Published in final edited form as:

Urology. 2018 April ; 114: 133–138. doi:10.1016/j.urology.2018.01.014.

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

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Abstract

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 post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND).

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

RESULTS: 1,105 patients who underwent a PC-RPLND of which 145 patients 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 ($p=0.037$). 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 <1cm 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 <1cm should not be precluded from RPLND.

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Keywords

Embryonal Carcinoma; Orchiectomy; Retroperitoneal lymph node dissection; Chemotherapy

Introduction:

The American Cancer Society (ACS) estimates that approximately 8,500 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). Post chemotherapy 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 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 two standard regimes currently used in the treatment of good risk GCT are three cycles of bleomycin, etoposide and cisplatin (BEP X 3) or four cycles of etoposide and cisplatin (EP X 4) 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.

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 under-staged 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 post chemotherapy lymph node dissection (PC-RPLND) can be a challenging undertaking that has historically been associated with high morbidity rates compared to 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 two cohort of patients; one with pure EC at orchiectomy (n=145) and one 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 orchiectomies 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. In order 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 versus good). Patient cancer-specific survival was determined from the date of post-chemotherapy 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 post-chemotherapy RPLND until the date of recurrence or until the most recent patient contact. We were missing date of recurrence for five 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 >1cm is present following induction chemotherapy⁷. Various studies have however demonstrated the presence of mature teratoma or viable cancer in residual lymph node masses <1cm, providing a rationale for PC-RPLND in any case of residual lymph node mass⁸. 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 International Germ Cell Cancer Collaborative Group (IGCCCG) risk compared to those with EC at orchiectomy (Table 1; p=0.037). Patients with EC histology had significantly lower pre-diagnosis AFP and HCG levels but did not differ on LDH 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, $p<0.0001$). 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, $p=0.017$). 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 while 27% of other histology patients underwent a modified unilateral approach 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 follow-up was 10% (95% CI 8.5%, 13%) and 3.1% (95% CI 1.2%, 8.0%) for mixed histologies vs. EC histology, respectively (Table 3). The probability of a recurrence at 5 years was significantly greater by 7.3% among those with mixed histologies (95% CI 3.7%, 11%) and at 10, 15, and 20 years of follow up the recurrence-free survival probability among those with EC remained significantly greater than those with mixed histologies (Table 3). 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 EC histologies, respectively. Cancer-specific mortality was significant greater among patients with mixed histologies at 5 years of follow up (difference 2.9%, 95% CI 0.097%, 5.7%) and at 10, 15, and 20 years of follow up cancer-specific mortality remained lower among those with EC (Table 3).

Supplementary Figures 1 and 2 display the overall Kaplan Meier curves (95% CI) for the outcomes of recurrence-free survival and cancer-specific survival, respectively. After adjusting for IGCCCG risk we did not find sufficient evidence to suggest that recurrence-free survival differs by histology type (HR= 0.36; 95% CI 0.09, 1.48; $p=0.2$) nor that histology type was associated with cancer-specific survival (HR= 0.50; 95% CI 0.07, 3.70; $p=0.5$) however, the confidence intervals do not exclude meaningfully differences in survival by histology type.

As shown in Table 4, among the 145 patients who had EC, 111 (77%) had no residual disease at RPLND, 28 (19%) had mature teratoma, 5 (3%) had viable cancer and 1 (1%) patient had somatic-type malignant transformation of a teratoma. 15% of patients with EC and a maximum node less than 1 cm had residual disease and 29% of patients with EC and a node greater than 1 cm had residual disease. Among the patients who had mixed histologies 45% had no residual disease at RPLND. 36% of patients with mixed histology and a maximum node less than 1 cm had residual disease and 57% of patients with mixed histology and a node greater than 1 cm had residual disease. As the risk of residual disease is relatively high among those with a maximum node less than 1 these patients should not be precluded from PC-RPLND.

