

Postchemotherapy Retroperitoneal Lymph Node Dissection in Patients With Nonseminomatous Testicular Cancer: A Single Center Experiences

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Background: Testicular cancer accounts for about 1 - 1.5% of all malignancies in men. Radical orchiectomy is curative in 75% of patients with stage I disease, but advanced stage with retroperitoneal lymph node involvement needs chemotherapy. All patients who have residual masses ≥ 1 cm after chemotherapy should undergo postchemotherapy retroperitoneal lymph node dissection (PC-RPLND).

Objectives: Treatment of advanced nonseminomatous testicular cancer is usually a combination of chemotherapy and surgery. We described our experience about postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) in our center.

Patients and Methods: In a retrospective cross-sectional study between 2006 and 2011, patients with a history of postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) in Imam Khomeini hospital were evaluated. All patients had normal postchemotherapy serum tumor markers and primary nonseminomatous cancer. We reviewed retrospectively clinical, pathological, and surgical parameters associated with PC-RPLND in our center.

Results: Twenty-one patients underwent bilateral PC-RPLND. Mean age was 26.3 years (ranged 16 - 47). Mean size of retroperitoneal mass after chemotherapy was 7.6 cm. Mean operative time was 198 minutes (120 - 246 minutes). Mean follow-up time was 38.6 months. Pathologic review showed presence of fibrosis/necrosis, viable germ cell tumor and teratoma in 8 (38.1%), 10 (47.6%) and 3 (14.28%) patients, respectively. One patient in postoperative period of surgery and three patients in two first years after surgery were expired. Of 17 alive patients, only two (11.8%) had not retrograde ejaculation.

Conclusions: PC-RPLND is one the major operations in the field of urology, which is associated with significant adjunctive surgeries. In appropriate cases, PC-RPLND was associated with good cancer specific survival in tertiary oncology center.

Keywords: Teratoma; Germ Cell Tumor; Tumor

1. Background

Testicular cancer accounts for about 1% - 1.5% of all malignancies in men and 5% of urological tumors in general. A report published in 2008 showed that 6.15% of urological cancers in Iran contributed to testicular neoplasia (1). Radical orchiectomy is curative in 75% of patients with stage I disease, but in advanced stages with retroperitoneal lymph node involvement is not sufficient and necessitates chemotherapy. All patients with residual masses ≥ 1 cm after chemotherapy should undergo postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) (2). Complication rates following PC-RPLND are higher than the primary RPLND ranging from 7% to 30% with a mortality rate of about 1% (3). Nephrectomy and vascular surgery are the most frequent adjunctive surgeries in patients undergoing PC-RPLND (4-6). Some authors recommend

tumorectomy-only and modified template RPLND to reduce the risk of retrograde ejaculation and improve the quality of life, but at the time the standard surgical therapy is full-bilateral RPLND and if feasible is nerve sparing. It has been shown that in at least 7% - 32% of patients, teratoma or viable germ cell tumor (GCT) are discovered outside the boundaries of a modified template dissection and these may remain if tumorectomy-only is applied (7-9).

Histological findings of retroperitoneal residual lesions may be necrosis, teratoma or viable GCT. Teratoma is considered as chemoresistant tumor; therefore, surgery is the mainstay treatment in patients with teratoma in PC-RPLND specimen, while variable GCT requires adjuvant chemotherapy. Therefore, surgery not only determines the next step in the treatment, but also

has diagnostic and therapeutic role. Variable GCT and teratoma are often present in 10% - 20% and 35% - 55% of PC-RPLND specimen, respectively. Complete necrosis in the residual mass and complete resection are two important prognostic factors. It has been investigated that complete resection after primary chemotherapy would increase long-term disease free survival to 95%. Overall long-term relapse rate in these patients is 6% - 9% (10). In a retrospective review, we analyzed medical records and treatment-related outcomes of patients who underwent PC-RPLND in our center along with reviewing relevant surveys.

2. Objectives

Treatment of advanced nonseminomatous testicular cancer is usually a combination of chemotherapy and surgery. We described our experience about postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) in our center.

3. Patients and Methods

In a retrospective cross-sectional study between 2006 and 2011, medical records of patients with history of PC-RPLND in Imam Khomeini hospital (Tertiary oncology center) were studied. Patients with primary nonseminomatous tumor and history of chemotherapy (three or four cycles of BEP) were enrolled in our study. Patients with primary seminomatous tumor or incomplete resection were excluded. All patients had normal tumor markers preoperative. In our center, PC-RPLND was performed via a transperitoneal bilateral dissection approach by two experienced uro-oncologist. Two closed-suction drains left in place until drainage volume reached less than 50 mL. In our center, patients are reevaluated six weeks after completeness of chemotherapy and surgery was performed if the residual mass was equal or more than 1 cm. Factors including age, time of hospitalization, primary pathology, retroperitoneal lesion size (according to the greatest dimension in CT-scan), permanent pathology, associated surgery and its complications and survival of patients in follow-up visits were recorded. This research was performed in accordance with the declaration of Hel-

sinki and subsequent revision and approved by the ethical committee of Tehran University of Medical Sciences.

