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Original Article

Clinico-pathological outcomes of post- primary and salvage chemotherapy retroperitoneal lymph node dissection for mixed germ cell tumors, King Hussein Cancer Center experience

Mikst germ hücreli tümörlerde primer kemoterapi ve kurtarma kemoterapisi sonrası retroperitoneal lenf düğümü diseksiyonunun klinikopatolojik sonuçları: Kral Hüseyin Kanser Merkezi deneyimi

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ABSTRACT

Objective: We sought to characterize clinical and pathologic outcomes of advanced mixed germ cell tumors after retroperitoneal lymph node dissection for post-chemotherapy residual masses.

Material and methods: Between January 2006 and November 2015, 56 patients underwent retroperitoneal lymph node dissection (RPLND) for residual masses of greater than 1 cm after receiving either primary chemotherapy or salvage chemotherapy. Retrospective review of the patients' characteristics, clinical, pathological, and treatment outcomes were performed after institutional review board (IRB) and ethics committee approval.

Results: The mean age at diagnosis was 30 years. Ninety percent of the patients received 3-4 cycles of BEP (bleomycin/etoposide/cisplatin) as primary chemotherapy, and 29% of them salvage chemotherapy prior to lymph node dissection. The mean size of the residual masses after chemotherapy was 6 cm. The histological findings were necrosis in 30%, viable tumor in 34% and teratoma in 36% of the retroperitoneal masses. The mean time to relapse after RPLND was 11 months, out of 9 relapses, 6 were in the retroperitoneum, 1 in the lung and 1 in the kidney and 1 in the contralateral testicle.

Conclusion: Our results indicated higher incidence of viable germ cell tumor in the retroperitoneal residual masses after primary and salvage chemotherapy when compared with previously reported global incidence rates.

Keywords: Chemotherapy; lymph node dissection; mixed germ cell tumors; retroperitoneal.

ÖZ

Amaç: Kemoterapi sonrası rezidüel kitleler için retroperitoneal lenf düğümü diseksiyonu yapılan ilerlemiş mikst germ hücreli tümörlerin klinik ve patolojik sonuçlarını tanımlamaya çalıştık.

Gereç ve yöntemler: Ocak 2006 ile Kasım 2015 tarihleri arasında 56 hasta, primer kemoterapi veya kurtarma kemoterapisi sonrasında 1 cm'den daha büyük rezidüel kitleler için retroperitoneal lenf düğümü diseksiyonu (RPLDD) ameliyatı olmuştur. Kurumsal inceleme kurulu ve etik kurulun onayından sonra hastaların klinik özellikleri, klinik, patolojik ve tedavi sonuçları geriye dönük olarak gözden geçirilmiştir.

Bulgular: Tanı anında yaş ortalaması 30 idi. Hastaların %90'ı primer kemoterapi olarak 3-4 kür BEP (bleomisin/etopozit/sisplatin) ve %29'u lenf düğümlerinin diseksiyonundan önce kurtarma kemoterapisi almıştı. Kemoterapi sonrası rezidüel kitlelerin ortalama büyüklüğü 6 cm idi. Retroperitoneal kitlelerdeki histolojik bulgular %30'unda nekroz, %34'ünde canlı tümör hücresi ve %36'sında teratom şeklindeydi. RPLDD'den sonra tümör nüksüne kadar ortalama 11 ay geçmişti. Dokuz tümör nüksü retroperitonda (n=6), akciğerde (n=1), böbrekte (n=1) ve diğer testiste (n=1) idi.

Sonuç: Bulgularımız primer ve kurtarma kemoterapisinden sonra retroperitoneal rezidüel kitlelerde canlı germ hücreli tümörün bulunma insidansının daha önce uluslararası yayınlarda raporlananlara göre yüksek olduğunu göstermiştir.

Anahtar sözcükler: Kemoterapi, lenf düğümü diseksiyonu; mikst germ hücreli tümörler; retroperitoneal.

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Introduction

Testicular cancer is the most common solid malignancy in young men and most of the patients are diagnosed during early stages in the Western hemisphere.[1] Since 1970s, cisplatin-based chemotherapy has resulted in excellent treatment response and typically, most patients have been treated with 3 or 4 courses of cisplatin- based chemotherapy. The etiology and pathogenesis of testicular cancer remain widely unknown and flow of data is mostly coming from western countries. However, limited data are available about testicular cancer behavior and response to treatment in other parts of the world. A growing worldwide incidence has been described and it has been already pointed out that the presentation of the disease is changing.

The aim of the present study was to evaluate the clinical and pathologic outcomes after chemotherapy for non-seminomatous mixed germ cell tumors in a tertiary referral King Hussein Cancer Center center in the Middle East.

