

Retroperitoneal Lymph Node Dissection in Patients With High Risk Testicular Cancer

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Purpose: In patients with testicular cancer the percent of embryonal carcinoma and lymphovascular invasion in the primary tumor have been identified as risk factors for occult metastatic disease. We reviewed differences between primary and post-chemotherapy retroperitoneal lymph node dissection in patients at high risk.

Materials and Methods: Patients who underwent retroperitoneal lymph node dissection at our institution from 1993 to 2006 were identified and the clinical charts were reviewed. A total of 247 patients with orchiectomy specimens containing greater than 30% embryonal carcinoma were identified and perioperative data were obtained.

Results: Of 247 patients 133 (53%) had greater than 30% embryonal carcinoma, including 76 (57%) with combined lymphovascular invasion. Median followup was 3.49 years. Of the patients 76 (57%) and 57 (43%) underwent primary and post-chemotherapy retroperitoneal lymph node dissection, respectively, of whom most received bleomycin, etoposide and cisplatin. Positive lymph nodes were identified at surgery in 37 (49%) and 35 patients (61%) with primary and post-chemotherapy retroperitoneal lymph node dissection, respectively. Of patients with negative pathological findings at surgery surveillance computerized tomography postoperatively identified retroperitoneal masses in 2 (5%) and 3 (14%) of those who underwent a primary and a post-chemotherapy procedure, respectively. Operative data on the primary vs post-chemotherapy groups showed an estimated blood loss of 166 vs 371 cc, an operative time of 2.7 vs 3.3 hours and a hospital stay of 4.4 vs 4.7 days. There were no deaths in either group.

Conclusions: Patients with greater than 30% embryonal carcinoma with or without lymphovascular invasion are at significant risk for metastatic disease and they can be successfully treated with primary retroperitoneal lymph node dissection. Recurrence rates based on computerized tomography evaluation were low and similar between the chemotherapy and nonchemotherapy treated groups.

Abbreviations and Acronyms

AFT = α fetoprotein
CS = clinical stage
CT = computerized tomography
ECP = embryonal carcinoma predominance
HCG = human chorionic gonadotropin
LVI = lymphovascular invasion
NSGCT = nonseminomatous germ cell tumor
P-RPLND = primary RPLND
PC-RPLND = post-chemotherapy RPLND
PS = pathological stage
RPLND = retroperitoneal lymph node dissection

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CARCINOMA of the testis remains the most common malignancy in males who are 15 to 35 years old. In the last 30 years management has evolved with the development of effective

multimodal therapy and a significant improvement in the cure rate from approximately 60% in the 1970s to 98% in 2000 in most cases. RPLND remains an integral component of the

treatment and cure of testicular cancer. Extensive anatomical studies have confirmed the primary landing zones for dissemination in the retroperitoneum. RPLND not only stages cases with increased accuracy compared with imaging, but also limits the followup and side effects associated with chemotherapy. Furthermore, RPLND avoids the need for frequent imaging with its attendant increased risk of secondary malignancies many years later.¹ In cases of low volume, low risk disease RPLND alone provides up to a 90% cure rate. In the setting of high risk disease that mandates adjuvant chemotherapy RPLND provides the additional benefits of excluding the risk of teratoma and/or viable tumor in the retroperitoneum. With the introduction of modified template RPLND and nerve sparing approaches the morbidity associated with this procedure is minimal when performed by expert hands at dedicated tertiary medical centers.

Histological studies have identified patients at high risk for metastatic disease. Many of these studies have shown that the percent of embryonal carcinoma as well as vascular and lymphatic invasion in the primary tumor are independent risk factors for recurrence.²⁻⁴ Heidenrich et al positively predicted 88% of CS I cases with greater than 80% embryonal carcinoma and positive vascular invasion as being PS II.² Conversely 91.5% of CS I cases with less than 45% embryonal carcinoma and absent vascular invasion were free of metastatic disease. The Testicular Cancer Intergroup study also reported that combining the percent of embryonal carcinoma with vascular invasion accurately predicted PS II disease in 86% of patients.⁵

The indication for primary chemotherapy in these patients at high risk remains a debate. Depending on the precise definition of risk factors 20% to 50% of patients at high risk who receive chemotherapy harbor metastatic disease.⁶⁻¹⁰ This means that 50% to 80% of patients given chemotherapy for high risk disease are treated unnecessarily. Further long-term studies of primary treatment with chemotherapy vs RPLND in patients at high risk are warranted.

