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Original Paper

Comparison of Histological Results from the Resection of Residual Masses at Different Sites After Chemotherapy for Metastatic Non-seminomatous Germ Cell Tumours

J.T. Hartmann,[1] M. Candelaria,[1] M.A. Kuczyk,[2] H.-J. Schmoll[3] and C. Bokemeyer[1]

[1]University Medical Center II, Department of Hematology, Oncology and Immunology, Eberhard-Karls-University, Otfried-Müller-Str. 10, D-72076 Tübingen; [2]Department of Urology, Hannover University Medical School, Hannover; and [3]Department of Hematology and Oncology, Martin-Luther-University, Halle, Germany

Cisplatin-based combination chemotherapy is considered standard treatment for patients with metastatic testicular cancer. However, despite the normalisation of serum tumour markers, 25–50% of patients will demonstrate residual neoplastic masses on radiological examination after completion of chemotherapy. The management of patients presenting with multiple residual masses at different localisations remains particularly difficult. This report summarises the histological findings and the clinical outcome of 27 patients with metastatic non-seminomatous germ cell tumours who underwent multiple resections for residual masses at different localisations after first-line cisplatin-based chemotherapy at Hannover University Medical School between 1980 and 1995. Fifty-six resections were performed (27 retroperitoneal interventions, 21 thoracotomies, 4 resections of hepatic lesions, 3 neck dissections, 1 craniotomy). No surgery-related mortality was observed. 8 patients (30%) showed dissimilar histological findings at sequential or one-stage resections. 5 of these demonstrated less favourable pathological features (mature teratoma or undifferentiated tumour) at the second operation, while only necrosis ($n = 3$) or teratoma ($n = 2$) had been found following the first operation. Tumour necrosis was documented more frequently at thoracotomy ($n = 15/21$) compared to retroperitoneal lymph node excision ($n = 17/27$). By univariate analysis, completeness of surgery (R0 resection) and the histological finding of necrosis or differentiated teratoma were associated with improved relapse-free and overall survival. After a median follow-up period of 33 months (range 1–167), 19 of 26 (73%) evaluable patients are alive; 18 of 27 (67%) patients have continuous no evidence of disease (1 patient with recurrent disease was lost to follow-up). Since the histological findings in postchemotherapy residuals may vary between different anatomical sites and no prediction seems possible, patients are best managed by excision of all present tumour masses if technically feasible. Necrosis identified at thoractomy should not lead to omission of retroperitoneal lymph node resection since there was, in accordance to other authors, a trend that the retroperitoneum harbours unfavourable histological findings more frequently. © **1997 Elsevier Science Ltd.**

Key words: testicular cancer, non-seminomatous germ cell tumour, residual tumour masses, multiple surgical interventions

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INTRODUCTION

WITH THE introduction of cisplatin combination chemotherapy regimens complete remission rates in patients with metastatic non-seminomatous germ cell tumours (NSGCT) range from 50 to 70% [1]. The normalisation of the serum

Correspondence to J.T. Hartmann.
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tumour markers alpha-fetoprotein (α-FP) and beta-human chorionic gonadotropin (β-HCG) usually demonstrates a favourable response to chemotherapy. However, despite marker normalisation, postchemotherapy residual masses are often detectable, especially in patients with large-volume metastatic disease at diagnosis. The nature of these masses remains unclear until resection and histological evaluation is carried out. Therefore, most investigators recommend surgical excision of all residual masses if technically possible [2–9], since the presence of residual undifferentiated tumour may indicate the need for additional chemotherapy [10–12].

Up to 35% of patients with disseminated advanced testicular cancer will have residual masses at more than one localisation after completion of chemotherapy [13]. Only small series of this subgroup of patients are available [4, 9, 13, 14]. Currently, there is no concensus on whether patients with residual masses at different localisations should be resected at all tumour sites or if the extent of surgical interventions could be reduced in selected patients when necrosis is found in one of the removed specimens. The current report evaluates the clinical characteristics, chemotherapy treatment, surgical interventions, and the histological findings classified as necrosis/fibrosis, mature teratoma and undifferentiated tumour in patients following first-linc cisplatin-based chemotherapy for metastatic NSGCT. At least two surgical interventions at different anatomical sites had to be performed for patients to be eligible. It was the aim of this retrospective analysis to study the distribution of histological findings at different localisations of patients with testicular cancer undergoing multiple resections.