Material and methods

After institutional review board (IRB) approval, the research protocol was submitted to the ethics committee of our center for consideration, comment, guidance and approval according to the laws and regulations of the country and the international norms and standards before the study onset. Retrospective review of testicular cancer data was performed for patients who underwent post-chemotherapy (primary and salvage chemotherapy) and retroperitoneal lymph node dissection for mixed germ cell tumor between January 2006 and November 2015. Written approval was obtained from each patient before the operation. Clinical and pathologic data were reviewed for patients' demographics, retroperitoneal residual mass size, recurrence and mortality rates during follow-up period, histopathology of the orchiectomized specimens and retroperitoneal mass. Histopathologically residual retroperitoneal masses were classified based on the presence of fibrosis/ necrosis, teratoma or viable tumor. Then, viable tumor was further characterized as embryonal, choricarcinoma, yolk sac or seminoma. The size of the residual masses was estimated based on the findings of CT scan performed prior to surgery and largest diameter of the mass was taken into consideration during analysis. Patients with pure seminoma in the testicular or in the RPLND specimens according to pathology reports were excluded from the study. Two patients lost to follow up immediately after RPLND. No age limit was considered during the selection process. Relevant statistical analysis was done in the department of statistics of our center. The mean, minimum, and maximum values were calculated for a set of variables which are included in Tables 1, and 2. Time intervals between the RPLND and the last follow- up appointment were calculated in months for all patients. Since this investigation was a retrospective study without any control group, advanced comparative statistical analyses were not performed.

Table 1. Demographic characteristics of the patients

Variable	No. of patients (%)	Mean	Range
No. of patients	56		
Mean age at RPLND: years (range)	30		
Median follow-up period: months (range)	34		
No. of chemotherapy cycles prior to PC-RPLND		4	0-5
Greatest dimension of retroperitoneal mass (cm)		6	1-14
Recurrence rate	9 (16)		
Mortality rate	4 (7)		
Patients with prior chemotherapy (n)			
First-line (BEP) (primary)	40 (71)		
Second-line (TIP, VeLP) (salvage)	16 (29)		

Results

The mean age of the patients at diagnosis was 30 years and the median follow-up period was 34 months (Table 1). Between January 2006 and November 2015, 56 patients underwent retroperitoneal lymph node dissection (RPLND) for residual masses either after primary chemotherapy (40 patients) or after salvage chemotherapy [vinblastine, ifosfamide, and cisplatin (VeIP) or paclitaxel, ifosfamide and cisplatin (TIP)]. Ninety percent of the patients received 3-4 cycles of BEP (bleomycin/etoposide/cisplatin) as primary chemotherapy (Table 1). Meanwhile, 16 patients (29%) received salvage chemotherapy. The mean size of the residual masses after chemotherapy was 6 cm (1-14 cm). Histopathological examination of the orchiectomy materials revealed the presence of mixed germ cell, pure embryonal, pure yolk sac tumors and teratoma in 82, 7, 7, and 4 % of the specimens, respectively (Table 2).

The histological findings of the residual masses were reported as necrosis in 30%, viable tumor in 34% and teratoma in 36% of the specimens. In addition, histopathology reports of the residual masses harvested from the patients who had undergone salvage chemotherapy indicated presence of necrosis in 25%, viable tumor in 44% and teratoma in 32% of the specimens, respectively (Table 2).

During follow-up period 9 patients had relapse. The mean time to relapse after surgery was 11 months, The relapses were detected in

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Table 2. Tumor demographics

Variable	No. of patients (%)
Histology of testicular primary tumor	
Mixed	46 (82)
Embryonal	4 (7)
Yolk sac	4 (7)
Teratoma	2 (4)
Histology of retroperitoneal lymph nodes	
Teratoma	20 (36)
Viable tumor	19 (34)
Fibrosis/necrosis	17 (30)
In salvage chemotherapy	16
Viable tumor	7 (44)
Fibrosis	4 (25)
Teratoma	5 (31)
In primary chemotherapy	40
Viable tumor	12 (30)
Fibrosis	13 (33)
Teratoma	15 (38)

the retroperitoneum (n=6), in the lung (n=1), in the kidney (n=1) and in the contralateral testicle (n=1) (Table 3). All patients who had relapse, had undergone surgery after salvage chemotherapy. Four patients who had received salvage chemotherapy exited, and the mean time to death was 27 months after surgery.

