Clinical Outcome of Retroperitoneal Lymph Node Dissection after Chemotherapy in Patients with Pure Embryonal Carcinoma in the Orchiectomy Specimen

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OBJECTIVE To determine the pathologic findings and clinical outcome of patients with pure embryonal carcinoma (EC) of the testis who were diagnosed with testis cancer from January 1989 to January 2013 who underwent an orchiectomy, cisplatin-based chemotherapy and a postchemotherapy retroperitoneal lymph node dissection (PC-RPLND).

METHODS We compared those patients with 100% EC with those with mixed nonseminomatous germ cell tumor pathology who underwent a PC-RPLND.

RESULTS Of 1105 patients who underwent a PC-RPLND, 145 had pure EC. Twenty-six percent of patients presented with metastatic disease outside the retroperitoneum. Patients with mixed histologies tended to have worse International Germ Cell Cancer Collaborative Group risk compared to those with EC at orchiectomy (P = .037). Histology at PC-RPLND revealed fibrosis or necrosis in 76%, mature teratoma in 19% and viable cancer in 4%. Over one-third of the patients had a residual mass of <1 cm prior to RPLND; of whom 15% harbored mature teratoma in PC-RPLND histology. The Kaplan–Meier estimated probability of recurrence at 5 years of follow-up was 3.1% (95% CI 1.2%, 8.0%) for EC histology, 7.3% lower than mixed histology. For cancer-specific mortality, the Kaplan–Meier estimated probability at 5 years was 4.6% (95% CI 3.3%, 6.3%) and 1.7% (95% CI 0.4%, 6.8%) for mixed and pure EC histologies, respectively.

CONCLUSION Approximately 20% of patients with pure EC had teratoma at PC-RPLND. We have shown that those with a maximum node size of <1 cm should not be precluded from RPLND. UROLOGY ■■: ■■–■■, 2018. © 2018 Elsevier Inc.

The American Cancer Society estimates that approximately 8500 new cases of testicular cancer will be diagnosed in the United States during 2015. The majority of testicular cancers are of germ cell origin (95%), of which 50% are nonseminomatous germ cell tumors (NSGCTs). Postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) is an important component in the management of many patients with metastatic NSGCT. NSGCTs are usually mixed tumors and teratoma often exists at metastatic sites with other germ cell tumor (GCT) elements, therefore cure often requires chemotherapy to eradicate chemo-sensitive elements and surgery to remove chemo-resistant teratomatous components. This successful integration of multimodal therapy has resulted in improved survival rates for metastatic GCT seen over the past few decades. The 2 standard regimes currently used in the treatment of good risk GCT are 3 cycles of bleomycin, etoposide, and cisplatin or 4 cycles of etoposide and cisplatin.[1]

Embryonal carcinoma is the second most common germ cell tumor of the testis encountered in pure form, after seminoma.[2] Previous studies have demonstrated that in cases of mixed GCTs of the testis, the proportion of EC strongly correlates with the development of metastasis in clinical stage I disease.[3] There is a paucity of data in the literature examining pure EC in the setting of metastatic disease.

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Retroperitoneal lymph node dissection is advocated at our institution for a number of reasons. Firstly, based on the results of surveillance series, the retroperitoneum is the initial and often the only site of metastatic disease in up to 90% of patients. Secondly, up to 30% of patients will be clinically understaged on radiographic imaging.[4] Furthermore, recurrences in the retroperitoneum often represent fatal disease, as patients who died of testicular cancer who have distant metastases usually have bulky retroperitoneal disease.[5] The retroperitoneum is also the most common site for late recurrence of teratoma and viable GCT.[6] However a postchemotherapy lymph node dissection (PC-RPLND) can be a challenging undertaking that has historically been associated with high morbidity rates compared with primary RPLND.

Our objective in this retrospective review was to determine the pathologic findings and clinical outcomes of patients with pure embryonal carcinoma (EC) of the testis who underwent an orchiectomy, followed by chemotherapy and a PC-RPLND at Memorial Sloan Kettering Cancer Center. We hypothesize that patients with pure EC at orchiectomy who have a residual mass following chemotherapy are more likely to progress after RPLND compared to those with mixed NSGCT.

