Long-term Survival of Good Risk Germ Cell Tumor Patients following Post-chemotherapy Retroperitoneal Lymph Node Dissection: A comparison of BEPx3 vs. EPx4 and treating institution

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Conflicts of interest: none

MicroAbstract

The purpose of the study was determine is survival differences exist between BEP x3 vs. EP x4 for good risk testicular cancer patients. In 223 patients, we found a nonsignificant trend toward improved survival when men where treated with BEPx3 compared to EP x4.

Abstract:**Background:**

Patients with International Germ Cell Cancer Collaborative Group (IGCCCG) good risk testicular cancer may receive either 4 cycles of etoposide and cisplatin (EP) or 3 cycles of bleomycin, etoposide, and cisplatin (BEP). We sought to examine differences in survival following PC-RPLND between patients receiving EPx4 compared to BEPx3.

Patients and Methods:

The Indiana University Testis Cancer database was queried to identify IGCCCG good risk PC-RPLND patients who received either EPx4 or BEPx3 induction chemotherapy. The primary outcome was overall survival (OS). Kaplan-Meier plots were generated for the EPx4 and BEPx3 groups and compared using the log-rank test. Cox regression analysis was used to determine risk of mortality.

Results:

A total of 223 patients met inclusion criteria between 1985 and 2011. Induction chemotherapy consisted of EPx4 in 45 (20%) patients and BEPx3 in 178 (80%). Most patients (78%) received their chemotherapy at outside institutions and were subsequently referred for PC-RPLND. The location of treating institution did not influence outcomes significantly when comparing similar chemotherapy regimens in this good risk cohort. The 10-year OS for the EPx4 and BEPx3 groups were 91% and 98%, respectively (log-rank $p < 0.01$). The adjusted risk of death in the EP x 4 group demonstrated a nonsignificant trend of 3 times greater compared to the BEP x3 group, (HR 3.1, 95% CI 0.8-12.0, $p = 0.10$).

Conclusions:

The regimen of BEPx3 resulted in a trend toward improved survival, however, this did not reach statistical significance. The location of treating institution seems less important in this risk group of patients.

Keywords: testicular neoplasms, bleomycin, lymph node excision, propensity score, survival analysis

Introduction

The National Comprehensive Cancer Network (NCCN) currently recommends either 3 courses of bleomycin, etoposide, and cisplatin (BEP x3) or 4 courses of etoposide and cisplatin (EP x4) for good risk metastatic testicular cancer.¹ This recommendation is based on randomized trial data that have sought to decrease morbidity and maintain efficacy in this subgroup of patients with excellent cure rates.²⁻⁴ In phase III trials, BEP x3 was numerically superior, but not statistically significant in overall survival.^{5,6}

Only a portion of patients in those randomized trials went on to PC-RPLND. Further subdividing good risk patients into those who required post chemotherapy retroperitoneal lymph node dissection (PC-RPLND) for residual RP masses provides insight into treatment responses. Our institution recently published data on the histologic response of retroperitoneal (RP) tumors to induction chemotherapy which showed higher proportions of active cancer in the EP x4 group compared to the BEP x3 group.⁷ However, comparisons in overall survival between BEP x3 and EP x 4 in the subgroup with residual RP masses that require PC-RPLND are limited in the literature.

This retrospective study evaluated overall survival in good risk patients who underwent post chemotherapy retroperitoneal dissection (PC-RPLND) and received either BEP x3 or EP x4.

Materials and Methods

The prospectively maintained Indiana University Testis Cancer database was queried to identify patients who underwent a PC-RPLND from 1985 to 2011. A total of 1,815 patients were identified. Exclusion criteria included induction chemotherapy other than BEP or EP (n=352), IGCCCG intermediate or poor risk classification (n=593), or unavailable serum tumor markers (n=321), any combination of BEP and EP regimens (n=323). Three additional patients were excluded due to unclear risk category, nonstandard radiotherapy use, and findings of primitive neuroectodermal tumor (PNET). The remaining 223 patients with good risk disease who received either BEP x 3 or EP x 4 cycles with all available data points made up the study cohort. These patients had received only the induction chemotherapy regimen and serum tumor markers had normalized prior to RPLND. The primary outcome of this study was overall survival. Death was determined by chart review, referring physician confirmation, or National Death Index data.

