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Excision of Residual Masses After Platinum Based Chemotherapy for Non-Seminomatous Germ Cell Tumours

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Abstract—*Between January* 1980 *and June* 1987, 42 *patients receiving platinum based combination chemotherapy for advanced non-seminomatous germ cell tumours had residual masses, detected by computed tomography, after four or six treatment courses without tumour marker evidence of active disease. Resection of retroperitoneal* (n = 32), *pulmonary* (n = 4) *or thoracoabdominal* (n = 2) *disease revealed residual malignancy in nine patients* (21%), *differentiated teratoma in* 14 (33%) *and fibrosis or necrosis in* 15 (36%). *Laparotomy showed no evidence of a mass in four instances.*

Of the 42 *patients*, 14 *had malignant teratoma undifferentiated in the primary tumour only one of whom* (7%) *had evidence of malignancy in the specimen resected post-chemotherapy. Conversely, six of* 15 *patients* (40%) *whose primary tumour was malignant teratoma intermediate had residual malignant tissue after treatment.*

With a median follow up of 36 *months from post-chemotherapy surgery*, 36 *patients* (86%) *are continuously disease-free. Relapses occurred in one of nine patients with residual malignancy* (11%), *three of* 14 *with differentiated teratoma* (21%), *one of* 15 *with necrosis or fibrosis* (7%) *and in one patient who had a normal laparotomy. Four patients have died from their tumours, but two are currently disease-free following further surgery and chemotherapy for relapse.*

Neither primary nor post-chemotherapy histology was predictive of relapse, and although relapse was numerically more common in patients whose residual mass was incompletely excised (three of 12), *this was not statistically significant.*

INTRODUCTION

THE PROGNOSIS for most patients with metastatic non-seminomatous germ cell tumours (NSGCT) has been dramatically improved by the use of platinum containing chemotherapy regimens [1]. Currently more than 95% of patients with nodal disease less than 5 cm or pulmonary metastases less than 2 cm are disease free and probably cured 2 years from diagnosis [2]. However, treatment failure is still regrettably frequent in patients with very large volume tumours [3] and this may relate to the emergence of drug resistance in parallel with the number of tumour cell divisions [4] or the inability of chemotherapy to eradicate tumour from sites of bulk disease.

In NSGCT a significant proportion of patients with high and intermediate volume tumours as defined by the Medical Research Council (MRC) [3] will only achieve a partial radiological remission after combination chemotherapy, although biochemical remission may be complete. The precise nature of persisting radiological abnormalities can only be determined by surgical excision.

Since 1980, the practice in Glasgow has been to resect, as far as possible, residual post-chemotherapy masses in nodal areas, liver and lungs. We report the outcome for such patients in relation to the histology of the resected specimen and the extent of the surgical excision.

PATIENTS AND METHODS

Between January 1980 and June 1987, 42 patients receiving chemotherapy as initial treatment for metastatic NSGCT underwent post-chemotherapy surgery. All were staged at presentation in accordance with the Royal Marsden Hospital classification [5], using computed tomography (CT) of chest, abdomen and pelvis with measurement of human

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chorionic gonadotrophin (hCG) and a α-foetoprotein (AFP). Eligible patients were entered into EORTC trials, those with no evident testicular primary lesion or very high volume disease by MRC criteria [3] received alternative platinum containing regimens (Table 1). A minority of patients presenting with very high tumour marker levels, an hCG >10,000 u/l or AFP >1000 u/ml received six chemotherapy cycles to ensure treatment continued after marker remission. Those with very high volume tumour or extragonadal disease have been treated since 1986 with a new, intensive combination (BOP/VIP) and have all received six chemotherapy cycles. Repeat CT scans were performed on completion of chemotherapy and any lymph node >1.5 cm, lung or liver lesion >1 cm was considered for excision provided that the patient was in marker remission. Those with any evidence of malignant tumour post-chemotherapy, whether completely resected or not, received further chemotherapy. Additionally, four patients were given post-operative irradiation.

For this report, histology of the post-chemotherapy masses excised has been reviewed by a single pathologist and classified according to the Indiana criteria [6]. This defines malignancy as severe cytological atypia only if evidence of an infiltrative growth pattern or large nodules of cartilage (>5 mm diameter) are also present. As a result of this pathology review, three patients were retrospectively considered to have residual malignancy and five patients were erroneously treated as having residual malignancy, when histological reassessment classified them as cytological atypia only.