We performed a retrospective chart review to evaluate patients with greater than 30% embryonal carcinoma with and without LVI. In addition, we further stratified this group into those who underwent P-RPLND vs PC-RPLND to detect any similarities and/or differences between these 2 groups.

MATERIALS AND METHODS

All patients undergoing RPLND through Brigham and Women's Hospital and Dana Farber Cancer Center from 1993 to 2006 were candidates for study inclusion. All patients with orchiectomy specimens showing greater

than 30% embryonal carcinoma were identified and perioperative data were obtained. Followup was done by chart review. Only complete medical records were used in the study to ensure that all necessary information was available and accurate. Complete medical records were defined as containing information from a preoperative clinic visit to the last documented followup visit. These data were extracted from the Brigham and Women's Hospital RPLND computerized database and analyzed accordingly. This project was approved by the Brigham and Women's Hospital institutional review board.

At our institution all patients are evaluated at a multidisciplinary clinic and counseled regarding the options of active surveillance, surgery and/or chemotherapy. All cases were preoperatively staged with tumor markers (AFP, HCG and lactate dehydrogenase), CT of the abdomen-pelvis and CT of the chest or chest x-ray. All orchiectomy and RPLND specimens were reviewed and reports were confirmed by pathologists at Brigham and Women's Hospital. All pathology reports showed a confirmed histology and the percent of embryonal carcinoma in the orchiectomy specimens. In addition, all orchiectomy pathological reports denoted the presence or absence of LVI, defined as identifiable tumor cells within the lumen of an artery, vein or lymphatic vessel.

The decision to perform primary chemotherapy vs RPLND in these patients at high risk is outlined. Patients were counseled initially at a multidisciplinary clinic and offered observation, RPLND and/or chemotherapy as primary treatment options pending the initial presentation (orchiectomy histology, imaging and tumor markers) and they were then followed accordingly. These patients include those with CS I and II disease with most patients with CS II electing chemotherapy as primary treatment. When there was suspicion for residual disease via a mass on CT and/or increased tumor markers, patients were offered PC-RPLND.

Data were entered into a computerized database and analyzed. Differences between P-RPLND and PC-RPLND cases based on continuous variables were compared using Student's *t* test. The chi-square test was used to test for differences in proportions between these groups. Recurrence in patients with P-RPLND and PC-RPLND was evaluated using survival analysis. All factors were considered simultaneously. No model selection algorithm was used. Outcomes in the P-RPLND and PC-RPLND groups were then tested using logistic regression analysis.

RESULTS

A total of 247 patients who underwent RPLND at Brigham and Women's Hospital and Dana Farber Cancer Center between 1993 and 2006 were identified, including 133 (53%) with greater than 30% embryonal carcinoma. Of these 133 patients 76 (57%) had combined LVI. Median followup was 3.49 years. There were no perioperative deaths.

P-RPLND and PC-RPLND were performed in 76 (57%) and 57 patients (43%), respectively, of whom most received bleomycin, etoposide and cisplatin. Table 1 shows a comparison of these 2 groups. The

Table 1. Demographics and preoperative clinical characteristics in 133 patients

Characteristics	P-RPLND	PC-RPLND
No. pts	76	57
Mean age	24	28
No. CS (%):		
I	50 (88)	15 (26)
II	26 (12)	42 (74)
Orchiectomy histology:		
% Embryonal Ca	75.3	71.2
No. teratoma (%)	34 (45)	32 (56)
No. yolk sac tumor (%)	27 (36)	24 (42)
No. LVI (%)	41 (53.4)	35 (61.4)
Mean followup (yrs)	3.1	4.2

average percent of embryonal carcinoma in the P-RPLND and PC-RPLND groups was 75.3% and 71.2%, respectively. When the 20 P-RPLND and 9 PC-RPLND cases of pure embryonal carcinoma were excluded from analysis, the mean percent of embryonal carcinoma was 66.5% and 65.8%, respectively.

CS I was noted in 50 (88%) and 15 (26%) P-RPLND and PC-RPLND cases, respectively. Regarding CS II there were 26 (12%) and 42 (74%) cases, respectively. The P-RPLND and PC-RPLND groups had 39 (51%) and 22 cases (39%) of PS I, respectively. Regarding PS II disease there were 37 (49%) and 35 (61%) cases, respectively (table 2). Of the 37 cases of P-RPLND and PS II disease 16 were pN1, 20 were pN2 and 1 was pN3. PS II PC-RPLND pathological evaluation revealed that 13 cases were pN1, 19 were pN2 and 3 were pN3. A total of 28 patients (80%) with PC-RPLND and PS II had teratoma in the retroperitoneum.

