

Optimal management of testicular cancer: from self-examination to treatment of advanced disease

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Abstract: Germ-cell cancer is the most common solid tumor in men aged 15 to 35 years and has become the model for curable neoplasm. Over the last 3 decades, the cure rate has increased from 15% to 85%. This improved cure rate has been largely attributed to the introduction of cisplatin-based chemotherapy. In stage I seminoma and nonseminoma, cure rates approach 100% and treatment is governed by patient choice based on the perceived morbidities of each therapy and personal preferences. For seminoma, treatments include surveillance, radiotherapy, and single course carboplatin. For nonseminoma, treatments include surveillance, retroperitoneal lymph node dissection (RPLND), and adjuvant chemotherapy. Low volume (<3 cm) stage II seminoma is typically managed with radiotherapy while higher volume (>3 cm) stage II and stage III disease treated with chemotherapy. Positron emission tomography (PET) imaging can differentiate active cancer versus necrosis for postchemotherapy residual masses. PET-positive masses are managed with either surgery or second-line chemotherapy. Low volume (<5 cm) stage II nonseminoma with normal serum tumor markers may be managed with either RPLND or chemotherapy. Patients with persistently elevated serum tumor markers and larger volume stage II and stage III disease are managed with systemic chemotherapy. As with seminoma, good risk patients are typically treated with 3 courses of bleomycin, etoposide, and cisplatin (BEP) and intermediate and poor risk patients are treated with 4 courses. Residual postchemotherapy masses should be resected due to the uncertainty of the histology with 50% to 60% harboring residual teratoma or active cancer. The majority of patients completing initial therapy who relapse do so within 2 years. A minority of patients (2%–3%) recur after 2 years and this phenomenon is termed late relapse. Excluding chemo-naïve patients, late relapse disease is typically managed surgically with 50% being cured of disease. Current therapeutic challenges in testis cancer include the accurate prediction of postchemotherapy histology to avoid surgery in patients harboring fibrosis only, improved therapy in platinum-resistant and platinum-refractory disease, and the understanding of the biology of late relapse.

Keywords: testicular cancer, self-examination, advanced disease

Introduction

Testicular cancer remains the most common solid tumor in young men with an anticipated 8,500 new cases in the United States in 2009. With the introduction of cisplatin based chemotherapy, the survival has increased from 60% in the 1970's to over 90% in the current era. Appropriate treatment selection is governed by tumor histology, TNM stage, IGCCCG risk classification, along with patient and physician preference. The following manuscript will attempt to guide patient treatment from presentation to cure.

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Diagnosis and staging

Clinical presentation of germ cell cancer

The most common presentation of testicular cancer relates to the site of origin and typically presents as a nodule or painless swelling in one gonad. Typically on self exam, a patient feels a solid, painless nodule or growth in the testicle. A painful testis is the next most common symptom, and in 10% of cases this pain is acute on onset.¹ Testicular pain at presentation is possibly secondary to hemorrhage or mass effect and has been linked to rapid tumor growth observed in nonseminomatous germ cell tumors (NSGCT). Seminomas have a slower growth rate and more often present with a painless mass. Sandeman reported testicular pain as the initial presenting symptom in 47% and 38% of nonseminoma and seminoma patients, respectively.²

Trauma is observed in 10% of patients with testicular cancer.³⁻⁶ Trauma was once regarded as a risk factor, because the enlarged gonad secondary to malignancy is more prone to injury and injury itself leads to recognition of the pre-existing tumor.³ Other red herrings, including epididymo-orchitis, torsion, hydrocele, and hernias, all lead to misdiagnosis and delay in diagnosis. Although nearly two-thirds of patient with testicular cancer have an abnormal semen analysis at presentation, infertility as an initial complaint is uncommon (<5%).⁷⁻⁹

Despite the external location of the male gonad, allowing accessibility for both self-exam and physician-performed exam, delay of diagnosis for testicular cancer continues to occur. Delay of diagnosis is not uncommon, with a reported mean delay-time of about 26 weeks.¹⁰ While a few investigators more recently have shown a reduction in diagnostic delay attributable to increased efforts at education and recognition,¹¹⁻¹³ these rates have remained relatively steady over time.¹²

Due to the relative rarity of testis cancer, many health care professionals may not recognize the array of presenting symptoms associated with testicular cancers, attributing these symptoms to a more common inflammatory condition leading to further delays in recognition and referral to a specialist. Common initial diagnoses include trauma, hydrocele, and infection. With the presumed diagnosis of orchitis/epididymitis, re-evaluation in the clinic is necessary to monitor response to antibiotics. The identification of a retroperitoneal mass in the young adult male is typically not a diagnostic dilemma, and metastatic or primary retroperitoneal germ-cell tumor is first on a rather short differential including lymphoma and sarcoma.¹⁴⁻¹⁷

Diagnosis

Initial diagnosis is typically made with a radical orchiectomy through an inguinal incision. Prior to surgery, serum tumor

markers including α -fetoprotein (AFP), β -human gonadotropin (β -HCG) and lactate dehydrogenase (LDH) should be obtained and followed post-orchietomy to determine the half life kinetics (half life time: AFP < 7 days; β -HCG < 3 days). At times, tissue diagnosis is made with an extra-gonadal biopsy (retroperitoneal mass, cervical mass ECT). In these cases, orchiectomy may be delayed after the introduction of chemotherapy depending on clinical scenario.

