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RETROPERITONEAL LYMPH NODE DISSECTION IN PATIENTS WITH LOW STAGE TESTICULAR CANCER WITH EMBRYONAL CARCINOMA PREDOMINANCE AND/OR LYMPHOVASCULAR INVASION

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ABSTRACT

Purpose: The outcome after primary retroperitoneal lymph node dissection (RPLND) was analyzed in patients with clinical stage I-IIA nonseminomatous germ cell testicular cancer with embryonal carcinoma predominance (ECP) or lymphovascular invasion (LVI).

Materials and Methods: Between 1989 and 2002, 267 patients with clinical stage I-IIA nonseminomatous germ cell testicular cancer, and ECP and/or LVI underwent RPLND. Patient information was obtained from a prospective database. Median followup was 53 months.

Results: Overall 42% of patients had pathological stage (PS) II disease, of whom 54% had low volume (PN1) disease and 16% had retroperitoneal teratoma. The 5-year progression-free probability was 90% overall, 90% for PS I and 86% for PN1. All patients with relapse were continuously free of disease following standard chemotherapy with or without resection of residual masses and the 10-year actuarial overall survival was 100%. When adjuvant chemotherapy was restricted to patients with PN2 disease, the estimated 5-year relapse rate was 9% and an estimated 72% of patients avoided chemotherapy.

Conclusions: The low risk of systemic relapse in patients with PS I and PN1 after RPLND alone combined with the 16% incidence of retroperitoneal teratoma and the favorable morbidity profile supports RPLND over primary chemotherapy for the treatment of patients with low stage disease with ECP and/or LVI who are not candidates for surveillance. An estimated 72% of patients are spared the potential toxicity of chemotherapy if adjuvant therapy is restricted to patients with PN2. After primary RPLND and selective adjuvant chemotherapy late recurrence is distinctly uncommon and long-term cancer control is anticipated in essentially all patients.

KEY WORDS: testis; testicular neoplasms; neoplasms, germ cell and embryonal; neoplasm staging; treatment outcome

Patients with low stage nonseminomatous germ cell testicular cancer (NSGCT) and evidence of embryonal carcinoma predominance (ECP) or lymphovascular invasion (LVI) are generally considered candidates for additional therapy after orchiectomy due to the high risk of failure on surveillance. The preferred intervention in these patients is controversial because more than 98% are cured by primary retroperitoneal lymph node dissection (RPLND) or cisplatin based chemotherapy.[1–5]

The rationale for RPLND is based on evidence that the retroperitoneum is the initial site of metastatic spread in more than 80% of patients. However, proponents of primary chemotherapy argue that patients with ECP and/or LVI frequently have occult distant metastases based on the 23% to 37% reported relapse rate in those with negative retroperitoneal nodes and the 22% to 57% relapse rate for pathological stage (PS) II disease.[1,2,6] Studies of the outcome of clinical stage (CS) I cases after 2 cycles of adjuvant chemotherapy show a relapse rate of 2% to 7%.[3–5]

We analyzed the cancer control rate and postoperative chemotherapy requirements in patients with CS I-IIA testicular cancer in whom ECP and/or LVI was managed by RPLND. Because the reported size criteria of retroperitoneal nodes used to distinguish CS I from IIA varies from 3 mm to 1.5 cm, we analyzed the outcome in all patients with CS I and IIA NSGCT.

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PATIENTS AND METHODS

Between 1989 and 2002, 410 patients with normal post-orchiectomy serum α-fetoprotein (AFP) and β-human chorionic gonadotropin (HCG) underwent RPLND for the management of CS I and IIA NSGCT. Of these patients 267 had evidence of ECP and/or LVI in the primary tumor and they are the focus of this study. At our institution compliant patients with CS I without ECP or LVI are considered candidates for surveillance but primary chemotherapy is not offered to those with CS I, and normal post-orchiectomy AFP and HCG. Patient information was obtained from a prospective database. Although several patients underwent initial orchiectomy at the referring institution, all specimens were reviewed by pathologists at our institution prior to RPLND. Patients were considered to have ECP if it composed more than 50% of the tumor in the orchiectomy specimen. The presence of LVI was assigned if aggregations of tumor cells were seen within the lumen of an artery, vein or lymphatic vessel.

Cases were staged preoperatively with AFP, HCG, lactate dehydrogenase, computerized tomography (CT) of the

abdomen-pelvis and chest CT or chest x-ray. Pathological stage was assigned according to the 2002 American Joint Committee on Cancer classification, that is PN0—negative retroperitoneal nodes histologically, PN1—5 or fewer positive nodes and no node greater than 2 cm, PN2—any node 2.1 to 5 cm, 6 or more positive nodes, or extranodal extension and PN3—any node greater than 5 cm.