Discussion

Testicular germ cell tumor is the most common solid tumor in men between the ages of 15 and 35 in the United States.[1] Multimodality approach in the treatment has been used and resulted in significant improvement in cure of the disease with 5-year survival rates of more than 90 percent.[2,3] RPLND is the standard of care in the management of patients with testicular germ cell tumors, who have residual masses after chemotherapy and salvage chemotherapy. RPLND provides accurate pathologic staging and predicts further management for patients who have residual viable tumors.[4] Classically, pathological examination of residual masses in previous studies revealed findings of necrosis or fibrosis in 40% to 50%, teratoma in 35% to 40% and viable malignant cells in 10% to 15% of the patients.[5]

Present study has indicated incidence rates of necrosis, viable tumor, and teratoma as 30, 34, and 36% which are slightly higher than those previously reported. Late presentation with advanced stage was characteristic feature of this study supported by large mean size of the residual masses approaching to 6 cm in diameter. As expected, incidence of viable tumor after salvage chemotherapy was higher (44%). Similar data are coming from a region where the incidence of testicular cancer is presumed to

Table 3. Pateints who developed relapse

Age	Size of the largest residual mass (cm)	Pathology of the retroperitonium	Site of relapse (RPLN/lung)	Outcome (dead/alive)	Time interval between RPLAND and last F/U (days)
31	3	Nonseminomatuous GCT	Retroperitoneal lymph nodes	Dead	12
37	5	Seminoma	Retroperitoneal lymph nodes	Dead	46
35	2.6	Mature epithelial cell component (skin) and benign columnar epithelium in addition to hyalinized acellular tissue	Retroperitoneal lymph nodes	Alive	2
23	5	Columnar epithelium, cartilage and immature neural tissue	Retroperitoneal lymph nodes	Alive	13
17	2	Right para-aortic lymph node free of tumor (0/6)	Retroperitoneal lymph nodes	Alive	32
26	5	Embryonal carcinoma, yolk sac and mature teratoma	Retroperitoneal lymph nodes	Alive	50
18		Metastatic tumor composed of yolk sac tumor, embryonal carcinoma and foci of mature teratoma	Kidney and ureteral wall	Dead	27
43	1	Metastatic mixed germ cell tumor (90% seminoma and 10% embryonal carcinoma)	Left testis	Alive	4
40	11	Teratoma (mature glandular, squamous epithelium and cartilage	Lung	Dead	24

be lower than that of Europe and North America. Limited comparative data about germ cell tumor behavior is available from Middle East. Al Othman et al.[6], reported 16 male patients who had RPLND after chemotherapy and they reported incidence rates of 13, 50, and 37% for the presence of viable GCT, fibrosis, and teratoma, respectively.

Reliable predictive model of the pathology of residual masses after chemotherapy is yet to be established. Thus, appropriate approach to residual masses following chemotherapy remains a controversial issue. However, potential advantage of avoiding further chemotherapy in cases of necrosis and cure of the patient with teratoma outweigh presumably, unnecessary surgery in case of necrosis/fibrosis.[7,8]

Steyerberg et al.[9] created a multivariate logistic model to predict variables for necrosis in the residual retroperitoneal masses based on data from 556 patients who had undergone post- chemotherapy RPLND and they found normal tumor markers, elevated lactate dehydrogenase levels, absence of teratoma in the orchiectomy specimens, small-sized retroperitoneal masses before application of chemotherapy, and significant reduction in retroperitoneal mass size following chemotherapy for specimens with necrosis but also a 20% false- negative rate which was considered too high. Incomplete resection of residual retroperitoneal masses, the size of residual retroperitoneal masses and the finding of teratoma and viable tumor at RPLND were suggested as independent predictors of the disease progression and relapse.[10] For non-seminomatous germ cell tumor, residual mass of 1 cm or more is a conventional indication for surgery after chemotherapy. Still several studies have shown that relatively small size of residual masses (<2 cm) is considered as one of the most significant predictor for the presence of necrosis in RPLND specimens retrieved after chemotherapy.[9]

Although absence of teratoma in the primary tumor has been suggested as predictor of absence of teratoma in the retroperitonum, our data indicated that 30% of the patients with teratoma in the retroperitoneal residual masses had no evidence of teratoma in the primary tumor.[7] In spite of benign nature of teratoma, untreated disease may have a lethal potential due to progressive local growth around vital structures or malignant transformation and its classical unresponsiveness to conventional cisplatin-based chemotherapy regimens. Thus, early resection of teratoma in the retroperitoneum after chemotherapy provides excellent prognosis and avoids the complications of late surgery.[8,11]

