Current Oncology Reports (2019) 21: 5
https://doi.org/10.1007/s11912-019-0758-6

GENITOURINARY CANCERS (DP PETRYLAK AND JW KIM, SECTION EDITORS)

Management of Residual Mass in Germ Cell Tumors After Chemotherapy

Costantine Albany[1] · Kenneth Kesler[2] · Clint Cary[3]

Published online: 21 January 2019

Abstract

Purpose of Review The purpose of this review is to educate medical oncologists on the management of patients with residual germ cell tumors and the role of surgical resection after platinum-based chemotherapy.

Recent Findings Patients with non-seminomatous testicular cancer and residual enlarged retroperitoneal lymph nodes > 1 cm following induction chemotherapy with normal tumor markers should undergo a post-chemotherapy retroperitoneal lymph node dissection. All patients with primary mediastinal non-seminoma should undergo surgical resection of the mediastinal mass post-chemotherapy. These are complex surgeries and require expert surgeons in high-volume centers. Patients with advanced testicular seminoma who have residual masses less than 3 cm after chemotherapy can be observed without further intervention. Patients with a residual mass > 3 cm should be evaluated with PET scan after 6 weeks of chemotherapy. Residual mass with negative PET scan can be followed by surveillance while a positive PET scan requires further work up to rule out active disease.

Keywords Chemotherapy · Residual mass · Testis cancer · Primary mediastinal · Germ cell tumor · Retroperitoneal lymph node dissection · Seminoma · Non-seminoma · Teratoma

Introduction

Germ cell tumors (GCT) are the most common cancers in men between the ages of 15 and 35 years. They are divided into seminomatous and non-seminomatous germ cell tumors (NSGCT). Cisplatin-based combination chemotherapy along with surgical interventions such as retroperitoneal lymph node dissection (RPLND) has translated into superior disease-specific survival.

This article is part of the Topical Collection on *Genitourinary Cancers*

✉ Costantine Albany
calbany@iu.edu

Kenneth Kesler
kkesler@iupui.edu

Clint Cary
kcary@iupui.edu

[1] Department of Medicine, Indiana University School of Medicine, 535 Barnhill Dr. RT 473, Indianapolis, IN 46202, USA

[2] Department of Surgery, Indiana University School of Medicine, 545 Barnhill Dr EH 212, Indianapolis, IN 46202, USA

[3] Department of Urology, Indiana University School of Medicine, 535 Barnhill Dr., Indianapolis, IN 46202, USA

Management of Residual Non-seminoma Mass

Residual Retroperitoneal NSGCT

Optimal management of residual mass following chemotherapy for NSGCT is a subject of ongoing debate. Depending on the presentation at diagnosis, 20–50% of patients who undergo cisplatin-based chemotherapy for metastatic GCT have significant residual retroperitoneal disease [1]. All patients who have residual masses ≥ 1 cm after chemotherapy should undergo post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) as 40–45% of cases harbor mature teratoma and viable GCT in 10–15% of patients [2]. Full bilateral PC-RPLND is a standard approach to large residual masses. In appropriately selected patients with low-volume disease before and after chemotherapy, a modified template PC-RPLND has durable long-term efficacy without risk of in-field recurrences, does not interfere with the oncologic outcome, and decreases treatment-associated morbidity [2, 3•].

Patients with teratoma in the PC-RPLND specimen have excellent disease-free survival of 75–80%, while those with viable GCT have a decreased chance of survival [4, 5]. Patients who achieve a complete serologic response and no radiographic residual mass less than 1 cm after chemotherapy have an

excellent prognosis with estimated 15-year recurrence-free survival (RFS) and cancer-specific survival (CCS) rates were 90% and 97%, respectively [6, 7]. These men can be safely observed without adjunctive regional surgery. However, there is a controversy over the optimal management of these patients [8]. The expert urologist should review the pre-chemotherapy and post-chemotherapy imaging to determine the extent and size of residual disease. The ESMO Consensus Conference on testicular germ cell cancer [9] and Indiana University [10] suggest that patients who achieve complete remission (residual retroperitoneal lesion < 1 cm) do not require PC-RPLND.