Clinical and pathologic characteristics were determined by electronic and paper chart review. These variables included age at surgery, year of surgery, year of diagnosis, receipt of chemotherapy at Indiana (yes/no), histology of primary tumor, prechemotherapy serum tumor markers, prechemotherapy retroperitoneal (RP) mass size, preoperative RP mass size, and RP histology. Overall survival time was calculated from the date of surgery until the date of death or the last date the National Death Index was queried.

Pearson chi-square, Fisher's exact test, and the Student's t test were used to compare clinical and pathologic differences between groups. Continuous variables that were not normally distributed were evaluated with the Mann-Whitney U test. Kaplan-Meier plots were generated for the EPx4 and BEPx3 groups and compared using the log-rank test. To determine if differences existed by location where chemotherapy was

delivered (Indiana University vs. outside institution) or if there were differences between those who were not treated with chemotherapy at Indiana University, sensitivity analyses were performed to evaluate the potential impact on RP histology and overall survival.

Multivariable analysis was performed using the Cox proportional hazard regression model. The primary outcome was death. All deaths were caused by disseminated germ cell tumor or treatment-related side effects. In order to account for baseline differences between treatment groups, propensity scores were generated using logistic regression for the propensity to receive EPx4. Variables included in the logistic regression model to generate propensity scores were determined a priori as potential confounders and included age, date of diagnosis, histology of primary site, pre-chemotherapy serum tumor markers, and pre-chemotherapy RP mass size. This generated a propensity score for each patient to determine the predicted probability for each patient to have received EP x 4. Overlap in propensity scores were assessed between groups using histogram plots. Given the low event rate, the multivariable Cox regression model only included the propensity score variable and the primary covariate of interest, (i.e. EP vs. BEP), to generate the most parsimonious model. Univariable and propensity-score adjusted cox proportional hazard regression models were created to evaluate the association between induction chemotherapy regimen and overall survival. The proportional hazards assumption was tested using Schoenfeld residuals. All statistical tests were 2-sided with significance at $p < 0.05$. Stata (version 12.1 IC) statistical software was used to conduct the analyses. This study was approved by the Indiana University Institutional Review Board.

Results

A total of 178 patients who received BEPx3 induction chemotherapy were identified and compared to 45 who received EPx4. The bleomycin cohort was younger, diagnosed and treated in earlier years, and was more likely to receive induction chemotherapy at Indiana University (all $p<0.003$)(Table 1). All 45 patients who received EP x4 were treated with chemotherapy at outside institutions. Patients who received EP x4 were treated according to the referring medical oncologist preferences prior to presenting to Indiana. None of the 45 patients had underlying lung disease prohibitive for receiving bleomycin based on medical record review; however, 7 patients in the EP group were ≥ 50 years old.

There was no difference in RP mass size between the two groups either before chemotherapy or in the preoperative setting (Table 1). The preoperative RP mass size was $>5\text{cm}$ in 56 of the 178 (32%) patients who received BEP x 3 compared to 14 of 45 (31%) patients who received EP x4. The patients who received BEP x3 had active cancer in 13 (7.8%) patients PC-RPLND specimens compared to 14 (31.9%) patients who received EP x4. Additionally, 115 (65%) patients who received BEP x3 were found to have teratoma in the RP specimen compared to 21 (47%) patients who received EP x4, ($p<0.001$).

Table 2a displays the RP histology of the 175 patients treated with chemotherapy outside of Indiana University. This again demonstrates the increased proportion of patients in the EP x4 group (31%) having active cancer compared to only 9% in the BEP x3 group, ($p=0.002$). We then evaluated if there was any RP histology differences between those who received BEP x3 at Indiana compared to those who received BEP x3 at outside institutions (Table 2b). There were no statistical differences in RP histology noted in these 2 groups, ($p=0.29$).

