Original Article

A retrospective analysis of patients undergoing postchemotherapy retroperitoneal lymph node dissection and metastasectomy in advanced nonseminomatous germ cell tumors

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ABSTRACT

Introduction: Postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) and metastasectomy play an important role in the management of advanced-stage nonseminomatous germ cell tumors (NSGCT). We aimed to analyze preoperative parameters that could predict postoperative histology.

Materials and Methods: We analyzed the data of 72 patients who underwent PC-RPLND and 14 patients who underwent metastasectomy after receiving cisplatin- or carboplatin-based chemotherapy for advanced stage NSGCT at our institute from 1994 to 2015. Clinical and pathological parameters such as the histology of orchidectomy, RPLND and metastasectomy, serum tumor markers, and the pre and post chemotherapy retroperitoneal lymph node size were recorded.

Results: Seventy-two patients with a mean age of 28 years underwent PC-RPLND. Of the various variables evaluated, only percentage change in nodal size was found to be statistically significant in predicting necrosis ($P = 0.004$). A decrease of 75% was found to predict the necrosis with a specificity of 100%. There was 84.6% concordance between the histology of RPLND and that of metastasectomy.

Conclusion: A 75% reduction in tumor size is highly predictive of absence of viable tumor or teratoma, however larger series are required to confirm these findings. RPLND histopathologies have a high concordance with metastasectomy histology and thus can be used as a guide to tailor further management.

INTRODUCTION

Testicular tumors are rare malignancies comprising 1.5% of all the tumors affecting men. Nearly 95% of the tumors are germ cell tumors, of which 40%–45% are nonseminomatous germ cell tumors.[1] With the recent advances in multimodality treatment, they have an excellent prognosis, with survival rates approaching to 90%. Nearly 27% of the patients present with advanced stage, and upfront chemotherapy forms the initial treatment. Based on the biochemical and radiological response, further surgical management is planned. The histology of the postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) determines further course of treatment. Current guidelines recommend additional chemotherapy for patients with viable tumor. However, this leads to unnecessary morbidity for patients with only necrosis, hence there is an ongoing search for factors that can predict necrosis in PC-RPLND specimen. Similarly, any residual metastatic masses are also surgically resected. We analyzed our PC-RPLND and metastasectomy data to correlate the respective histologies and to look for factors that can predict necrosis.

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MATERIALS AND METHODS

A retrospective analysis was performed that included all the patients who underwent PC-RPLND or metastasectomy from 1994 to 2015 for advanced-stage nonseminomatous germ cell tumors (NSGCT). The prechemotherapy tumor markers, orchidectomy, RPLND and metastasectomy histologies, and pre- and post-chemo radiological size of the retroperitoneal lymphnodes were recorded. The longest dimension of the largest node/nodal mass was measured. All patients received 3–4 cycles of bleomycin-, etoposide-, and cisplatin-based chemotherapy. The institute policy is to perform RPLND for all residual nodes of size ≥1 cm, provided the tumor markers have normalized. Patients with raised tumor markers received salvage chemotherapy. Tumor response was calculated as the percentage difference between the largest transverse nodal diameter pre- and post-chemotherapy. All statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., IBM, Chicago, USA) and Student's *t*-test was used for nonparametric variables and the Chi-square test was used for categorical variables with the level of significance set at $P < 0.05$. Receiver operating curves were drawn for significant variables.

RESULTS

A total of 72 patients underwent PC-RPLND at our center from 1994 to 2015. The clinicopathological profile of the patients is presented in Table 1. One patient underwent orchidectomy at some other center and the slides were not available for review whereas another one patient had extragonadal or burnt-out primary. Two patients had seminoma in the orchiectomy specimen, however in view of the raised serum tumor markers, they were treated as NSGCT. Nine patients had prechemotherapy imaging performed at some other center and hence the nodal size was not available for evaluation. Nearly 55.5% of the patients had Stage III disease, with lung being the most common site of metastasis, followed by liver. Of the 72 patients, 3 patients underwent postsalvage chemotherapy surgical resection, 1 underwent desperation RPLND, and 1 patient underwent surgery for recurrence in the para-aortic region. Table 2 shows the histopathological analysis of the PC-RPLND specimens.

A comparison of the PC-RPLND with the orchidectomy histology [Table 3] showed a 41.4% discordance rate. Nearly 32.1% (9 out of 29) of the patients had teratomatous elements in PC-RPLND specimen without teratoma in the orchidectomy specimen.

