Eur J Cancer Clin Oncol, Vol. 25, No. 12, pp. 1739–1743, 1989.
Printed in Great Britain

0277-5379/89$3.00 + 0.00

Successful Treatment of Patients in Whom Germ Cell Tumour Masses Enlarged on Chemotherapy While Their Serum Tumour Markers Decreased

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Abstract—*Enlargement of tumour masses with a fall or no change in tumour marker levels was noted in eight of 287 patients during chemotherapy for NSGCT at the Charing Cross and Mount Vernon Hospitals between 1977 and 1988.*

These eight patients had elements of differentiated teratoma in the primary specimen and in five the enlarging masses showed cystic change on CT scan. The increase in tumour mass occurred within 6 months of starting treatment. At surgery, four patients were found to have differentiated teratoma and have been followed for 15 months to 5 years without relapse. Two patients who also had some areas of embryonal carcinoma in the resected specimens had post-operative chemotherapy and are alive disease free at 8 and 24 months respectively.

Two patients died: one post-operatively of uncontrolled haemorrhage secondary to aortic rupture and the second of acute myeloid leukaemia following 8 years of intermittent therapy for unresectable differentiated teratoma.

The successful outcome in six of these eight patients suggests that enlarging teratomatous masses on chemotherapy can be managed by surgical resection and, when active tumour is present, by the use of post-operative chemotherapy.

INTRODUCTION

MOST PATIENTS with metastatic non-seminomatous germ cell tumours (NSGCT) obtain a long-term disease-free remission with chemotherapy. When there is minimal metastatic disease overall survival is greater than 90% and even with extensive metastatic disease using platinum based chemotherapy survival is between 70 and 80% [1–4].

Response to therapy is judged by decreases in the size of detectable masses and in serum levels of human chorionic gonadotrophin (HCG), alphafoetoprotein (AFP) and lactate dehydrogenase (LDH). Enlargement of tumour masses during or after chemotherapy is usually cause for concern in solid tumours and would normally indicate a poor prognosis. However NSGCT tumours may contain elements of differentiated teratoma which if remaining after treatment may be totally resected with good prognosis [5, 6].

In this report, we have evaluated eight patients who developed a measurable increase in tumour mass during initial chemotherapy while their serum marker levels were either decreasing or in whom levels were never elevated. The overall survival of this group was not adversely affected by the increase in tumour mass.

Accepted 2 August 1989.
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METHODS

Patients presenting to or referred to Charing Cross Hospital between 1977 and 1987 or Mount Vernon Hospital between 1984 and 1987 were included in this study. All the notes and X-rays of the patients studied were reviewed (K.T. and B.W.) and the tumour masses were measured at the commencement of chemotherapy and at the time of mass increase. Using the CT and ultrasound scans for the abdominal masses the volumes were calculated using the formula of a cylinder ($2/3\ \pi\ r^2 \times h$) with the maximum AP and transverse diameters of the mass used to calculate the radius (r) and the number of cuts in which the mass was visible on the CT to calculate the height (h). For the two patients who had increasing size of disease in the thorax the volume of a sphere (πr^3) was used again calculating the radius from the maximum diameter of the mass on the CT. Histology of the initial and

Table 1. Patient characteristics

Patient No.	Age Sex	Vol. of disease pre-chemotherapy (cm^3)	Vol. increase (%)	Treatment	Outcome
1	23 M	1746	160	Cervical node biopsy Laparotomy	Died Ruptured aorta
2	15 M	110	145	Laparotomy	Died Acute myeloid leukaemia
3	19 M	9.4	129	Laparotomy	Post-operative chemotherapy Alive NED 2 years
4	15 F	Undetectable	To 261 cm^3	Laparotomy	Persistent liver abnormality Alive NED 18 months
5	26 M	24.6	547	Laparotomy	Alive NED 18 months
6	23 M	33.0	90	Laparotomy	Post-operative chemotherapy Alive NED 8 months
7	19 M	0.7	95	Thoracotomy Laparotomy	Persistent para-aortic abnormality Alive 15 months
8	24 M	0.9	150	Bilateral lung wedge resections	Alive NED 4.5 years

NED — no evidence of disease
Patient 4 had undetectable disease on scans so absolute volume stated not volume increase (%).

subsequent surgical specimen was independently reviewed (F.J.P. and M.H.B.).