All patients have been regularly examined post-operatively with serial chest X-rays and tumour marker measurements. Those who had malignant disease in resected specimens have also undergone repeat CT scans following surgery and 6–12 months later to confirm the absence of relapse. Subsequent treatment for relapse has been non-standardized; all patients have received further chemotherapy with platinum or carboplatin usually combined with ifosfamide and etoposide.

RESULTS

Thirty-six patients who achieved a marker complete remission (AFP <3 u/ml, hCG <4 u/l) and six whose tumours were non-marker producing, had residual CT scan abnormalities consistent with metastatic disease on completion of chemotherapy. Pretreatment details of these patients, the chemotherapy they received and the surgery performed are shown in Table 2. No significant abnormality was found within the abdomen in four patients despite a radiological appearance consistent with retroperitoneal lymphadenopathy. One of these patients and four others had small (<0.5 cm) white nodules on the small bowel serosa, which showed a fibrotic reaction histologically. Early in the study, when the importance of complete resection was less well documented, biopsy of residual tumour was performed in two patients. Since 1983, total excision has been impossible in six instances, as a result of inability to separate tumour from major vessels.

Surgery was well tolerated despite thoraco-abdominal incisions ($n = 2$) for *en bloc* resection of retroperitoneal and retrocrural lymphadenopathy or concurrent bilateral thoracotomy ($n = 2$). There was no surgical mortality and morbidity was minor. The median post-operative hospital stay was 6 days.

Of the 42 patients, nine (21%) had evidence of malignancy by the Indiana criteria [6] in post-chemotherapy masses excised completely ($n = 5$) or incompletely ($n = 4$) from the retroperitoneum. No residual malignancy was found in any specimen

Table 1. Chemotherapy regimens

BEP	Bleomycin 30 mg i.v. infusion or i.m. weekly × 12 Etoposide 120 mg/m² i.v. days 1, 3, 5 Platinum 20 mg/m² i.v. days 1–5	q 3 weekly × 4	
PVB	Platinum 20 mg/m² i.v. days 1–5 Vinblastine 0.15 or 0.2 mg/kg or 6 mg/m² Bleomycin 30 mg i.v. infusion or i.m. weekly × 12	days 1, 2	q 3 week × 4 or 6
Alternating PVB – BEP – PVB – BEP			
(BOP/VIP)	Bleomycin 30 mg i.v. infusion Oncovin 2 mg i.v. Platinum 50 mg/m² i.v. days 1 and 2 VP16–213 75–100 mg/m² i.v. days 1, 3, 5 Ifosfamide 1–1.2 g/m² + MESNA 0.6 g/m² and MESNA 0.6 g/m² infused over subsequent 8 h Platinum 20 mg/m² i.v. days 1–5	day 1 i.v. days 1–5	q 10 days × 3

Table 2. Details of patients undergoing post-chemotherapy surgery

	$n = 42$		
Median age	30 years (range)	(17–63)	
Pretreatment tumour stage:		IIB	3
		IIC	20
		III	2
		IV Lung	10
		Liver	6
		Brain	1
Pretreatment tumour markers:	hCG $n = 17$	median 9054 (20–318,000 u/l)	
	AFP $n = 19$	median 1150 (40–15,000 u/ml)	
Chemotherapy:	BEP	$n = 7$	
	PVB	$n = 15$	
	PVB/BEP	$n = 8$	
	BOP/VIP	$n = 10$	
	Other	$n = 2$	
Surgery:			
Laparotomy $n = 36$:	19 complete excision retroperitoneal mass		
	1 complete excision hepatic mass		
	12 incomplete excision retroperitoneal mass		
	4 normal laparotomy		
Laparotomy and thoracotomy $n = 4$:		2 unilateral	
		2 bilateral	
Thoracotomy only $n = 2$			

of mediastinal node, lung or liver, and two patients with malignant disease in the retroperitoneum had differentiated teratoma and necrotic tumour in the mediastinum and lungs respectively. Fourteen patients (33%) had differentiated teratoma and 15 (35%) necrosis, fibrosis or reactive histology.

