ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211247

Postchemotherapy retroperitoneal residual mass resection for germ cell testicular tumors: a single-center experience

Serdar Kalemci[1], Fuat Kizilay[1], Kasim Emre Ergun[1*], Bayram Aliyev[1], Adnan Simsir[1]

SUMMARY

Objective: Postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) plays an important role in the management of advanced germ cell testicular tumors. Bilateral template lymph node dissection is considered a standard treatment in postchemotherapy residual masses; however, modified unilateral templates have gained acceptance in patients with unilateral residual disease. In this study, we aimed to demonstrate the perioperative and oncological outcomes of the patients with advanced testicular cancer who underwent unilateral modified template PC-RPLND in our center.

Methods: This is a retrospective study in which patients who underwent PC-RPLND in a referred center between 2004 and 2021 were investigated. All patients had three or four cycles of chemotherapy and retroperitoneal residual masses. Data were retrospectively collected from medical, operative, radiology, and pathology records and analyzed.

Results: A total of 57 patients underwent PC-RPLND. The mean age was 32.7±8.1 years (19–50). According to the disease stage at presentation, there were 39 patients with stage 2 and 18 patients with stage 3. The average tumor size after chemotherapy was 57.6±2.7 mm (25–117). The overall complication rate was 35% (20/57 patients). No grade 4 and 5 complications were observed. Pathologic review demonstrated the presence of teratoma in 28 (49.1%) patients, fibrosis and/or necrosis in 15 (26.3%) patients, and viable germ cell tumor in 14 (24.5%) patients. The mean follow-up was 69.4 months (8–201). During follow-up after surgery, 14 (24.5%) deaths occurred due to advanced disease.

Conclusion: PC-RPLND is a major component of the management of advanced testicular germ cell cancer. Our study demonstrated that modified unilateral template is an effective and safe procedure in the postchemotherapy setting for selected patients.

Keywords: Retroperitoneal lymph node dissection. Testicular cancer. Germ cell tumor. Nonseminoma. Seminoma.

INTRODUCTION

Testicular cancer is the most common solid malignancy among males aged 15–35 and represents 1% of adult neoplasms and 5% of urological tumors[1]. Since the past decade, the incidence of testicular cancer has been rising in many countries. Northern European countries have the highest incidence rates, while Eastern European, Asian, African, and South American countries have the lowest[2]. The majority of malignant testicular tumors are germ cell tumors (GCTs), accounting for 95% of all cases, and GCTs are classified into seminomas and non-seminomatous GCTs[3]. In the vast majority of patients with stage 1 disease, radical orchiectomy is curative, although those with advanced stages require chemotherapy[4]. The majority of patients achieve complete remission after chemotherapy, although a significant number will still have postchemotherapy masses.

Surgical resection of postchemotherapy residual retroperitoneal masses is an essential component of multimodality treatment for patients with advanced testicular cancer receiving systemic chemotherapy. The optimal management of residual mass after chemotherapy for non-seminomatous testicular cancer is still being debated. Patients with non-seminomatous testicular cancer and residual retroperitoneal lymph nodes > 1 cm following chemotherapy should undergo a postchemotherapy retroperitoneal lymph node dissection (PC-RPLND)[5,6]. In these patients, following the first-line bleomycin, etoposide, and cisplatin (BEP) chemotherapy, only 6–10% of residual masses contain active cancer, 50% have postpubertal teratoma, and 40% comprise necrotic-fibrotic tissue only[7]. Seminomas are extremely sensitive to chemotherapy, but residual masses are detected after chemotherapy in 66–80% of patients with advanced disease. Fluorodeoxyglucose-positron emission tomography (FDG-PET) is recommended with residual masses after treatment of seminoma due to its high negative predictive value[8]. Surveillance is advised for residual lesions less than 3 cm in size or lesions larger than 3 cm in size with a negative FDG-PET. In patients with postchemotherapy residual masses <3

[1]Ege University Faculty of Medicine, Department of Urology – Izmir, Turkey.
*Corresponding author: kasimemreergun@gmail.com
Conflicts of interest: the authors declare there is no conflict of interest. Funding: none.
Received on January 19, 2022. Accepted on February 01, 2022.

cm, FDG-PET is optional[8,9]. PC-RPLND should be considered a treatment option in patients with postchemotherapy residual masses >3 cm with a positive FDG-PET scan.