With only 5 recurrences and 2 cancer-specific deaths among those patients with EC, we do not have enough events to power comparisons for these outcomes. The patient who had somatic-type malignant transformation of a teratoma had only limited follow-up but did not die or recur within that time. There were no recurrences or deaths among the 5 patients with embryonal carcinoma who had viable cancer at RPLND pathology based on a median follow up time of 14 years (IQR: 13, 15). There were 2 recurrences among those with a mature teratoma and 3 among those with no residual disease. There were 2 cancer-specific deaths both of whom had a persistent nodal mass of greater than 1 cm in diameter prior to RPLND and had no residual cancer after RPLND. One of the patients died at 3 months and the other 4.5 years after RPLND. The patient who died at 3 months after RPLND had unresectable liver disease and had progression of disease.

The majority of patients in both cohorts underwent induction chemotherapy (first line) only. Seven percent of patients in the EC group had second-line chemotherapy and 13% of the mixed histologies group had second-line chemotherapy.

Discussion:

Patients presenting with metastatic disease will require multimodal therapy with surgery and chemotherapy. Embryonal carcinoma is relatively common among testicular germ cell tumors; the majority will have embryonal elements as a component of a mixed germ cell tumor. However, only 10% present as pure (100%) embryonal carcinomas. In clinical stage one disease, the presence of a high proportion of embryonal carcinoma in the primary tumor is a risk factor for the development of metastatic disease.⁹ It is unknown from the existing literature whether this results in a worse outcome for patients with pure EC at orchiectomy who undergo a PC-RPLND compared to those with mixed germ cell tumors. The characteristic histological features of embryonal carcinoma are cells with large, pleomorphic vesicular nuclei, having one or more large nucleoli, dense cytoplasm, ill-defined cytoplasmic membranes, numerous mitotic figures and frequent apoptotic bodies¹⁰.

The size of residual mass following chemotherapy has traditionally been used to consider further treatment. A number of surgeons continue to base the decision to perform a PC-RPLND on residual mass size following chemotherapy, obviating resection in patients with masses <1cm¹¹. Some authors have reported that residual masses smaller than 2cm are considered to be one of the most significant predictors for finding necrosis only at PC-RPLND¹². However, more recent studies have demonstrated that a third of retroperitoneal masses <2cm after chemotherapy harbored either teratoma or viable carcinoma⁸. Currently predictive models and imaging modalities cannot reliably predict the finding of fibrosis at PC-RPLND. We confirm that a non-negligible proportion of patients (15%) with the largest mass being 1 cm harbored teratoma which indicates that the decision to perform a PC-RPLND should not be based on imaging modalities and among this patients an RPLND should be performed.

PC-RPLND establishes what histological elements are present in the residual mass. Traditional series reported PC-RPLND pathology as necrosis or fibrosis in 40-50%, teratoma in 35-40%, viable GCT in 10-15% and non germ cell carcinoma in <1%¹³. In

Carver *et al.* the incidence of microscopic mature teratoma in the residual retroperitoneal mass was 23% which is in keeping with our findings of an incidence of 15%¹⁴. Patients in the Carver *et al.* study included all NSGCT at orchiectomy who had a post-chemotherapy RPLND whereas we restricted to our cohort to those with pure embryonal carcinoma at orchiectomy¹⁴. We would expect our rates to be lower as none of the patients in our cohort had any teratoma in their orchiectomy specimen which may explain the smaller incidence of mature teratoma in our study. Absence of teratoma in the primary testis tumor does not exclude finding teratoma in the RP mass. This study confirms that patients with 100% pure EC do not have worse outcomes than those with mixed histology as both received the same treatment (induction chemo + PC-RPLND).