Histology

Tumor classification includes seminoma and non-seminoma. As seminoma does not produce AFP, patients with a pure seminoma primary and an elevated serum AFP are categorized as a non-seminoma. The remaining histologic subtypes include: embryonal cell carcinoma, teratoma (mature and immature), yolk sac tumor and choriocarcinoma.

Serum tumor markers

AFP is secreted by embryonal cell carcinoma, teratoma, and yolk sac tumor but not by pure choriocarcinoma or pure seminoma. All patients with choriocarcinoma and 40% to 60% of patients with embryonal cell carcinoma have elevated levels of bHCG. Approximately 10% of patients with pure seminoma have an elevated bHCG with typical levels less than 500 U/L. Approximately 50% to 70% of patients with NSGCT have an elevated serum AFP and 40% to 60% have an elevated bHCG. Measured together, up to 90% of patients present with elevation of one or both serum tumor markers. Fewer patients with clinical stage 1 (CS1) disease present with elevated serum tumor markers with up to 33% of patients having both markers normal at presentation.

Staging and prognostic classification

Staging includes chest x-ray (CXR) or computerized tomography (CT) and abdominal/pelvic CT scan. Along with imaging, post orchiectomy serum tumor markers are repeated. The TNM staging system is seen in Table 1.¹⁸ In addition to the TNM staging system, the IGCCCG classification defines patients into risk groups based on histology, location of the primary, location of metastases and level of AFP, β -HCG and LDH (Table 2.)¹⁹

Seminoma

CSI

Despite no evidence of metastatic disease on CXR or abdominal/pelvic CT, approximately 20% of patients with CS1 seminoma harbor occult lymphatic disease and will subsequently relapse. Risk factors for harboring microscopic disease include size of the primary tumor >4 cm and

Table 1 TNM Classification of tumors of the testis

T-Primary tumor	
Tx:	Cannot be assessed
T0:	No evidence of primary tumor
Tis:	Intratubular cancer (CIS)
T1:	Limited to testis and epididymis, no vascular invasion
T2:	Invades beyond tunica albuginea or has vascular invasion
T3:	Invades spermatic cord
T4:	Invades scrotum
N-Regional lymph nodes	
Nx:	Cannot be assessed
N0:	No regional lymph node metastasis
N1:	Lymph node metastasis <2 cm or multiple nodes, none >2 cm and <6 positive nodes
N2:	Nodal mass >2 cm and <5 cm or >6 nodes positive
N3:	Nodal mass >5 cm
M-Distant metastasis	
Mx:	Cannot be assessed
M0:	No distant metastasis
M1:	Distant metastasis present in nonregional lymph nodes or lungs
M2:	Non pulmonary visceral metastasis
S-Serum tumor markers	
Sx:	Markers not available
S0:	Marker levels within normal limits
S1:	LDG < 1.5 × nl, hCG < 5000 and AFP < 1000
S2:	LDH 1.5–10 × nl, hCG 5000–50000, AFP 1000–10000
S3:	LDH > 10 nl, hCG > 50000, AFP > 10000

infiltration of the rete testis. The 5-year relapse rate for patients with 0, 1, and 2 risk factors is 12, 16, and 32%, respectively.²⁰ The cure rate for CS1 seminoma approaches 100% and treatments include surveillance, adjuvant radiotherapy and single-agent carboplatin. Mainstay management of CS1 seminoma in North America is typically radiotherapy or surveillance.

Adjuvant radiotherapy

Adjuvant radiotherapy is associated with a relapse rate of 3%–4% with recurrences located outside the irradiated field, most commonly in the pelvis.^{21–23} The targeted field is defined by the upper edge of thoracic vertebra 11 and the lower edge of lumbar vertebra 5. Ipsilateral to the primary tumor, the lateral margin should extend to the renal hilum and the contralateral margin includes the processus transversus of the lumbar vertebrae. Radiation dose for most centers range from 25 to 35 Gy in 15 to 10 daily fractions. In a prospective, randomized trial, the Medical Research Council (MRC) found no difference in relapse rates comparing 20 Gy versus 30 Gy.²⁴ Toxicity is generally mild and mostly limited to gastrointestinal symptoms. To further minimize toxicity, the MRC randomized target volume to include the pelvis (dog leg, DL), versus para-aortic only (PA). With no difference in relapse-free

survival (96% vs 97%) in the PA vs DL arm, the PA arm had an improved short-term recovery of spermatogenesis though a higher rate of pelvic recurrence (2% vs 0%).²⁵

Though the relapse rate is low with adjuvant radiotherapy (<4%), up to 80% of patients with CS1 disease are unnecessarily over treated. Furthermore, patients receiving radiotherapy are at a higher risk of developing a secondary malignancy versus no therapy at all (though the incidence of a secondary malignancy is very low). Patient follow-up post radiotherapy is simplified due to the low risk of relapse and typically CT scans can be omitted, though some physicians may recommend CT scans in patients receiving a PA template due to the small risk of pelvic recurrences.

