Original Article

Predictors of viable germ cell tumor in postchemotherapeutic residual retroperitoneal masses

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Abstract

Objective: The aim of this study was to identify predictors of viable germ cell tumor (GCT) in postchemotherapeutic residual retroperitoneal masses.

Materials and Methods: The pertinent clinical and pathologic data of 16 male patients who underwent postchemotherapeutic retroperitoneal lymph node dissection (PC-RPLND) at King Faisal Specialist Hospital and Research Centre between 1994 and 2005 were reviewed retrospectively. It was found that all patients received cisplatin-based chemotherapy for advanced testicular GCT.

Results: Out of the 16 male patients, 2 (13%), 8 (50%), and 6 (37%) had viable GCT, fibrosis, and teratoma, respectively. Ten (10) of the patients with prechemotherapeutic S1 tumor markers did not have viable GCT, and two of the six patients who had prechemotherapeutic S2 tumor markers have viable GCT. All tumor marker levels normalized after chemotherapy even in patients with viable GCT. Four patients had vascular invasion without viable GCT. Furthermore, four patients had more than 60% embryonal elements in the original pathology, but only 1 had viable GCT at PC-RPLND. Four of the five patients with immature teratoma had teratoma at PC-RPLND but no viable GCT; however, out of the four patients with mature teratoma, one had viable GCT and two had teratoma at PC-RPLND. Of the two patients with viable GCT, one had 100% embryonal cancer in the original pathology, prechemotherapeutic S2 tumor markers, history of orchiopexy, and no vascular invasion; the other patient had yolk sac tumor with 25% embryonal elements and 40% teratoma in the original pathology, and prechemotherapeutic S2 tumor markers.

Conclusion: None of the clinical or pathological parameters showed a strong correlation with the presence of viable GCT in PC-RPLND. However, patients with ≥S2 may be at higher risk to have viable GCT. Further studies are needed to clarify this.

Key Words: Chemotherapy, germ cell tumor, predictor, retroperitoneal lymph node dissection

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INTRODUCTION

Cisplatin-based chemotherapy is highly effective for treating advanced nonseminomatous testicular germ cell tumor (GCT) and, thus, decreases the morbidity from this disease. After chemotherapy, residual retroperitoneal lesions may be detected by computed tomography.[1-6] Postchemotherapeutic retroperitoneal lymph node dissection (PC-RPLND) is the standard approach to remove masses of 10 mm or larger and perform pathologic investigation.[7-9] These masses may be completely benign (necrosis or fibrosis) in 40-50% of the patients or having teratoma elements in 30-40% of the patients. Only 10-20% of patients have viable cancer.[10]

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Resection of benign tissue has no therapeutic value. Unnecessary resection exposes the patient to the risk of complications, and is expensive. Several patient's characteristics have been identified as predictors of residual retroperitoneal masses, such as histologic findings, levels of three serum tumor markers (alpha fetoprotein [AFP], human chorionic gonadotropin [hCG], and lactate dehydrogenase [LDH]), presence of teratoma elements in the primary tumor, size of the residual mass measured by CT, and change in the mass size induced by chemotherapy.[1,11] Clinical trials have been conducted to develop a prognostic model incorporating all these predictors. For example, meta-analysis for variable factors and two similar cohorts from the United States and Europe have been used for model development and validation.[1,12] Therefore, we aimed to identify the predictors of viable GCT in postchemotherapeutic residual retroperitoneal masses.

MATERIALS AND METHODS

The medical records of 16 male patients who underwent PC-RPLND at King Faisal Specialist Hospital and Research Centre between 1994 and 2005 were reviewed retrospectively. All the patients received cisplatin-based chemotherapy for advanced testicular GCT before RPLND. Resected masses containing necrosis, teratoma, or viable GCT were included in the analysis. The following clinical and pathologic parameters pertinent to viable GCT in the residual retroperitoneal masses were examined: presence of viable GCT, fibrosis, or teratoma; levels of tumor markers before and after chemotherapy; primary histologic diagnosis; presence of vascular invasion; type of chemotherapy, history of cryptorchidism, and the original tumor stage and elements.