The optimal approach to PC-RPLND has proven to be more contentious. In the postchemotherapy setting, bilateral nerve-sparing RPLND is the standard option. In selected patients, ipsilateral template resection with nerve preservation has been shown to produce comparable long-term oncologic results to bilateral systematic resections[4,10]. In this study, we present the results of 57 patients undergoing PC-RPLND for retroperitoneal residual mass after chemotherapy for germ cell testicular tumors. We aimed to present our surgical experience and evaluate oncological results, complications, and survival of PC-RPLND procedures performed at our institution.

METHODS

Patient population and inclusion criteria

Between May 2004 and March 2021, patients with primary non-seminomatous or seminomatous testicular tumor and history of chemotherapy after orchiectomy were enrolled in our study. All 62 patients who underwent open PC-RPLND for residual mass in the retroperitoneal area in a single center were included in this study. All of the patients underwent radical orchiectomy for primary diagnosis, and all patients received three or four cycles of chemotherapy prior to surgery according to their prognostic group. Patients with extragonadal tumor, previous RPLND prior to chemotherapy, and previous salvage chemotherapy were excluded from the study. Before PC-RPLND, all patients underwent computed tomography of the chest and abdomen 6–8 weeks following the last cycle of chemotherapy, and measurement of the serum tumor markers was taken.

Data collection

Data were retrospectively collected from medical, operative, radiology, and pathology records and analyzed. Five patients with incomplete data were excluded from the study. Follow-up data were available for 57 patients. Preoperative demographic and clinical variables included age, clinical stage, initial pathology of testicular tumor, preoperative chemotherapy status, size of the retroperitoneal mass, and time to RPLND. Operative and postoperative variables included pathology of retroperitoneal mass, intraoperative complication status, estimated blood loss, length of hospital stay (LOH), and oncologic outcomes. Intraoperative and postoperative complications were recorded according to Clavien-Dindo classification system[11]. The 2016 Tumor Node Metastasis (TNM) classification of the International Union Against Cancer is used for clinical staging and classification of prognostic groups[12].

Surgical technique

Patients were placed in supine position, and a midline incision was made. After obtaining the intra-abdominal access, a medial rotation of the colon was made to create the retroperitoneal space. Modified template resection limits for right-sided tumors consist of the ureter (lateral), the midpoint of the aorta (medial), bifurcation of iliac vessels (inferior), and and renal hilum (superior), and for left-sided tumors consist of ureter (lateral), there are midpoint of vena cava (medial), bifurcation of iliac vessels (distal), and renal hilum (superior). Lymph nodes in these areas were packed and dissected. Care was taken to avoid major vessels and sympathetic trunk injury during dissection. If the residual mass is close to the ureters, a double J ureteral catheter was placed before RPLND, in order to identify and avoid damage to the ureters.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 17.0 (Chicago, IL, USA) program. The categorical variables were compared using the chi-square and continuous variables were evaluated by Mann-Whitney U test. Kaplan-Meier test was used to calculate the survival of patients. Statistical significance was accepted as p-value <0.05.