Our group at Indiana University reported long-term experience with 141 patients who underwent surveillance after they achieved a complete remission (residual mass < 1 cm and normal tumor markers) following induction chemotherapy. Over a median follow-up was 15.5 years, 12 patients (9%) recurred within 1 year, eight of whom had no evidence of disease. Four patients died, all within 12 months of induction chemotherapy. Importantly, no patients recurred with pure teratoma. Five patients had a late relapse (two of which were in the retroperitoneum) all of whom had no evidence of disease at long-term follow-up. The only predictor of relapse and cancer-specific survival (CSS) was the International Germ Cell Consensus Classification (IGCCCG) risk classification. The presence of teratoma in the primary orchiectomy tumor was not predictive of relapse nor CSS [6]. A similar study by Kollmannsberger and colleagues followed 161 patients with < 1 cm masses after chemotherapy and CSS was 100%. Eight of the ten relapses were teratoma all treated with PC-RPLND at the time of relapse successfully [7].

Investigators at other centers advocate retroperitoneal lymph node resection in all cases of NSGCT irrespective of residual mass size after chemotherapy. The basis for this recommendation is that all patients with metastatic disease require surgery to eradicate microscopic teratoma, and the risk of residual microscopic teratoma that may undergo malignant transformation and ultimately have a deleterious effect on outcome [11]. However, microscopic teratomas may remain clinically insignificant, in which case, resection would probably only add morbidity without improving outcome [12]. While late relapse or malignant transformation of teratoma can occur, it is very rare [13].

Although some cancer centers still recommend PC-RPLND for all testis cancer patients with retroperitoneal disease who achieved complete response to chemotherapy, other experts agree that PC-RPLND should be performed only if lymph nodes ≥ 1 cm persist following chemotherapy. Beyond radiographic size criteria, if there is teratoma in the orchiectomy specimen, this predicts for an 85% probability of teratoma in the retroperitoneum after chemotherapy. However, even in the absence of teratoma in the orchiectomy specimen, there is about a 45% chance of teratoma in the retroperitoneum after chemotherapy [14].

PC-RPLND should be performed 4–6 weeks after the last dose of chemotherapy in order to allow patients to recover their blood counts. Patients should have tumor marker done within 1 to 2 weeks pre-surgery to make sure no serological relapse at the time of surgery.

Concomitant Surgeries

In about 20% of patients undergoing PC-RPLND, large residual masses can surround and encase vital structures requiring adjunctive surgery. The most common concomitant procedure includes a left nephrectomy and occasionally *en bloc* vena caval and aortic resection with graft placement [15, 16]. GCT can invade the vena cava and present with a tumor thrombus that should not be mistaken for deep venous thrombosis [17, 18]. Resection of these masses along with tumor thrombectomy or even inferior vena cava (IVC) resection with or without reconstruction is often curative [19, 20]. Indications for IVC resection included tumor encasement or encroachment, post-chemotherapy desmoplastic compression, or thrombus with tumor or clot in which cavotomy and thrombectomy cannot be performed [21].

Following chemotherapy, approximately 50–70% of patients will have residual disease in the retroperitoneum depending upon the bulk of disease at presentation, and up to 35% will have radiographic evidence of liver, lung, or neck metastasis [12]. Complete surgical resection of all residual extra-retroperitoneal masses is indicated if the PC-RPLND revealed teratoma. It might be acceptable to perform a simultaneous surgical resection of multiple disease sites in selected patients. However, the combined procedures must be technically feasible with acceptable morbidity. Otherwise, a staged approach should be used [22].