The relationship between pathology of the primary tumour and that found in the post-chemotherapy mass is shown in Table 3. The majority of patients with residual malignant disease had MTI initially, and 40% of patients with MTI who underwent post-chemotherapy surgery had malignant tumour resected. Conversely, most patients with a primary MTU had fibrosis or necrosis in the resected specimen and the incidence of residual malignancy was low (7%).

The median duration of patient follow up is 36 months (range 6–95 months) from post-chemotherapy surgery. Thirty-six patients (86%) remain in complete remission including eight of nine with residual malignancy. The only patient in this category whose tumour has relapsed had a retroperitoneal biopsy followed by extensive chemotherapy and irradiation. Three patients had residual malignancy by the Indiana criteria [6] on pathology review though this was not appreciated at the time.

Table 3. Histology of tumour resected post-chemotherapy in relation to that of the primary lesion

	Normal laparotomy	Fibrosis/necrosis reactive tissue	Differentiated teratoma	Malignancy
Primary pathology				
None $n = 3$		2		1
Seminoma + raised				
AFP $n = 1$		1		
MTD $n = 6$		1	5	
MTI $n = 15$	2	2	5	6
MTU $n = 14$	2	8	3	1
MTT $n = 3$		1	1	1
		36%	33%	21%

MTD = malignant teratoma differentiated; MTI = malignant teratoma intermediate (teratocarcinoma); MTU = malignant teratoma undifferentiated (embryonal carcinoma); MTT = malignant teratoma trophoblastic (choriocarcinoma). Histopathological classification according to the criteria of the British Testicular Tumour Panel [10].

They received no further treatment and are disease-free at 16, 24 and 35 months.

There have been five relapses among the remaining 33 patients (15%). These include one patient with stage IV lung and liver disease who had a normal laparotomy and liver biopsy showed reactive changes only. He relapsed with pulmonary disease, having previously achieved a radiological CR at this site. Three patients had differentiated teratoma excised from the retroperitoneum. One patient had an incomplete excision and post-operative irradiation; he relapsed with differentiated teratoma in the mediastinum 44 months after initial laparotomy. A second patient with incomplete excision of TD relapsed in brain at 5 months. The patient who underwent complete excision of TD had retroperitoneal recurrence of MTU, the primary testicular pathology, at 22 months. The fifth relapse followed resection of necrotic paraaortic nodes, in a patient with Stage IVH disease at presentation: tumour was evident radiologically in the retroperitoneum and liver. Of the six patients who have relapsed, four have died from their disease. Two patients are disease-free, one 30 months after complete excision of differentiated teratoma in a mediastinal node and one 6 months from a second laparotomy, consolidation chemotherapy and irradiation.

The probability of residual malignancy or subsequent tumour relapse appears independent of initial tumour stage, volume or pretreatment levels of tumour markers (Table 4). The frequency of both residual malignancy and relapse was higher in patients whose primary pathology was MTI than any other subtype, though this did not reach statistical significance. Relapse was also numerically more common in patients whose residual masses were incompletely excised (three of 12) and those whose tumours contained differentiated teratoma (three of 14). However, the presence of residual malignancy did not increase the frequency of relapse which occurred in one of nine patients (11%) with malignancy in the resected specimen, though most of these patients received further treatment.

DISCUSSION

The management of patients with residual tumour after platinum based combination chemotherapy for NSGCT remains controversial. As non-invasive techniques are unable to predict the histology of these masses, most centres advocate surgical excision. This may also be of therapeutic value, as the frequency of subsequent relapse is reported to correlate with the completeness or otherwise of resection [7]. The current study would tend to confirm this observation.

Our data indicate that the pathology found in residual masses depends in part on the histology of the primary tumour. The majority of differentiated teratomas followed treatment for MTD or MTI whereas chemotherapy for MTU tended to result in fibrosis or necrosis, as has been reported previously [7, 8]. However, in our patient population, residual malignancy was found mostly in patients whose primary disease was MTI though others have shown a similar incidence in treated MTI and MTU [7].

Few of our patients had tumour resected from both retroperitoneum and lungs or mediastinum, however the discrepancy between pathology above and below the diaphragm is of note. In a similar study [9], residual malignant disease was found most frequently in the retroperitoneum (eight of nine cases), supradiaphragmatic malignancy was found in only four of these eight patients. Four additional patients had differentiated teratoma in retroperitoneal lymph nodes with necrosis or fibrosis in pulmonary masses [9]. Thus, if excision is of therapeutic benefit, masses need to be excised from all sites as extrapolation of pathological data from one tumour mass to another may be inaccurate in a significant proportion of cases.

