn, 2007) The 2 and 5-year recurrence free survival for the 99 patients was 86% and 75%, with a mean follow up of 42 months, suggesting that in large volume masses, recurrence rates are also noteworthy. As a result, follow-up of teratoma at PC RPLND need include serial abdominal CT scan.

The presence of active cancer at PC RPLND portends a poor prognosis, and it has been standard practice to give two courses of adjuvant chemotherapy. In this population, Spiess reported the 5 year disease-free survival rate to be 50%. (Spiess et al., 2007) An international study group on testis cancer reported the outcomes of 238 patients with active cancer at PC RPLND. Variables predictive of survival included incomplete surgery, viable malignant cells > 10% of surgical specimen, and poor or intermediate IGCCC risk category. (Fizazi et al., 2001)Patients with no adverse factors experienced a 5-year progression free survival of 90% compared to 41% for 2 or more risk factors. Furthermore, on multivariate analysis postoperative chemotherapy was associated with a significantly better progression free survival ($p < 0.001$), but not overall survival ($p = 0.26$). Thus, while adjuvant chemotherapy does not improve overall survival, it does reduce recurrence rates to 30%, and thereby avoids the morbidity of second line chemotherapy for those who do not recur.

2.3.3 Follow-up after PC RPLND

PC RPLND follow-up is based upon retroperitoneal pathology. Patients with necrosis are at low risk of relapse, and follow-up should include physical exam, serial chest imaging and serum tumor markers. Routine abdominal imaging is not necessary in this population. In addition to the routine follow-up necessary for necrosis, patients with teratoma are at some risk of retroperitoneal relapse, and therefore require serial abdominal CT scans. Follow-up for active cancer should be tailored individually, though will include physical exam, serum tumor markers, chest X-ray and abdominal imaging.

2.3.4 Summary: Induction chemotherapy and PC RPLND

Following induction chemotherapy for clinical stage II or III disease, patients with a complete response to chemotherapy are most commonly managed with observation. Patients with a persistent retroperitoneal mass and negative serum tumor markers routinely undergo PC RPLND. 45% of PC RPLND patients will harbor necrosis, with a relapse rate of 5%. 45% harbor teratoma with relapses ranging from 5-20%, depending on mass size. The 10% of patients with active cancer in their retroperitoneum at PC RPLND are treated with adjuvant chemotherapy to improve disease-free survival. Adjuvant chemotherapy has yet to demonstrate improved overall survival in this population.

2.4 Special considerations in stage II and III disease

2.4.1 Induction chemotherapy failure

Patients with disease relapse or disease progression despite first line chemotherapy are candidates for salvage therapy. Disease progression may be identified by persistently elevated tumor markers or increasing mass size. A minority of such patients will have anatomically confined disease that is amenable to surgical resection, and may undergo "desperation surgery". (S. D. Beck, Foster, Bihrle, Einhorn, & Donohue, 2005; Murphy et al., 1993) For the remaining patients with multifocal disease, treatment options include salvage chemotherapy with cisplatin plus ifosfamide plus vinblastine, (Loehrer, Gonin, Nichols, Weathers, & Einhorn, 1998) or paclitaxel (Motzer, Sheinfeld, et al., 2000) for four courses, or high-dose chemotherapy with autologous hematopoietic stem-cell transplantation to rescue the bone marrow from the myeloablative effect of chemotherapy. (Einhorn et al., 2007; Motzer, Mazumdar, et al., 2000; Rick et al., 1998)

2.4.2 Determining the extent of dissection at PC RPLND

Many patients from the 1970's and 1980's undergoing post chemotherapy surgery had high volume residual disease and the decision to perform a full, bilateral RPLND was therefore rational and appropriate. Since chemotherapy is now being administered for relatively low volume retroperitoneal disease, and since these tumors are typically restricted to the primary landing zone of the affected testicle, the question has arisen as to the appropriateness of full bilateral PC RPLND in this population.