Following RPLND 2 cycles of etoposide-cisplatin (EP × 2) as adjuvant therapy was given to most patients with PN2–3 due to the high risk of relapse and to select those with PN1 for anticipated noncompliance or due to strong patient insistence for psychological or occupational reasons. Postoperatively patients were seen monthly in year 1, every second month in year 2, every third month in year 3, every fourth month in year 4, every 6 months in year 5 and annually thereafter. At each visit patients were evaluated by a history, physical examination, chest x-ray and serum tumor markers. Baseline abdominal CT was routinely obtained 4 months after RPLND. Median followup after RPLND was 53 months (range 1 to 169).

Progression-free probability (PFP) was estimated using the Kaplan-Meier method and survival differences between subgroups were assessed using the log rank test. Patients receiving adjuvant chemotherapy were excluded from the analysis of disease progression. All statistical analysis was performed using SPSS, version 10.0 statistical software (SPSS, Chicago, Illinois).

RESULTS

The table lists preoperative clinical features. Overall 196 cases (73%) were CS I and 71 (27%) were CS IIA. Regarding the presence of ECP and LVI, 84 patients (31%) had the 2 risk factors, 27 (10%) had ECP without LVI and 156 (58%) had LVI without ECP, of whom only 20 did not have evidence of EC in the primary tumor.

Overall 155 patients (58%) had PS I disease, including 129 (66%) with CS I and 26 (37%) with CS IIA. Of the 112 patients (42%) with PS II 60 (54%) had PN1 and 52 (46%) had PN2 disease. A total of 18 patients (16%) with PS II had teratoma in the retroperitoneum (7% overall). Compared with patients with 1 risk factor only the presence of ECP and LVI was associated with a higher rate of PS II (54% vs 37%, $p = 0.009$) but the proportion of patients with PS II with PN2 disease was not significantly greater (53% vs 42%, $p = 0.2$).

Adjuvant chemotherapy was administered in 56 patients (50%) with PS II, including 22% with PN1 and 83% with PN2. All patients who received adjuvant chemotherapy were continuously free of disease. Compared with patients with 1 risk factor those with PN1 disease, ECP and LVI were not significantly more likely to receive adjuvant chemotherapy (29% vs 18%, $p = 0.3$).

In the absence of adjuvant chemotherapy disease progression was observed in 26 of 211 patients overall and the 5-year PFP was 87% (95% CI 82 to 92). Four patients (1.5%) experienced disease relapse in the retroperitoneum, of whom all underwent modified template dissection. Three of these patients had PS I and 1 had PN1 disease. With nerve sparing techniques modified templates have now been abandoned and no retroperitoneal recurrences have been observed following full bilateral template dissections. The 5-year PFP was 90% (95% CI 85 to 95) for PS I and 86% (95% CI 76 to 96) for PN1. Disease recurrence was observed in 5 of 9 PN2 cases (56%) that did not receive adjuvant chemotherapy. A total of 25 patients were salvaged with EP × 4 chemotherapy, of whom 6 underwent resection of residual masses. Subsequently all were continuously free of disease. One patient had late EC recurrence in an interaortocaval lymph node 8.5 years after initial RPLND. This patient remained free of recurrence for 1 year following repeat RPLND and adjuvant EP × 2. Considering all patients, including the 56 who received adjuvant chemotherapy, 5-year PFP was 90% (95% CI 86 to 94) and 10-year actuarial overall survival was 100%, that is 33 patients at risk at 10 years. Considering patients with PS I and PN1 the presence of ECP and LVI was not associated with a higher risk of relapse compared with that in patients with 1 risk factor (5-year PFP 80% vs 92%, $p = 0.5$).

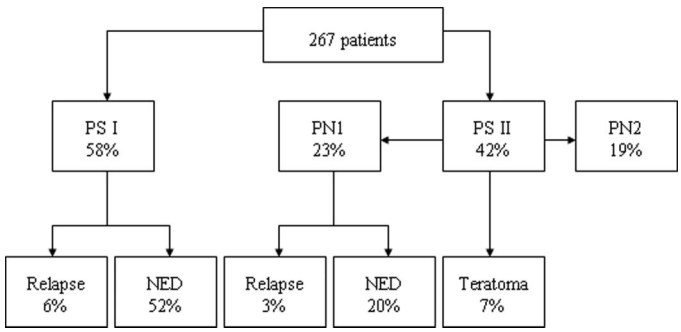
Post-RPLND chemotherapy requirements were estimated in the 267 patients in this study based on the proportion with PN2 and the actuarial 5-year relapse rate in patients with PS I and PN1 (see figure). For the purpose of analysis patients with PN2 would have received adjuvant EP × 2, and patients with PS I and PN1 would have been observed after RPLND and would have received EP × 4 for relapse only. An estimated 52% of patients would have been over treated by RPLND due to PS I without relapse at 5 years. Postoperative chemotherapy was required in an estimated 28% of patients, including as adjuvant therapy in 19% for PN2, for PS I relapse in 6% and for PN1 relapse in 3%. Patients required an average of 0.7 cycles of chemotherapy. Of the 81% of patients with PS I and PN1 an estimated 89% would have been free of progression at 5 years after RPLND alone.

