Published in final edited form as:

J Urol. 2015 February ; 193(2): 513–518. doi:10.1016/j.juro.2014.08.081.

Rates of Teratoma and Viable Cancer at Post-Chemotherapy Retroperitoneal Lymph Node Dissection after Induction Chemotherapy for Good Risk Non-Seminomatous Germ Cell Tumors

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Abstract

Purpose—Patients with good risk nonseminomatous germ cell tumors receive induction chemotherapy with either 4 cycles of etoposide and platinum (EPx4) or three cycles of bleomycin, etoposide, and platinum (BEPx3). We report the histologic results at post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) after induction chemotherapy in patients treated either with EP or BEP for good risk NSGCT.

Materials and Methods—PC-RPLND was performed in 579 patients following induction chemotherapy. Five-hundred five patients were treated with EPx4 and 74 patients were treated with BEPx3 or BEPx4. Clinical and pathologic features are reported.

Results—No difference in the frequency of viable residual cancer was observed between BEP and EP (5% vs 6%, respectively, $P=NS$). Teratoma was more prevalent in the BEP group vs. EP (57% vs. 34%, respectively, $p<0.001$). On multivariate analysis, patients that received induction BEP had a 2-fold greater risk of harboring teratoma at PC-RPLND (OR 2.0, 95% CI 1.0, 4.0, $p=0.04$). When excluding patients that received BEPx4, patients that received BEPx3 still had a 3.7 fold increased risk of having teratoma in the retroperitoneum (OR 3.7, 95% CI 1.5, 8.9, $p=0.004$). Relapse-free survival and disease-specific survivals were not different between the two regimens.

Conclusion—Viable cancer was equally uncommon after treatment with both regimens. Overall, relapse-free, and disease-specific survivals did not differ. The discrepancy between regimens in

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the frequency of teratoma is not explained, but may be due to an unrecognized selection bias than an effect of the regimen.

Introduction

In 1997 the International Germ Cell Cancer Collaborative Group (IGCCCG) revised the prognostic factor based staging system for metastatic germ cell tumors (GCT).¹ This classification assigns risk based on location of metastasis and nadir serum tumor marker level after orchiectomy and has been used primarily to standardize chemotherapy regimens and assign risk in clinical trials. Patients with good risk GCT include men with a testicular or primary retroperitoneal GCT, no non-pulmonary visceral metastases, and good risk serum marker levels (AFP < 1000 ng/ml, HCG < 5000 ng/ml, and LDH < 1.5 x normal). Cure rates for patients with good risk GCT exceed 90% with appropriate chemotherapy and surgical resection.²

Two standard treatments are currently used in the treatment of good risk GCT: three cycles of bleomycin, etoposide, and cisplatin (BEPx3) or four cycles of etoposide and cisplatin (EPx4).²³⁴⁵ The long term follow-up results of good risk patients treated with both BEPx3 and EPx4 have been reported with excellent complete response results and long term survival rates.²³ EP x 4 has been the standard of care at MSKCC in the treatment of men with good risk GCTs due to its excellent long term results and the complete avoidance of the pulmonary and vascular (Raynaud's phenomenon) complications associated with bleomycin.

Post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) is also advocated at MSKCC for men undergoing chemotherapy for good risk GCT because it is known that at least 30% will harbor either viable cancer or teratoma, depending on size of residual mass.² While several groups have reported similar efficacy for EP and BEP, these reports do not include post-chemotherapy surgery data. The interpretation of the results is therefore hampered by inadequate follow-up to detect the consequence of additional chemotherapy for relapsed viable cancer and late recurrence of teratoma.

Beck et al. reported rates of teratoma after PC-RPLND in 2002 for patients treated at Indiana University. Stage-for-stage, when comparing histologies in patients treated with PC-RPLND at Indiana vs. MSKCC, the rates of teratoma are higher in the cohort of patients treated at Indiana University.⁶⁷⁸ We therefore sought to examine the differences in histology, and specifically teratoma and viable cancer, in good risk GCT patients who underwent PC-RPLND at MSKCC and were treated with either EPx4 or BEPx3.