Surveillance

Surveillance is an acceptable treatment modality and is rationale in that 80% of patients are destined never to relapse, need no further therapy after orchiectomy and are over treated with any additional adjuvant therapy, and the 20% that do relapse remain curable.

Relapses are typically located in the retroperitoneum (84% to 100% of cases) and a quarter of these have either recurrences greater than 5 cm or with distant disease.²⁰ For local recurrence less than 3 cm, we recommend radiotherapy, for recurrences >3 cm or distant disease, treatment consists of cisplatin based chemotherapy.

Relapses may occur as late as 10 years after orchiectomy requiring longer follow-up than for stage 1 NSGCT.

Adjuvant carboplatin chemotherapy

The MRC and EORTC randomized 1,477 patients with CS1 seminoma to one cycle of carboplatin or 20–30 Gy PA radiotherapy.²⁶ At a median follow-up of 6.5 years, the 5-year disease free survival was similar in both arms at 95%. Despite these results, the trial was designed as a non-inferiority trial to exclude a risk of relapse <3% with carboplatin and this end point was not reached.

A greater number of retroperitoneal relapses were observed in the carboplatin arm though less developed a second primary compared to patients receiving adjuvant XRT. Concerns of long term toxicity, and rate and sites of recurrences has limited the general adoption of this therapy in managing CS1 seminoma in the United States.

CS2

Historically, in attempt to avoid the toxicity of platinum based chemotherapy, low stage (<5 cm) retroperitoneal seminoma had been managed with radiotherapy. In a study from the

Table 2 IGCCCG Classification of prognostic groups

Prognosis	Proportion of patients	5-year survival	Non-seminoma	Seminoma
Good	56%	90%	Testis or extragonadal retroperitoneal tumor <i>and</i> low markers <ul style="list-style-type: none"> • AFP < 1000 • <i>and</i> βHCG < 5000 • <i>and</i> LDH < 1.5 \times NL And no non-pulmonary visceral metastases (NPVM)	Any primary location Any marker level And no NPVM
Intermediate	28%	80%	Testis or extragonadal retroperitoneal tumor <i>and</i> intermediate markers <ul style="list-style-type: none"> • AFP 1000–10000 • βHCG 5000–50000 • LDH 1.5–10 \times NL And no NPVM	Any primary location And the presence of any NPVM Any marker level
Poor	16%	50%	Primary mediastinal germ cell tumor Or Testis or extragonadal retroperitoneal tumor <ul style="list-style-type: none"> • <i>and</i> the presence of NPVM • <i>and/or</i> high markers <ul style="list-style-type: none"> ◦ AFP > 10000 ◦ βHCH > 50000 ◦ LDH > 10 \times NL 	

Royal Marsden Hospital, 10% of patients with clinical stage 2A (CS2A) disease relapsed, 18% of CS2B disease relapsed and 38% of CS2C relapsed after radiotherapy.²⁷ Therefore patients with retroperitoneal disease less than 5 cm had a fairly low relapse rate post radiotherapy.

Investigators from Germany reported outcome of 66 patients with CS2A and 21 patients with CS2B treated with median radiotherapy dose of 30 Gy and 36 Gy, respectively.²⁸ The relapse-free survival at 6 years was 95.3% and 88.9% for CS2A and CS2B, respectively.

As the toxicity of chemotherapy has decreased over the last 2 decades, at Indiana University, we recommend that small volume disease (<3 cm) be treated with radiotherapy and larger size (>3 cm) CS2 and all CS3 disease be treated with cisplatin-based chemotherapy.

Surgery

In seminoma, the management of a post chemotherapy (PC) residual mass has been a controversial matter as the histology of the residual mass usually represents fibrosis rather than persistent seminoma. Investigators at Memorial Sloan-Kettering advocate surgery for all residual PC masses larger than 3 cm.²⁹ Due to the high incidence of fibrosis (70% to 80%) many centers including Indiana University take a more conservative approach and perform serial CT imaging and only intervene if there is disease progression.

Positron emission tomography (PET) scan has been used to differentiate between persistent germ cell tumors and fibrosis. PET scan cannot distinguish teratoma from necrosis as both are biologically inert and thus has a limited role in NSGCT. As teratoma is not typically an issue in seminoma, PET scans have been used to differentiate the histology of residual PC masses. The SEMPET trial assessed 56 PET scans in 51 patients with metastatic pure seminoma with residual PC masses. All 19 cases with residual lesions >3 cm and 35 of 37 (95%) with residual masses <3 cm were correctly predicted by PET.³⁰ The specificity, sensitivity, positive predictive value, and negative predictive value were 100%, 80%, 100%, and 96%, respectively.