PATIENTS AND METHODS

A series of 109 patients underwent excision of residual masses after completion of chemotherapy at the Department of Hematology/Oncology at Hannover University Medical School from 1980 to 1995. Only patients undergoing surgery after first-line chemotherapy were included. Patients receiving chemotherapy between two surgical operations were excluded from this analyses. 27 patients were identified as eligible requiring at least two surgical interventions. The second resection was commonly performed 2–8 weeks after the first surgical intervention, except in 5 patients when simultaneous operation procedures were conducted. None of the included patients were treated with radiation therapy. The median age at diagnosis was 26 years (range 15–44). All patients in our series had primary tumours of testicular origin. The staging investigations prior to chemotherapy consisted of physical examination, laboratory testing including serum tumour markers α-FP, β-HCG and LDH (lactate dehydrogenase), chest X-ray and abdominal and thoracic CT scans. Patients were classified according to Indiana University Classification [15]: 1 patient was classified as "minimal disease" with small bilateral metastases in the lung (4%). 6 patients had "moderate" (22%) and 20 "advanced disease" (74%). Patients received different cisplatin-containing chemotherapy regimens as follows: PEB (cisplatin/etoposide/bleomycin) $n = 12$ (44%), PVB (cisplatin/vinblastine/bleomycin) $n = 3$ (11%), PEI (cisplatin/etoposide/ifosfamide) $n = 7$ (26%), PEBOI (cisplatin/etoposide/bleomycin/vincristine/ifosfamide) $n = 5$ (19%) [16–19]. Primary histology at diagnosis, according to the British Tumour Panel [20], was malignant teratoma undifferentiated (MTU) in 15 (56%), malignant teratoma intermediate (MTI) in 5 (19%) and malignant teratoma trophoblastic (MTT) in 7 patients (26%). Postchemotherapy staging consisted of physical examination, laboratory determination of serum tumour marker levels, chest X-ray and CT scans of the initially involved sites. The tumour markers were normalised in all patients before surgery. Size criteria for performing a retroperitoneal intervention was a minimum residual mass of 1 cm and in a thoracic site of 0.5–1 cm in diameter at CT scan. To restrict the surgical intervention, retroperitoneal surgery was routinely a lumpectomy. In case of the intra-operatively finding of undifferentiated tumour, a formal RPLND (retroperitoneal lymph node dissection) was performed. The findings at postchemotherapy surgery were histologically classified as necrosis/fibrosis, mature teratoma or undifferentiated tumour. Tumour marker stains were routinely prepared if undifferentiated tumour was suspected. If undifferentiated tumour was resected in at least one site, patients routinely received two additional cycles of cisplatin-based chemotherapy, mainly the combination PEI. Salvage chemotherapy was applied after completion of both surgical interventions and a time period of physical recovery. Of 5 patients with undifferentiated tumour as the first histological diagnosis, 2 patients received surgery simultaneously at both sites and 3 patients went on to a second resection, with the intention of achieving maximal tumour debulking prior to the start of salvage chemotherapy. Complete resection (R0) was defined as the excision of all tumour residuals with clear surgical margins. Patients were classified as having an incomplete resection by evidence of large residual masses as determined at surgery (macroscopic residual tumour-RII resection) or if the surgical margins were not clear by histological evaluation of the resected specimens (microscopic residual tumour-RI resection).