The retrocrural space is a small triangular area within the most inferior posterior mediastinum and is bordered by two diaphragmatic crura. This area includes the aorta, the azygos and hemiazygos veins, nerves, thoracic duct, and lymph nodes, which are called the retrocrural lymph nodes [23]. Resection of retrocrural mass is exceptionally challenging and require expert thoracic surgeon along with the urologist at the time of RPLND. Access to this area can be approached either from a trans-abdominal trans-diaphragmatic technique [24] or with a thoracotomy. However, exposure of this area can be complex thus experienced surgeons in high-volume centers are beneficial [25•]. For patients presenting with bilateral pulmonary metastasis, we prefer staging pulmonary metastasectomy typically beginning with the lung most extensively involved. If pathology demonstrates teratoma, then contralateral pulmonary metastasectomy is also performed. Patients with less than 6 peripheral pulmonary nodules can usually be surgically managed with thoracoscopy. Otherwise, a thoracotomy approach is utilized. If unilateral

lung pathology demonstrates necrosis only then the contralateral lung can be observed, due to a high rate (95%) of pathologic concordance between the two lungs [26].

The Role of Induction Chemotherapy Before PCRPLND

In a modern surgical cohort from Indiana in men with good-risk GCT, the inclusion of bleomycin did not increase the risk of pulmonary morbidity, operative difficulty, or non-pulmonary postoperative complications after PC-RPLND [27••]. Recent data have evaluated the histologic findings following induction chemotherapy with or without bleomycin for good-risk disease [28, 29]. The Indiana group evaluated 226 patients and found a higher incidence of residual cancer in the group treated initially with four cycles of etoposide and cisplatin (22.9%) compared to the group treated with three cycles of bleomycin, etoposide, and cisplatin (7.8%). Conversely, the Memorial Sloan Kettering group found a higher incidence of residual teratoma in the BEP group 53% vs. 32% in the EP group. Randomized trial data has not demonstrated a statistically significant survival benefit of one regimen over another in good-risk patients. However, the recent histologic studies demonstrating differences in residual cancer vs. teratoma with no increased surgical or pulmonary morbidity with the inclusion of bleomycin are noteworthy.

The Role of Adjuvant Chemotherapy After PCRPLND

The histopathologic findings in post-chemotherapy surgical specimens determine the need for further treatment and surveillance protocol. In general, in bulky RPLN, pure necrotic tissue is found in 50%, teratoma in 35%, and viable tumor in 10–15% of the post-chemotherapy-resected masses [30]. If pathology post-surgery showed viable residual GCT after first-line cisplatin-based chemotherapy, there is a high chance of relapse and are generally recommended to receive two postoperative cycles of cisplatin-etoposide (EPx2) chemotherapy [31]. In an international study group, the 5-year progression-free survival (PFS) rate was 64%, and the 5-year overall survival (OS) rate was 73%. Three factors were independently associated with both PFS and OS: complete resection ($P < .001$), < 10% of viable malignant cells ($P = .001$), and a good International Germ Cell Consensus Classification (IGCCC) group ($P = .01$). After adjustment on the three prognostic factors, postoperative chemotherapy was associated with a significantly better PFS ($P < .001$) but not with better OS. Patients in the favorable risk group had a 100% 5-year OS, with or without postoperative chemotherapy. Postoperative chemotherapy appeared beneficial in both PFS ($P < .001$) and OS ($P = .02$) in the intermediate-risk group but was not statistically beneficial in the poor-risk group [32].

The histologic finding of malignant transformation of teratoma in the PC-RPLND specimen has been associated with a poor prognosis [33••]. Complete surgical resection has the best chance of cure. These patients should receive adjuvant chemotherapy composed of cyclophosphamide, doxorubicin, and vincristine (CAV) alternating with ifosfamide plus etoposide for 5 consecutive days given every 3 weeks for a maximum of six cycles [34, 35•].