DISCUSSION

The high rate of retroperitoneal disease, the 16% observed incidence of retroperitoneal teratoma in patients with PS II and the low rate of systemic relapse in those with PS I and PN1 supports RPLND as the preferred intervention in patients with low stage testicular cancer with ECP and/or LVI who are not candidates for surveillance. Primary chemotherapy for CS I-IIA and normal serum tumor markers expose a substantial proportion of patients who have disease confined to the testis (an estimated 52% in our study) to the potential long-term toxicity of chemotherapy. In addition, primary chemotherapy alone is ineffective therapy for retroperitoneal teratoma. With RPLND an estimated 72% of patients are

Preoperative characteristics of patients with clinical stages I–IIA NSGCT with ECP and/or LVI managed by primary RPLND

Characteristic	No. Pts (%)
Total No.	267
Ca:	
I	196 (73)
IIA	71 (27)
Orchiectomy histology:	
ECP	156 (58)
Teratoma	134 (50)
Yolk sac tumor	125 (47)
EC present	247 (93)
LVI	240 (90)
Risk group:	
ECP + LVI	84 (31)
ECP only	27 (10)
LVI only	156 (58)



Estimated chemotherapy requirements in 267 patients with clinical stages I-IIA NSGCT with ECP and/or LVI managed by RPLND. *NED*, no disease evidence.

spared the toxicity of chemotherapy if adjuvant therapy is restricted to those with PN2 disease, the overall estimated long-term relapse rate is 9% with virtually no late recurrences and long-term cure is achieved in essentially all patients.

ECP and LVI are the 2 most frequently reported histological factors that predict retroperitoneal metastases. Heidenreich et al reported a 40% to 50% rate of PS II in patients with LVI or ECP alone and a 91% rate in those with ECP and LVI.[7] Patients with these features are generally recommended to undergo additional therapy after orchiectomy due to the high risk of relapse on surveillance. Proponents of primary chemotherapy cite the 23% to 37% relapse rate in these patients at high risk with PS I, suggesting that metastases bypass the retroperitoneum in 32% to 50% in whom RPLND represents ineffective therapy.[1,2,6] However, the 10% relapse rate for PS I in our series combined with the 42% PS II rate indicates that the retroperitoneum is the initial site of metastases in 88% of patients with CS I-IIA with ECP and/or LVI. The majority of patients with PS II had low volume (PN1) disease and an estimated 86% were cured after RPLND alone, emphasizing the therapeutic efficacy of RPLND. The low 5-year relapse rate in patients with PS I and PN1 (10% and 14%, respectively) indicates that the risk of systemic metastases is low.

An important consideration in the treatment of patients with low stage testicular cancer is the 16% to 30% incidence of retroperitoneal teratoma in those with PS II.[8] Teratoma is resistant to chemotherapy and unresected disease poses a significant threat to patients who are treated with chemotherapy alone. Although it is histologically benign, the biological potential of teratoma is unpredictable. It may grow and become unresectable, undergo malignant transformation or result in late recurrence, of which all may have lethal consequences. Late recurrence of testicular cancer is resistant to chemotherapy and long-term cancer control is achieved in less than 50% of patients.[9]

The potential long-term toxicity of chemotherapy should caution against its liberal use in patients with low stage testicular cancer. After 2 cycles of cisplatin based chemotherapy ototoxicity is reported in 15% of patients and 10% to 16% experience sensory peripheral neuropathy.[4,10] The risk of pulmonary toxicity after 2 cycles of bleomycin is low[11] but Raynaud's phenomenon is observed in a substantial proportion of patients (up to 30% after standard doses).[12] A 0.2% to 0.5% risk of secondary leukemia is associated with cumulative etoposide doses of 2 gm/m^2 or less and there is no safe lower limit.[13] There is a 7-fold increased risk of late cardiovascular events in patients receiving standard cisplatin based chemotherapy and it is uncertain if 2 cycles are associated with lower risk.[12] In contrast, primary RPLND is associated with a 1% to 2% risk of small bowel obstruction and a 5% or less risk of anejaculation when nerve sparing techniques are used.[14,15] Given the increased long-term toxicity of chemotherapy, it should be reserved for patients with a high risk of distant metastases. Of note, an estimated 52% of patients overall in our study had disease confined to the testicle due to PS I and relapse-free status at 5 years.