Overall, there were 13 deaths during a median follow up of 127 months. Of the 178 patients treated with BEP x3, 7 (4%) died of disease. Conversely, of the 45 patients treated with EP x4, 6 (13%) died of disease. Of the 13 deaths, 12 were due to recurrent germ cell tumor. The other patient died from complications related to myelodysplastic syndrome. This patient was treated with salvage TIP (paclitaxel, ifosfamide, cisplatin), then with high-dose chemotherapy (HDCT) and stem cell transplant. The 10-year OS for the entire cohort was 97% (95% CI 94-99). The 10-year OS for patients who received EPx4 was 91% (95% CI 78-97) compared to 98% for those who received BEPx3 (95% CI 93-99)($p<0.001$) (Figure 1). In patients found to have active cancer in the PC-RPLND specimen, the 10-year OS was 54% in the EPx4 group (95% CI 17-80) compared to 89% in the BEPx3 group (95% CI 43-98). Those patients who did not have active cancer in the RP specimen did very well regardless of chemotherapy regimen with long-term survival approaching 100%, (Figure 2). The unadjusted risk of death was 7.6 times higher in the EPx4 group compared to the BEPx3 group, (HR 7.6, 95% CI 2.26-25.4, $p=0.001$). After propensity-score adjustment, the risk of death in the EP x 4 group was 3 times higher, however, this was no longer statistically significant, (HR 3.1, 95% CI 0.8-12.0, $p=0.10$, Table 2c). To further assess the impact of age we performed Kaplan Meier sensitivity analyses stratified by age $>$ or $<$ 40 years old, which demonstrated no differences in results. Additionally, we added age as a covariate in our propensity-score adjusted cox model with no significant change in results.

There were 4 seminoma patients who had an elevated AFP at presentation and 2 patients had biopsies of neck masses consistent with teratoma. For this reason, we also conducted a sensitivity analysis excluding all seminoma patients and the survival results were unchanged.

Figure 3 demonstrates overall survival based on location where chemotherapy was delivered. Figure 3a depicted a worse survival for patients treated with EP x4

treated outside Indiana compared to BEP x3 patients treated outside Indiana, log rank $p=0.004$. Figure 3b depicts a borderline statistically worse survival in patients treated with BEP x 3 outside Indiana compared to patients treated with BEP x 3 at Indiana, $p=0.05$. However, these curves are almost mirror images of one another and thus may not be of clinical significance.

Discussion

This study has 2 main findings. First, the unadjusted overall survival for good risk patients who underwent a PC-RPLND was worse for those who received EPx4 compared to BEP x3. However, the difference in survival became non-significant after propensity-score adjustment, despite a continued trend for worse survival. This trend of worse survival is interesting given the increased proportion of patients having active residual germ cell tumor found in the RP specimen in the EP x4 group. Second, the effect of treating institution (Indiana vs. outside) did not seem to have a large effect on survival in this good risk cohort of patients when comparing similar chemotherapy regimens.

This data adds to the published literature demonstrating a numerically superior advantage of including bleomycin in the induction chemotherapy regimen.⁴⁻⁶ In the phase III French trial comparing BEP x3 to EP x4, Culine et al. demonstrated the 4-year OS to be numerically worse in the EP x4 group (93% vs. 97%, $p=0.082$). The randomized ECOG trial comparing BEP x3 to EP x3 also demonstrated a worse OS for the EP group (86% vs. 95%, $p=0.01$), albeit this trial only utilized 3 cycles of EP.⁴ More recently, a retrospective study from Memorial Sloan Kettering Cancer Center (MSKCC) compared IGCCCG good risk patients treated with BEP x3 to those treated with EP x4 who subsequently underwent a PC-RPLND.⁸ This study also demonstrated a small numerically but not statistically worse disease free survival in those patients who received EP x4 compared to the BEP x3 group, (98% vs. 100%, $p=0.32$).

The numerically superior survival in the BEP group in the current study is likely a function of the retroperitoneal histology at the time of PC-RPLND. Only 7% of those treated with BEP had residual germ cell cancer in the RP specimen compared to 31% of patients treated with EP. Without robust randomized trial data with adequate power and follow up, tumor response rates should be used as a surrogate for treatment efficacy.

Patients with residual cancer in the retroperitoneum after induction chemotherapy have demonstrated a decreased progression free survival (PFS) and OS. Fizazi et al. found that patient with > 10% viable cancer in post chemotherapy residual masses had a PFS and OS of 55% and 63% respectively compared to 71% and 82% in residual masses with <10% viable cancer.⁹ An Indiana University study showed that of the 34 patients with viable cancer in the completely resected PC-RPLND specimen, 27 received post-operative cisplatin based chemotherapy. There were seven patients who did not receive post-operative chemotherapy, all of whom relapsed.¹⁰ Spiess et al. showed that presence of viable tumor in the PC-RPLND specimen was a predictor of PFS ($p=0.03$).¹¹ In our current series, patients in the EP x4 group had increased rates of active cancer in their PC-RPLND specimens and a trend toward decreased survival.