Primary Mediastinal Non-seminoma GCT

Primary mediastinal non-seminoma germ cell tumors (PMNSGCTs) are extragonadal germ cell tumors that arise in the anterior mediastinum. They are histologically identical to testicular GCT; however, the biology and prognosis are substantially different [36]. PMNSGCTs represent the most challenging group of malignant GCT to treat and classified as poor risk per the IGCCCG criteria [37, 38]. Survival outcome is dependent on both chemotherapy and a skilled thoracic surgeon. They should be treated with four cycles of etoposide (VP16), ifosfamide and cisplatin (VIP) combination chemotherapy followed by surgical resection of the residual tumor even if there is an elevation in tumor markers [39, 40••]. We recommend ifosfamide instead of bleomycin to prevent pulmonary complications as these patients require extensive thoracic surgical resection. These recommendations are based on a large retrospective study from Indiana University, 158 patients underwent post-chemotherapy operations for PMNSGCT. Ten (6%) operative deaths occurred, nine of which were attributed to respiratory failure, and 26 (18%) patients experienced postoperative complications, including 9 with respiratory failure. None of 17 recent patients who received chemotherapy regimens that did not contain bleomycin experienced pulmonary complications ($p = 0.12$ vs patients who received bleomycin). Operative survivors were followed up a median of 34 months. Multivariable analysis demonstrated that the post-chemotherapy pathologic complete necrosis vs teratoma, persistent viable cancer, and elevated serum tumor markers after operation were independently predictive of survival [41]. Primary mediastinal seminoma represents a good-risk disease with a cure rate near 100% when treated with BEP × 3 or EP × 4. No surgical resection is needed post-chemotherapy.

Management of Residual Retroperitoneal Seminoma Mass

Classical seminoma is exquisitely sensitive to chemotherapy; however, up to 66–80% of patients with advanced disease may have residual masses post-chemotherapy. The primary

concern in these men is determining whether those residual masses contain viable seminoma. This will dictate whether the patient needs further treatment or just active surveillance. Currently, fluorine-18 deoxyglucose (FDG)–positron-emission tomographic–CT (FDG-PET/CT) is the best non-invasive modality for predicting the presence of viable residual tumor in patients with post-chemotherapy residual masses [42]. FDG-PET/CT has been recommended in international guidelines in the evaluation of post-chemotherapy seminoma residuals based on the SEMPET trial [43, 44]. Early reports on the use of FDG-PET in detecting viable seminoma indicated specificity of 100% and sensitivity of 80%. However, in a confirmatory study, the PET sensitivity, specificity, negative predictive value, and positive predictive value were 50%, 77%, 91%, and 25%, respectively, before the 6-week cutoff and 82%, 90%, 95%, and 69% after the 6-week cutoff. PET accuracy significantly improved from 73% before to 88% after the cutoff ($P = 0.032$) [43].

Watchful waiting is recommended for residual lesions < 3 cm or lesions ≥ 3 cm with negative FDG-PET scan. In seminoma, post-chemotherapy residual masses of up to 3 cm represent necrosis in 97–100%, and FDG-PET is not recommended. FDG-PET has a high negative predictive value to discriminate viable tumor from necrosis. Positive predictive value for FDG-PET has been shown to be low: 25% if performed before 6 weeks after the end of chemotherapy and 69% after this cutoff. There is a lack of data regarding the optimal management strategy for FDG-PET-positive residual lesions.

In a retrospective study, Cathomas et al. identified 90 patients with metastatic seminoma and residual PET-positive lesions after chemotherapy. Median time from last day of chemotherapy to PET scan was 6.9 weeks. Post PET, 26 patients underwent resection, and 9 had a biopsy. The histology of the resected specimen was necrosis only in 25 patients (78%) and vital seminoma in 7 cases (22%). Only, 17% of seminoma patients with a positive post-chemotherapy FDG-PET relapsed. All relapsed patients received successful salvage chemotherapy apart from one who died from treatment. Relapses occur rapidly and can be successfully salvaged. FDG-PET has a very low positive predictive value even if performed 6 weeks after the end of chemotherapy (19%). The authors recommend repeating an FDG-PET scan 8–12 weeks after a positive first FDG-PET scan. Resections of PET-positive residuals may be performed after a 2nd positive scan, but represent an over treatment for 70–80% of patients [45]. Regression of post-chemotherapy residual masses in patients with seminoma is reported in 50 to 60% of cases, with the median time to the resolution being 13 to 18 months [46].