During the first 2 years after treatment, patients were followed 3-monthly, during the third year 6-monthly and thereafter the patients were seen annually. For all patients alive, the current status as of June 1995 was recorded. The Kaplan–Meier method [21] was used to determine the overall (OS) and disease free (DFS) survival distributions assessed from the date of the last surgical intervention. Analysis was based on numbers of patients. For each patient, the worst result of the operations (complete/incomplete resection) and histological findings were taken into account. Progression or relapse were defined as a new elevation of tumour markers or histological proof of recurrent undifferentiated tumour. The progression- or relapse-free period ended in progression or relapse in 9 cases. The histological finding of mature teratoma without evidence of undifferentiated tumour cells was not considered as relapse. Survival curves according to different prognostic parameters were compared using the log-rank test. As a cut-off level for significance, a P value of 0.05 was used.

RESULTS

As first surgical intervention, retroperitoneal surgery was performed in 25 (93%) and thoracotomy in 2 patients (7%). All patients required at least a second surgical intervention, 2 patients (7%) had retroperitoneal surgery, 18 patients (67%) had a thoracotomy, 4 (15%) had resection of hepatic lesions, 1 craniotomy (4%) and 2 (7%) supraclavicular lymph node dissections. The histological findings at

Table 1. Distribution of histological findings at sequential or one-stage resections of multiple residual masses after first-line chemotherapy for patients with testicular cancer

Localisation	Necrosis *n* (%)	Differentiated teratoma *n* (%)	Undifferentiated tumour *n* (%)
Retroperitoneum ($n = 27$)	17 (63%)	3 (11%)	7 (26%)
Lung ($n = 21$)	15 (71%)	2 (10%)	4 (19%)
Liver ($n = 4$)	4 (100%)		
Supraclavicular LN ($n = 3$)	1 (33%)		2 (66%)
CNS ($n = 1$)			1 (100%)
Total ($n = 56$)	37 (66%)	5 (9%)	14 (25%)

No. of patients = 27 (56 operations).
CNS, central nervous system; LN, lymph nodes.

the first surgical procedure after chemotherapy showed necrosis/fibrosis in 18 patients (67%), differentiated teratoma in 4 (15%) and undifferentiated tumour in 5 patients (19%). During the second intervention, necrosis/fibrosis, differentiated teratoma and undifferentiated tumour were found in 18 (67%), 1 (4%), 8 patients (30%), respectively. Two additional patients underwent a third surgical intervention yielding undifferentiated tumour (neck dissection) and necrosis/fibrosis (thoracotomy) (Table 1). 10 patients had undifferentiated tumour in at least one resected specimen (37%). 6 of 9 patients who relapsed after postchemotherapy surgery had tumour recurrence at previously resected sites. 5 of them (83%) had received incomplete resections. The other recurrences occurred in mediastinal lymph nodes after thoracotomy for lung metastases and after retroperitoneal surgery in one patient; in the second patient with retroperitoneal lymph node dissection and craniotomy, both complete resections, a growing mass at cranial CT scan, which was not localised at the site of the preceding intervention, was detected, and the third patient developed bone meastases 38 months after sequential resection at lung and retroperitoneum. A significant correlation between the completeness of resection and the histological finding was detectable, since all patients with undifferentiated tumour in the first and 4 of 7 patients with undifferentiated tumour in the second operation were only incompletely resectable ($P = 0.0003$ and $P = 0.032$, respectively). 8 of 27 patients (30%) showed dissimilar histological findings at multiple surgical procedures (Table 2). 5 of these 8 patients demonstrated a less favourable histopathological feature at the second resection: 3 patients with necrosis/fibrosis at first resection had undifferentiated tumour; 2 patients with teratoma at the first intervention had undifferentiated tumour in the following resected specimen. In 18 patients who underwent both retroperitoneal and thoracical resection, a less favourable finding was found in 2 patients at the retroperitoneal site and in 1 patient at thoracotomy. Considering all surgical interventions, necrosis was more frequently found at thoracotomy ($n = 15/21$) compared to retroperitoneal surgery ($n = 17/27$), corresponding to the higher number of complete resections (86%) at thoractomy versus 77% in the retroperitoneum. Of the 2 patients who underwent bilateral thoracotomy, 1 patient showed necrosis at both sites and the other had dissimilar findings with differentiated teratoma at the first and undifferentiated tumour at the operated site. All resections of hepatic lesions showed necrotic tissue ($n = 4$).