RESULTS

The total number of patients treated with POMB/ACE chemotherapy for NSGCT during this period was 287. During the period 1977 to 1988, 67 patients underwent removal of residual disease and 63 of the 91 procedures performed on the patients were abdominal lymph node dissections (Kulkarni, R.P. personal communication). We have identified a sub-group of eight patients who had an early increase in tumour mass with either normal levels or a decrease in serum markers and who went to surgery to remove bulk disease within a further 4 months of the tumour mass increase (Table 1). No patient treated for NSGCT during this period had primary chemoresistant disease with enlarging tumour masses with increasing or unchanged serum markers. In the subgroup of patients identified, seven were males with primary testicular tumours and one was a female with a primary ovarian tumour. Table 1 shows patient characteristics and demonstrates that bulk disease is not a feature of this syndrome prior to chemotherapy. Histology review showed that in all patients the initial specimen had elements of differentiated teratoma and, although all the secondary surgical specimens had predominately differentiated tissue, two patients (Nos. 3 and 6) still had areas of embryonal carcinoma within the secondary surgical specimen. These two patients were given post-operative chemotherapy.

Six (75%) of the patients had complete macroscopic surgical removal of tumour. In one patient, although the disease at laparotomy was only differentiated teratoma, as a result of mesenteric involvement it proved inoperable and later enlarged despite further chemotherapy. He had controllable disease for a total of 8 years using interferon [6] but then the patient developed acute myeloid leukaemia and died within a few months. In a further patient the aorta was torn during the removal of 3 kg of differentiated teratoma. It was so friable it could not be satisfactorily grafted and the patient died as a result of uncontrolled haemorrhage.

In two patients with abdominal and thoracic disease only the disease in the lung was found to have increased while the abdominal disease was unchanged.

The median disease volume increase was 155% with a range of 90–547%. In the two patients who required post-operative chemotherapy on the basis of the histology found at surgery there was only a moderate sized mass before chemotherapy and only 90–129% increase in disease. Thus initial disease volume or extent of disease increase before surgery do not predict for the histological findings. The increase in mass size occurred within the first 2–6 months of treatment. All patients had surgery within

Table 2. Serum marker evaluation and time to increasing disease and surgery

Patient	Serum markers at presentation βHCG	αFP	Serum markers at time of increasing disease βHCG	αFP	Time to increasing disease (months)	Time to surgery (months)
1	29,900	12,120	N	N	3	3
2	192	6550	N	N	4	2
3	<2	<2	<2	<2	2	2
4	<2	8,562	N	18	2	2
5	3540	644	N	6	3	1
6	3	9	N	N	2	1
7	628	9724	N	8	3	4
8	<1	248	N	6	6	1

Time to increasing disease in months is from date of pre-treatment scan.
Time to surgery in months is from date of scan showing increasing size of disease.

4 months of the assessment of increasing disease volume.

Two patients had normal serum markers at presentation and throughout treatment. In the six patients with at least one serum tumour marker elevated at diagnosis one or both of the serum tumour markers had fallen to normal at the time of the increase in tumour mass (Table 2). The fall in serum markers of at least 1 log in these patients suggests the increasing mass was due to differentiating tumour which does not produce elevated circulatory HCG or AFP, and not the occurence of primary chemoresistant disease. The female patient with a germ cell tumour of the ovary had no detectable residual disease after initial surgery and was treated because of an elevated level of AFP. She developed a clinically palpable abdominal mass within 2 months of starting chemotherapy but this contained only mature germ cell elements and was successfully resected. Two of the male patients had Stage 1 disease at diagnosis and developed para-aortic nodes between 6 months to 1 year of follow up and were then treated with chemotherapy. One of these patients had embryonal tumour at surgery and went on to receive post-operative chemotherapy and remains disease free and the second had no further treatment after bilateral lung wedge resections for mature teratoma.