4. Results

We gathered information of 21 patients with a mean age of 26.3 ± 7.2 years (ranged 16 - 47 years). The primary tumor was in the right and left testes in 14 and 7 patients, respectively. (R/L = 2). One case had a history of right orchiopey at age five, with primary tumor of mixed embryonal and yolk sac tumor on the same side. In other cases, primary testicular tumor pathology was mixed embryonal, yolk sac tumor and teratoma. The mean hospitalization was 4.5 days (ranged 3 - 7 days). The mean follow-up was 38.57 ± 7.6 months (ranged 10 - 56 months) and average tumor size after chemotherapy was 76 ± 23 mm (ranged 27 - 178 mm). Mean operative time was 168 ± 24.7 minutes (ranged 120 - 246 minutes). Seven patients (33.3%) received additional surgery as follows; three patients required vascular procedures including caval resection in two and aortic resection and substitution in one. Four patients (19.04%) required nephrectomy (3/1, left/right kidney). A patient with a 68-mm mass adjacent to the left renal hilum showed diminished nephrogram and atrophy during postoperative follow-up. Five patients (20.83%) needed transfusion. One patient required re-exploration for bleeding and underwent nephrectomy due to renal blood vessels injury and died on postoperative day.

Three deaths occurred during two years after surgery. One patient had pulmonary metastasis, the second from pulmonary and brain metastases and the last from retroperitoneal recurrence with multiple metastases. Among 17 alive patients (80.95%), antegrade ejaculation was preserved in only two patients (11.76%) Demographics and peri-operative characteristics of patients are shown in Table 1. In two years after surgery, recurrence was experienced by two patients; both had primary pathology of teratoma. They underwent operation for the second time.

Final retroperitoneal pathology revealed necrosis in 8 (38.09%), teratoma in 10 (47.61%) and viable germ cell tumor in 3 (14.28%) patients. The characteristics and perioperative variables of patients were stratified according to their final pathology (Table 2).

Table 1. Demographics and Perioperative Characteristics of Patients

Variables	Pathology		
	Teratoma (N = 10)	Viable GCT (N = 3)	Fibrosis and Necrosis (N = 8)
Age range, y	28 (19 - 41)	25.8 (19 - 47)	24.6 (16 - 38)
Tumor size range, mm	91.4 (68 - 178)	72.3 (46 - 124)	64.3 (27 - 74)
Mean operative time range, min	180 (150 - 246)	170 (150 - 190)	154 (120 - 170)
Adjunctive vascular surgery, no	2	1	0
Adjunctive nephrectomy	3	1	0
Survival (alive patients/total)	10/10	0/3	8/8
Retrograde ejaculation (patients/total)	10/10	3/3	6/8

Table 2. Summary of Results Regarding the Pathology Findings of Postchemotherapy RPLND ^a

Literature	Pathology		
	Necrosis	Teratoma	Viable Germ Cell Tumor
Heidenreich et al. (11)	65.9	12.4	21.6
Aprikian et al. (12)	45	42.5	12.5
Djaladat et al. (6)	28	39	32
Oldenburg et al. (13)	67	26	7
Albers et al. (14)	35	34	31
Ozen et al. (9)	33.3	45.3	21.3

^a The values are presented as %.

5. Discussion

Chemotherapy is the optimal treatment for testicular cancer with retroperitoneal lymph node involvement. All patients with residual masses equal to or more than 1 cm after chemotherapy should undergo PC-RPLND. In this study, necrosis contributed to 38.1% of histologic findings, teratoma 47.6% and viable GCT the remaining 14.3%. Our results support the findings of other studies.

Several studies reported different prevalence of teratoma, necrosis and viable GCT Table 2. Post chemotherapy RPLND was first reported over 40 years ago by Comisarow et al. They recommended PC-RPLND after chemotherapy or relapse following primary RPLND (15).

Improvements in chemotherapy techniques have led to lesser incidence of viable germ cell tumor (GCT) presence in PC-RPLND specimen and more fibrosis and necrosis, while no significant change in the rate of teratoma has been noted (16).