For biopsy confirmed residual seminoma, a multidisciplinary tumor board should discuss the morbidity of surgical resection. PC-RPLND may be an option for patients with small-volume disease owing to the limited long-term morbidity with modern operative techniques. However, in patients with significant residual tumor, who have received chemotherapy, these surgeries are technically demanding because of the desmoplastic reaction associated with seminoma tissue following chemotherapy. In a retrospective study from IU, the 5-year CSS for PC-RPLND was 54% [47]. Only a minority of patients achieved a durable cure from surgery alone. Thus, our preferred approach at Indiana University is to use tandem HDCT with carboplatin-etoposide plus stem cell transplant for most patients with relapsed/residual seminoma as it achieved 90% cure rate in this group of patients [48••]. We recommend against the use of radiation as second-line therapy for stage II seminoma that relapsed after first-line platinum-based chemotherapy.

Pitfalls in the Management of Residual Disease Post-chemotherapy

Salvage chemotherapy is not appropriate for residual mass and normal tumor markers. These masses represent teratoma, necrosis, or less commonly residual cancer and must be treated with surgical resection as described above. Additionally, a growing mass following chemotherapy with normalized serum tumor markers should be surgically resected because invariably represents a growing teratoma.

Salvage chemotherapy should be used only when the tumor markers α-fetoprotein (AFP) or human chorionic gonadotrophin (hCG) are rising. AFP can be elevated in non-malignant conditions such as alcohol abuse, hepatitis, cirrhosis, biliary tract obstruction, and in other conditions such as Fanconi anemia. Some individuals have familial, hereditary, mildly elevated serum AFP levels in the range of 15 to 30 ng/mL. Patients with this hereditary syndrome can present with elevated AFP levels as high as 40 or 50 ng/mL. However, the level remains the same throughout chemotherapy and follow-up [49].

Similarly, hCG could be falsely elevated in patients using marijuana [50]. These should not be an indication for salvage chemotherapy unless there is a clear and sustained rise in tumor markers. Elevated tumor markers levels as a result of progressive cancer will generally show a consistent pattern of increasing values with subsequent measurements.

Conclusion

The management of residual mass in germ cell tumors after chemotherapy should be evaluated in a multidisciplinary tumor board. Surgeries such as retroperitoneal lymph node dissection and thoracotomy to remove primary mediastinal germ cell tumors are complex and require expertise available only at high-volume centers. Salvage chemotherapy is not appropriate for residual non-seminoma GCT with normal tumor