DISCUSSION

Once serum tumour markers are normal and chemotherapy is completed a proportion of patients with NSGCT have residual disease [7] and it is recommended that this should be removed surgically. Histology reveals either no evidence of disease with necrosis and fibrosis, active germ cell elements or mature teratoma [8–10]. Approximately one-third of patients fall into each category and further treatment and outcome depends on the histology that is found at second surgery.

It has been demonstrated that there is a subgroup of patients in whom serum tumour markers increase at the beginning of treatment but unless the tumour mass increases at the same time this is not necessarily a poor prognostic factor and is probably related to tumour lysis [11]. A rise in AFP levels during therapy may be due to hepatotoxicity from cisplatin and methotrexate if the level plateaus and there is not enlargement of tumour masses [12]. In this report we have established a separate group of patients in whom the disease as measured by serum tumour marker evaluation responds to chemotherapy but the tumour mass itself increases in size within the first 6 months of treatment.

A prior report of enlarging masses of differentiated teratoma was published by Logothetis *et al.* in 1982 [13]. They reported six patients who form two separate groups. In the first group of three patients without residual post chemotherapy disease enlarging masses were noted 3–5 months post-chemotherapy. In two of the three, surgery was undertaken without further chemotherapy and revealed mature teratoma, but the third patient received several courses of chemotherapy for suspected recurrent disease prior to surgery which also demonstrated only mature teratoma. In the second group of three patients, there were persistent enlarging masses at the end of chemotherapy with normal serum markers and all received alternative drug regimes on the assumption of active chemoresistant disease. When chemotherapy did not lead to tumour shrinkage, salvage surgery was undertaken and revealed only mature teratomatous elements. No further treatment was given and no relapses occurred. Thus these patients were somewhat different from those reported here as the enlarging masses of mature teratoma occurred either at the end of treatment or 3–5 months after treatment was completed. It is notable that four of the six patients received chemotherapy on the assumption that the enlarging masses were due to active disease. Most

of the patients were seen during the pre-CT scan era and therefore evaluation was done clinically or using chest radiographs unlike our patients who were largely evaluated using serial CT scans to complement clinical evaluation.

Pre-treatment characteristics of our subgroup of patients did not reveal that marker levels or site or size of disease differ in comparison to the remainder of NSGCT patients so that close monitoring of all patients is essential. However, this subgroup of patients did show elements of mature teratoma in the initial histological specimen. In addition, five of the eight patients had cystic changes on the CT or ultrasound scan done at the time of enlarging disease suggesting the presence of differentiated elements (Fig. 1). If patients have enlarging masses with falling tumour markers on chemotherapy early surgical resection is advisable. It is possible that if earlier surgery had been performed in the two patients in this study who have died their tumours might have been easier to resect and their operations could have been successful.

The post-operative management is dependent on the histological findings and serum tumour markers. Further chemotherapy is indicated either when active germ cell elements are found at surgery or when serum markers remain elevated, unless there is only a persistent plateau of the AFP thought to be due to drug toxicity [12].

The subgroup of patients with enlarging masses but falling or undetectable serum tumour markers can be anticipated to have an excellent prognosis with early surgery and appropriate post-operative management. Although no patients with primary drug-resistant tumours were identified in the Charing Cross series from 1977 to 1988, a similar early surgical approach is recommended as it might be the only chance of eradicating drug resistant disease in an otherwise poor prognosis subgroup.