RESULTS

The mean age of the patients was 25 years (range, 16-41 years). Only one patient had a history of cryptorchidism. Figure 1 shows the results of the pathologic examination, and Table 1 shows the tumor staging. Of the 16 patients, 2 (13%) had viable GCT, 8 (50%) had fibrosis or necrosis, and 6 (37%) had teratoma in the resected masses.

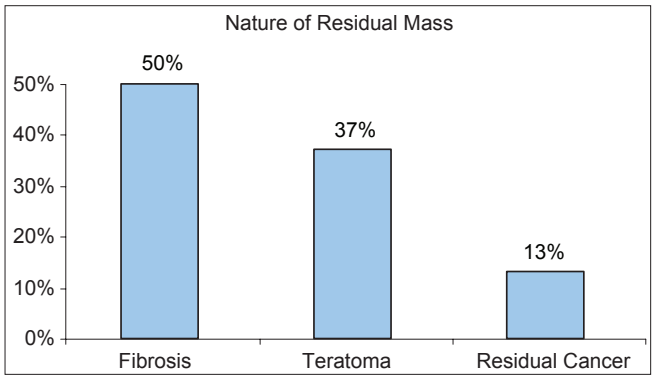

Figure 1: Pathologic finding after PC-RPLND: Postchemotherapeutic retroperitoneal lymph node dissection

All the patients had elevated tumor marker levels before chemotherapy. 10 (62.5%) and 6 (37.5%) patients had prechemotherapeutic S1 and S2 tumor markers, respectively. However, the tumor marker levels normalized after chemotherapy, even in the patients with viable GCT. None of the patients with prechemotherapeutic S1 tumor markers had viable GCT at the time of PC-RPLND, but two (33.3%) of the six patients with prechemotherapeutic S2 tumor markers had viable GCT at this time. Table 2 shows a comparison of the prechemotherapeutic tumor markers and pathologic findings.

Vascular invasion was found in four patients (25%); most of these patients had fibrosis at PC-RPLND, none had viable GCT, and only one had teratoma. Six patients (56.2%) had embryonal elements in the original pathology, which were less than 40% in five patients and more than 60% (pure embryonal cancer) in one patient.

Nine patients had teratoma in the original pathology (orchiectomy specimen). Five (5) of these patients had immature teratoma; pathologic examination after PC-RPLND revealed that four patients had mature teratoma and one had fibrosis or necrosis. Among the remaining four patients who had mature teratoma in the original pathology, two had mature teratoma, one had fibrosis, and one had yolk sac tumor at the pathologic examination after PC-RPLND.

Of the two patients with viable GCT at PC-RPLND, one had embryonal cancer with prechemotherapeutic S2 tumor markers, 100% embryonal elements in the original pathology, history of orchiopexy, and no vascular invasion. The second patient had yolk sac cancer with prechemotherapeutic S2 tumor markers, 25% embryonal elements in the original pathology, and 40% mature cancer in the original pathology.

Table 1: Tumor staging

Stage	*N* (%)
T1	7 (43.75)
T2	2 (12.5)
T3	1 (6.2)
Undetermined	6 (37.5)

Table 2: Prechemotherapeutic tumor markers according to the pathologic findings at the PC-RPLND

Marker	Fibrosis	Teratoma	Viable tumor
S1	6 (60)	4 (44)	–
S2	2 (33.3)	2 (33.3)	2 (33.3)

The values represent n (%), PC-RPLND: Postchemotherapeutic retroperitoneal lymph node dissection

DISCUSSION

Predicting the pathologic findings of postchemotherapeutic residual retroperitoneal masses and the need for resection can prevent unnecessary major surgery and avoid treatment-related morbidity. The decision to proceed with PC-RPLND is largely dependent on the radiologic finding of 1 cm or larger residual retroperitoneal masses after chemotherapy.

The European Organization for Research and Treatment of Cancer (EORTC) and the Medical Research Council (MRC) developed a prediction model containing three dichotomous and three continuous predictors.[1] The dichotomous predictors are the presence of teratoma elements in the primary tumor (no versus yes), determined as teratoma differentiated or malignant teratoma intermediate, and the prechemotherapeutic levels of AFP and hCG (normal versus elevated). The continuous predictors are the prechemotherapeutic level of LDH (expressed as the natural logarithm of the standardized value), square root of the maximum diameter of the residual mass measured on CT in millimeters after chemotherapy, and change in the diameter per 10% induced by chemotherapy.[1,2] This model may help refine the selection of candidates for resection. Resection may be withheld from a subgroup of patients with enlarged postchemotherapeutic lymph nodes and high probability of benign tissue, whereas patients with normal-sized postchemotherapeutic lymph nodes and relatively low probability of benign tissue may benefit from resection.