RESULTS

A total of 62 patients who underwent postchemotherapy open PC-RPLND were evaluated. Of them, 57 patients with a mean age of 32.7±8.1 years (range 19–50) were included in the study. The primary testicular tumor sides were in the right and left testis in 33 (57.8%) and 24 (42.2%) patients, respectively. The pathology of primary tumor demonstrated non-seminomatous germ cell (n=35, 61.4%), seminoma (n=8, 14%), and mixed GCT (n=14, 24.5%). According to the disease stage at presentation, there were 39 patients with stage 2 and 18 patients with stage 3. The primary chemotherapy regime in 41 (71.9%) patients was standard three or four cycles of BEP, 8 (14%) patients received epirubicin and cisplatin (EP) for bleomycin toxicity, 4 (7%) patients received etoposide, ifosfamide, and cisplatin (VIP), and another 4 (7%) patients received alternative individualized chemotherapy regimens. The average tumor size after chemotherapy was 57.6±2.7 mm

(25–117 mm). Baseline demographics and patient characteristics are shown in Table 1.

Open PC-RPLND via an anterior abdominal approach was performed in all patients. The mean LOH was 8.4±7.5 days. The overall complication rate was 35% (20/57 patients). There was no grade 4 and grade 5 complications (perioperative death). Eight of these complications were occurred in the intraoperative period, of which four were bleeding requiring blood transfusion and four were major vascular (inferior vena cava or aorta) injuries requiring surgical intervention. In all, 12 patients suffered from postoperative complications, of which 8 were Clavien-Dindo grades 1 and 2 and 4 were Clavien-Dindo grade 3b. Complications are summarized in Table 2.

Final retroperitoneal mass pathology demonstrated teratoma in 28 (49.1%) patients, fibrosis and/or necrosis in 15 (26.3%) patients, and viable GCT in 14 (24.5%) patients. The mean follow-up was 69.4±54.5 months (8–201). During follow-up after surgery, 14 (24.5%) deaths occurred due to advanced disease. Overall survival rate was 75.5%, with a median follow-up of 47 months. Kaplan-Meier survival curves are presented in Figure 1.

DISCUSSION

In this study, we aimed to present our surgical experience and demonstrate that modified unilateral template is an effective and safe procedure in the postchemotherapy setting. In the treatment of metastatic testicular cancer, surgical excision of remaining masses after chemotherapy is still an integral and crucial aspect of the treatment[13]. For patients undergoing RPLND after chemotherapy, a full bilateral dissection is currently recommended. Patients with advanced disease who have received chemotherapy may benefit from a unilateral, modified template RPLND[4]. Both procedures can be performed by open, laparoscopic, or robotic-assisted laparoscopic approach. In our study, we examined oncologic outcomes following postchemotherapy open unilateral modified template RPLND in patients with clinical stage II and III diseases. In these patients, RPLND is a key part of multidisciplinary treatment, but surgery requires

Table 2. Grading of surgical complications.

Grade	Complication	n
1	Ileus Wound infection	4 2
2	Blood transfusion Deep vein thrombosis Damage of IVC or aorta	4 2 4
3b	Wound dehiscence Coloileal anastomosis leakage Small intestine necrosis	2 1 1
Total (%)		20 (35)

IVC, inferior vena cava.

Table 1. Patient characteristics.

Characteristic	Non-seminomatous (n=49)	Seminomatous (n=8)	p-value
Age (years)	32.4 (19–46)	39.1 (30–50)	0.042
Site of primary tumor, n			
Right	29	4	0.660
Left	20	4	
Tumor size, cm (biggest diameter)	4.72 (1.5–9.2)	6.8 (3.5–12)	
Stage of disease, n			
Stage II	34	5	0.657
Stage III	15	3	
Histology of residual mass, n			
Teratoma	30	2	
Necrosis/fibrosis	8	4	0.215
Viable GCT	11	2	
Perioperative complication	15	5	0.136
Mean estimated blood loss	194 (140-400)	234 (115-440)	0.451
Length of hospitalization (days)	7.8 (3-50)	9.2 (6-21)	0.657
Mean follow-up (months)	68.6 (8-201)	75.6 (24-112)	0.732
Survival (death patients/total)	13/49	1/8	0.339