In the absence of a reliable model to predict the pathology of residual masses after chemotherapy, the role of some imaging techniques has been investigated. FDG-PET (18-Fluoro-deoxyglucose positron emission tomography) scan prior to surgery but after chemotherapy has been investigated, and found that FDG-PET accurately identified patients who had residual necrosis/fibrosis, teratoma or viable cancer post- induction chemotherapy. However, FDG-PET does not offer any benefit over CT in primary staging performed with the intention of discriminating the nature of the residual masses. Although a positive PET scan is highly suggestive of residual viable cancer, false-negative rates of up to 40% have been reported in a prospective trial by Oechsle et al.[12] In contrary, PET scan has more utility in patients with disseminated seminoma treated with chemotherapy where it has a higher sensitivity and specificity for the determination of residual viable disease.[13]

Although the germ cell tumor is highly responsive to chemotherapy, the success rate of chemotherapy is lower after failure of the first- line chemotherapy. The present study revealed 16% relapse rate after chemotherapy and surgery during the follow-up period with a mean time to recurrence of 11 months and all relapses occurred in patients who received surgery after salvage chemotherapy with outcomes congruent with previously reported data. Previous studies reported a relapse rate ranging between 6 and 14%.[14,15] The present study has its limitations. First, the limitations are inherent to retrospective analysis. Second, additional follow-up may affect long-term oncologic or survival outcomes. Third, the number of patients is small compared to large cohorts previously reported from western hemisphere. However, this study provides some insight into testicular cancer in a region where very limited flow of data is available.

In conclusion, our results reveals higher incidence of viable tumor in the retroperitoneum after primary and salvage chemotherapy in comparison with previously reported data.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of King Hussein cancer center.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11-30. [CrossRef]
2. Foster R, Bihrle R. Current status of retroperitoneal lymph node dissection and testicular cancer: when to operate. Cancer Control 2002;9:277-83.
3. Beck SD, Foster RS. Long-term outcome of retroperitoneal lymph node dissection in the management of testis cancer. World J Urol 2006;24:267-72. [CrossRef]
4. Motzer RJ, Jonasch E, Agarwal N, Beard C, Bhayani S, Bolger GB, et al. Testicular Cancer, Version 2.2015. J Natl Compr Canc Netw 2015;13:772-99.
5. Vergouwe Y, Steyerberg EW, Foster RS, Sleijfer DT, Fossa SD, Gerl A, et al. Predicting retroperitoneal histology in postchemotherapy testicular germ cell cancer: a model update and multicentre validation with more than 1000 patients. Eur Urol 2007;51:424-32. [CrossRef]
6. Al Othman K, Al Hathal N, Mokhtar A. Predictors of viable germ cell tumor in postchemotherapeutic residual retroperitoneal masses. Urol Ann 2014;6:27-30. [CrossRef]
7. Carver BS, Bianco FJ, Jr., Shayegan B, Vickers A, Motzer RJ, Bosl GJ, et al. Predicting teratoma in the retroperitoneum in men undergoing post-chemotherapy retroperitoneal lymph node dissection. J Urol 2006;176:100-4. [CrossRef]
8. Fizazi K, Tjulandin S, Salvioni R, Germa-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.
9. Steyerberg EW, Keizer HJ, Fossa SD, Sleijfer DT, Toner GC, Schraffordt Koops H, et al. Prediction of residual retroperitoneal mass histology after chemotherapy for metastatic nonseminomatous germ cell tumor: multivariate analysis of individual patient data from six study groups. J Clin Oncol 1995;13:1177-87.
10. Shayegan B, Carver BS, Stasi J, Motzer RJ, Bosl GJ, Sheinfeld J. Clinical outcome following post-chemotherapy retroperitoneal lymph node dissection in men with intermediate- and poor-risk nonseminomatous germ cell tumour. BJU Int 2007;99:993-7. [CrossRef]
11. Motzer RJ, Amsterdam A, Prieto V, Sheinfeld J, Murty VV, Mazumdar M, et al. Teratoma with malignant transformation: diverse malignant histologies arising in men with germ cell tumors. J Urol 1998;159:133-8. [CrossRef]
12. Oechsle K, Hartmann M, Brenner W, Venz S, Weissbach L, Franzius C, et al. [18F]Fluorodeoxyglucose positron emission tomography in nonseminomatous germ cell tumors after chemotherapy: the German multicenter positron emission tomography study group. J Clin Oncol 2008;26:5930-5. [CrossRef]
13. Hinz S, Schrader M, Kempkensteffen C, Bares R, Brenner W, Krege S, et al. The role of positron emission tomography in the evaluation of residual masses after chemotherapy for advanced stage seminoma. J Urol 2008;179:936-40. [CrossRef]
14. Einhorn LH, Williams SD, Loehrer PJ, Birch R, Drasga R, Omura G, et al. Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. J Clin Oncol 1989;7:387-91.
15. Horwich A, Sleijfer DT, Fossa SD, Kaye SB, Oliver RT, Cullen MH, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. J Clin Oncol 1997;15:1844-52.