Acknowledgements—We thank Mr K.W. Reynolds and Mr J. Bradley for their surgical help with these patients. Dr Rustin and Dr Tonkin are supported by the Cancer Research Campaign.

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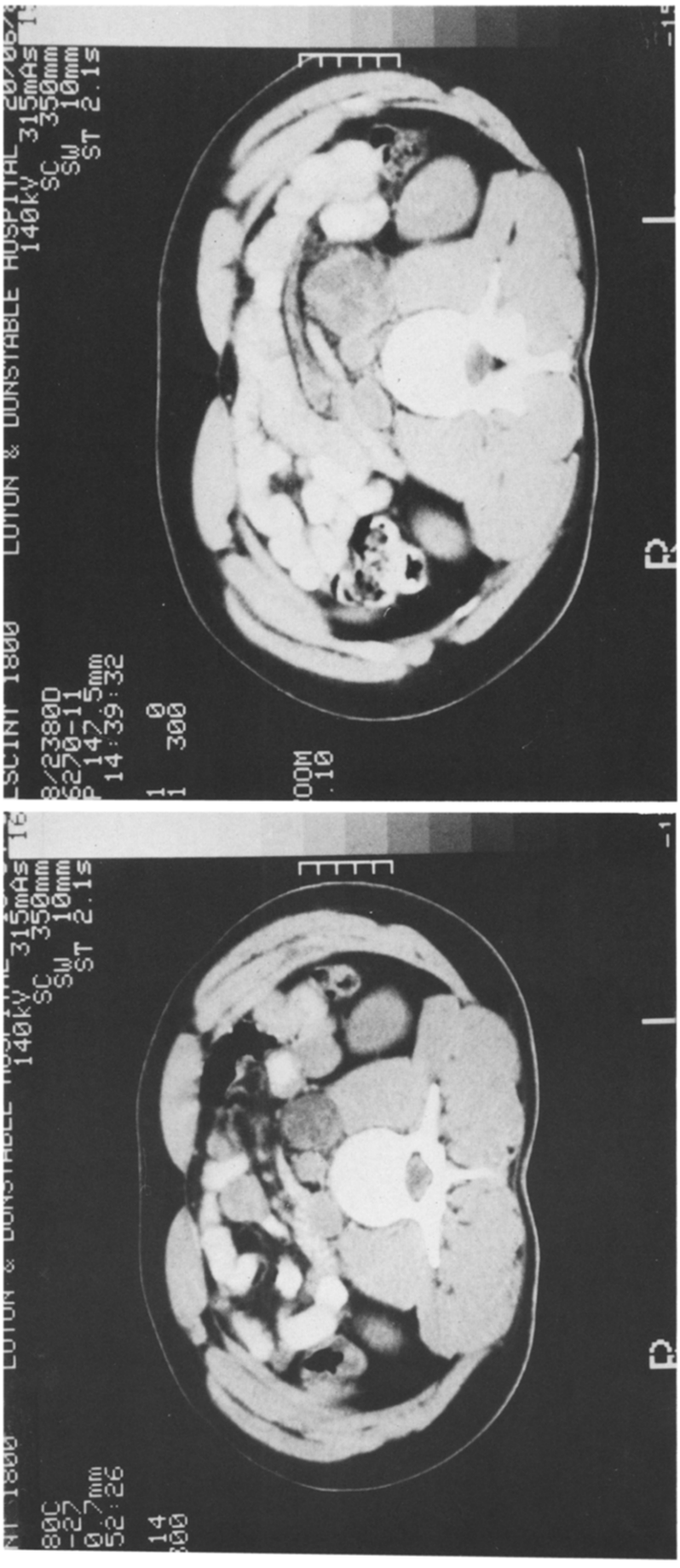

Fig. 1. Left para-aortic mass in patient 6 (left) at start of chemotherapy which had a volume of 33 cm³ and (right) 9 weeks after start of chemotherapy when volume had increased to 63 cm³ and appeared cystic.