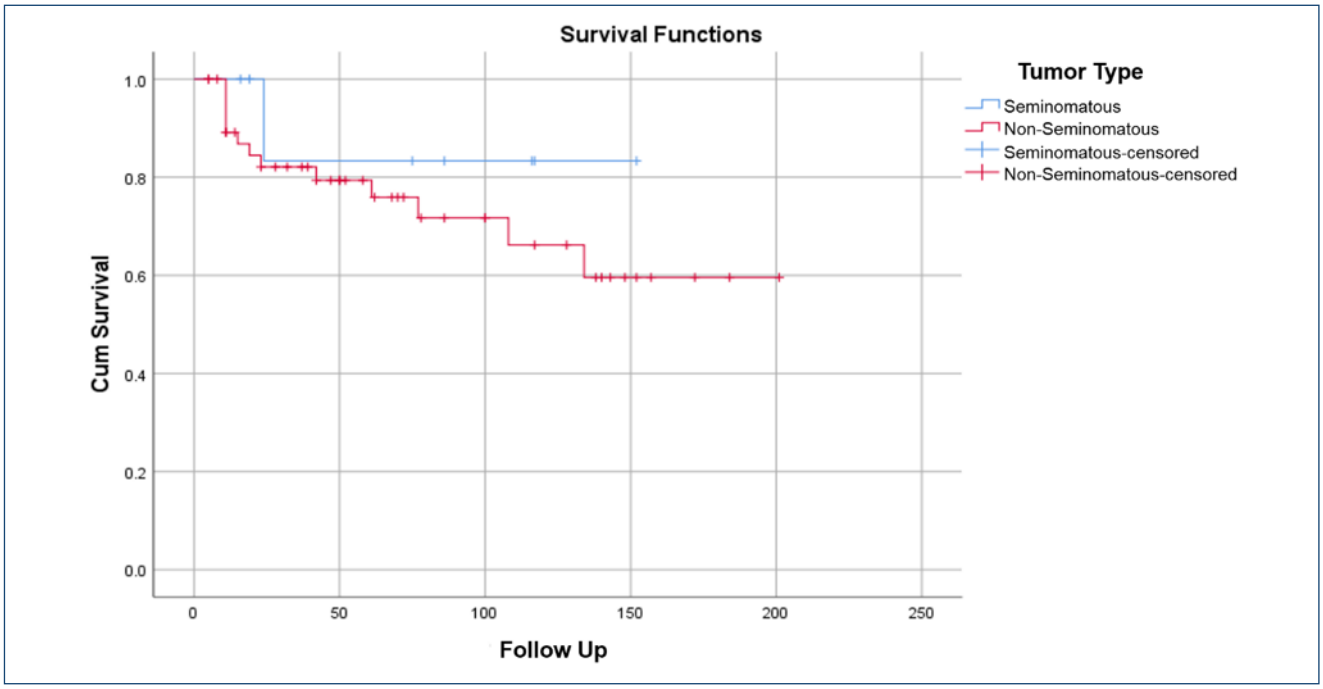

Figure 1. Kaplan-Meier survival curve for cancer-specific survival stratified by tumor type.

a high level of competence and may cause many serious intraoperative and postoperative surgical complications. Therefore, these patients should be managed in centers with a high volume of testicular cancer patients.