markers. PET scan are used to evaluate residual retroperitoneal seminoma after 6 weeks of chemotherapy. A negative scan is rarely associated with relapse. However, a positive PET scan should be repeated and conformed by a biopsy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Hendry WF, Norman AR, Dearnaley DP, Fisher C, Nicholls J, Huddart RA, et al. Metastatic nonseminomatous germ cell tumors of the testis: results of elective and salvage surgery for patients with residual retroperitoneal masses. Cancer. 2002;94:1668–76.
2. Heidenreich A, Pfister D, Witthuhn R, Thüer D, Albers P. Postchemotherapy retroperitoneal lymph node dissection in advanced testicular cancer: radical or modified template resection. Eur Urol. 2009;55:217–24.
3. • Cho JS, Kaimakliotis HZ, Cary C, et al. Modified retroperitoneal lymph node dissection for post-chemotherapy residual tumour: a long-term update. BJU Int. 2017;120:104–8 **This study reported long-term outcomes of modified-template post-chemotherapy retroperitoneal lymph node dissection in selected patients with low-volume metastatic non-seminomatous germ cell tumour and showed durable long-term efficacy without risk of in-field recurrences**.
4. Carver BS, Shayegan B, Serio A, Motzer RJ, Bosl GJ, Sheinfeld J. Long-term clinical outcome after postchemotherapy retroperitoneal lymph node dissection in men with residual teratoma. J Clin Oncol. 2007;25:1033–7.
5. Beck SD, Foster RS, Bihrle R, et al. Long-term outcome for patients with high volume retroperitoneal teratoma undergoing post-chemotherapy surgery. J Urol. 2009;181:2526–32.
6. Ehrlich Y, Brames MJ, Beck SD, et al. Long-term follow-up of cisplatin combination chemotherapy in patients with disseminated nonseminomatous germ cell tumors: is a postchemotherapy retroperitoneal lymph node dissection needed after complete remission? J Clin Oncol. 2010;28:531–6.
7. Kollmannsberger C, Daneshmand S, So A, Chi KN, Murray N, Moore C, et al. Management of disseminated nonseminomatous germ cell tumors with risk-based chemotherapy followed by response-guided postchemotherapy surgery. J Clin Oncol. 2010;28:537–42.
8. Saxman SB, Finch D, Gonin R, Einhorn LH. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: the Indian University experience. J Clin Oncol. 1998;16:702–6.
9. Honecker F, Aparicio J, Berney D, Beyer J, Bokemeyer C, Cathomas R, et al. ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. Ann Oncol. 2018;29:1658–86.
10. Beck SD, Foster RS. Management of the post chemotherapy subcentimeter residual mass: the case for observation. World J Urol. 2009;27:485–8.
11. Sheinfeld J. Risks of the uncontrolled retroperitoneum. Ann Surg Oncol. 2003;10:100–1.
12. Daneshmand S, Djaladat H, Nichols C. Management of residual mass in nonseminomatous germ cell tumors following chemotherapy. Ther Adv Urol. 2011;3:163–71.
13. Geldart TR, Gale J, McKendrick J, et al. Late relapse of metastatic testicular nonseminomatous germ cell cancer: surgery is needed for cure. BJU Int. 2006;98:353–8.