In a retrospective review from Indiana University, 24 PET scans were reviewed from 19 patients who had received primary or salvage chemotherapy for metastatic seminoma.³¹ Twelve PET scans were read as negative and none of these patients relapsed giving a negative predictive value of 100%. Twelve PET scans were read as positive. PET scans identified all 8 patients who had persistent disease after chemotherapy giving them a sensitivity of 100%. However, 4 positive PET scans led to surgical resections of residual masses revealing only fibrosis or inflammation (false-positive). The positive predictive value for PET scans was 67%.

In seminoma, a negative PET scan indicates a low likelihood of persistent seminoma after chemotherapy.

However, a positive PET scan does not necessarily confer a high probability of persistent seminoma. Positive PET scans should be viewed as a tool in conjunction with other clinical variables to determine if therapy is indicated. Treatment is usually surgery for those masses that can be resected with acceptable morbidity or second-line chemotherapy for more complex cases.

Nonseminomatous germ cell tumors CSI

Despite dramatic advances in cure, controversy remains regarding the optimal management of CSI nonseminomatous germ cell tumors (NSGCT), defined as disease limited to the testicle with normal abdominal and chest computed tomographic (CT) scans, and normal serum tumor markers post orchiectomy. The presentation of CSI NSGCT is associated with a 30 to 50% incidence of occult retroperitoneal metastases (pathologic stage B, PSB) creating the controversy regarding “the best” treatment modality. Currently, 3 approaches are considered for treatment in CSI NSGCT: retroperitoneal lymph node dissection (RPLND); surveillance; and primary chemotherapy, all with equal cure rates at 99%.

Risk stratification: CSI

The primary issue in the adjuvant treatment of patient with CSI NSGCT is tailoring treatment to those 30% of patients who have occult metastatic disease and are destined to relapse on a surveillance program. Observation without risk assessment will result with the treatment of recurrence in about one third of patients with multiple courses of chemotherapy and potential resection of residual masses. RPLND as well as adjuvant chemotherapy without risk assessment will over treat about 70% of patients. It is therefore essential to identify risk factors identifying patients at high risk of occult metastatic disease.

The Medical Research Council (MRC) in Great Britain has performed the first major study for identifying risk factors for relapse in CSI NSGCT.³² The multivariate analysis revealed four prognostic factors predictive of recurrence: vascular invasion of the primary tumor, lymphatic invasion, the presence of embryonal carcinoma, and the absence of yolk sac tumor. A prospective MRC trial based on these prognostic variables found the presence of at least three of these four factors to be predictive for relapse in 48% of patients.³³ Vascular invasion was the predominant finding. Conversely, those patients with zero to two risk factors were found to recur on surveillance about 20% of the time.

Multiple other studies have identified similar risk factors for relapse with embryonal cell carcinoma dominant tumors and the presence of lymphovascular invasion consistently being the most powerful predictors. Vergouwe et al performed a review of studies assessing predictors of occult metastases and identified 23 publications reporting on 2,587 patients.³⁴ Overall 759 (29.3%) patients had occult metastasis. Pooled univariate odds ratios identified that lymphovascular (LVI), embryonal carcinoma (EC) > 50%, pathologic stage pT2–4 versus pT1, and MIB-1 staining >70% as the strongest predictors. Though somewhat variable, high risk groups, with the presence of either or both lymphovascular invasion and embryonal dominant primary carry an approximate 50% recurrence rate. Low risk groups without either pathologic variable, had a relapse rate of <20%.

The ability for accurate risk stratification would enable directed therapy: arguably retroperitoneal lymph node dissection (RPLND) or primary chemotherapy for the high-risk group and observation for the low-risk group. Even with this stratification, 50% of high-risk patients will be over treated when otherwise cured with orchiectomy. Likewise, 20% of the low-risk group will be destined to relapse on surveillance and subjected to systemic chemotherapy and possible post chemotherapy RPLND.

Surveillance

The rationale for surveillance includes the low rate of progression (overall 30% for all comers and only as high as 50% for the “high risk group”), and patients who do relapse remain curable. Irrespective of risk classification, RPLND or immediate chemotherapy, will subject 100% of patients to therapy while benefiting only 30% and up to 50% based on risk classification. That is, even in the high risk group, 50% of patients are unnecessarily treated with RPLND or chemotherapy.

The group from Toronto reported on 371 patients with CS I NSGCT placed on an active surveillance protocol.³⁵ The median follow-up was 6.3 years and the median time to relapse was 7.1 months. Lymphovascular invasion and pure embryonal cell carcinoma were independent predictors of relapse. In the initial cohort (prior to 1992), 66/157 patients were high risk and 54.5% relapsed versus 18.7% for the low risk group. In the later cohort (after 1992), 59/214 patients were high risk and 49.2% recurred versus 14.2% for the low risk group. In total, 104 (28%) patients relapsed. The disease specific survival (DSS) was 99.2%.