The excision of postchemotherapy residual masses in the retroperitoneal area is a major procedure with several intraoperative and postoperative difficulties. In a recent population-based study, the incidence of intraoperative and postoperative complications was higher for bilateral PC-RPLND than for unilateral PC-RPLND and they found that lymphatic leakage was the most common complication[14]. In another study in which primary and PC-RPLND complications were compared, the authors stated that the risk and severity of intraoperative and postoperative complications were higher with PC-RPLND though no significant difference was found between the two groups in terms of complication rates[15]. In our PC-RPLND series, no intraoperative or perioperative death was observed. Although the complication rate was at an acceptable level in our study, none of the patients had Clavien-Dindo grade 4 or 5 complications. In one patient who had Clavien-Dindo grade 3b complication, surgical intervention was performed again under general anesthesia due to abdominal evisceration secondary to postoperative ileus. In a large study of 603 patients who underwent PC-RPLND for clinical stages II and III, there were 144 complications in 125 (20.7%) patients, and the mortality rate was 0.8%[16]. In a recent systematic review comparing outcomes of different PC-RPLND techniques, 100 (29%) of 347 patients undergoing modified unilateral PC-RPLND experienced complications, and 27(8%) patients experienced grade 3 and 4 complications[17]. In a study comparing primary and PC-RPLND surgeries, it was emphasized that intraoperative and postoperative complications were more common in the PC-RPLND group without statistically significant difference, and ileus constituted the majority of postoperative complications in both groups[15]. In our study, we found that the hospitalization period was prolonged in patients with ileus especially in the postoperative period and two patient needed adjuvant surgery due to abdominal evisceration and two patients due to coloileal anastomosis leakage and intestinal necrosis. Patients undergoing PC-RPLND are more likely to develop complications due to factors such as a large volume of disease, a postchemotherapy desmoplastic reaction, and aggressive/extensive retroperitoneal dissection. In addition, the decrease in pulmonary reserves of these patients after chemotherapy, especially in those receiving bleomycin therapy, adds an additional burden to the perioperative and postoperative morbidities of the patients.

Fibrosis/necrosis, teratoma, and viable GCT are the most common findings after PC-RPLND. In a single-institution series of 504 patients who underwent PC-RPLND, 51% of

cases had fibrosis/necrosis, 37% had teratoma, and 15% had viable GCT[7]. A similar rate was found in another series of 152 patients from two tertiary referral centers, 84 (55.2%) patients had necrosis/fibrosis, 45 (29.6%) had mature teratoma, and 23 (15.1%) had vital cancer in the surgical specimens[4]. Reviewing our series, teratoma contributed to 49.1% of histopathological findings of retroperitoneal masses, fibrosis/necrosis to 26.3%, and viable GCT to the remaining 24.5%. In a clinical model for analyzing residual masses after chemotherapy, authors demonstrated that models that predict patients with non-seminoma with either necrosis or viable cancer after is irrelevant and not reliable and highlighted PC-RPLND should not be performed in these patients, as residual seminoma was not detected in 97% of patients with seminoma who received adequate systemic chemotherapy[18]. In a recent study, the levels of a new serum biomarker micro-RNA 371 were found significantly associated with clinical stage, primary tumor size, and response to treatment, and all histologic subtypes, except teratoma, express this micro-RNA. Compared with classical serum tumor markers, it was found to have a higher sensitivity and specificity of over 90%. After further validation, this marker could be considered in the management of GCTs even in advanced stages[19]. In another study, it was underlined that the levels of this marker decreased significantly after chemotherapy in patients with advanced disease and confirmed that it was not expressed at all in teratoma[20]. This novel biomarker should be considered in cases where the use of the classical tumor markers is inconclusive, postchemotherapy residual masses in seminoma and non-seminoma.

In our series, 14 patients died from disease progression. Our overall survival rate was 75.5%, with a median follow-up of 47 months. In a study demonstrating the long-term data of 100 patients who underwent modified left or right unilateral PC-RPLND, they reported a 99% survival rate at a 10-year follow-up. Unlike our study, this study consisted of only patients with a limited retroperitoneal limited disease on the affected testis side and normal serum tumor markers after systematic chemotherapy[21]. In our study, residual mass resection pathology was reported as viable GCT in 10 of the patients who died due to advanced disease during follow-up. In a study with similar survival rates as ours, 60% of the patients who died during follow-up had a GCT in the final pathology[22]. In another study investigating the pathological data and clinical results of patients who underwent RPLND after multiple chemotherapy regimens, it was emphasized that the predictors of worse disease-specific survival were the detection of a retroperitoneal mass larger than 5 cm and GCT[23]. Furthermore, in this study, a 5-year disease-specific survival rate of 74% was reported, which is also consistent with our study.