A MSKCC study demonstrated disparate results regarding RP histologic findings compared to our current study. In the MSKCC cohort, rates of viable cancer in the PC-RPLND specimen were 6% in the EP x4 group vs. 5% in the BEP x3 group.⁸ Preoperative lymph node sizes varied significantly between the two groups in the MSK study. Seventy percent of patients in the EP group had lymph nodes less than 2cm compared to only 35% in the BEP x3 group. Eight percent of patients in the EP x4 group had lymph nodes greater than 5 cm compared to 27% in the BEP x3 group. Despite this difference in preoperative RP mass size, the BEP x3 group had a lower rate of viable cancer in the PC-RPLND specimen. Furthermore, the suggestion that BEP leads to a biological development of teratoma in the retroperitoneum is unfounded. This is more likely a statistical issue after the exclusion of multiple patients treated with BEP x4, patients with masses greater than 1.1cm, and limited outcome events resulting in an overfit logistic model. This is evidenced by the extremely wide confidence intervals in that study.

When evaluating the effect of treating institution on outcomes, we did not see large differences based on where patients received their induction chemotherapy. However, the regimen received (BEP vs. EP) did maintain important differences in RP histology outcomes and survival. For example, when only evaluating patients receiving chemotherapy outside Indiana University, the EP x4 group still had significantly more residual cancer in the RP compared with BEP x3 (31% vs. 9%, $p=0.002$). Conversely, when assessing patients treated with BEP, regardless of treating institution, there were no statistical differences in RP histology between those that received BEP at Indiana University (2%) compared to those receiving it at outside institutions (9%) ($p=0.29$). Furthermore, the Kaplan-Meier OS results remained significantly worse for the EP group when limited to patients who received their chemotherapy outside Indiana University, (Figure 3a). Moreover, the survival curves of patients treated with BEP at Indiana University compared to those treated with BEP at outside institutions are essentially mirror images of one another.

This retrospective study does have limitations worth highlighting. First, we are unable to control for variance in treatment regimens (i.e. dose reductions) and cannot describe overall response rates apart from the PC-RPLND patients. There is also a referral and selection bias of patients referred and treated at our institution. Nevertheless, it is our belief that this subset of good risk patients can guide our current understanding on the subject. Since it is difficult to power a study adequately to detect significant differences in overall survival, studying patients with residual tumors after chemotherapy can be a surrogate for subsequent salvage therapy. Second, the limited number of deaths in this good risk cohort of patients reduces any definitive conclusion to be drawn from these results. However, this trend of numerically worse outcomes in the EP x4 group adds to similarly published outcomes. Third, a number of these patients received their induction chemotherapy at an outside institution. None of the 45 patients

in the EP group received chemotherapy at Indiana University and only 27% (48 of 178) received BEP x3 at our institution. Recent criticism has suggested that this accounts for the difference seen between the groups due to the relative dose intensity delivered.¹² However, the sensitivity analyses demonstrated similar RP histology and survival outcomes in the BEP group regardless of whether they were treated at Indiana University or elsewhere. Even though patients with IGCCCG poor risk features have been shown to have worse survival when treated at low volume centers¹³, it may not be prudent to assume that a significant portion of this good risk population treated at lower volume centers received inadequate care.

These limitations notwithstanding, our findings have significant implications for patients and providers. In this cohort of good risk patients, there are clear differences in the RP histology between the 2 chemotherapy regimens with a higher incidence of residual germ cell cancer in the EP group. This can influence the necessity for additional chemotherapy with its subsequent additive long-term side effects and can ultimately impact survival. Since a future randomized trial in this setting is unlikely to occur, this data provides medical oncologists with histologic and survival outcomes comparing the 2 chemotherapy regimens, which can assist in decision-making and counseling of patients. One caveat in which we would prefer EP x4 rather than BEP x3 is in patients > age 50, regardless of smoking history.