In some studies, patients with necrosis/fibrosis in final pathology were alive. It provokes this question whether we can predict this pathology and avoid major surgery. In the presence of only necrosis in final pathology of residual masses, surgery would not be helpful. Therefore, a number of researchers attempted to predict the presence of necrosis in residual masses. Different predictive factors of necrosis have been identified. These items were level of α FP before chemotherapy, primary size of retroperitoneal mass, size of residual mass after chemotherapy and degree of tumor shrinkage after chemotherapy (14, 17).

Although several other studies showed that size is not a predictive parameter alone and 20% - 33% of patients with residual Masses equal or less than 2 cm had vital tumors (13, 18). Finally, suggested models could not predict necrosis in residual specimen with reliable accuracy and RPLND remains necessary for residual tumors.

In our study, we performed bilateral RPLND associated with approximately 90% retrograde ejaculation. Although this complication can compromise quality of life of patients, controversy still exists regarding the benefit of modified PC-RPLND. Numerous attempts have been made to limit boundaries of dissection and perform RPLND within a restricted template without

compromising gains in survival or increasing retroperitoneal relapse rates. Appropriate patient selection criteria have been established for modified template PC-RPLND, which in summary includes intraoperative frozen section analysis of residual mass demonstrating necrosis, low volume tumor, left-sided primary tumor and small residual mass (12, 19). On the other hand, it has been proven that greater diameter of residual mass is associated with higher possibility of extratemplate metastasis, for example size of lesion 1 cm and 5 cm lead to 8% and 25% of extratemplate involvement, respectively. Overall, it has been shown that at least 7% - 32% of patients have teratoma or viable GCT outside boundaries of a modified template dissection. Therefore, even if modified template RPLND is applicable in some situations, full-bilateral RPLND remains the standard of care (8, 19). Another option, suggested as an investigation to preserve antegrade ejaculation is nerve sparing PC-RPLND with preserved ejaculatory function in 75% of patients (20, 21).

In postoperative period, one of our patients died due to bleeding. The most common additional surgery was nephrectomy performed in 19% of patients. Three patients underwent aorta resection and graft interposition and caval resection. Totally, complications occurred in 20% - 35% of patients and mortality rate in 0.8% - 1%. In case of tumor extension into the renal hilum, nephrectomy is inevitable and pathology of nephrectomy specimen is proved to be involved in more than a half of patients (4). In several studies nephrectomy was performed in 5% - 19% of cases (4-6) and is known as the most common additional procedure followed by PC-RPLND. Spitz and colleagues retrospectively reviewed 1790 patients and reported the overall incidence of nephrectomy was 14.8% (265 of 1790) at PC RPLND. They showed that a higher incidence is observed in patients with mass size more than 10 cm and histology of viable GCT rather than teratoma and necrosis (22). IVC involvement that requires resection is seen in 7% - 11% (22, 23) and usually tumor encasement of the inferior vena cava with or without invasion is the main reason of IVC resection.

In a study performed on 85 patients, Djaladat et al. reported additional surgery requirement in 28 patients (32.94%). The most common adjuvant surgeries were nephrectomy and vascular procedures (29% of 33% of adjuvant surgeries). They suggested excellent outcomes with low operative morbidity and mortality will be obtained when experienced surgeons perform such aggressive operations (6). Therefore, it seems that PC-RPLND must be performed in a well-equipped center with vascular surgeon and urologist.

Several factors are correlated with prognosis of patients undergoing PC-RPLND including number of dissected lymph nodes, complete necrosis in residual mass, complete resection, aggressive surgery in case of teratoma (24, 25). In this study, the mean follow-up was 38 months, 17 patients (80%) were alive without any evidence of active disease. Three patients in follow-up died due to brain and liver metastasis with final pathology of viable germ cell tumor and two additional chemotherapy cycles. This finding is not statistically reportable because of low sample volume, but shows that viable germ cell tumors have worse outcome. Two patients with teratoma had recurrence who underwent salvage surgery indicating the importance of complete resection in PC-RPLND. Fizazi et al. reviewed the outcome of 238 patients and showed that the 5-year overall survival rate is more than 70% (26). Heidenreich et al. reported 10-year disease free survival rate of 70% in 71 patients. In some studies, complete resection followed by primary chemotherapy has led to long-term disease free survival rate of 95% (11).

PC-RPLND is an integral component in the management of advanced NSGCTs. PC-RPLND is one of the major operations in the field of urology which might be associated with other considerable procedures. Therefore, it is better to be performed in tertiary care referral centers.

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Authors' Contributions

All the authors were involved in operations and Alireza Ghadian and Amir Arbab contributed in analysis and writing of the manuscript.

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