A univariate analysis [Table 4] was conducted to assess the variables that can predict the presence of necrosis in the PC-RPLND specimen. Only percentage change in the nodal size was found to be statistically significant. Data for change in nodal size were available for 63 patients and on performing a receiver operating characteristic (ROC) analysis, a 75% reduction in the size predicted necrosis with 100% specificity [Figure 1].

Table 5 shows clinicopathological data from patients who underwent metastasectomy. Fourteen patients

Table 1: Clinicopathological profile of the patients

Clinical parameter	Results
Number of patients	72
Mean age of the patients (years) (range)	28 (6-48)
Stage distribution, *n* (%)	
II	32 (44.4)
III	40 (55.5)
IGCCCG risk group for Stage III, *n* (%)	
Good	12 (30)
Intermediate	8 (20)
Poor	20 (50)
Place of orchidectomy, *n* (%)	
Institute	24 (33.3)
Outside	43 (59.7)
Undescended testes	5 (6.9)
Mean size of the nodes (prechemotherapy) (cm) (*n*=67)	6.6
Median marker levels (range)	
Serum AFP (ng/ml)	435 (1-110,868)
Serum β-HCG (IU/l)	339 (0-119,147)
Serum LDH (IU/l) (*n*=59)	900 (20-21,179)
Number of patients with teratomatous elements in orchidectomy specimen (*n*=70), *n* (%)	41 (58.6)
Median number of chemotherapy cycles (range)	3 (3-6)

IGCCCG=International Germ Cell Cancer Collaborative Group, AFP=Alpha-fetoprotein, HCG=Human chorionic gonadotropin, LDH=Lactate dehydrogenase

Table 2: Histological analysis of post chemotherapy retroperitoneal lymph node dissection

Clinicopathological parameter (no. of patients)	Result
Mean size of the nodes pre chemotherapy (*n*=63) (±SD) (cm)	7.05±3.81
Mean size of the nodes post chemotherapy (*n*=68) (±SD) (cm)	4.04±2.59
Mean nodal yield (*n*=70)	22.93±10.17
PC RPLND histology (*n*=72) (%)	
Necrosis	33 (45.83)
Viable tumor (with or without teratoma)	7 (9.7)
Teratoma only	32 (44.44)

PC RPLND=Postchemotherapy retroperitoneal lymph node dissection, SD=Standard deviation

Table 3: Comparison of presence of teratomatous elements in orchidectomy and retroperitoneal lymph node dissection specimen

Orchidectomy	RPLND		Total
	Teratoma absent	Teratoma present	
Teratoma absent	20	9	29
Teratoma present	20	21	41
Total	40	30	70

RPLND=Retroperitoneal lymph node dissection

Table 4: Univariate analysis for predicting necrosis in retroperitoneal lymph node dissection specimen

Predictive Factor	Presence of necrosis (±SD)	Absence of necrosis (±SD)	*P*
Age (years)	29.4±7.41	27.5±7.34	0.27
Serum AFP (ng/ml)	5084.4±19,394.7	4481.7±9559.4	0.87
Serum βHCG (IU/l)	7775.8±20,673.8	9237.8±21,852.5	0.77
Serum LDH (IU/l)	1228.9±1648.8	2054.5±3716.1	0.26
Presence of teratoma in orchidectomy	16	25	0.1
ICGCCS			
Good risk	8	4	0.28
Intermediate risk	3	5	
Poor risk	8	12	
Size of nodes prechemotherapy (cm)	6.2±3.6	7.7±3.8	0.09
Percentage change in size of nodes	51.03±22.7	26.49±37.6	0.004

RPLND=Retroperitoneal lymph node dissection, SD=Standard deviation, AFP=Alpha-fetoprotein, HCG=Human chorionic gonadotropin, LDH=Lactate dehydrogenase

Table 5: Clinicopathological data of metastasectomy for nonseminomatous germ cell tumor testes

Site of metastasectomy	Number of patients, *n* (%)
Pulmonary metastasis only	7
Extra pulmonary metastasis	
Liver alone	2
Lung and liver	1
Lung and mediastinal nodes	1
Mediastinal node and SCL node	1
SCL node	2
Metastasectomy histology	
Necrosis	8 (57.14)
Viable tumor	0
Teratoma	6 (42.85)

SCL=Supraclavicular lymph node

underwent a metastasectomy either during or after the RPLND. On analyzing the histopathology, there was an 84.6% concordance between the histology of RPLND and metastasectomy specimens and 69.2% concordance between orchidectomy and metastasectomy specimens.