Similar results were recently published from combined series of 223 patients from British Columbia and Oregon.²⁰

59 (29%) patients relapsed at a median time of 4 months, 88% relapsed within 2 years and only 7 patients relapsed beyond 2 years. Treatment consisted of chemotherapy in 98% of relapses with 78% achieving a complete clinical response. Only 12 of 223 patients (5%) required PC RPLND. DSS was 100% after a median follow up of 52 months.

Patterns of relapse

The retroperitoneum is the most common site of recurrence. On a pooled analysis, Albers reported that approximately 60% of recurrences will be observed in the RP, 25% in the lungs and 10% will be diagnosed based on elevated serum tumor markers alone.³⁶ Most recurrences are diagnosed with CT scan or elevated serum TM.

Follow-up

Though follow-up schemes vary, it is generally accepted that as the relapse rate is higher in the first 2-years, follow-up should be more intensive during this time period. Schematics should include a combination of physical exam, CXR, serum TM, and abdominal/pelvic CT scan. A randomized trial evaluated CT scans at 3 and 12 months versus 3, 6, 9, 12, and 24 months and found no benefit in more frequent CT scans. This study involved 414 patients with a median follow-up of 40 months though only 10% of patient were considered high risk based on vascular invasion.³⁷ Suggested guidelines can be obtained via national organizations including the National Comprehensive Cancer Network (NCCN). These guidelines should be individualized based on the unique clinical and pathologic features for each patient.

Arguments against surveillance include compliance and an increase burden of treatment for those patients that do relapse. Relapses on surveillance are usually treated with 3 courses of BEP or 4 course of EP with a quarter requiring PC surgery. Patients with retroperitoneal relapse only with normal serum tumor markers may be considered for primary RPLND. Compliance has been a concern when placing patients on a surveillance protocol with studies showing up to a third of patients missing at least one clinic visit.^{38,39} The concern of non-compliance is that it may translate into a decrease disease specific survival. A national surveillance study in New Zealand failed to correlate non-compliance with compromise in cure.⁴⁰ In this study only 12% of patients were non-compliant. In determining the best treatment for each individual with CS1 NSGCT, patients felt to be unreliable and likely to have poor compliance would likely be better served being steered away from surveillance as a treatment modality.

Adjuvant chemotherapy

The administration of chemotherapy after orchiectomy in CS1 NSGCT nearly eliminates the risk of relapse. A pooled analysis of 13 studies involving 1043 patients revealed a relapse rate of 1.6% with 6 patients (0.6%) dying of disease.⁴¹ All but two of these series involved 2 courses of platinum-based chemotherapy.

With continued data documenting the long-term side effects of chemotherapy,⁴² knowing that 50% to 70% of CS1 patients are unnecessarily exposed to chemotherapy (ie, were never destined to relapse) along with the young population being treated and the fact that other treatment modalities exist with equal cure rates with a lower risk of receiving chemotherapy, this form of management has not gained wide acceptance in the United States.

Primary RPLND

RPLND for CS1 nonseminoma has a staging and therapeutic capability. In patients with low volume retroperitoneal metastatic disease, surgical cure with retroperitoneal lymph node dissection only and without adjuvant chemotherapy occurs at the 65% to 90% level.^{43–46} Indiana University reported on the outcome of 464 patients with CS1 NSGCT from 1965–1989 with a mean follow-up of 96.2 months.⁴⁷ In this analysis, 323 (70%) patients had pathologic stage A (PSA) disease with 37 (11%) relapsing, with an overall survival of 99.4%. There were 2 deaths.

PSB disease was identified in the remaining 112 (30%) patients. Of these, 64 did not receive adjuvant chemotherapy of whom 22 (34%) relapsed with 1 death. None of the 48 patients receiving adjuvant chemotherapy relapsed.

Recently the results of RPLND in patients with so-called high risk, CS1 disease treated at Indiana University were reviewed.⁴⁸ High risk was defined by the 2 criteria of embryonal predominance and vascular invasion in the orchiectomy specimen. Embryonal predominance was defined as embryonal carcinoma present at a level greater than any other histologic subtype in the orchiectomy specimen. The presence of each risk factor predicted PSB disease at the 46.5% level. Of patients with PSB disease who elected not to receive adjuvant chemotherapy only a third had recurrence after RPLND, indicating that two-thirds of these high risk patients were cured with retroperitoneal lymph node dissection only. Therefore, even in so-called high risk patients, retroperitoneal lymph node dissection retains its therapeutic capability. Interestingly, the only identified consequence of primary RPLND in high risk patients compared to the general population with CS1 NSGCT was that those with high risk features who proved to have PSA

disease had a recurrence rate of 20% versus 10% in the general population undergoing RPLND.

