Predictors of Positive Retroperitoneal Lymph Nodes in Patients With High Risk Testicular Cancer

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Purpose: Percent of embryonal carcinoma and lymphovascular invasion in the primary tumor are risk factors for occult retroperitoneal metastatic disease. High risk patients with clinical stage I and IIA nonseminomatous germ cell tumor who underwent primary retroperitoneal lymph node dissection were identified to discern any other risk factors for metastatic disease.

Materials and Methods: Patients who had undergone retroperitoneal lymph node dissection at our institution from 1993 to 2009 were identified and clinical charts were reviewed. A total of 90 patients with orchiectomy specimens containing more than 30% embryonal carcinoma who underwent primary retroperitoneal lymph node dissection were identified and perioperative data were obtained.

Results: Of 353 patients 90 (25%) had greater than 30% embryonal carcinoma and underwent primary retroperitoneal lymph node dissection. Of these patients 45 (50%) had lymphovascular invasion. Median followup was 1.1 years. Positive lymph nodes identified at retroperitoneal lymph node dissection were noted in 30 (46%) and 15 (60%) patients with clinical stage I vs clinical stage II disease. On multivariate analysis embryonal carcinoma (OR 1.02, 95% CI 1.00–1.04) and lymphovascular invasion (OR 3.52, 95% CI 1.43–8.67) were associated with positive lymph nodes at retroperitoneal lymph node dissection. The positive predictive value for 100% embryonal carcinoma was 65.5%, although the negative predictive value for 30% embryonal carcinoma was 85.7%.

Conclusions: Embryonal carcinoma and lymphovascular invasion were significantly and independently associated with the risk of occult retroperitoneal metastatic disease. These results should be considered when counseling patients about appropriate treatment options.

Key Words: lymph node excision; testicular neoplasms; carcinoma, embryonal

Abbreviations and Acronyms

CSI = clinical stage I
CSII = clinical stage II
LVI = lymphovascular invasion
P-RPLND = primary retroperitoneal lymph node dissection
PSI = pathological stage I
PSII = pathological stage II
RPLND = retroperitoneal lymph node dissection

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Of all clinical stage I nonseminomatous germ cell tumors, approximately 30% will harbor metastatic disease to the retroperitoneum.[1] Current treatment options include active surveillance, chemotherapy and/or RPLND. RPLND remains an integral component in the treatment and cure of testicular cancer not only by staging cases more precisely than imaging, but also by limiting the followup and side effects associated with chemotherapy.[2,3] Furthermore, RPLND avoids the need for frequent imaging and the attendant increased risk of secondary malignancies developing many years later.[4] With the introduction of modified template nerve sparing approaches, the morbidity associated with this procedure is minimal.[5,6]

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To identify patients at risk for metastatic disease prior studies have confirmed that percent embryonal carcinoma and LVI in the primary tumor are independent risk factors for occult metastasis.[7–9] Heidenreich et al positively predicted 88% of patients with CSI disease with greater than 80% embryonal carcinoma and positive vascular invasion had PSII disease.[7] Conversely 91.5% of patients with CSI disease with less than 45% embryonal carcinoma and absent vascular invasion were free of metastatic disease. The Testicular Cancer Intergroup study revealed that combining percent embryonal carcinoma with vascular invasion accurately predicted PSII disease in 86% of patients.[10]

The indication for primary chemotherapy in these high risk patients remains a debate with some groups recommending 2 cycles of platinum based chemotherapy and open RPLND reserved as an alternative treatment.[11] Depending on the precise definition of risk factors, up to 50% of these high risk patients who receive chemotherapy harbor metastatic disease.[12] Therefore, 50% of patients given chemotherapy for high risk disease are treated unnecessarily, thus exposing these often young patients to the lifelong risks of secondary malignancies[3] and cardiopulmonary toxicities.[13,14] Prior studies have demonstrated the successful treatment of high risk patients with P-RPLND.[12,15] In the current study high risk cases of clinical stage I and IIA nonseminomatous germ cell tumor treated with P-RPLND were reviewed to elucidate any other risk factors for metastatic disease.

MATERIALS AND METHODS

All patients undergoing RPLND at Brigham and Women's Hospital and Dana Farber Cancer Center from 1993 to 2009 were candidates for inclusion in this study. All patients with orchiectomy specimens of greater than 30% embryonal carcinoma were identified and perioperative data were obtained. These data were extracted from the Brigham and Women's Hospital RPLND computerized database and analyzed accordingly.[12] This project was approved by the institutional review board at Brigham and Women's Hospital.

At our institution all patients are evaluated in a multidisciplinary clinic, and are counseled regarding the options of active surveillance, surgery and/or chemotherapy as previously described.[12] All cases were preoperatively staged with tumor markers (α-fetoprotein, human chorionic gonadotropin and lactate dehydrogenase), abdominopelvic computerized tomography and computerized tomography 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 had confirmed histology and percent embryonal carcinoma in orchiectomy specimens. In addition, all orchiectomy pathological reports denoted the presence or absence of LVI defined as the presence of identifiable tumor cells within the lumen of an artery, vein or lymphatic vessel.

Data were entered into a computerized database and analyzed. Differences between P-RPLND and RPLND pathological findings based on continuous variables were compared using the Student's t test. A chi-square test was used to test for differences in proportions among these groups of patients. All variables significantly associated with positive nodes on univariate analysis at $p = 0.05$ or better were used in the logistic regression model. Embryonal carcinoma greater than 30% was evaluated as a categorical variable. Since orchiectomy pathological stage is based largely on the presence or absence of LVI, we did not include orchiectomy stage in the multivariate analysis.

RESULTS

A total of 353 patients who underwent RPLND at Brigham and Women's Hospital and Dana Farber Cancer Center between 1993 and 2009 were identified. Of these patients 90 (25%) had greater than 30% embryonal carcinoma and underwent P-RPLND. Of these patients 45 (50%) had combined LVI. Median followup was 1.1 years. There were no perioperative deaths.

Patient demographics and primary tumor characteristics according to pathological stage at RPLND are summarized in the table. Positive lymph nodes identified at RPLND were noted in 30 (46%) and 15 (60%) patients with CSI vs CSII disease. There was no difference in patient age or clinical stage between the groups. Average percent embryonal carcinoma in PSI vs PSII was 68.2% vs 81.4%, respectively ($p = 0.011$). All other histological subtypes were similar in either group. Patients with PSII disease had a significantly higher percentage of LVI (66.7% vs 33.3%, $p = 0.003$) which corresponded with orchiectomy pathological stage ($p = 0.006$).

On multivariate analysis embryonal carcinoma (OR 1.02, 95% CI 1.001–1.040, $p = 0.038$) and LVI (OR 3.52, 95% CI 1.43–8.67, $p = 0.006$) were associated with positive lymph nodes at RPLND. The positive predictive value for 100% embryonal carci-

Patient demographic data and preoperative clinical characteristics

	Pathological Stage I	Pathological Stage II	p Value
No. pts	45	45	
Mean pt age	29	30	0.587
No. CSI (%)	35 (77.8)	30 (66.7)	0.347
No. CSII (%)	10 (22.2)	15 (33.3)	
No. Ca (%):			
Choriocarcinoma	5 (11.1)	3 (46.67)	0.714
Seminoma	17 (37.8)	10 (22.2)	0.167
Teratoma	24 (53.3)	18 (40.0)	0.291
Yolk sac	21 (46.7)	12 (26.7)	0.079
No. orchiectomy stage (%):			
pT1	29 (64.4)	15 (33.3)	0.006
pT2 or greater	16 (35.6)	30 (66.7)	