DISCUSSION

Testicular cancer is the most common malignancy among men of 20–40 years of age. The mean age of our cohort was 28 years, which is consistent with the presentation of NSGCT in the younger age groups as compared to seminoma.[2] Cryptorchidism increases the relative risk of testicular malignancy by 4–6 times.[3] We had five patients with undescended testes. Almost 55% of our patients had NSGCT with distant metastasis, of which 47.5% belonged to the poor International Germ Cell Cancer Collaborative Group (IGCCCG) risk group. This is in contrast with the original IGCCCG criteria, wherein 16% were classified as poor risk and 56% as good risk.[4] As ours is a referral center, patients with advanced stage and those with delayed diagnosis are treated more often than good-risk patients. Due

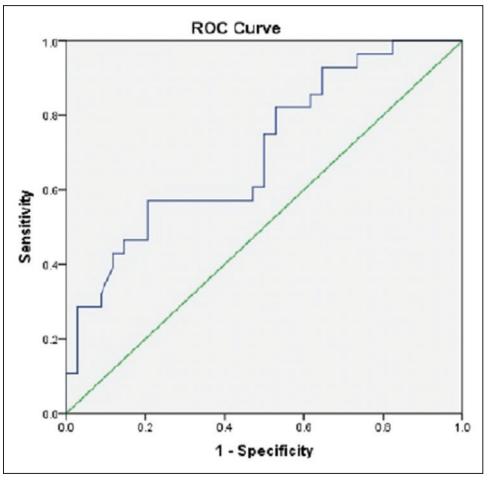

Figure 1: Receiver operating characteristic curve estimating the tumor response for predicting necrosis

to the same reason, 59.7% of the patients had undergone orchidectomy at some other center.

The current standard of care for advanced-stage NSGCT testes includes 3–4 cycles of chemotherapy followed by biochemical and radiological response assessment. If the markers have normalized, the present National Comprehensive Cancer Network guidelines recommend RPLND for residual retroperitoneal nodes ≥1 cm followed by metastasectomy for residual disease at other sites.[5] These recommendations are based on the histological evaluation of PC-RPLND and metastasectomy specimens in various retrospective series.

The literature suggest that resected PC-RPLND specimens will demonstrate necrosis, teratoma, and viable malignancy in 40%, 45%, and 15% of the cases respectively, although the recent series have shown a reduction in the percentage of viable tumors, probably due to advancement in multimodality treatment.[6] Our series also shows a 9.5% rate of viable tumor in the RPLND histology, which could be attributed to the same. Following salvage chemotherapy, the chances of viable tumor increases to 50% and that of necrosis drops to 10%.[7]

As surgery for necrosis would not be beneficial, studies have tried to predict the histology at RPLND by various preoperative parameters including the presence of teratoma in the primary orchidectomy specimen, postchemotherapy nodal size, IGCCCG risk, marker level, and percentage reduction in tumor size. In their earliest series, Donohue *et al.*, asserted that in patients with no teratoma in the original specimen and tumor volume reduction of >90%, RPLND can be avoided.[8] Steiner *et al.* showed teratoma-in the primary tumor and prechemotherapy alfa-fetoprotein (AFP) levels as most significant predictors.[9] In one of the largest analyses to predict teratoma in PC-RPLND, Carver *et al.* found teratoma or yolk sac histology in the primary tumor,

relative change in nodal size before and after chemotherapy, and no requirement for second-line chemotherapy as the significant factors.[10] Several models based on large databases have been constructed to predict PC-RPLND histology. Steyerberg *et al*. devised a model to predict necrosis based on the absence of teratoma elements in the primary tumor, prechemotherapy normal AFP, normal human chorionic gonadotropin, elevated lactate dehydrogenase levels, a small prechemotherapy or postchemotherapy mass, and a large reduction in the mass size during chemotherapy.[6] Vergouwe *et al*. proposed a model, which used the levels of three serum tumor markers, the presence of teratoma elements in the primary tumor, the size of the residual mass measured on computed tomography (CT), and the change in mass size induced by chemotherapy to predict histology. This model was later validated in more than 1000 patients.[11] However, these models have been criticized for their high false-negative rates. Other smaller studies have shown a mixed result in predicting teratoma.[12-14]