This study has several limitations. First is the retrospective nature of this study. Second, since information about the retrograde ejaculation status of the patients in the postoperative period is not reported in the database, this detail was not included in the study. Third, we did not use the bilateral modified RPLND technique, which may have affected the oncological outcomes. Another limitation is that there is no mention of additional adjuvant therapy.

CONCLUSIONS

We present the results of a single-center PC-RPLND procedure for advanced testicular tumors. PC-RPLND has a complementary role in the management of advanced GCTs, particularly non-seminoma. After chemotherapy, the majority of patients achieve complete remission, although a significant number will still have postchemotherapy masses. We hypothesized that a modified unilateral PC-RPLND would be equally effective in managing the masses in the retroperitoneum oncologically. In optimally diagnosed and well-evaluated patients with residual masses following systemic chemotherapy for advanced testicular cancer, modified PC-RPLND can be regarded as a safe surgical procedure. In particular, PC-RPLND procedures should be performed in high-volume clinics with extensive experience in the treatment of advanced testicular cancer. Centralizing the treatment of these patients is important in terms of disease control and prevention of perioperative mortality. The prediction of viable GCTs in these patients with newly developed tumor markers seems promising.

AUTHORS' CONTRIBUTIONS

SK: Conceptualization, Formal Analysis, Methodology, Project administration, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **FK:** Conceptualization, Investigation, Methodology, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. **KEE:** Data curation, Formal Analysis, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft. **BA:** Data curation, Resources, Validation. **AS:** Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33. https://doi.org/10.3322/caac.21654
2. Gurney JK, Florio AA, Znaor A, Ferlay J, Laversanne M, Sarfati D, et al. International trends in the incidence of testicular cancer: lessons from 35 years and 41 countries. Eur Urol. 2019;76(5):615-23. https://doi.org/10.1016/j.eururo.2019.07.002
3. Rajpert-De Meyts E, McGlynn KA, Okamoto K, Jewett MAS, Bokemeyer C. Testicular germ cell tumours. Lancet. 2016;387(10029):1762-74. https://doi.org/10.1016/S0140-6736(15)00991-5
4. Heidenreich A, Pfister D, Witthuhn R, Thuer D, Albers P. Postchemotherapy retroperitoneal lymph node dissection in advanced testicular cancer: radical or modified template resection. Eur Urol. 2009;55(1):217-24. https://doi.org/10.1016/j.eururo.2008.09.027
5. Hendry F, Norman A, Dearnaley D, Fisher Cyril, Nicholls J, Huddart R, et al. Metastatic non-seminomatous germ cell tumors of the testis: results of elective and salvage surgery for patients with residual retroperitoneal masses. Cancer. 2002;94(6):1668-76. https://doi.org/10.1002/cncr.10440
6. Sheinfeld, J. The role of adjunctive postchemotherapy surgery for non-seminomatous germ-cell tumors: current concepts and controversies. Semin Urol Oncol. 2002;20(4):262-71. https://doi.org/10.1053/suro.2002.36977
7. Carver BS, Serio AM, Bajorin D, Motzer RJ, Stasi J, Bosl GJ, et al. Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. J Clin Oncol. 2007;25(35):5603-8. https://doi.org/10.1200/JCO.2007.13.6283
8. Bachner M, Loriot Y, Gross-Goupil M, Zucali PA, Horwich A, Germa-Lluch JR, et al. 2-^{18}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(1):59-64. https://doi.org/10.1093/annonc/mdr052