A contemporary series was recently published from our institution evaluating the efficacy of primary RPLND in patients with PSB1 NSGCT. This population included 118 patients, none of whom received adjuvant chemotherapy. At a minimum follow-up of 2 years, and median follow-up of 43 months, the 5-year disease free survival was 68%. The median follow-up in patients without recurrence was 67.4 months and the median time to recurrence was 5.0 months. Pathologic features including number and histologic subtype of the metastatic lymph nodes failed to predict recurrence.^{49,50} Despite the inability to predict risk factors of recurrence in this population, RPLND cures patients with metastatic disease alone and without adjuvant chemotherapy.

Important in the philosophy of treating low stage germ-cell cancer is the goal of achieving cure by a single treatment modality. As demonstrated in the studies referenced above, primary RPLND cures 70% of patients with PSB disease. Two courses of adjuvant chemotherapy administered to patients with PSB disease does eliminate the risk of recurrence for those 30% destined to relapse but adds to patient morbidity and unnecessarily exposes chemotherapy for those 70% otherwise cured with surgery.^{51,52} If the rationale is to administer post operative chemotherapy (2 courses) in patients with PSB disease in order to avoid recurrence and not rely on surgery for cure, we feel that surveillance is better suited. If this is the case, those patients on surveillance who do relapse would avoid surgery and still be cured with 3 courses chemotherapy.

With the introduction of nerve sparing technique, the morbidity from retroperitoneal lymph node dissection is essentially that of a laparotomy.⁵³⁻⁵⁵ 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.⁵⁶ We recently reviewed the last 75 primary retroperitoneal lymph node dissections performed at our institution.⁵⁷ In this population the mean operative time was 132 minutes, mean blood loss was 207 mL. We routinely do not place nasogastric tubes in primary or post chemotherapy surgery, and in this series only 2 patients had NG tubes. Clear liquids were started on day 1 with the mean hospital stay of 2.8 days (range: 2-4 days). This series demonstrates that in a contemporary cohort the morbidity of open primary RPLND is essentially limited to the incision.

Overview CS1 NSGCT

The treatment of CS1 disease should be patient driven irrespective of risk grouping as even in the “high risk group”

only 50% harbor micrometastatic disease and the remaining 50% are cured with orchiectomy alone. The advantages and disadvantages of each treatment modality should be discussed along with the perceived short and long term morbidity taking into account the uniqueness of each patient and available resources.

Clinical stages 2 and 3

CS2 NSGCT includes patients with evidence of retroperitoneal metastases based on clinical staging (CT scan). Patients with serum TM normalization post orchiectomy with small volume (<5 cm) retroperitoneal disease may be treated with either chemotherapy or primary RPLND. CS2 patients with persistently elevated serum TM post orchiectomy and all cases of CS3 disease are treated with cisplatin-based chemotherapy. Patients with a complete radiographic response to chemotherapy are observed while patients with persistent radiographic disease undergo PC surgery.

Primary RPLND

The rationale to proceed with primary RPLND in CS2 NSGCT with normal serum TM is multifactorial. Not all retroperitoneal tumors (CS2) represent metastatic disease and therefore would not respond to systemic chemotherapy. These patients would therefore require PC surgery due to this “persistent mass”. Donohue reported on 174 CS2 patients undergoing primary RPLND from 1965 to 1989, 41 patients (23%) were in fact pathologic to PS1 or pathologic stage 1.⁵⁸

Furthermore, patients with teratoma in the orchiectomy specimen may have teratoma in the retroperitoneum and more likely to have a persistent mass post chemotherapy and require RPLND. Therefore this subset may have a higher likelihood of dual therapy (chemotherapy and surgery) for cure.

Alternatively, primary RPLND would eradicate retroperitoneal teratoma and potentially cure the patient while avoiding systemic therapy. If retroperitoneal pathology reveals active cancer (with or without teratoma), surgery remains curative in 50% to 70% of patients. Surgery should be a consideration for all patients presenting with CS2 disease with normal serum TM especially those with teratoma in the primary.

Chemotherapy

Systemic therapy for metastatic germ cell tumors consists of cisplatin-based chemotherapy. For good risk disease, the accepted standard is 3 courses of bleomycin, etoposide, and cisplatin (BEP).^{59,60} Due to concerns of pulmonary toxicity, patients with a strong smoking history or older than 50 years

of age can be alternatively managed with 4 courses of EP. Standard therapy for intermediate and poor risk disease remains 4 courses of BEP. Randomized trials evaluating high dose chemotherapy (HDCT) versus BEP \times 4 in poor risk patients as initial therapy failed to show an improved outcome in the HDCT arm.⁶¹

Depending upon the patient population selected, about 70% of patients treated with first line chemotherapy will obtain a complete clinical response with normalization of serum tumor markers and complete resolution of all metastatic disease. The policy at Indiana University, in agreement with the European Germ Cell Cancer Consensus Group,²⁰ is to observe these patients as only 3% to 5% will relapse.^{62,63}

Patients not achieving a complete clinical response, with residual radiographic tumor and serum tumor marker normalization routinely undergo PC RPLND. Pathology of the residual mass at PC surgery consists of necrosis in 45%, teratoma in 45% and cancer in 10%.