The overall incidence of residual malignancy (21%), differentiated teratoma (33%) and fibrosis or necrosis (36%) in our series is comparable to that in other studies [7–9]. The high and increasing frequency of differentiated teratoma has been attributed to more effective primary chemotherapy. This may either promote maturation [11] or result in more complete elimination of malignant components thereby revealing a previously unrecognized differentiated cell population [12]. The latter hypothesis would correspond with the observation that treated MTI (or MTD), which includes a differentiated component, is most commonly associated with residual TD [current data, 7–9].

The capacity for TD to revert subsequently to less differentiated malignancy is unknown, although our data would suggest that this is at least possible. Only one of the three patients with resected TD relapsed with a totally differentiated tumour histologically. A similar phenomenon of phenotypic reversion from differentiated tumour in residual masses to less well differentiated histology at relapse has been previously reported [13].

The prognosis for residual malignant disease varies between reported series, with 22–89% of patients relapse free [6, present data] using similar criteria to define malignancy. The Indiana group [6] have classified residual malignancy principally on the basis of stromal invasion, though they also included the presence of solid mesenchymal or epithelial nodules. They found residual malignancy in nine of 55 patients (16%), a similar proportion to that in our series (21%). However, despite complete resection of residual malignancy in the Indiana

Table 4. Patient characteristics in relation to post-chemotherapy histology and outcome

		All patients $n = 42$	Residual malignancy $n = 9$	Relapse $n = 6$	
Pretreatment tumour volume					
MRC criteria [3]	Low	6	1	—	
	High	18	4	3	
	Very high	17	4	3	
Pretreatment tumour stage					
Royal Marsden Hospital Classification [9]	IIB	3	1	—	
	IIC	20	6	3	
	III	2	1	—	
	IV	17	1	3	
Pretreatment tumour markers					
	hCG median	9054	$n = 3$ 9323	$n = 3$ 14 200	
	AFP median	1150	$n = 5$ 4015	$n = 3$ 4015	
Pretreatment histology					
	none	4	1	—	
	MTD	6	—	—	
	MTI	15	6	4	$P = 0.11$
	MTU	14	1	2	
	MTT	3	1	—	
Surgery:					
Complete excision		26	5	2	
Incomplete excision		12	4	3	$P = 0.17$
Other		4	—	1	
Pathology					
Fibrosis/necrosis		15	—	1	
Differentiated teratoma		14	—	3	$P = 0.32$
Malignancy		9	9	1	
Other (normal laparotomy)		4	—	1	
Post-surgery chemotherapy					
Yes		9	6	1	
No		33	3	5	
Post-surgery irradiation					
Yes		4	2	2	
No		38	7	4	

patients, and the fact that the majority (six of nine) received post-operative chemotherapy, the relapse rate was higher than in our experience. Other studies using different criteria fall between these extremes [7, 9].

There is a significant relapse rate in patients with no evident malignancy in resected post-chemotherapy masses; 15% in this series and a similar frequency in others [7] even when patients with incomplete resection are omitted [6]. This may be due to minute foci of malignant disease being overlooked as clearly only limited numbers of random tissue blocks can be examined. Alternatively, relapse may occur from occult metastatic disease. Two of six patients relapsing in our series had stage IVH disease at presentation and, although the liver post-chemotherapy was normal radiologically, macroscopically at laparotomy and histologically, it is possible that residual disease was not recognised at this site. Newer imaging methods may resolve this point.

Our pathology review identified three patients whose residual malignant disease was unrecognized at the time, one of whom had an incomplete resection yet all are currently disease-free. This raises the question of whether cells characterized as histologically malignant will necessarily behave in a neoplastic manner. Such an inability to identify the malignant phenotype from morphological appearance might explain the wide differences between

series in terms of relapse rate and the apparent lack of correlation between outcome and post-surgical treatment.

In summary, the reasons for treatment failure in these patients are likely to be variable. Incomplete resection of differentiated teratoma and residual malignancy, even if completely excized, are more important in other studies than in our experience. Nevertheless, we continue to advocate as radical surgery as circumstances permit in conjunction with additional chemotherapy for patients in whom malignant disease is found.

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