14. Beck SD, Foster RS, Bihrle R, et al. Teratoma in the orchiectomy specimen and volume of metastasis are predictors of retroperitoneal teratoma in post-chemotherapy nonseminomatous testis cancer. J Urol. 2002;168:1402–4.
15. Stephenson AJ, Tal R, Sheinfeld J. Adjunctive nephrectomy at post-chemotherapy retroperitoneal lymph node dissection for nonseminomatous germ cell testicular cancer. J Urol. 2006;176:1996–9 **discussion 1999**.
16. Cary KC, Beck SD, Bihrle R, Foster RS. Clinical and pathological features predictive of nephrectomy at post-chemotherapy retroperitoneal lymph node dissection. J Urol. 2013;189:812–7.
17. Moore CJ, Daneshmand S, Kondagunta GV, Nichols CR. Management of difficult germ-cell tumors. Oncology (Williston Park). 2006;20:1565–70 1575; **discussion 1575-1566**.
18. Johnston P, Beck SD, Cheng L, et al. Incidence, histology and management of intraluminal thrombus at post-chemotherapy retroperitoneal lymph node dissection. J Urol. 2013;190:874–7.
19. Duty B, Daneshmand S. Resection of the inferior vena cava without reconstruction for urologic malignancies. Urology. 2009;74:1257–62.
20. Quinones-Baldrich W, Alktaifi A, Eilber F, Eilber F. Inferior vena cava resection and reconstruction for retroperitoneal tumor excision. J Vasc Surg. 2012;55:1386–93 **discussion 1393**.
21. Beck SD, Lalka SG. Long-term results after inferior vena caval resection during retroperitoneal lymphadenectomy for metastatic germ cell cancer. J Vasc Surg. 1998;28:808–14.
22. Tognoni PG, Foster RS, McGraw P, et al. Combined post-chemotherapy retroperitoneal lymph node dissection and resection of chest tumor under the same anesthetic is appropriate based on morbidity and tumor pathology. J Urol. 1998;159:1833–5.
23. Restrepo CS, Eraso A, Ocazionez D, Lemos J, Martinez S, Lemos DF. The diaphragmatic crura and retrocrural space: normal imaging appearance, variants, and pathologic conditions. Radiographics. 2008;28:1289–305.
24. Fadel E, Court B, Chapelier AR, Droz JP, Dartevelle P. One-stage approach for retroperitoneal and mediastinal metastatic testicular tumor resection. Ann Thorac Surg. 2000;69:1717–21.
25. • Albany C, Adra N, Snavely AC, et al. Multidisciplinary clinic approach improves overall survival outcomes of patients with metastatic germ-cell tumors. Ann Oncol. 2018;29:341–6 **This study showed that multidisciplinary clinic approach to GCT at high-volume cancer center is associated with improved OS outcomes. These finding are especially relevent to the surgical resection of residual mass after chemotherapy**.
26. Besse B, Grunenwald D, Flechon A, et al. Nonseminomatous germ cell tumors: assessing the need for postchemotherapy contralateral pulmonary resection in patients with ipsilateral complete necrosis. J Thorac Cardiovasc Surg. 2009;137:448–52.
27. •• Calaway AC, Foster RS, Adra N, et al. Risk of bleomycin-related pulmonary toxicities and operative morbidity after postchemotherapy