No treatment-related mortality was observed. After a median follow-up of 33 months, 19 of 26 evaluable patients (73%) are alive 18/27 (67%) with continuous no evidence of disease. 7 patients died, 1 patient with recurrent disease was lost to follow-up. Patients with complete removal of residual masses at both interventions had a significantly better outcome compared to patients with at least one incomplete operation (DFS: 89% versus 13%, $P = 0.0002$; OS: 96% versus 25%, $P = 0.007$). The histological findings of necrosis/differentiated teratoma were associated with a more favourable DFS and OS compared to the finding of undifferentiated tumour (OS: 87% versus 22%, $P = 0.0003$; DFS: 96% versus 33%, $P = 0.008$).

DISCUSSION

Cisplatin-based combination chemotherapy is considered standard treatment for patients with metastatic testicular cancer. 15–35% of patients, especially those with bulky disease, will have tumour masses detectable after completion of chemotherapy, most often localised in the retroperitonal space [2]. Postchemotherapy resection of these residual tumour masses as part of the treatment concept has resulted in long-term cure rates of 60–80% [22–24]. A special problem is the management of patients presenting with multiple residual masses at different localisations after chemotherapy. Most investigators support the excision of all tumour residuals since there is no reliable instrument that allows the histological subtypes of necrosis/fibrosis, differentiated teratoma and undifferentiated tumour to be distinguished except surgical resection and histological examination of the tissues [25–27]. There is no consensus about the abdominal surgical procedure, which is an important issue in patients planning to undergo multiple operations. On the one hand, the patient could be managed by a restricted intervention, e.g. lumpectomy, but on the other, a formal RPLND is often done [13] and feasible as part of a one-stage intervention with simultanous thoracotomy [9]. At our centre, a limited surgical intervention with only resection of the enlarged tumour mass (lumpectomy) is usually performed. In case of evidence of undifferentiated tumour in the histological examination, all lymph nodes in this site are resected.

Table 2. Comparison of histological results from first and second resection

Histology	Histology			
	Necrosis	Differentiated teratoma	Undifferentiated tumour	Total
Necrosis	15	1	2	18
Differentiated teratoma	–	1	–	1
Undifferentiated tumour	3	2	3	8
Total	18	4	5	27

Table 3. Reported data of overall and disease-free survival from patients after multiple resections of residual masses after chemotherapy for metastatic testicular cancer

No. of patients	Survival		Median follow-up period in months (range)	[Ref.]
	Disease-free	Overall		
15	73%	n.g.	29 (1–58)	[4]
27	n.g.	83%*	36 (n.g.)	[14]
24‡	n.g.	79%	60 (n.g.)	[9]
38	66%	n.g.	84† (5–146)	[13]
27	67%§	73%	33 (1–167)	Current series

* Only patients with minimum follow-up of 12 months. † Of surviving patients. ‡ Including 2 patients with incomplete marker normalisation after chemotherapy. § 26 patients evaluable.
n.g., not given

The histological findings at surgery are of prognostic value and will lead to further treatment in 10–20% of patients presenting with undifferentiated tumour [11]. Approximately 30–40% of resected specimens will show mature teratoma and these patients benefit from surgery because of prevention of local tumour growth and of a possible transformation into malignant undifferentiated teratoma [28, 29]. Patients with necrosis/fibrosis in all resected sites will have no improvement of prognosis and it would be of benefit to identify these patients prior to the operation in order to prevent surgery-related morbidity and mortality.

By comparing the response to chemotherapy, we found a relatively high rate of 37% undifferentiated tumour in resected specimens of patients presenting with multiple residual tumour localisations. Other rates available from the literature concerning this subgroup of patients ranged from 13 to 27% [3, 6, 9, 12, 13]. Dissimilar histological results at different anatomical localisations were detected in a high number of patients (8/27; 30%), in accordance with other investigations, ranging from 25 to 47% [3, 6, 9, 12, 13]. With one exception [6], all other investigators and our results demonstrated more unfavourable findings with retroperitoneal surgery compared to thoracotomy [3, 9, 12, 13]. Considering all 27 patients in our study, there was a trend towards the retroperitoneum harbouring unfavourable histological findings more frequently. Our data seem to suggest that patients with necrosis at retroperitoneal excision have a high probability of necrosis found at thoracotomy, while necrosis at thoracotomy did not predict for necrosis found at the retroperitoneal site.