Proponents of modified dissections note that with appropriate patient selection, the risk of extra-template disease and its clinical significance is low. In 1992, investigators from Memorial Sloan-Kettering published a series of 113 patients undergoing full bilateral PC RPLND, with an 8% incidence of disease (cancer/teratoma) identified in the contralateral landing zone. (D. P. Wood, Jr., Herr, Heller, et al., 1992) This cohort all presented with "bulky disease", and were treated with cisplatin- or carboplatin-based chemotherapy. Based upon these findings, the authors concluded that a modified dissection should be considered in patients with 1) no palpable residual tumor mass, 2) a left primary tumor, or 3) a right primary tumor and no evidence of cancer/teratoma on frozen section analysis of the residual mass. Fossa et al. reported the results of 87 patients with residual masses less than 20 mm undergoing modified PC RPLND. (Oldenburg, et al., 2003) Pathology revealed necrosis in 67%, teratoma in 26%, and cancer in 7%. Five relapses occurred in this study, with no recurrences in the retroperitoneum, indicating that the template of dissection was

adequate. Indiana University recently reported outcomes of 100 patients undergoing a modified post chemotherapy dissection. (S.D.W. Beck, Foster, Bihrle, & Donohue, 2005) The selection criteria included low-volume retroperitoneal disease (< 5 cm) both pre- and postchemotherapy, restricted to the primary landing zone of the affected testicle. Pathology revealed cancer in 2%, teratoma in 62% and necrosis in 36%. Three patients relapsed, all outside the boundaries of a full bilateral dissection, and the 2-year progression free survival was 95%. Others have also demonstrated the safety of a modified PC RPLND in select patients, (Ehrlich, Yossepowitch, Kedar, & Baniel, 2006; Rabbani et al., 1998) thus it appears that a modified dissection may be appropriate in select patients.

Though limited dissection is appropriate in a subset of patients, the vast majority of patients undergoing PC RPLND require a full, bilateral dissection.

2.4.3 Complicated PC RPLND

Complicated PC RPLND is defined as: 1) PC RPLND after more than induction chemotherapy ("salvage RPLND"), PC RPLND after previous RPLND ("redo RPLND"), or PC RPLND in the setting of persistently elevated markers or progression of disease after chemotherapy ("desperation RPLND"). (Donohue, et al., 1998)

Indiana University reported the outcomes of patients undergoing "complicated" RPLND. The incidence of active cancer at "salvage" RPLND was 50%, with an overall survival of 50% to 60%. There appeared to be no benefit with adjuvant chemotherapy in this population. Overall survival for the 188 patients undergoing "redo" surgery was 63%. Memorial Sloan-Kettering reported a 67% 5-year disease specific survival for 57 patients undergoing redo surgery. (McKiernan et al., 2003) Historically, persistent serum tumor marker elevation after chemotherapy has been considered a relative contraindication to surgery, due to supposed systemic disease and low chance of cure with local therapy alone. These "desperation" patients were therefore treated with salvage chemotherapy. Over the last 15 years, however, several centers have experienced surgical cures in this population. (S. D. Beck, R. S. Foster, R. Bihrle, L. H. Einhorn, et al., 2005; Eastham, Wilson, Russell, Ahlering, & Skinner, 1994; Murphy, et al., 1993; D. P. Wood, Jr., Herr, Motzer, et al., 1992) Thus, a subset of patients with elevated serum tumor markers after chemotherapy are curable with surgery. Approximately 50% of patients undergoing post chemotherapy surgery with elevated serum tumor markers are alive at 5-years. Half of these patients are found to harbor viable non-teratomatous germ cell tumor, and a third of these are alive at 5-years. Interestingly, this small subset population observes no benefit from adjuvant chemotherapy. Clearly, there is a role for surgery in selected patients with elevated serum tumor markers. The decision to proceed with surgery *in lieu* of second or third line chemotherapy involves identifying patients that are unlikely to obtain a complete response with systemic therapy, are of acceptable surgical candidacy, are harboring resectable tumors which could potentially be curable with negative margins, and following resection are offered acceptable morbidity profiles.