We estimated that a policy of primary RPLND and adjuvant chemotherapy for PN2 only would result in an overall 5-year relapse rate of 9% and chemotherapy would be avoided in 72% of patients. Overall patients are calculated to receive an average of 0.7 cycles of chemotherapy compared with 2.5 cycles if they received primary chemotherapy, assuming 2 cycles of bleomycin and EP for CS I, and 4 cycles of EP for CS IIA. In our study 13 patients (22%) with PN1 received adjuvant EP $\times$ 2 and 9 (17%) with PN2 were observed after RPLND. The overall 5-year estimated relapse rate was 13% and 82 patients (31%) received chemotherapy as adjuvant therapy or treatment for relapse.

Even with the selective use of adjuvant chemotherapy in our study the observed 10% overall relapse rate after RPLND is higher than the 2% to 4% relapse rate reported in studies of 2 cycles of primary chemotherapy for NSGCT in patients with CS I.[3–5] However, the 7% overall incidence of retroperitoneal teratoma observed in our study suggests that the relapse rate in these studies should be higher. There are several explanations for this apparent discrepancy. 1) Not all patients in these adjuvant chemotherapy studies had LVI or ECP and the incidence of retroperitoneal metastases may have been low. 2) Unresected teratoma may present late and followup in these studies was insufficient to capture these events. 3) There may exist a subset of patients with retroperitoneal teratoma who will not have clinically evident recurrence.

An important point to emphasize about patients with relapse after RPLND is that all are chemotherapy naïve. All patients with relapse in our study were successfully salvaged with good risk chemotherapy regimens and they subsequently remained continuously free of disease at a median followup of 53 months. In contrast, all relapses following primary chemotherapy are chemoresistant, requiring surgical resection and/or salvage chemotherapy regimens. Of the 6 published studies of chemotherapy for CS I 4 described cancer related deaths in 1.4% to 5% of patients, illustrating the inability to salvage all patients with relapse.

Numerous risk stratification schemes have been developed based on the histological features of the primary tumor to identify low stage patients at high risk for occult metastases in whom additional therapy is warranted but only 1 of these models has been prospectively validated.[16] Several studies have demonstrated that patients with ECP and LVI are at higher risk for retroperitoneal metastases than those with only 1 risk factor but the association of these factors with a higher risk of systemic disease is less certain.[7,17] In our study the presence of ECP and LVI was associated with a higher rate of retroperitoneal disease compared with ECP or LVI alone. However, patients with PS I and PN1 with ECP and LVI who did not receive adjuvant chemotherapy did not experience a significantly higher rate of relapse compared with those with 1 risk factor only. Increased post-orchiectomy AFP and/or HCG are the only factors that reliably predict systemic disease in patients with low stage NSGCT in whom primary chemotherapy is the preferred treatment option.[18]

Surveillance is an acceptable alternative option for in patients with CS I, ECP and LVI, and normal post-orchiectomy AFP and HCG. However, patient compliance is essential. Noncompliance rates of up to 80% have been reported in surveillance series and these patients frequently have relapse with advanced disease.[19] The inability to salvage all cases is highlighted by the 2% to 5% reported cancer specific death rate reported in several surveillance series.[20]

CONCLUSIONS

RPLND is the preferred treatment option in patients with low stage testicular cancer with ECP and/or LVI who are not candidates for surveillance, given the 42% incidence of retroperitoneal metastases (including teratoma in 16%), the low risk of occult systemic disease and the favorable morbidity profile of RPLND compared with primary chemotherapy. Up to 72% of patients avoid chemotherapy after primary RPLND. Late recurrence is distinctly rare and long-term cure is anticipated in virtually all patients.

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EDITORIAL COMMENT

The preferred treatment in patients with clinical low stage testicular cancer with the associated risk factors of ECP (greater than 50%) or LVI remains 1 of the few major controversies in the treatment of testicular cancer. A recent publication of the European Consensus Group on Diagnosis and Treatment of Germ Cell Cancer recommended 2 cycles of adjuvant chemotherapy with bleomycin, etopicide and platinum or an active surveillance strategy with nerve sparing RPLND reserved for patients unwilling to undergo either of these strategies.[1] Proponents of primary chemotherapy have based their recommendation on the high likelihood of systemic disease and subsequent recurrence after RPLND.

These authors evaluated 267 patients with clinical stage I or IIa nonseminomatous germ cell tumor with the associated risk factors of LVI and/or ECP. Of the patients 58% were found to have pathological stage I disease with negative nodes and a low lapse rate of 10%. Patients with minimal nodal involvement (pathological stage N1a) comprised 23% of the series and had a low relapse rate of 14%.

This study of carefully defined and carefully followed patients mitigates the strength of the argument for primary chemotherapy in patients with these factors. Nerve sparing RPLND in such patients provides an excellent likelihood of cure without associated additional therapy, and with acceptable short-term and long-term toxicity.

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