Conclusion

Good risk testicular cancer patients who received BEPx3 have less residual cancer in the RP specimen at the time of PC-RPLND. It is less clear if this leads to an improvement in survival compared to those who received EPx4 as induction chemotherapy in this retrospective analysis. We continue to favor BEP x3 as induction chemotherapy in good risk patients assuming there are no underlying lung conditions and patients are younger than 50 years of age.

Clinical Practice Points:

- While not statistically significant, there is a numerically worse survival when good risk patients are treated with EPx4 when compared to BEPx3.
- Treating institution did not seem to have an effect on survival in good risk patients comparing BEP chemotherapy regimens.

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Figure Legend:

Figure 1. Kaplan-Meier curves for Overall Survival stratified by chemotherapy received

Figure 2. Overall Survival stratified by chemotherapy regimen and RP histology.

Figure 3a-b. Overall Survival assessed by location of where chemotherapy regimen was received. 3a: Overall Survival in patients who only received chemotherapy outside of Indiana University. 3b: Overall Survival in patients who received BEP x3 stratified by location of where regimen was received.

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A total of 223 patients met inclusion criteria between 1985 and 2011. Induction chemotherapy consisted of EPx4 in 45 (20%) patients and BEPx3 in 178 (80%). Most patients (78%) received their chemotherapy at outside institutions and were subsequently referred for PC-RPLND. The location of treating institution did not influence outcomes significantly when comparing similar chemotherapy regimens in this good risk cohort. The 10-year OS for the EPx4 and BEPx3 groups were 91% and 98%, respectively (log-rank $p < 0.01$). The adjusted risk of death in the EP x 4 group demonstrated a nonsignificant trend of 3 times greater compared to the BEP x3 group, (HR 3.1, 95% CI 0.8-12.0, $p = 0.10$).

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Introduction

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Table 2a displays the RP histology of the 175 patients treated with chemotherapy outside of Indiana University. This again demonstrates the increased proportion of patients in the EP x4 group (31%) having active cancer compared to only 9% in the BEP x3 group, ($p=0.002$). We then evaluated if there was any RP histology differences between those who received BEP x3 at Indiana compared to those who received BEP x3 at outside institutions (Table 2b). There were no statistical differences in RP histology noted in these 2 groups, ($p=0.29$).

Overall, there were 13 deaths during a median follow up of 127 months. Of the 178 patients treated with BEP x3, 7 (4%) died of disease. Conversely, of the 45 patients treated with EP x4, 6 (13%) died of disease. Of the 13 deaths, 12 were due to recurrent germ cell tumor. The other patient died from complications related to myelodysplastic syndrome. This patient was treated with salvage TIP (paclitaxel, ifosfamide, cisplatin), then with high-dose chemotherapy (HDCT) and stem cell transplant. The 10-year OS for the entire cohort was 97% (95% CI 94-99). The 10-year OS for patients who received EPx4 was 91% (95% CI 78-97) compared to 98% for those who received BEPx3 (95% CI 93-99)($p<0.001$) (Figure 1). In patients found to have active cancer in the PC-RPLND specimen, the 10-year OS was 54% in the EPx4 group (95% CI 17-80) compared to 89% in the BEPx3 group (95% CI 43-98). Those patients who did not have active cancer in the RP specimen did very well regardless of chemotherapy regimen with long-term survival approaching 100%, (Figure 2). The unadjusted risk of death was 7.6 times higher in the EPx4 group compared to the BEPx3 group, (HR 7.6, 95% CI 2.26-25.4, $p=0.001$). After propensity-score adjustment, the risk of death in the EP x 4 group was 3 times higher, however, this was no longer statistically significant, (HR 3.1, 95% CI 0.8-12.0, $p=0.10$, Table 2c). To further assess the impact of age we performed Kaplan Meier sensitivity analyses stratified by age $>$ or $<$ 40 years old, which demonstrated no differences in results. Additionally, we added age as a covariate in our propensity-score adjusted cox model with no significant change in results.

There were 4 seminoma patients who had an elevated AFP at presentation and 2 patients had biopsies of neck masses consistent with teratoma. For this reason, we also conducted a sensitivity analysis excluding all seminoma patients and the survival results were unchanged.