In a quantitative overview of 996 PC-RPLNDs, predictors were analyzed for each study and combined in a pooled odds ratio (OR). The predictors of necrosis were teratoma-negative primary tumor (OR = 5.1), normal tumor markers before chemotherapy (AFP, OR = 2.8; hCG, OR = 1.9; both AFP and hCG, OR = 5.7), small postchemotherapeutic abdominal mass (≤20 mm, OR = 3.7), large shrinkage (≥90%, OR = 3.1), and lung resection versus abdominal resection (OR = 1.7). Cancer was found in only 4% of the residual retroperitoneal masses measuring ≤20 mm^3.

Donahue *et al.* reported that men with no teratoma in the primary orchiectomy specimen undergoing PC-RPLND have greater than 90% volume reduction in retroperitoneal metastasis. None of the 15 patients in their series had teratoma or viable GCT in the resected specimens. They concluded that PC-RPLND could safely be omitted in these patients.[4]

Carver *et al.* conducted a study to predict teratoma in the retroperitoneum in men undergoing PC-RPLND and concluded that significant variables predictive of teratoma includes teratoma in the primary tumor, yolk sac in the primary tumor, relative change in nodal size before and after chemotherapy, and no requirement for second-line chemotherapy.[5] Multiple predictive clinical variables should be used to identify patients at risk for teratoma in the retroperitoneum after chemotherapy for advanced nonseminomatous testicular GCT. Dexeus *et al.* analyzed the clinical and radiologic correlation of retroperitoneal metastasis from GCT and reported that increase in the size of retroperitoneal metastasis by CT predicts an increased likelihood of a residual mass after chemotherapy irrespective of whether the tumor pathology involves teratoma or embryonal cancer.[6,8]

In the current study, despite the small sample size, the pathologic findings after PC-RPLND were similar to those reported in the literature (13% viable GCT, 50% fibrosis, and 37% teratoma). The higher the tumor marker levels before chemotherapy, the more likely is viable GCT to be found in the retroperitoneum. The two patients with viable GCT after PC-RPLND had increased prechemotherapeutic S2 tumor marker levels, although they normalized after chemotherapy. A similar finding was reported for the three dichotomous predictors in the prediction model developed by the EORTC and MRC.[1,9] Vascular invasion was found in 25% of the patients but was not related to any patient with viable GCT after PC-RPLND. Among the four patients with more than 60% embryonal elements in the primary pathology, one had viable GCT (embryonal cancer) and another had yolk sac tumor with 25% embryonal elements and 40% teratoma in the primary pathology. Mosharafa reported the strongest associations of histologic subtypes in mixed GCTs between teratoma and yolk sac tumor.[7]

Teratoma elements were found in 9 of the 16 patients (56%) in this study. Among the five patients with immature teratoma in the primary pathology, four had teratoma and one patient had yolk sac tumor in the retroperitoneum during PC-RPLND. The presence of benign or malignant teratoma in the primary tumor is a strong predictor of the presence of a tumor in the retroperitoneum, irrespective of whether it is viable GCT or teratoma.[1,9]

Although extensive predictive modeling has been attempted to define the appropriate postchemotherapeutic surgical candidates on the basis of various clinical and pathologic parameters, the accuracy of these models is controversial. To date, complete removal of all postchemotherapeutic residual masses in nonseminomatous testicular GCTs remains the standard of care and allows improved prognostication of the long-term oncologic and functional outcomes.[10] In 2008, Heidenreich *et al.* concluded that PC-RPLND represents a major part of the interdisciplinary management of advanced testicular cancer after systemic chemotherapy and complete resection of all residual masses results in a long-term disease-free survival of 95%.[11]

CONCLUSION

None of the clinical or pathological parameters who underwent the study showed a strong correlation with presence of viable GCT in PC-RPLND. However, patients with ≥S2 may be at higher risk to have viable GCT. Further studies are needed to clarify this.

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