Methods

After obtaining Institutional Review Board approval, we interrogated the prospective MSKCC Testis Cancer Registry and identified 579 patients with good risk GCT who were treated between 1989 and 2009 with induction chemotherapy followed by PC-RPLND after normalization of serum tumor markers. There were 505 patients who received EPx4 and 79 who received BEP. MSKCC risk criteria were used to assign good-risk status until August 1994;⁹ thereafter, the IGCCCG criteria were used. In the cohort of patients treated before 1994, all patients were retrospectively reviewed and were included in this study if their

clinical features were consistent with good risk status based on the IGCCCG criteria. The treatment plan for EPx4 has been described previously.⁹ Sixty-three patients had clinical stage I disease at initial diagnosis and subsequently received chemotherapy. Of these patients, 25 had induction chemotherapy for elevated serum tumor markers (clinical stage I-S), and 38 had relapse during surveillance for clinical stage I disease. Most patients who received BEP were treated at other institutions and referred to MSKCC for PC-RPLND. The treatment schedule with BEP has also been described previously.⁴ Twenty eight patients were given chemotherapy outside of MSKCC for good risk NSGCT and received BEPx4 as their induction regimen. A separate analysis excluding these patients treated with BEPx4 was also performed. Before 1999, modified templates were used. After 1999, full bilateral RPLND was performed. Computerized tomography results were used, when available, to measure transverse diameter of pre-chemotherapy and pre-surgery lymph nodes.

Categorical variables were compared using the chi-square or Fisher's exact test. Logistic regression was carried out for both univariate and multivariate analyses to test for factors that were associated with the presence of teratoma in the retroperitoneum at PC-RPLND. When performing logistic multivariate regression for lymph nodes less than 1.1 cm, node size was analyzed by 0.1 cm increments. Lymph node size was analyzed as a continuous variable in all analyses. Survival analysis was performed using the Kaplan-Meier method, and comparisons were made using the log-rank test. Statistical analysis was performed using the Stata® software package 8.2. A P value <0.05 was considered statistically significant.

Results

Baseline patient features including age, orchiectomy histology, clinical stage, pre-chemotherapy lymph node size, pre-surgery lymph node size, and year of surgery are listed in Table 1. Median patient age for the EP and BEP group was 31 years (IQR 25, 37) and 31 years (IQR 24, 36), respectively. Mixed GCT histology was the most common histology in both groups. All patients underwent PC-RPLND after induction chemotherapy; RPLND histology is listed in Table 2. Fibrosis was more prevalent in the EP group than the BEP group (60% vs. 39%, respectively, $p=0.001$). Pure teratoma was more prevalent in the BEP group compared to the EP group (53% vs. 32%, respectively, $p=0.001$). Presence of any teratoma was more prevalent in the BEP group vs. the EP group (57% vs. 34%, respectively, $p<0.001$). Rates of viable GCT at PC-RPLND were similar in both groups (BEP 5%, EP 6%).

Univariate analysis was performed examining the likelihood of teratoma in the retroperitoneum based on clinical and pathologic features (Table 3). Higher clinical stage was inversely and significantly associated with presence of teratoma in the RP. Presence of yolk sac or teratoma at orchiectomy, pre-surgery lymph node size, and BEP chemotherapy were all associated with presence of teratoma at RPLND (Table 3). On multivariate analysis, patients who received BEP were more likely to have teratoma found at PC-RPLND (OR 2.0, 95% CI 1.0, 4.0, $p=0.04$), even when accounting for other variables such as teratoma in the orchiectomy specimen and pre-surgery LN size (Table 4). Excluding patients who received BEPx4, multivariate analysis revealed that patients who received BEP were still more likely

to have teratoma in the retroperitoneal lymph nodes removed at PC-RPLND (OR 3.7, 95% CI 1.5, 8.9, $p=0.004$).

Since patients with small residual lymph nodes after chemotherapy are often observed without PC-RPLND at other institutions, we examined the risk of teratoma in patients with residual masses less than 1.1 cm after chemotherapy. In the cohort of patients with residual lymph node size less than 1.1 cm, those who received BEP remained more likely to have teratoma in the retroperitoneum at the time of PC-RPLND (OR 4.6, 95% CI 1, 17, $p=0.03$). Excluding patients who received BEP x 4 with post-chemotherapy lymph nodes less than 1.1 cm, the likelihood of teratoma in patients who received BEP vs. EP was even higher (OR 10.3, 95% CI 1.8, 59, $p=0.008$).

After complete PC-RPLND, there was no significant difference in 5 or 10-year relapse free survival or disease specific survival in patients that received BEP or EP (Figure 1).