Figure 3 demonstrates overall survival based on location where chemotherapy was delivered. Figure 3a depicted a worse survival for patients treated with EP x4

treated outside Indiana compared to BEP x3 patients treated outside Indiana, log rank $p=0.004$. Figure 3b depicts a borderline statistically worse survival in patients treated with BEP x 3 outside Indiana compared to patients treated with BEP x 3 at Indiana, $p=0.05$. However, these curves are almost mirror images of one another and thus may not be of clinical significance.

Discussion

This study has 2 main findings. First, the unadjusted overall survival for good risk patients who underwent a PC-RPLND was worse for those who received EPx4 compared to BEP x3. However, the difference in survival became non-significant after propensity-score adjustment, despite a continued trend for worse survival. This trend of worse survival is interesting given the increased proportion of patients having active residual germ cell tumor found in the RP specimen in the EP x4 group. Second, the effect of treating institution (Indiana vs. outside) did not seem to have a large effect on survival in this good risk cohort of patients when comparing similar chemotherapy regimens.

This data adds to the published literature demonstrating a numerically superior advantage of including bleomycin in the induction chemotherapy regimen.⁴⁻⁶ In the phase III French trial comparing BEP x3 to EP x4, Culine et al. demonstrated the 4-year OS to be numerically worse in the EP x4 group (93% vs. 97%, $p=0.082$). The randomized ECOG trial comparing BEP x3 to EP x3 also demonstrated a worse OS for the EP group (86% vs. 95%, $p=0.01$), albeit this trial only utilized 3 cycles of EP.⁴ More recently, a retrospective study from Memorial Sloan Kettering Cancer Center (MSKCC) compared IGCCCG good risk patients treated with BEP x3 to those treated with EP x4 who subsequently underwent a PC-RPLND.⁸ This study also demonstrated a small numerically but not statistically worse disease free survival in those patients who received EP x4 compared to the BEP x3 group, (98% vs. 100%, $p=0.32$).

The numerically superior survival in the BEP group in the current study is likely a function of the retroperitoneal histology at the time of PC-RPLND. Only 7% of those treated with BEP had residual germ cell cancer in the RP specimen compared to 31% of patients treated with EP. Without robust randomized trial data with adequate power and follow up, tumor response rates should be used as a surrogate for treatment efficacy.

Patients with residual cancer in the retroperitoneum after induction chemotherapy have demonstrated a decreased progression free survival (PFS) and OS. Fizazi et al. found that patient with > 10% viable cancer in post chemotherapy residual masses had a PFS and OS of 55% and 63% respectively compared to 71% and 82% in residual masses with <10% viable cancer.⁹ An Indiana University study showed that of the 34 patients with viable cancer in the completely resected PC-RPLND specimen, 27 received post-operative cisplatin based chemotherapy. There were seven patients who did not receive post-operative chemotherapy, all of whom relapsed.¹⁰ Spiess et al. showed that presence of viable tumor in the PC-RPLND specimen was a predictor of PFS ($p=0.03$).¹¹ In our current series, patients in the EP x4 group had increased rates of active cancer in their PC-RPLND specimens and a trend toward decreased survival.

A MSKCC study demonstrated disparate results regarding RP histologic findings compared to our current study. In the MSKCC cohort, rates of viable cancer in the PC-RPLND specimen were 6% in the EP x4 group vs. 5% in the BEP x3 group.⁸ Preoperative lymph node sizes varied significantly between the two groups in the MSK study. Seventy percent of patients in the EP group had lymph nodes less than 2cm compared to only 35% in the BEP x3 group. Eight percent of patients in the EP x4 group had lymph nodes greater than 5 cm compared to 27% in the BEP x3 group. Despite this difference in preoperative RP mass size, the BEP x3 group had a lower rate of viable cancer in the PC-RPLND specimen. Furthermore, the suggestion that BEP leads to a biological development of teratoma in the retroperitoneum is unfounded. This is more likely a statistical issue after the exclusion of multiple patients treated with BEP x4, patients with masses greater than 1.1cm, and limited outcome events resulting in an overfit logistic model. This is evidenced by the extremely wide confidence intervals in that study.