2.4.4 Surgical management of pulmonary extraperitoneal disease

Selection of patients for pulmonary resection typically includes patients with residual lung nodules and normal serum tumor markers after chemotherapy. Much like PC RPLND,

resection of residual teratoma or active cancer in the pulmonary system can be therapeutic and therefore the morbidity of thoracotomy is justified. Conversely, resection of residual necrosis is a staging procedure only.

Efforts to predict pulmonary histology prior to surgical resection have been somewhat successful. Excluding series with less than 100 patients, there are 2 retrospective studies identifying variables predictive of pulmonary histology. Tognini et al reviewed 143 post chemotherapy patients who underwent resection of residual retroperitoneal and chest disease under the same anesthetic. (Tognoni et al., 1998) Pathologic concordance between pulmonary and retroperitoneal masses existed in 77.5% of patients with necrosis, 70% with teratoma, and 69% with active cancer. For surgery-naïve patients experiencing normalization of tumor markers following first line chemotherapy, a pathologic concordance between pulmonary and retroperitoneal masses of 86% for patients with necrosis was seen. An international, multicenter, retrospective review evaluated the concordance of retroperitoneal and pulmonary histology in 215 patients. (Steyerberg et al., 1997) The strongest predictor of pulmonary histology was the histology found at PC RPLND -- if PC RPLND histology revealed necrosis, the probability of necrosis at thoracotomy was 89%.

As such, patients with small pulmonary nodules may be observed with serial chest imaging. Masses which enlarge on observation are thus identified, and represent the small proportion of patients with residual disease in the form of teratoma (5%) or active cancer (1-4%). Such patients could conceivably then undergo surgical resection without a decrease in their expected survival rate. In fact, in subgroups with pulmonary nodules and necrosis in the retroperitoneum, such an approach would spare more than 90% of patients the morbidity of thoracotomy.

There is no data comparing immediate resection of residual pulmonary nodules versus delayed resection upon progression. Decision-making with regard to residual pulmonary mass resection must take into account technical feasibility, patient morbidity and potential benefit, future access to health care, and of course patient preference.

2.4.5 Surgical management of nonpulmonary extraperitoneal disease

NSGCT metastatic to extraperitoneal sites beyond the pulmonary system are quite rare, and require specific site-based therapeutic approaches.

Residual post-chemotherapy mediastinal or neck masses are typically removed either at time of RPLND or as a staged procedure.

Brain metastases occur in 1% of patients, and Cisplatin-based chemotherapy is recommended as initial therapy in patients with brain metastases at initial presentation. Balmaceda et al reported a 57% complete response rate in 68 patients with brain involvement with chemotherapy alone. (Balmaceda et al., 1996) Surgical resection should be considered for residual disease. Radiotherapy does not appear to influence survival in this select population, and confers considerable morbidity by way of declining functional cognitive status.

Indiana University demonstrated that approximately 70% of resected liver lesions are necrosis and the histologic concordance between retroperitoneal histology and liver histology is 94.4% for necrosis, 25.9% for teratoma and 38.5% for active cancer. (Jacobsen et

al.) With this data in mind, observation of liver metastases should be considered when retroperitoneal histology reveals necrosis or when the volume and/or location of the hepatic involvement require a significant surgical undertaking. If the mass enlarges on surveillance, then surgery or second-line chemotherapy should be considered.

2.4.6 Management of late relapse

Late relapse of testis cancer is defined as recurrence of disease later than 2 years after initial successful treatment. In a pooled analysis of 5880 patients, late relapse occurred in 119 of 3704 (3.2%) patients with non-seminoma. The retroperitoneum is the predominant site of relapse, followed by the lung, and 70% present with an elevated AFP. About 40% to 50% of patients with late relapse are curable, predominantly through surgery, as these tumors are by and large chemoresistant. (Baniel, et al., 1995; George et al., 2003)

2.5 Summary: Management options for clinical stage II and III non-seminomatous germ cell tumor of the testis

Patients with low-volume clinical stage II disease with normal serum tumor markers may undergo primary RPLND *in lieu* of systemic chemotherapy. Surgery alone without chemotherapy can cure 50-70% of patients with pathologic stage II disease. The remainder are cured with chemotherapy at relapse.