METHODS

After obtaining institutional review board approval, the prospectively maintained Memorial Sloan Kettering Cancer Center Testis Cancer Registry was queried for men who had undergone an RPLND between 1989 and 2013 following induction or salvage chemotherapy. We identified 2 cohort of patients; 1 with pure EC at orchiectomy (n = 145) and 1 with mixed histology at orchiectomy (n = 960). Only patients with 100% EC were included in the pure EC group and those patients with a fraction of EC were added to the mixed histologies group. We excluded men who had RPLNDs performed at outside institutions however; patients who had orchietomies performed elsewhere were included.

Our aim was to compare cancer-specific outcomes by histology type as well as to investigate whether histology affected predictors of cancer-specific outcomes. To determine whether histology type was associated with either recurrence-free or cancer specific survival, we employed multivariable Cox proportional hazards regression adjusting for International Germ Cell Cancer Collaborative Group (IGCCCG) risk (poor or intermediate vs good). Patient cancer-specific survival was determined from the date of postchemotherapy RPLND until death from testis cancer or death from another cause or until the last date the patient was known to be alive. Recurrence-free survival was determined from date of postchemotherapy RPLND until the date of recurrence or until the most recent patient contact. We were missing date of recurrence for 5 patients who died of testis cancer; we defined their date of recurrence as their death date. Patients who had refractory disease or recurred prior to their RPLND date (n = 106) were not included in the recurrence analysis.

Separately by histology type, we report the breakdown of histology after first RPLND by the diameter of the maximum node on CT prior to RPLND dichotomized at 1 cm. Currently, PC-RPLND is recommended if a residual mass of >1 cm is present following induction chemotherapy.[7] Various studies have however demonstrated the presence of mature teratoma or viable cancer in residual lymph node masses <1 cm, providing a rationale for PC-RPLND in any case of residual lymph node mass.[8] We also wished to test the association between recurrence-free and cancer-specific survival and histology after RPLND as well as dichotomized maximum node size prior to RPLND using separate univariable Cox proportional hazards regression. All analyses were conducted using Stata 12.0 (Stata Corp., College Station, TX).

RESULTS

We identified 145 patients with pure ECs at orchiectomy and 960 metastatic testis cancers with mixed histologies. All patients were treated with cisplatin-based chemotherapy prior to RPLND based on their risk group as per the 1997 IGCCCG classification system. Baseline patient characteristics by histology type at orchiectomy are displayed in Table 1. Patients with mixed histologies tended to have worse IGCCCG risk compared with those with EC at orchiectomy (Table 1; $P = .037$). Patients with EC histology had significantly lower prediagnosis alpha fetoprotein and human chorionic gonadotropin levels but did not differ on lactate dehydrogenase levels (Table 1). Among those who had EC histology, 99% of their testis cancer was diagnosed on orchiectomy, which was significantly greater than the 74% of cases with other histology diagnosed (Table 1, $P < .0001$). At orchiectomy, EC patients had a greater probability of intratubular germ cell neoplasia and lymphovascular invasion but on average, had 1 cm smaller tumors and tended to have worse T stage (Table 1). Patient characteristics based on RPLND findings are displayed in Table 2. Patients who had EC histology were, on average, one year younger with a median age among those with mixed histologies of 30 years and 29 years among those with EC (Table 2, $P = .017$). At RPLND, those with EC had a higher incidence of nerve sparing surgery. The total number of nodes and the proportion of patients with positive nodes on RPLND were significantly greater among those with mixed histologies (Table 2). Over 50% of EC patients had a modified unilateral approach during their RPLND whereas 27% of other histology patients underwent a modified unilateral approach, and 28% of other histology patients underwent a modified bilateral approach (Table 2). All modified templates were performed before 1999.

In total, there were 104 patients who had a recurrence of their testis cancer and 40 who died of their disease. The median follow-up time among those who did not die of disease was 5.9 years (IQR: 2.3, 10.6). The Kaplan–Meier estimated probability of recurrence at 5 years of