Teratomas are tumors containing well or incompletely differentiated elements from at least two germ cell layers. They are present in 47% of the adult germ cell tumors and in 15% of patients with disseminated NSGCT.[1] They do not respond to chemotherapy and require surgical resection, as there is a risk of malignant transformation or a growing teratoma syndrome, both of which are potentially lethal complications. In Donohue *et al*.'s study, seven of nine patients with teratomatous elements had either teratoma or viable tumor in the RPLND specimen.[8] In a study of eighty patients who had teratoma in the orchiectomy specimen, Williams *et al*. found 72% concordance with RPLND histology.[15] However, Beck *et al*., from their retrospective review of Indiana University database, found that 48% of the patients without teratoma in the orchidectomy specimen had teratoma in the RPLND specimen.[16] In another small series, lack of teratoma in the orchidectomy specimen could not predict its absence in the retroperitoneum.[17] Our series showed a 68.1% concordance rate between PC-RPLND and orchiectomy histology. However, on univariate analysis this was not significant for predicting necrosis. Nine patients had teratoma in the RPLND specimen despite being absent in the orchiectomy specimen. Although the presence of teratoma in the orchiectomy specimen increases the chances of its presence in the RPLND, its absence does not rule out the probability of the same.

Prechemotherapy tumor marker levels have been studied to predict PC-RPLND histology and have been a part of almost all the proposed models including Vergouwe *et al*. and Princess Margaret Model.[11,18] In other small series by Steiner *et al*. and Akaza *et al*., variable levels of serum AFP were found to correlate with the presence of necrosis.[9,19] In our series, none of the tumor markers were found to predict necrosis.

Radiological response to chemotherapy has been studied as a marker to predict the RPLND histology. Donohue *et al*. used tumor volume as a measure to compare pre- and post-chemotherapy sizes.[8] In the model described by Vergouwe *et al*., they used square root of the maximum diameter of the residual mass and the change in diameter/10%.[11] A recent study by Miranda Ede *et al*. evaluated the response by measuring the difference between the longest transverse diameters of the largest mass on the CT scan. They suggested a cutoff level of 35% for predicting necrosis with 73% sensitivity and 82% specificity.[12] We have utilized a similar method in our series to evaluate the response. In a model proposed by the Princess Margaret Hospital, change in mass size was directly utilized as a variable.[18] In our patients, on univariate analysis, tumor response significantly predicted the presence of necrosis. On plotting the ROC curve (area under the curve = 0.703), a tumor response of 75% predicted necrosis with 100% specificity . All the nodes that increased in size while on chemotherapy showed viable tumor or teratoma.

Residual masses at extraretroperitoneal sites will be seen in 30% of the patients and metastasectomy forms an integral part of the management for these patients. Lungs are the most common site followed by mediastinal and cervical nodes. Studies indicate that necrosis (60%) will be more commonly seen as compared to teratoma (30%) or viable tumor (10%) at these sites.[1] In our series, 53.8% had necrosis and the remaining had teratoma, none had viable tumor. Various series have reported a discordance rate of 22%–35% between RPLND and thoracotomy histology.[20-22] In their series of 215 patients undergoing thoracic metastasectomy, Steyerberg *et al*. reported an 89% concordance rate between RPLND and metastasectomy histology for the presence of necrosis. Other reported predictors of fibrosis in thoracotomy specimens include primary tumor histology, prechemotherapy tumor marker levels, percentage reduction in the mass size after chemotherapy, and number of metastasis.[23] However, higher discordance rates are noted when nonpulmonary sites are also included. Nakamura *et al*. reported 31.9% discordance between RPLND and metastasectomy histology.[24] Nearly 46% of our patients had extrapulmonary postchemotherapy residual masses. Our data also showed an 84.6% concordance between the RPLND and metastasectomy histology, however concordance between metastasectomy and primary orchidectomy histology was low. For pulmonary metastasis, only one patient had discordant histology.

Even though retrospective in nature, our study shows a significant correlation between tumor response to chemotherapy and the RPLND histology, which has been consistently shown by other series also. A statistically interpreted cutoff has been calculated, which can be further evaluated as a means to avoid RPLND. We included three patients post salvage chemotherapy in our analysis as markers

were normalized post chemotherapy, suggesting treatment response, however patients undergoing desperation RPLND and surgery for para-aortic recurrence were excluded. Many institutions, including ours, omit RPLND in the presence of subcentimetric nodes, however this policy has been challenged. A documented response of 75% as a cutoff for avoiding RPLND in residual masses of >1 cm can be used as a hypothesis for future large-scale studies. A high cutoff is chosen as we need a higher specificity; to avoid missing viable tumor or teratoma. As seen in the literature, there is a high concordance between RPLND and metastasectomy histology in our study also, although it will require larger sample size to come to definite conclusions regarding avoiding metastasectomies based on RPLND histology.

CONCLUSION

We conclude that a 75% reduction in the retroperitoneal node size post chemotherapy is highly predictive of absence of viable tumor or teratoma, however larger series are required to confirm these findings. RPLND histopathologies have a high concordance with metastasectomy histology and thus can be used as a guide to tailor further management.

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