9. De Santis M, Becherer A, Bokemeyer C, Stoiber F, Oechsle K, Sellner F, et al. 2-^{18}fluoro-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(6):1034-9. https://doi.org/10.1200/JCO.2004.07.188
10. Rick O, Bokemeyer C, Weinknecht S, Schirren J, Pottek T, Hartmann JT, et al. Residual tumor resection after high-dose chemotherapy in patients with relapsed or refractory germ cell cancer. J Clin Oncol. 2004;22(18):3713-9. https://doi.org/10.1200/JCO.2004.07.124
11. Clavien PA, Strasberg SM. Severity grading of surgical complications. Ann Surg. 2009;250(2):197-8. https://doi.org/10.1097/SLA.0b013e3181b6dcab
12. Brierley JE, Gospodarowicz M, Wittekind C. The TNM classification of malignant tumours. 8th ed. Hoboken, NJ: Wiley; 2016. p 190-4.
13. Heidenreich A, Thuer D, Polyakov S. Postchemotherapy retroperitoneal lymph node dissection in advanced germ cell tumours of the testis. Eur Urol. 2008;53(2):260-72. https://doi.org/10.1016/j.eururo.2007.10.033
14. Gerdtsson A, Håkansson U, Törnblom M, Jancke G, Negaard H, Glimelius I. Surgical complications in postchemotherapy retroperitoneal lymph node dissection for nonseminoma germ cell tumour: a population-based study from the Swedish Norwegian Testicular Cancer Group. Eur Urol Oncol. 2020;3(3):382-89. https://doi.org/10.1016/j.euo.2019.08.002
15. Subramanian VS, Nguyen CT, Stephenson AJ, Klein EA. Complications of open primary and post-chemotherapy retroperitoneal lymph node dissection for testicular cancer. Urol Oncol. 2010;28(5):504-9. https://doi.org/10.1016/j.urolonc.2008.10.026
16. Baniel J, Foster RS, Rowland RG, Bihrle R, Donohue JP. Complications of postchemotherapy retroperitoneal lymph node dissection. J Urol. 1995;153(3 Pt 2):976-80. PMID: 7853586
17. Rosenvilde JJ, Pedersen GL, Bandak M, Lauritsen J, Kreiberg M, Wagner T, et al. Oncological outcome and complications of post-chemotherapy retroperitoneal surgery in non-seminomatous germ cell tumours – a systematic review. Acta Oncol. 2021;60(6):695-703. https://doi.org/10.1080/0284186X.2021.1905176
18. Albers P, Weissbach L, Krege S, Kliesch S, Hartmann M, Heidenreich A, et al. Prediction of necrosis after chemotherapy of advanced germ cell tumors: results of a prospective multicenter trial of the german testicular cancer study group. J Urol. 2004;171(5):1835-8. https://doi.org/10.1097/01.ju.0000119121.36427.09
19. Dieckmann K-P, Radtke A, Geczi L, Matthies C, Anheuser P, Eckardt U, et al. Serum levels of MicroRNA-371a-3p (M371 Test) as a new biomarker of testicular germ cell tumors: results of a prospective multicentric study. J Clin Oncol. 2019;37(16):1412-23. https://doi.org/10.1200/JCO.18.01480
20. Leão R, van Agthoven T, Figueiredo A, Jewett MAS, Fadaak K, Sweet J, et al. Serum miRNA predicts viable disease after chemotherapy in patients with testicular nonseminoma germ cell tumor. J Urol. 2018;200(1):126-35. https://doi.org/10.1016/j.juro.2018.02.068
21. Cho JS, Kaimakliotis HZ, Cary C, Masterson TA, Beck S, Foster R. Modified retroperitoneal lymph node dissection for post-chemotherapy residual tumour: a long-term update. BJU Int. 2017;120(1):104-8. https://doi.org/10.1111/bju.13844
22. Nowroozi M, Ayati M, Arbab A, Jamshidian H, Ghorbani H, Niroomand H, et al. Postchemotherapy retroperitoneal lymph node dissection in patients with nonseminomatous testicular cancer: a single center experiences. Nephrourol Mon. 2015;7(5):e27343. https://doi.org/10.5812/numonthly.27343
23. Eggener SE, Carver BS, Loeb S, Kondagunta GV, Bosl GJ, Sheinfeld J. Pathologic findings and clinical outcome of patients undergoing retroperitoneal lymph node dissection after multiple chemotherapy regimens for metastatic testicular germ cell tumors. Cancer. 2007;109(3):528-35. https://doi.org/10.1002/cncr.22440