Overall there were 6 (8%) and 5 (9%) recurrences in the P-RPLND and PC-RPLND groups, respectively. Recurrence was identified by tumor marker increases and/or CT. Median time to recurrence was 1.4 and 1.1 years in the P-RPLND and PC-RPLND groups, respectively. Of patients with P-RPLND and recurrence 4 underwent adjuvant chemotherapy for pulmonary metastases (1), mesenteric metastasis (1) and sub-cm retroperitoneal lymphadenopathy (2), while 2 are under observation for sub-cm retroperitoneal lymph nodes. Of patients with PC-RPLND and recurrence 1 under-

Table 2. Pathological results and recurrences

	No. P-RPLND (%)	No. PC-RPLND (%)	p Value
Overall	76	57	
PS:			
I	39 (51)	22 (39)	<0.0220
II	37 (49)	35 (61)	<0.0299
Recurrence:			
Overall	6 (8)	5 (9)	Not significant
After neg pathology results	2 (5)	3 (14)	Not significant

Table 3. Operative data

	P-RPLND	PC-RPLND	p Value
No. pts	76	57	
Mean operative time (hrs)	2.7	3.3	<0.0127
Mean estimated blood loss (cc)	166	371	<0.0001
Mean hospital stay (days)	4.4	4.7	Not significant
No. complications (%)	5 (7)	6 (11)	Not significant

went adjuvant chemotherapy and subsequent salvage RPLND for recurrent retroperitoneal lymphadenopathy, which proved to be teratoma. The other 4 patients were under observation for sub-cm retroperitoneal lymphadenopathy. Of patients with negative pathological findings at RPLND post-RPLND surveillance CT identified retroperitoneal masses in 2 (5%) and 3 (14%) of those with P-RPLND and PC-RPLND, respectively (table 2).

Operative data were analyzed and compared between the P-RPLND and PC-RPLND groups. The P-RPLND group had less blood loss (166 vs 371 cc, $p < 0.0001$) and shorter operative time (2.7 vs 3.3 hours, $p < 0.0127$) than the PC-RPLND group. Hospital stay was not significantly different between P-RPLND and PC-RPLND (4.4 and 4.7 days, $p < 0.4453$). Caution must be used when considering hospital stay because patients treated before 2000 had a hospital stay of around 4 days vs those who underwent surgery after 2000, who had a hospital stay of about 3 days. There were 5 perioperative complications (7%) in the P-RPLND group, including ileus in 2 cases, postoperative pain in 1, wound infection in 1 and chylous ascites/pain in 1. The PC-RPLND group had 6 (11%) perioperative complications, including ileus in 2 cases, postoperative pain in 2, chylous ascites/pain in 1 and injury to the aorta in 1. All patients responded to conservative treatment except the male patient who experienced injury to the aorta. The laceration was repaired and the patient received 10 U blood. Histopathological findings were negative and he had an otherwise uneventful hospital course. This patient had recurrent disease, requiring adjuvant chemotherapy and subsequent salvage RPLND for teratoma. He remains disease-free. There were no deaths in either group (table 3).

DISCUSSION

Surgical and medical management for high risk testicular cancer has been well described with disease-free survival in CS I-II cases approaching 100%.¹¹ Two factors that have been shown to lead to high rates of retroperitoneal metastasis after orchiectomy are ECP and LVI. Our retrospective chart review supports earlier findings that ECP and LVI are high risk factors predictive of metastatic disease.

Furthermore, analysis of P-RPLND vs PC-RPLND confirmed that surgical therapy for high risk testicular cancer is safe and P-RPLND for CS I and IIA-B disease can often spare the patient the potential long-term toxicity of chemotherapy compounded by radiation exposure from surveillance imaging.

Of the 133 cases of embryonal predominance in this study 65 (49%) were CS I and 68 (51%) were CS II. Clinical stage was a factor in patient selection for RPLND vs chemotherapy as the initial treatment modality with lower stage disease more often treated with P-RPLND as definitive therapy. Of patients with CS I disease 77% underwent P-RPLND, while 23% received primary chemotherapy followed by PC-RPLND. Conversely patients with CS II disease after orchiectomy preferentially underwent chemotherapy as primary treatment with PC-RPLND in 62% and P-RPLND in 38%.