Patients with elevated serum tumor markers, bulky clinical stage II disease, and all clinical stage III patients require induction chemotherapy. 70% of these patients will achieve CR, and these patients are observed, as the relapse rate is less than 5%. Patients with normalization of serum tumor markers and a persistent retroperitoneal mass routinely require PC RPLND. Outcome is dependent upon pathology.

Patients with more complicated disease require individualized therapy, which may involve salvage chemotherapy, surgery, or both. Relapses occurring more than two years since last treatment are best approached with surgery. Patients requiring "complicated" PC RPLND, presenting with late relapse, or harboring extraperitoneal disease are candidates for referral to tertiary centers of considerable experience in these difficult scenarios.

3. Explanation of terms and abbreviations

Adjuvant Chemotherapy – A term denoting chemotherapy that is administered after first receiving definitive local therapy (such as surgery). This second therapy is given to patients under the assumption that micrometastatic disease persists despite the initial local therapy.

CT A & P – Computed Tomography Scan of the Abdomen and Pelvis. Providing detailed information about the size and location of potential sites of metastatic testis cancer in the abdomen and pelvis, these scans are the pelvic imaging modality of choice for surveillance and investigation of nonseminomatous germs cell tumors.

CXR – Chest X-ray. A chest imaging modality for the surveillance and investigation of patients with nonseminomatous germ cell tumors of the testis.

Induction Chemotherapy – A term denoting chemotherapy that is administered as initial treatment where disease is too advanced for other modalities (such as surgery).

IVC – Inferior Vena Cava. Anatomical term for large vein coursing through retroperitoneum, returning venous blood to the right atrium. Metastatic testis cancer frequently intimately involved with this structure.

PC RPLND – Post-chemotherapy retroperitoneal lymph node dissection. Surgical procedure to remove all lymphatic tissue in the retroperitoneal space which lies between the ureters, superior to the common iliac vessels, and inferior to the crus of the diaphragm, performed after patient has received chemotherapy.

RPLND – Retroperitoneal lymph node dissection. Surgical procedure to remove all lymphatic tissue in the retroperitoneal space which lies between the ureters, superior to the common iliac vessels, and inferior to the crus of the diaphragm.

Salvage Chemotherapy – A term denoting chemotherapy given after relapse or progression of disease, despite prior induction chemotherapy

STM – Serum tumor markers. In nonseminomatous germ cell tumor of the testis, the most important markers are alpha fetoprotein (AFP), the beta subunit of human chorionic gonadotropin (βhCG) and lactate dehydrogenase (LDH). These proteins are easily isolated from blood samples, and are highly reliable in terms of their ability to quantify disease burden and/or assess response to therapy.

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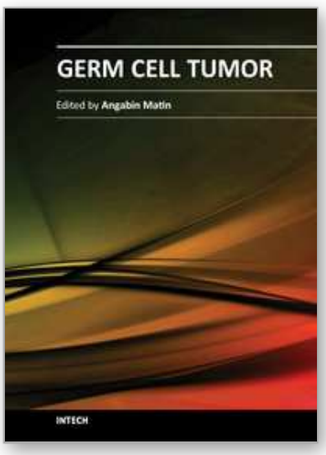

Germ Cell Tumor
Edited by Dr. Angabin Matin

ISBN 978-953-51-0456-8
Hard cover, 150 pages
Publisher InTech
Published online 30, March, 2012
Published in print edition March, 2012

The book aims to provide an overview of current knowledge regarding germ cell tumors. It deals with the clinical presentations, treatment modalities, the biology and genetics of germ cell tumors in children and adults. Most chapters are focused on testicular germ cell tumors whose incidence has been increasing in young males. Included are reviews on the pathogenesis, risk factors, diagnosis and treatment regimens applied to precursor, pre-invasive lesions as well as to seminomatous and non-seminomatous germ cell tumors of the testes. In addition, a review is included on the diagnosis and current management options for intracranial germ cell tumors in children. Authors have also contributed articles on the genetics and epigenetics of germ cell tumor development in humans and in the mouse model system. This book will be of interest to scientists, physicians and lay readers wishing to review recent developments in the field of germ cell cancers.

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