When evaluating the effect of treating institution on outcomes, we did not see large differences based on where patients received their induction chemotherapy. However, the regimen received (BEP vs. EP) did maintain important differences in RP histology outcomes and survival. For example, when only evaluating patients receiving chemotherapy outside Indiana University, the EP x4 group still had significantly more residual cancer in the RP compared with BEP x3 (31% vs. 9%, $p=0.002$). Conversely, when assessing patients treated with BEP, regardless of treating institution, there were no statistical differences in RP histology between those that received BEP at Indiana University (2%) compared to those receiving it at outside institutions (9%) ($p=0.29$). Furthermore, the Kaplan-Meier OS results remained significantly worse for the EP group when limited to patients who received their chemotherapy outside Indiana University, (Figure 3a). Moreover, the survival curves of patients treated with BEP at Indiana University compared to those treated with BEP at outside institutions are essentially mirror images of one another.

This retrospective study does have limitations worth highlighting. First, we are unable to control for variance in treatment regimens (i.e. dose reductions) and cannot describe overall response rates apart from the PC-RPLND patients. There is also a referral and selection bias of patients referred and treated at our institution. Nevertheless, it is our belief that this subset of good risk patients can guide our current understanding on the subject. Since it is difficult to power a study adequately to detect significant differences in overall survival, studying patients with residual tumors after chemotherapy can be a surrogate for subsequent salvage therapy. Second, the limited number of deaths in this good risk cohort of patients reduces any definitive conclusion to be drawn from these results. However, this trend of numerically worse outcomes in the EP x4 group adds to similarly published outcomes. Third, a number of these patients received their induction chemotherapy at an outside institution. None of the 45 patients

in the EP group received chemotherapy at Indiana University and only 27% (48 of 178) received BEP x3 at our institution. Recent criticism has suggested that this accounts for the difference seen between the groups due to the relative dose intensity delivered.¹² However, the sensitivity analyses demonstrated similar RP histology and survival outcomes in the BEP group regardless of whether they were treated at Indiana University or elsewhere. Even though patients with IGCCCG poor risk features have been shown to have worse survival when treated at low volume centers¹³, it may not be prudent to assume that a significant portion of this good risk population treated at lower volume centers received inadequate care.

These limitations notwithstanding, our findings have significant implications for patients and providers. In this cohort of good risk patients, there are clear differences in the RP histology between the 2 chemotherapy regimens with a higher incidence of residual germ cell cancer in the EP group. This can influence the necessity for additional chemotherapy with its subsequent additive long-term side effects and can ultimately impact survival. Since a future randomized trial in this setting is unlikely to occur, this data provides medical oncologists with histologic and survival outcomes comparing the 2 chemotherapy regimens, which can assist in decision-making and counseling of patients. One caveat in which we would prefer EP x4 rather than BEP x3 is in patients > age 50, regardless of smoking history.

Conclusion

Good risk testicular cancer patients who received BEPx3 have less residual cancer in the RP specimen at the time of PC-RPLND. It is less clear if this leads to an improvement in survival compared to those who received EPx4 as induction chemotherapy in this retrospective analysis. We continue to favor BEP x3 as induction chemotherapy in good risk patients assuming there are no underlying lung conditions and patients are younger than 50 years of age.

Clinical Practice Points:

- While not statistically significant, there is a numerically worse survival when good risk patients are treated with EPx4 when compared to BEPx3.
- Treating institution did not seem to have an effect on survival in good risk patients comparing BEP chemotherapy regimens.

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Figure Legend:

Figure 1. Kaplan-Meier curves for Overall Survival stratified by chemotherapy received

Figure 2. Overall Survival stratified by chemotherapy regimen and RP histology.

Figure 3a-b. Overall Survival assessed by location of where chemotherapy regimen was received. 3a: Overall Survival in patients who only received chemotherapy outside of Indiana University. 3b: Overall Survival in patients who received BEP x3 stratified by location of where regimen was received.