The percent of embryonal carcinoma with or without LVI carries an increased risk of metastatic disease. Of the 133 study patients 54% harbored metastatic disease. Heidenreich et al successfully predicted PS in CS I cases based on the percent of embryonal carcinoma with or without LVI in 88% of 149.² The average percent of embryonal carcinoma in PS I and II cases in that study was 37.8% and 81.9%, respectively. Although we used greater than 30% as our threshold for ECP, the average embryonal component in our series was 75.3% in the P-RPLND group and 71.2% in the PC-RPLND group. These relatively high percents of embryonal carcinoma are closer to the greater than 80% cutoff used by Heidenreich et al. Above this cutoff they were able to accurately predict PS II status in 85.4% of cases compared to the less than 45% group, in which 88% were accurately staged as PS I. In our study 72 of 133 patients (54%) who underwent RPLND had retroperitoneal disease. Despite the difference in surgical treatment in these patients with ECP with or without LVI recurrence rates in the P-RPLND and PC-RPLND groups were similar at 8% and 9%, respectively, and there were no deaths in either group. Our findings are consistent with those in other reports identifying RPLND as safe and effective therapy for high risk NSGCT.^{2,12}

Several studies have supported primary chemotherapy for NSGCT testicular cancer with ECP and LVI.^{13,14} Bohlen et al reported that 2 cycles of cisplatin, vinblastine and bleomycin or bleomycin, etoposide and cisplatin were effective definitive treatment in 56 of 58 men with high risk CSI NSGCT.⁷ They reported 1 relapse of teratoma into the retroperitoneum and 1 patient was found to have seminoma in the contralateral testis. Only 57% of their patients had an embryonal component in the primary tumor and 9% had an embryonal component as well as LVI. Grade 4 toxicity was noted in 8% of

patients, of whom 1 could only tolerate 1 cycle of cisplatin, vinblastine and bleomycin due to paralytic ileus and 1 man experienced cardiac toxicity due to bleomycin, which ended chemotherapy prematurely.

Primary chemotherapy for high risk CS I testicular cancer has been favored over watchful waiting strategies because the psychological impact of knowing about the relatively high 27% to 35% relapse rate is taxing.⁷ Stephenson et al argued that for CS II NSGCT RPLND cannot be safely omitted after induction chemotherapy in patients with stable disease because the incidence of viable retroperitoneal disease in the form of teratoma or viable malignancy is on the order of 20%.¹³ The current study demonstrates that in high risk NSGCT cases RPLND performed at a high volume tertiary care center is a safe option with minimal morbidity, more accurate staging and an excellent oncological outcome. In addition, surgical management with RPLND avoids the more rigorous followup regimen with CT used for surveillance in primary chemotherapy cases.

Recent attention has also been given to routine CT and the risk at which it puts the patients for malignancy as a result of radiation exposure.^{1,15} Although no large-scale epidemiological studies of the cancer risk attributable to CT are presented in their review, Brenner and Hall noted that 1.5% to 2.0% of all cancers in the United States may be attributable to ionizing radiation from CT.¹ Patients are at an increased attributable lifetime risk for cancer with even 1 CT of the abdomen. This magnitude of risk is inversely proportional to patient age. This finding is of importance in our study population of men in the third decade of life with a life expectancy of greater than 40 years. If primary chemotherapy is used without PC-RPLND, these men undergo numerous CT scans as part of followup. The National Comprehensive Cancer Network guidelines for surveillance after primary chemotherapy for CS IA-B NSGCT include 6 or 7 abdominal CT scans during 5 years with CT every 12 to 24 months after 5 years.¹⁶ This is in contrast to the post-RPLND National Comprehensive Cancer Network guideline, which recommends 1 postoperative baseline abdominal CT scan.