Discussion

PC-RPLND is an essential component of care in patients with metastatic NSGCT. Many reports show the increasing likelihood of residual teratoma with increasing retroperitoneal lymph node size. Viable residual cancer is also more frequent in larger residual masses. Hence, PC-RPLND is the standard of care when residual retroperitoneal nodes size is greater than 1 cm in diameter. However, controversy exists when lymph node size is less than 1 cm in diameter, with MSKCC favoring PC-RPLND and others favoring surveillance until relapse. Direct comparisons of node histology after PC-RPLND in patients who have received BEP and EP have not been reported. Because of MSKCC's referral patterns, a large number of patients with GCT of all types are seen for primary therapy and many more referred for surgical management after chemotherapy in the community.

In this retrospective analysis of PC-RPLND following either BEP or EP for good risk disease, we found that residual viable GCT was equally infrequent after BEP and EP (5% and 6%, respectively, Table 2). Importantly, the median survivals of patients receiving BEP and EP were similar (95% and 96%, 5 and 10-year survival). These data support the notion that both chemotherapy regimens are equally effective in eradicating malignant GCT. Late relapses were extremely rare after both regimens. However, unexpectedly, we found that fibrosis was statistically more common after EP and teratoma statistically more common after BEP, regardless of the number of cycles or post-chemotherapy lymph node size. An explanation for the disparity in the frequency of fibrosis and teratoma between the two regimens is not immediately obvious and may therefore relate to differences between the two populations of patients, for which we were not able to control. Other potential explanations, such as bleomycin inducing differentiation of malignant GCT components into teratoma or some previously unappreciated activity of etoposide and cisplatin against teratoma (a chemo-resistant histology), are highly unlikely.

The goal of chemotherapy for patients with good risk GCTs has been to minimize treatment-related toxicity without compromising the efficacy of treatment. BEPx3 is a standard treatment for good risk GCT based on several randomized studies by the Southeastern

Cancer Study Group (SECSG) and European Organization for the Research and Treatment of Cancer (EORTC)/Medical Research Council (MRC) that have shown that BEPx3 is effective in the treatment of good risk GCT.³⁴ Randomized and non-randomized trials from MSKCC have also shown that EPx4 has also shown excellent long term results in the treatment of good risk GCT.²⁵ Two randomized trials compared the efficacy of EPx4 and BEP in patients with good-risk GCT. The EORTC published a trial in which the CR rate was lower in the EP arm without differences in relapses, time to progression, or survival after long-term follow-up.¹⁰ However, lower doses of etoposide (360mg/m² rather than 500mg/m²/cycle) were administered in both arms of this study and may have accentuated the benefit of bleomycin in the BEP arm. This hypothesis is supported by another randomized study which compared a reduced intensity BEPx4 regimen (etoposide 360mg/m² per cycle and bleomycin 30 units per cycle) to standard BEPx3 (with etoposide 500 mg/m² per cycle) and superior outcomes were observed with BEPx3 despite one less cycle of therapy.¹¹ A more recent randomized study comparing full doses of both regimens demonstrated similar rates of favorable response, event-free survival and overall survival.¹² The American Society of Clinical Oncology has concluded that both EPx4 and BEPx3 are standard treatment options in good-risk GCT.¹³

Toxicity from chemotherapy is an important consideration when choosing a chemotherapy regimen for good risk GCT. Both the EORTC and Genito-urinary group of French Federation of Cancer Centers (GETUG) have shown that BEP chemotherapy is associated with an increased rate of neurologic, dermatologic, and pulmonary toxicity relative to patients who receive EP.¹²⁴ EP minimizes potential bleomycin-associated toxicity such as pneumonitis (quite rare with BEPx3) and Raynaud's phenomenon, which does not occur with EPx4. Pulmonary toxicity is particularly relevant to the practice at MSKCC because post-chemotherapy surgery is advocated for most patients. While studies have not shown an increased rate of overall complications at PC-RPLND based on prior chemotherapy regimen,¹⁴ patients who have received pre-operative bleomycin need careful fluid and oxygen management in the post-operative period because they are at significantly increased risk of pulmonary complications after RPLND. While it is theoretically possible that the higher cumulative doses of etoposide and cisplatin in EPx4 as compared to BEPx3 could result in an increase in late toxicities such as infertility, leukemia, or other secondary malignancies, data supporting these concerns is lacking.