Patients with tumors that relapse or with tumors that progress despite first line chemotherapy are candidates for salvage therapy. A minority of patients will have anatomically confined disease and amendable to surgical resection.^{64,65} For the remaining majority of patients treatment options include salvage chemotherapy with cisplatin plus ifosfamide plus vinblastine,⁶⁶ or paclitaxel⁶⁷ for 4 courses or high-dose chemotherapy with autologous hematopoietic stem-cell transplantation to rescue the bone marrow from the myeloablative effect of chemotherapy.⁶⁸⁻⁷⁰

Post-chemotherapy RPLND

The surgical resection of necrotic tissue after chemotherapy offers no therapeutic benefit to the patient. Therefore, post chemotherapy surgery with the finding of necrosis is a staging procedure alone. The recurrence rate in this population is less than 5% and typically we would not re-image the retroperitoneum and follow the patient only with physical exam, chest imaging and serum tumor markers. Donohue and Foster reported a 93% progression free survival for patient harboring fibrosis only at PCRLND.⁷¹

Ideally patients with known residual fibrosis would be excluded from surgery though presently we are unable to accurately predict necrosis with the use of clinical parameters. The EORTC/MRC recently assessed the external validity of a prediction rule developed to predict the probability of retroperitoneal metastases being only necrosis after chemotherapy.³⁴ Patients with a high probability of necrosis might be offered surveillance as opposed to surgery. Criteria used to calculate the probability of benign histology included:

the absence/presence of teratoma in the primary tumor, pre-chemotherapy serum tumor marker levels, and maximal transversal mass size measured on CT before and after chemotherapy. In the validation set, only 4% of residual masses were classified as benign and would have received surveillance en lieu of surgery. Though the prediction rule accurately identified benign histology, so few patients met the classification criteria that the clinical usefulness of this tool remains limited.

Surgical resection of residual cancer or teratoma is rational and well accepted as both entities may grow and metastasize and lead to significant patient morbidity and even death. Teratoma is not sensitive to chemotherapy and therefore surgical resection is the only therapeutic option. Recurrence rate for resected teratoma is 10% or less with a greater chance of local (retroperitoneal) recurrence the larger the volume of disease.⁷² Donohue and Foster reported a 89% progression free survival for 273 patients harboring residual teratoma at surgery.⁷¹ Tait et al reported an observed relapse rate of 7% in 28 patients with completely resected teratoma at a median follow up of 37 months.⁷³ In an international study, Stenning et al reported similar results in a cohort of 153 patients undergoing PCRPLND.⁷⁴ The 2 year progression free survival for resected mature and immature teratoma was 86% and 89%, respectively. We recently reported recurrence rates after resection of large volume (>10 cm) teratoma.⁷⁵ The 2- and 5-year recurrence free survival for the 99 patients was 86% and 75% with a mean follow up of 42 months. Typically in the post chemotherapy setting after resecting residual teratoma we would recommend CT scans of the abdomen and pelvis periodically in addition to serial chest imaging, physical exam and serum tumor markers.

Active cancer is identified in 10% of patients after standard PC surgery. Donohue reported a relapse free rate of 70% in this population all of whom received adjuvant chemotherapy. Fizazi et reported on 238 patients with viable residual disease after first-line chemotherapy.⁷⁶ The 5-year progression free survival was 64%. Three variables significant on multivariate analysis were used to risk stratify this population and included: incomplete surgery, viable malignant cells >10%, and poor or intermediate IGCCC.

Patients with no adverse factors experienced a 5 year progression free survival of 90% compared to 41% for 2 or more risk factors. This International Study Group further compared progression free survival and overall survival in patients receiving and not receiving adjuvant chemotherapy. The 5-year relapse free rate for 166 patients receiving adjuvant chemotherapy was 69% compared to 52% for the 65 patients not receiving post operative chemotherapy ($P < 0.001$). On

multivariate analysis post operative chemotherapy was associated with a significantly better progression free survival ($P < 0.001$), but overall survival was not improved ($P = 0.26$). It seems that the presence of viable NSGCT portends a poor prognosis and as such, it has been standard practice to give 2 courses of adjuvant chemotherapy in this population.

Complicated post chemotherapy surgery

The term “complicated” RPLND (PCRPLND) applies to patients who have received more than induction chemotherapy only (salvage), have experienced a retroperitoneal recurrence after initial RPLND (redo), or have elevated serum TM or progression of disease during or immediately after chemotherapy (desperation). In this group there is a higher incidence of nephrectomy, aortic replacement and caval resection. This aggressive approach is justified as ensuring a complete resection with additional procedures provides a therapeutic benefit.