Large epidemiological studies have been performed that demonstrate an increased lifetime risk of secondary malignancy in testis cancer cases. In a population based study of 42,722 patients with testicular cancer the lifetime risk of leukemia after various treatments for seminoma and nonseminomatous germ cell testis cancer was quantified.¹⁷ This distinct population was chosen to evaluate the risk of secondary malignancy because the testis cancer survival rate exceeds 95% and long-term data were available through the Scandinavian cancer registry. There was investigation of risk by treat-

ment type as well as by histological type. The investigators concluded that the risk of acute myelogenous leukemia is higher in men who received chemotherapy for testicular cancer after 1975, which marks the introduction of platinum based chemotherapy. Similar findings were identified in a pooled analysis of nonseminoma survivors after the introduction and widespread adoption of etoposide.¹⁸ The excess leukemia cumulative risk was 0.23% 30 years after the diagnosis of testis cancer. In addition, platinum based chemotherapy regimens place patients at increased risk for metabolic syndrome and at possibly increased cardiovascular risk. A recent study by van den Belt-Dusebout et al showed that the risk of major late complications with secondary malignancy

or cardiovascular disease as a result of chemotherapy for testicular cancer was 1.9-fold greater compared to that in patients who underwent surgery.¹⁹ This risk was comparable to the effect of smoking.

CONCLUSIONS

Patients with greater than 30% embryonal carcinoma with or without LVI are at significant risk for metastatic disease and they may be successfully treated with primary RPLND. Recurrence rates based on CT evaluation were low and similar between the chemotherapy and nonchemotherapy treated groups.

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EDITORIAL COMMENT

In patients with CS I and IIA-B NSGCT with evidence of ECP and/or LVI, RPLND and primary chemotherapy with 2 (CS I), or 3 or 4 (CS IIA-B) cycles of cisplatin based regimens are accepted treatment options because each is associated with a survival rate that approaches 100%. Treatment decisions are

largely based on minimizing treatment related morbidity without compromising curability. There is increasing appreciation of the long-term toxicity of cisplatin based chemotherapy, specifically cardiovascular disease and secondary malignant neoplasms. The risk is similar to that associated with

cigarette smoking (reference 19 in article). In contrast, the short-term morbidity of RPLND performed by experienced surgeons is negligible. A 5% risk of ejaculatory dysfunction with nerve sparing and a 1% risk of small bowel obstruction are the greatest long-term sequelae. Thus, we have preferentially recommended RPLND in these patients except those at high risk for occult systemic disease. In these cases induction chemotherapy is preferred.¹

Patients with increased serum AFP or HCG and/or bulky (greater than 3 cm) adenopathy are likely to harbor systemic disease and there is a general consensus that they should receive chemotherapy. However, treatment for low stage NSGCT in patients with ECP and LVI without these factors is controversial. Advocates of chemotherapy for CS I argue that a large proportion of patients have systemic disease (a 28% relapse rate in patients with PS I has been reported) and chemotherapy is ultimately necessary in more than 80% with proven metastatic disease (PS II and/or relapse) (reference 3 in article). However, we observed a substantially lower risk of systemic disease in these patients.² The relapse rate in patients with PS I was 10% and only 25% of patients required chemotherapy as adjuvant therapy or to treat relapse.

The current article confirms the low risk of systemic disease in patients with low stage NSGCT with ECP with or without LVI who are treated with RPLND. Retroperitoneal disease was present in 37 of 76 patients (49%) but only 2 (3%) had systemic disease (metastasis to the lung and mesentery in 1 each). This result is similar to the 1.2% systemic relapse rate after RPLND that we recently reported.¹ This evidence indicates that treatment should be directed primarily at the retroperitoneum, for which RPLND is the preferred intervention. As these authors report, approximately half of patients with PS II

have microscopic lymph node involvement (pN1), for which RPLND alone is curative in up to 90%.¹ Likewise, approximately a third of patients with PS II have teratoma, which is resistant to chemotherapy.¹ It appears that only 27 patients (36%) in this study would require chemotherapy, assuming that adjuvant therapy was restricted to those with pN2-3 disease. Thus, 64% of patients would avoid the potential late toxicity of chemotherapy. The 5% retroperitoneal recurrence rate is somewhat higher than that reported from centers where a full bilateral template is routinely used, presumably due to the use of modified templates. Compared to chemotherapy routine surveillance CT after RPLND is unnecessary, thus avoiding the potential risks of SMN related to radiation exposure.³

Briefly, these authors confirm the safety and efficacy of RPLND in patients with CS I NSGCT and evidence of ECP or LVI, and they report that systemic disease is relatively uncommon in these patients. In patients with CS IIA-B disease a policy of RPLND in those with normal AFP and HCG, and less than 3 cm adenopathy with chemotherapy in all others is associated with a long-term survival rate of close to 100% and 25% of patients avoid chemotherapy (reference 13 in article).

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