The goal of post-chemotherapy RPLND is to completely resect teratoma or viable cancer in the retroperitoneum, which can be present in 25% and 5% of cases, respectively.^{152, 16} In the current study, patients who underwent post-chemotherapy surgery had a 2-fold increased risk of teratoma if they had received bleomycin as part of their induction therapy. This was true for all cohorts examined, including those patients who were treated appropriately with BEPx3, and those who had post-chemotherapy masses less than 1.1 cm in size. The latter finding is notable because at many centers, patients with post-chemotherapy masses less than 1 cm are managed with observation. Rarely, teratoma may grow, or undergo malignant transformation to chemoresistant somatic cancers such as sarcoma or carcinoma and invade into adjacent structures. There is a higher risk of late relapse if residual disease is not fully resected and this is particularly important for patients that harbor metastatic teratoma in the RP.¹⁷ While teratoma present in residual masses less than 1 cm appears to rarely progress in

patients with good risk disease, it is noted to occur more frequently in patients with intermediate and poor risk disease.^{18, 19} Therefore, clinicians need to be aware of these findings when making chemotherapy and PC-RPLND decisions.

The current study is limited by its retrospective nature and the fact that there were far more patients treated with EP than BEP. Therefore the differences observed may not be attributable to the chemotherapy regimen administered. The BEP patients referred to MSKCC seemed more likely to have larger pre-RPLND nodes (Table 1). Since the preferred good risk chemotherapy regimen differs by center, it is unlikely that any retrospective single institution study addressing this issue would be balanced for induction treatment or nodal size. In addition, since recommendations for post-chemotherapy surgical resection vary between institutions, any multicenter analysis, which would exclude some patients based on small post-chemotherapy nodal size, would be difficult to interpret. While many studies have consistently shown that teratoma can be present even in small masses in the RP after chemotherapy, the clinical behavior of these masses cannot be predicted. Since we cannot know prospectively which patient will unduly suffer from observation, we advocate complete resection after chemotherapy to maximize the chance of long term cure in what are usually very young men.

In summary, this retrospective analysis of patients with good risk GCT treated with induction chemotherapy followed by PC-RPLND has shown that overall rates of viable GCT, relapse and disease specific survival are equivalent in patients treated with EP and BEP. Despite accounting for factors that predict teratoma after chemotherapy such as teratoma or yolk sac in the orchiectomy specimen and pre-surgery RP node size, the rates of teratoma in the retroperitoneum were higher in the patients treated with BEP than EP. In the absence of a plausible biologic reason related to greater efficacy of EP against teratoma or greater capacity of BEP to cause in vivo differentiation, it is likely that the observed differences in the frequency of teratoma are related to an unrecognized selection bias. These findings should be considered when making chemotherapy and PC-RPLND decisions.

Acknowledgments

Supported by: The Sidney Kimmel Center for Prostate and Urologic Cancers and a T32 grant from the National Institute of Health (T32 CA082088) and The Capri Foundation

Key Definition of Abbreviations

NSGCT	nonseminomatous germ cell tumors
EP	etoposide and platinum
BEP	bleomycin, etoposide, and platinum
PC-RPLND	post-chemotherapy retroperitoneal lymph node dissection

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Figure 1.
Relapse Free Survival (EP vs. BEP)

Figure 2.
Disease Specific Survival (EP vs. BEP)

Table 1

Baseline patient characteristics. N=579 patients

	EP	BEP
	N(%)	N(%)
Patient No.	505 (87)	74 (13)
Age	31 (IQR 25, 37)	31 (IQR 24, 36)
Orchiectomy Histology		
Mixed Germ Cell Tumor	327(66)	48(67)
Pure Seminoma	32(6)	5(7)
Pure Embryonal	100(20)	11(15)
Pure Yolk Sac	3(1)	1(1)
Pure Teratoma	10(2)	5(7)
Fibrosis	9(2)	0(0)
Burnt Out Scar	14(3)	1(1)
Unclassified	2(1)	1(1)
Any Teratoma	205(41)	37(50)
Any Yolk Sac	200(40)	32(43)
Clinical Stage		
I	56(11)	7(10)
IIa	77(15)	8(11)
IIb/IIc	269(53)	33(45)
III	102(20)	25(34)
Pre-Surgery LN size (n=431)		
< 1.1 cm	125 (34)	6 (10)
1.1–2 cm	132(36)	15 (25)
2–5 cm	84(23)	23(38)
> 5 cm	30(8)	16(27)
Pre-Chemo LN size (n=453)		
< 2 cm	103 (26)	8(14)
2–5 cm	215(55)	32(54)
> 5 cm	16(19)	19(32)
Year of Surgery		
Before 1999	201(40)	28(38)
After 1999	304(60)	46(62)