Tables

Table 1. Demographic and clinical characteristics of 223 patients who underwent PC-RPLND

	Induction Chemotherapy		P-value	Propensity adjusted p-value
Characteristic	BEP x3 N=178 No. (%)	EP x4 N=45 No. (%)		
Age (median,range)	27 (15-52)	30 (18-71)	0.002	0.47
Year of Diagnosis (range)	1999 (1985-2010)	2003 (1989-2011)	0.003	0.76
Year of Surgery (range)	2000 (1985-2010)	2003 (1989-2011)	0.002	n/a
Orchiectomy histology			0.006	0.92
• NSGCT	172 (97)	38 (84)		
• Seminoma	6 (3)	7 (16)		
Pre-chemotherapy RP mass size			0.388	0.53
• <2cm	13 (7)	7 (16)		
• 2-5cm	87 (49)	19 (42)		
• 5-10cm	53 (30)	13 (29)		
• >10cm	25 (14)	6 (13)		
Preoperative RP mass size			0.99	n/a
• <2cm	27 (15)	7 (16)		
• 2-5cm	95 (53)	24 (53)		
• 5-10cm	39 (22)	10 (22)		
• >10cm	17 (10)	4 (9)		
Pre-chemotherapy serum tumor markers				
• β -HCG (mIU/mL)				
Mean (SD)	57.1 (172)	168.2 (693)	0.879	0.85
Median	0	0		
• AFP (ng/mL)				
Mean (SD)	71.2 (161)	120.0 (261)	0.456	0.99
Median	3	3.9		
• LDH (IU/L)				
Mean (SD)	120.5 (445)	173.2 (216)	0.145	0.35
Induction chemotherapy received at IU	48 (27)	0 (0)	n/a	n/a
Final RP pathology			<0.001	n/a
• Necrosis	50 (28)	10 (22)		
• Teratoma	115 (65)	21 (47)		
• Active Cancer	13 (7)	14 (31)		

RP: retroperitoneal, IU: Indiana University, NSGCT: Non-seminomatous germ cell tumor
n/a: Variables not including in the propensity score generation

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Pre-chemotherapy RP mass size <ul style="list-style-type: none"> • <2cm • 2-5cm • 5-10cm • >10cm 	13 (7) 87 (49) 53 (30) 25 (14)	7 (16) 19 (42) 13 (29) 6 (13)	0.388	0.53
Preoperative RP mass size <ul style="list-style-type: none"> • <2cm • 2-5cm • 5-10cm • >10cm 	27 (15) 95 (53) 39 (22) 17 (10)	7 (16) 24 (53) 10 (22) 4 (9)	0.99	n/a
Pre-chemotherapy serum tumor markers <ul style="list-style-type: none"> • β-HCG (mIU/mL) Mean (SD) Median • AFP (ng/mL) Mean (SD) Median • LDH (IU/L) Mean (SD) 	57.1 (172) 0	168.2 (693) 0	0.879	0.85
	71.2 (161) 3	120.0 (261) 3.9	0.456	0.99
	120.5 (445)	173.2 (216)	0.145	0.35
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RP: retroperitoneal, IU: Indiana University, NSGCT: Non-seminomatous germ cell tumor
n/a: Variables not including in the propensity score generation

Table 2a-c: a) Final RP pathology of the 175 patients receiving chemotherapy outside of Indiana University b) Final RP pathology of the patients receiving chemotherapy with BEP x3 at Indiana University vs. BEP x3 outside Indiana University c) Unadjusted and Adjusted Cox regression models for Overall Survival.

a)			
	BEP x3	EP x4	P-value
Necrosis	35 (27)	10 (22)	0.002
Teratoma	83 (64)	21 (47)	
Cancer	12 (9)	14 (31)	
b)			
	BEP x3 at IU	BEP x3 at OSH	P-value
Necrosis	15 (31)	35 (27)	0.29
Teratoma	32 (67)	83 (64)	
Cancer	1 (2)	12 (9)	
c)			
	Unadjusted HR	Propensity Adjusted HR	
EP vs. BEP	7.58 (2.26 – 25.4) p=0.001	3.1 (0.8 – 12.0) p=0.10	

OSH: Outside hospital

Figure 1. Kaplan-Meier curves for Overall Survival stratified by chemotherapy received

Log-rank $p < 0.001$

Figure 2. Overall Survival stratified by chemotherapy regimen and RP histology.

Log-rank $p=0.045$

Figure 3a-b. Overall Survival assessed by location of where chemotherapy regimen was received. 3a: Overall Survival in patients who only received chemotherapy outside of Indiana University. 3b: Overall Survival in patients who received BEP x3 stratified by location of where regimen was received.

Log-rank $p=0.05$