As expected, the completeness of surgical resection and the histological findings of necrosis/fibrosis or differentiated teratoma were identified as significant factors influencing both disease-free and overall survival. Table 3 compares our and other survival data available from the literature concerning patients with multiple resections at different sites.

The histological findings at different anatomical sites vary frequently and are not predictable. Maybe the use of positron emission tomography (PET) scanning with marked 2-fluoro-2-deoxyglucose molecules (FDG) will offer progress in this field in the near future. PET-FDG imaging may be useful for the detection of residual undifferentiated tumour. However, it remains difficult to distinguish between necrosis and differentiated teratoma in the residual mass [30]. Ongoing investigations will further clarify the role of PET for the management of residual masses after chemotherapy for testicular cancer. It may be speculated that the combination of a negative result at PET examination at all sites and necrotic tissue found in the retroperitoneum may identify patients who can be spared from further surgical resections.

Recently, Steyerberg and associates performed a meta-analysis containing data from 556 patients with NSGCT after chemotherapy in order to develop a model for the prediction of histology [31]. Predictive factors for necrosis were the absence of teratoma elements in the primary tumour, prechemotherapy normal tumour marker levels, small pre- or postchemotherapy masses and a >70% shrinkage of the mass during chemotherapy. To distinguish undifferentiated tumour from teratoma, a higher prechemotherapy LDH level, a larger postchemotherapy mass and smaller relative shrinkage of the mass during chemotherapy were of value in the second meta-analysis. This model enables necrosis to be distinguished reliably from other histologies, but is less valuable for the discrimination of undifferentiated tumour from mature teratoma. Steyerberg created a helpful instrument giving a basis for the decision to operate on patients immediately or to follow their residual tumours closely. However, as demonstrated in our patients requiring multiple resections, there is a high incidence of dissimilar histological findings in resected masses from different localisations in the same individual. Systemic chemotherapy might have different effects on each metastatic subpopulation depending on pharmacological and pharmacokinetic characteristics of the agents used, extent of metastases, blood delivery of the affected organ and local growth conditions of the tumour cells, resulting in a different effect of the treatment. The variation of histological results within one person shows that the prediction of histological findings in resected specimens remains difficult, since the prognostic criteria as reported above—perhaps with the exception of a relatively shrinkage of the lesion—were certainly identical for all lesions within 1 patient. Maybe the combination of the available modalities—the Steyerberg model and FDG-PET scanning—will achieve a meaningful advance in the prediction of histological findings.

In the meantime, surgical resection of residual tumours is still mandatory, either performed as a simultaneous or a staged procedure. In our series, 5 patients had a one-stage operation without major complications. 3 patients underwent abdominal surgical intervention (simultaneous resection of hepatic lesions and retroperitoneal lymph nodes). The other 2 patients had a lymph node excision at the neck and simultaneous retroperitoneal lymph node dissection. A

recently published investigation has shown that one-stage resection of neck, chest and abdominal residual masses may be a safe and feasible alternative in selected patients who require surgical intervention at multiple sites and fulfils the objective of rendering patients disease-free in a single operation procedure. No surgery-related death occurred but 2 patients suffered from complications, 1 with chylous ascites and chylothorax requiring percutaneous drainage and the other with an air leakage resolving with conservative management [9]. Since surgery-related mortality is considered to be very low and morbidity has decreased with modified operation techniques, patients with residual masses after chemotherapy are best managed by excision of all present localisations. Necrosis identified at thoractomy should not lead to the omission of patients from retroperitoneal lumpectomy because there is a trend that the retroperitoneum often contains unfavourable histological findings.

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