Table 2

Post-chemotherapy RPLND histology

	EP	BEP	
RPLND Histology	N(%)	N(%)	p value
Fibrosis	301 (60)	29 (39)	0.001
Teratoma	162 (32)	39 (53)	
Viable Cancer	31 (6)	4 (5)	
Malignant Transformation	6 (1)	1 (1)	
Any Teratoma	172(34)	42(57)	<0.001

Table 3

Univariate Analysis for presence of teratoma in RPLND specimen (n=579)

Teratoma in RPLND specimen	OR	95 % CI	p value
Clinical Stage			
I	Ref		
IIA	0.5	0.2 to 0.7	0.02
IIB/C	0.4	0.2 to 0.6	<0.001
III	0.3	0.1 to 0.5	<0.001
Any EC orchiectomy	1.4	0.95 to 2.2	0.08
Any Yolk Sac	2.5	1.7 to 3.5	<0.001
Any Teratoma	6.2	4.3 to 9.0	<0.001
Year of Surgery (Before 1999 vs. After 1999)	0.8	0.5 to 1.1	0.1
Pre-chemotherapy RP node size (continuous)	1.0	0.95 to 1.1	0.6
Pre-surgery RP node size (continuous)	2.9	2.1 to 4.0	<0.001
Chemotherapy (EP vs. BEP)	2.5	1.5 to 4.2	<0.001

Table 4

Multivariate analysis for presence of teratoma in RPLND specimen (n=432)

Variable	OR	95% CI	p-value
Clinical Stage			
I	ref		
IIa	0.9	0.3, 2.0	0.7
IIb/c	0.4	0.2, 0.8	0.02
III	0.3	0.1, 0.6	0.002
Any Yolk Sac	1.3	0.8, 2.1	0.3
Any Teratoma in primary tumor	4.3	2.7, 7.0	< 0.001
Pre-surgery RP node size	1.3	1.1, 1.5	<0.001
Year of surgery (before 1999 vs. after 1999)	0.7	0.4, 1.1	0.5
Chemotherapy (EP vs. BEP)	2.0	1.0, 4.0	0.04

Table 5

Multivariate analysis for presence of teratoma in RPLND specimen excluding patients that received BEP x 4 for good risk GCT (n=410)

Variable	OR	95% CI	p-value
Clinical Stage			
I	Ref		
IIA	0.9	0.4, 2.3	0.8
IIB/C	0.4	0.2, 0.8	0.01
III	0.2	0.08, 0.5	0.001
Any Yolk Sac	1.2	0.7, 2.1	0.4
Any Teratoma	4.3	2.6, 7.2	<0.001
Pre-surgery RP node size	1.6	1.3, 1.9	<0.001
Year of surgery (before 1999 vs. after 1999)	0.7	0.4, 1.2	0.2
Chemotherapy (EP vs. BEP)	3.7	1.5, 8.9	0.004

Table 6

Multivariate analysis for presence of teratoma in RPLND specimen for pre-RPLND lymph nodes ≥ 1.1 cm (n=190)

Variable	OR	95% CI	p-value
Clinical Stage			
I	Ref		
IIa	1.2	0.3, 4.5	0.8
IIb/c	0.5	0.1, 1.6	0.2
III	0.5	0.1, 2.0	0.3
Any Yolk Sac	1.0	0.4, 2.4	0.9
Any Teratoma	2.5	1.1, 5.6	0.02
Pre-surgery RP node size (0.1 cm increment)	1.0	0.9, 1.1	0.5
Year of surgery (before 1999 vs. after 1999)	0.4	0.2, 1.1	0.09
Chemotherapy (EP vs. BEP)	4.6	1.1, 17	0.03

Table 7

Multivariate analysis for presence of teratoma in RPLND specimen excluding patients who were treated with BEP x 4 for good risk GCT and with pre-RPLND lymph nodes ≥ 1.1 cm (n= 187)

Variable	OR	95% CI	p-value
Clinical Stage			
I	Ref		
IIa	1.3	0.3, 4.8	0.7
IIb/c	0.5	0.1, 1.6	0.2
III	0.5	0.1, 2.2	0.4
Any Yolk Sac	1.0	0.4, 2.2	1.0
Any Teratoma	2.5	1.1, 5.7	0.02
Pre-surgery RP node size (0.1 cm increments)	1.0	0.9, 1.1	0.4
Year of surgery (before 1999 vs. after 1999)	0.5	0.2, 1.2	0.1
Chemotherapy (EP vs. BEP)	10.3	1.8, 59	0.008