The risk of teratoma within residual masses mandates complete surgical resection. Teratoma is resistant to chemotherapy and the natural history of unresected teratoma is highly unpredictable. It may remain dormant or grow slowly, however it may also grow rapidly leading to local invasion. Furthermore a small percentage (<10%) may undergo somatic-type malignant transformation to a non-GCT malignancy such as adenocarcinoma, rhabdomyosarcoma or primitive neuroectodermal tumor) which is usually associated with a very poor prognosis^{15, 16}. Teratoma may also result in devastating late relapses. Late relapse beyond 2 years of primary treatment occurs in approximately 2-3% of patients with testicular cancer and has been shown to occur across all stages^{6, 17}. The overall prognosis for patients with late relapse of non seminomatous GCT is relatively poor with survival rates ranging from 30-40%⁶.

Conclusions:

In our study we demonstrate that despite the absence of more differentiated elements in the orchiectomy specimen, approximately 20% of patients with pure embryonal carcinoma will have teratoma in the resected tissue at PC-RPLND. Furthermore, we have shown that those with a maximum node size of <1cm should not be precluded from RPLND.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by: National Cancer Institute [P50-CA92629 and P30-CA008748], the Sidney Kimmel Center for Prostate and Urologic Cancers, and David H. Koch through the Prostate Cancer Foundation, the Richard Capri Foundation.

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Table 1:

Baseline patient characteristics by histology at orchiectomy. Values are displayed as median (interquartile range) or frequency (percentage).

Characteristics	Mixed Histologies (N=960; 87%)	Embryonal Carcinoma (N=145; 13%)	p-value *
Race			
White	874 (91%)	137 (94%)	0.7
Asian	29 (3.0%)	2 (1.4%)	
Black	22 (2.3%)	4 (2.8%)	
Other	8 (0.8%)	2 (1.4%)	
Native American	2 (0.2%)	0 (0%)	
Unknown	25 (2.6%)	0 (0%)	
Method of Diagnosis			
Abdominal Mass	13 (1.4%)	0 (0%)	<0.0001
Lymph Node Biopsy	123 (13%)	2 (1.4%)	
Orchiectomy	708 (74%)	143 (99%)	
Other	4 (0.4%)	0 (0%)	
Unknown	112 (12%)	0 (0%)	
Clinical Stage			
I	101 (11%)	11 (7.6%)	0.026
II	498 (52%)	93 (64%)	
III	358 (37%)	41 (28%)	
Unknown	3 (0.3%)	0 (0%)	
Pre-diagnosis AFP (N=732)	49 (6, 544)	6 (3, 22)	<0.0001
Pre-diagnosis HCG (N=495)	70 (7, 1082)	5 (2, 56)	<0.0001
Pre-diagnosis LDH (N=212)	8 (5, 68)	8 (5, 58)	0.5
International Germ Cell Cancer Collaborative Group Risk			
Poor	149 (16%)	5 (3.4%)	0.037
Intermediate	131 (14%)	6 (4.1%)	
Good	557 (58%)	51 (35%)	
Unknown	123 (13%)	83 (57%)	
Intratubular Germ Cell Neoplasia on First Orchiectomy	591 (62%)	115 (79%)	0.025
Unknown	132 (14%)	2 (1.4%)	
Lymphovascular Invasion on First Orchiectomy	476 (50%)	108 (74%)	<0.0001
Unknown	142 (15%)	2 (1.4%)	
T Stage on First Orchiectomy			
PT0	8 (0.8%)	0 (0%)	<0.0001
PT1	197 (21%)	20 (14%)	
PT2	249 (26%)	88 (61%)	
PT3	54 (5.6%)	28 (19%)	

Characteristics	Mixed Histologies (N=960; 87%)	Embryonal Carcinoma (N=145; 13%)	p-value *
PTIS	3 (0.3%)	0 (0%)	
Unknown	449 (47%)	9 (6.2%)	
Size of Tumor on First Orchiectomy (cm) (N=860)	3.4 (2.0, 5.3)	2.5 (2.0, 3.5)	<0.0001

* p-values determined by Wilcoxon Rank Sum for continuous variables and Fisher's exact test for categorical variables

Table 2:

Patient Characteristics at First RPLND. Values are displayed as median (interquartile range) or frequency (percentage).