Donohue et al analyzed 860 patients who underwent PCRPLND.⁷⁷ Relapse rates for patients with any one of the complicated factors mentioned above was 45% compared to 12% for patients without these factors. In the salvage population, the incidence of active cancer was 50% with an overall survival of 50% to 60% with no apparent benefit from adjuvant chemotherapy. In that same review, Donohue analyzed the effect of “redo” RPLND on patient outcome. That is, the significance of incomplete resection at initial surgery. An overall survival of 63% was observed in 188 patients undergoing redo RPLND versus 86% for 613 patients undergoing primary PCRPLND. Likewise, in a contemporary series, Memorial Sloan-Kettering reported a 67%, 5-year disease specific survival for 57 patients undergoing redo surgery.⁷⁸ Redo RPLND, probably the only prognostic variable not absolutely dictated by the biological aggressiveness of the disease, largely reflects prior inadequate retroperitoneal technique, underscoring the importance of complete surgical resection at initial RPLND.

Indiana University recently reviewed its experience of desperation RPLND to determine the therapeutic benefit of surgery in this population.⁶⁴ This study included 114 patients all with elevated serum tumor markers after either induction chemotherapy alone (50 patients) or salvage chemotherapy (64 patients). The 5-year overall survival was 54%. Sixty-one patients (53.5%) were alive with a median follow-up of 5 years. Fifty-three patients died of disease, with a median time to death of 8.0 months. Retroperitoneal pathology revealed germ-cell cancer in 53.5%, teratoma in 34.2%, and fibrosis in 12.2%, with 5-year survival rates of 31%, 77%, and 86%, respectively. Poor prognostic variables included a

rising β HCG, serum AFP level; redo RPLND, and germ cell cancer in the resected specimen.

Despite poor prognostic features, patients resistant to chemotherapy with persistent cancer can be cured a third of the time with aggressive surgery. Such a population would be unlikely to respond to and avoid surgery with additional chemotherapy, while only adding to morbidity. As such, it is our approach to proceed with surgery in selected patients with elevated serum tumor markers and resectable retroperitoneal disease and forgo either second or third line chemotherapy.

Late relapse

The majority of patients completing initial therapy who relapse do so within 2 years. A minority of patients (2%–3%) recur after 2 years and this phenomenon is termed late relapse. Late relapse disease is predominately a surgical disease as late relapse tumors are not likely to be cured with chemotherapy alone. Indiana University reported its experience with late relapse disease in a cohort of 83 patients.⁷⁹ The median interval from initial presentation to late relapse was 85 months. At late relapse, AFP was the most commonly elevated serum tumor marker (elevated in 52%) and the retroperitoneum and lung the most common sites of relapse. Forty-three of 49 patients who underwent surgery were rendered disease-free and 20 (46.5%) remained continuously disease free. Thirty-two patients received chemotherapy, but only 6 (18.8%) obtained a complete remission. Five of these patients remain continuously disease free after chemotherapy alone, including 3 who were chemotherapy naïve.

A German group recently reported their multi-institutional series of 122 patients presenting with late relapse disease.⁸⁰ In this series 50 of the 122 patients had pure seminoma at initial presentation; in contrast only 3 of 83 in the Indiana series were pure seminoma. The median time to late relapse was 42 months for seminoma and 64.5 months in nonseminoma. As in the Indiana series, the majority of patients (45/59 with nonseminoma) had an elevated serum AFP at late relapse. Likewise, the few responders to chemotherapy included seminomas and chemo-naïve cases. This group also concluded that surgery is required as a component of therapy.

At presentation of late relapse, over 50% of patients have an elevated serum AFP. Despite elevated markers, surgery is considered the primary treatment in patients with resectable disease. Unresectable disease should first be treated with systemic chemotherapy, followed by surgery for tumors now deemed resectable. Teratoma is the most frequent histology, with yolk sac tumor being identified in up to 50% of patients.

Survival is above 50% and approached 95% for single-site teratoma.

Conclusion

Testis cancer has become a model of a curable disease. For both CS1 seminoma and nonseminoma the survival regardless of treatment modality approaches 100%.

Management should be governed by patient choice with consideration of the unique toxicities of each available therapy. In CS1 disease, future research should be directed towards improved risk categorization.

In low volume (<3 cm) seminoma, management is typically radiotherapy with chemotherapy reserved for larger volume (>3 cm) or CS3 disease. Post chemotherapy PET scan is obtained to determine the need for further therapy in patients with pure seminoma.

In non-seminoma, low volume retroperitoneal disease may be managed with primary RPLND or chemotherapy while patients with elevated serum tumor markers, higher volume CS2 or CS3 disease treated with cisplatin chemotherapy based on risk classification.

With the inability to accurately predict retroperitoneal histology, surgery remains integral in the management of residual retroperitoneal masses after chemotherapy.

In metastatic germ cell cancer, further research is directed towards the treatment of poor risk disease and a better understanding of the biology of late relapse.

Disclosure

The author discloses no conflicts of interest.

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