retroperitoneal lymph node dissection in patients with good-risk germ cell tumors. J Clin Oncol. 2018. https://doi.org/10.1200/JCO.18.00431 **This study showed that the inclusion of bleomycin does not increase the risk of pulmonary morbidity, operative difficulty, or nonpulmonary postoperative complications after PC-RPLND in men with IGCCCG good-risk GCT.**

28. Cary KC, Pedrosa JA, Kaimakliotis HZ, Masterson TA, Einhorn LH, Foster RS. The impact of bleomycin on retroperitoneal histology at post-chemotherapy retroperitoneal lymph node dissection of good risk germ cell tumors. J Urol. 2015;193:507–12.
29. Kundu SD, Feldman DR, Carver BS, Gupta A, Bosl GJ, Motzer RJ, et al. Rates of teratoma and viable cancer at post-chemotherapy retroperitoneal lymph node dissection after induction chemotherapy for good risk nonseminomatous germ cell tumors. J Urol. 2015;193:513–8.
30. Fox EP, Weathers TD, Williams SD, Loehrer PJ, Ulbright TM, Donohue JP, et al. Outcome analysis for patients with persistent nonteratomatous germ cell tumor in postchemotherapy retroperitoneal lymph node dissections. J Clin Oncol. 1993;11:1294–9.
31. Nichols CR, Williams SD, Loehrer PJ, Greco FA, Crawford ED, Weetlaufer J, et al. Randomized study of cisplatin dose intensity in poor-risk germ cell tumors: a Southeastern Cancer Study Group and Southwest Oncology Group protocol. J Clin Oncol. 1991;9:1163–72.
32. Fizazi K, Tjulandin S, Salvioni R, Germà-Lluch JR, Bouzy J, Ragan D, et al. Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: prognostic factors and role of postsurgery chemotherapy–results from an international study group. J Clin Oncol. 2001;19:2647–57.
33.•• Giannatempo P, Pond GR, Sonpavde G, et al. Treatment and clinical outcomes of patients with teratoma with somatic-type malignant transformation: an international collaboration. J Urol. 2016;196:95–100 **International retrospective study that assessed the prognostic factors, treatments and outcomes in patients with malignant transformation of teratoma.**
34. Speir R, Cary C, Foster RS, Masterson TA. Management of patients with metastatic teratoma with malignant somatic transformation. Curr Opin Urol. 2018;28:469–73.
35.• Al-Hader AA, Jain A, Al-Nasrallah N, Einhorn LH. Metastatic malignant transformation of teratoma to primitive neuroectodermal tumor (PNET): results with PNET-based chemotherapy. Am J Clin Oncol. 2015;38:364–6 **This study evaluated the role of chemotherapy with cyclophosphamide+doxorubicin+vincristine (CAV) alternating with ifosfamide+etoposide (IE) in malignant transformation of teratoma to primitive neuroectodermal tumor (PNET).**
36. Albany C, Einhorn LH. Extragonadal germ cell tumors: clinical presentation and management. Curr Opin Oncol. 2013;25:261–5.
37. Albany C. Current medical management of patients with poor-risk metastatic germ-cell tumors. Curr Opin Urol. 2018;28:474–8.
38. Adra N, Althouse SK, Liu H, Brames MJ, Hanna NH, Einhorn LH, et al. Prognostic factors in patients with poor-risk germ-cell tumors: a retrospective analysis of the Indiana University experience from 1990 to 2014. Ann Oncol. 2016;27:875–9.
39. Schneider BP, Kesler KA, Brooks JA, Yiannoutsos C, Einhorn LH. Outcome of patients with residual germ cell or non-germ cell malignancy after resection of primary mediastinal nonseminomatous germ cell cancer. J Clin Oncol. 2004;22:1195–200.
40.•• Ranganath P, Kesler KA, Einhorn LH. Perioperative morbidity and mortality associated with bleomycin in primary mediastinal nonseminomatous germ cell tumor. J Clin Oncol. 2016;34:4445–6 **This study found high rate of post-operative pulmonary failure after bleomycin containing chemotherapy (BEP) in patients with PMNSGCTs. The results support the use of VIP in PMNSGCT patients prior to major thoracic surgical procedures.**
41. Kesler KA, Rieger KM, Hammoud ZT, Kruter LE, Perkins SM, Turrentine MW, et al. A 25-year single institution experience with surgery for primary mediastinal nonseminomatous germ cell tumors. Ann Thorac Surg. 2008;85:371–8.
42. Becherer A. PET in testicular cancer. Methods Mol Biol. 2011;727:225–41.
43. Bachner M, Loriot Y, Gross-Goupil M, Zucali PA, Horwich A, Germa-Lluch JR, et al. 2-(1)(8)fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) for postchemotherapy seminoma residual lesions: a retrospective validation of the SEMPET trial. Ann Oncol. 2012;23:59–64.
44. De Santis M, Becherer A, Bokemeyer C, et al. 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. J Clin Oncol. 2004;22:1034–9.
45. Cathomas R, Klingbiel D, David Bernard B et al. FDG PET scan (PET) positive residual lesions after chemotherapy (chemo) for metastatic seminoma: results of an International Global Germ Cell Cancer Group (G3) registry. J Clin Oncol. 2017;359:4521–1.
46. Mezvrishvili Z, Managadze L. Retroperitoneal lymph node dissection for high-risk stage I and stage IIA seminoma. Int Urol Nephrol. 2006;38:615–9.
47. Rice KR, Beck SD, Bihrle R, et al. Survival analysis of pure seminoma at post-chemotherapy retroperitoneal lymph node dissection. J Urol. 2014;192:1397–402.
48.•• Adra N, Abonour R, Althouse SK, et al. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumors: the Indiana University experience. J Clin Oncol. 2017;35:1096–102 **This large study from Indiana University showed that patients with relapsed metastatic GCT can be cured with second-line and even third-line high-dose chemotherapy (HDCT) and peripheral-blood stem-cell transplantation (PBSCT). Relapsed seminoma had high response rate with 90% cure with HDCT.**
49. Albany C, Einhorn L. Pitfalls in management of patients with germ cell tumors and slight elevation of serum alpha-fetoprotein. J Clin Oncol. 2014;32:2114–5.
50. Garnick MB. Spurious rise in human chorionic gonadotropin induced by marihuana in patients with testicular cancer. N Engl J Med. 1980;303:1177.