Characteristics	Mixed Histologies (N=960; 87%)	Embryonal Carcinoma (N=145; 13%)	p-value *
Age at RPLND	30 (24, 37)	29 (23, 34)	0.017
Surgery Approach Type RPLND			
Modified Bilateral	366 (38%)	41 (28%)	<0.0001
Modified Unilateral	256 (27%)	77 (53%)	
Full Bilateral	185 (19%)	24 (17%)	
Suprahilar	70 (7.3%)	1 (0.7%)	
Other	41 (4.3%)	2 (1.4%)	
Incomplete Resection	14 (1.5%)	0 (0%)	
Unknown	28 (2.9%)	0 (0%)	
Diameter of Maximum Node (cm) at RPLND (N=966)	2.2 (1.2, 5.0)	1.2 (0.9, 1.9)	<0.0001
RPLND Nerve Sparing	375 (39%)	79 (54%)	0.004
Unknown	55 (5.7%)	0 (0%)	
RPLND Desperation	48 (5.0%)	3 (2.1%)	0.047
Unknown	206 (21%)	1 (0.7%)	
Total Number of Nodes at RPLND (N=732)	39.0 (21.0, 59.0)	31.0 (21.0, 43.0)	0.038
Positive Nodes at RPLND	299 (31%)	26 (18%)	<0.0001
Unknown	270 (28%)	8 (5.5%)	

* p-values determined by Wilcoxon Rank Sum for continuous variables and Fisher's exact test for categorical variables

Table 3:

Kaplan Meier estimates (95% CI) for recurrence and cancer-specific mortality by histology type at orchiectomy and the difference. The difference was calculated as the Kaplan Meier estimate of those with EC subtracted from the estimate corresponding to those with other histology.

Recurrence			
Time (years)	Mixed Histology	EC	Difference
5	10% (8.5%, 13%)	3.1% (1.2%, 8.0%)	7.3% (3.7%, 11%)
10	12% (9.8%, 15%)	5.1% (1.9%, 13%)	7% (1.5%, 13%)
15	15% (12%, 20%)	5% (1.9%, 13%)	10% (4.0%, 16%)
20	15% (12%, 20%)	5% (1.9%, 13%)	10% (4.0%, 16%)
Cancer-Specific Mortality			
Time (years)	Mixed Histology	EC	Difference
5	4.6% (3.3%, 6.3%)	1.7% (0.4%, 6.8%)	2.9% (0.097%, 5.7%)
10	4.8% (3.5%, 6.6%)	1.7% (0.4%, 6.8%)	3.1% (0.26%, 5.9%)
15	5.2% (3.7%, 7.2%)	1.7% (0.4%, 6.8%)	3.5% (0.57%, 6.4%)
20	5.2% (3.7%, 7.2%)	1.7% (0.4%, 6.8%)	3.5% (0.57%, 6.4%)

Table 4:

Histology after first RPLND by the maximum node size in diameter dichotomized at 1 cm by histology type at orchiectomy. Values are displayed as frequency (percentage).

Embryonal Carcinoma at Orchiectomy		
	Maximum Node 1 cm in diameter (N=55; 38%)	Maximum Node > 1 cm in diameter (N=90; 62%)
Histology after First RPLND		
Malignant Transformation of Teratoma	0 (0%)	1 (1.1%)
Mature Teratoma	8 (15%)	20 (22%)
No Residual Disease	47 (85%)	64 (71%)
Viable Cancer	0 (0%)	5 (5.6%)
Mixed Histology at Orchiectomy		
	Maximum Node 1 cm in diameter (N=167; 20%)	Maximum Node > 1 cm in diameter (N=654; 80%)
Histology after First RPLND		
Malignant Transformation of Teratoma	0 (0%)	17 (2.6%)
Mature Teratoma	45 (27%)	306 (47%)
No Residual Disease	101 (60%)	272 (42%)
Viable Cancer	15 (9.0%)	48 (7.3%)
Unknown	6 (3.6%)	11 (1.7%)