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Eur J Cancer, Vol. 27, No. 6, pp. 695–698, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Long-term Follow-up of Non-seminomatous Testicular Cancer Patients with Mature Teratoma or Carcinoma at Postchemotherapy Surgery

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From 1979 to 1983 the EORTC GU Group treated 239 patients with disseminated non-seminomatous testicular cancer with combination chemotherapy comprising cisplatin, vinblastine and bleomycin in a prospectively controlled trial. The protocol required complete resection of residual masses after induction chemotherapy, provided that serum tumour markers were normal. 102 patients were operated on. 27 patients had mature teratoma (teratoma differentiated) in the resected specimens and 23 had viable cancer. Follow-up data were available for 26 and 22 of these patients, respectively. 23 of 26 patients (88%) with mature teratoma are alive and disease free after a follow-up of 53–110 months (median 92 months). 3 patients developed progressive disease; 1 died. A peculiar case of growing mature teratoma on the forearm is described. 13 of 22 patients (59%) with residual carcinoma are alive and disease free after a follow-up of 74–112 months (median 95 months). The prognosis of patients with carcinoma is shown to be correlated with the completeness of surgery, which in turn is correlated with the initial tumour mass before chemotherapy.
Eur J Cancer, Vol. 27, No. 6, pp. 695–698, 1991

INTRODUCTION

THE TREATMENT results of metastatic non-seminomatous germ-cell tumours have improved dramatically with the introduction of cisplatin combination chemotherapy. Survival rates beyond 3 years are reported to be 63–89% [1–5]. About half of the patients undergo postchemotherapy surgery, although the percentages in different series vary from 24%–70% [6, 7]. In about 20% of patients carcinoma is found in the resected specimens, 40% have mature teratoma (teratoma differentiated) and 40% have fibronecrotic tissue and normal architecture [6, 8–11]. Patients with residual viable cancer appear to have a high probability of disease progression [12, 13]. However, few reports are available about the long-term prognosis of patients with residual carcinoma [6, 13, 14] or mature teratoma [6, 15]. This report presents the analysis of such patients initially treated with cisplatin, vinblastine and bleomycin (PVB) in an EORTC GU Group Study [9].

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Revised 13 Mar. 1991; accepted 18 Mar. 1991.

Table 1. Type and macroscopic completeness of retroperitoneal surgery in 24 patients with mature teratoma

	RPLND		Biopsy	
	Bilateral	Unilateral	Excisional	Incisional
Surgery				
Complete	9	4	4	—
Incomplete	3	3	0	1

RPLND = retroperitoneal lymph-node dissection.

PATIENTS AND FOLLOW-UP

From 1979 to 1983 the EORTC GU Group entered 239 patients with disseminated non-seminomatous testicular cancer in a prospective randomised study. The patients received 4 cycles of induction chemotherapy with cisplatin, vinblastine and bleomycin, with a randomisation between 0.4 (100%) and 0.3 mg/kg/cycle (75%) of vinblastine. No difference between the treatment arms was found. The treatment results of this study have been reported elsewhere [9].

The protocol required complete macroscopic resection of residual masses after induction chemotherapy, provided that serum tumour markers were normal. Residual masses were determined by physical examination, chest X-rays, and computed tomography (CT) of chest and abdomen. 102 patients (43%) underwent exploratory surgery. All had normal serum concentrations of human chorionic gonadotropin (HCG) and alpha-fetoprotein (AFP) at that time. Of these 102 patients 52 (51%) had fibrosis and necrosis or normal architecture, 27 (26%) had mature teratoma and 23 (23%) had residual viable cancer in the resected specimens. In this paper an analysis is presented of time to progression, overall survival, completeness of post-chemotherapy surgery and treatment thereafter, and the relationship of these factors with histology of the primary tumour and extent of disease at the start of chemotherapy. All patient charts were reviewed by R.L.H.J. Data were available for 26 patients with mature teratoma, and for 22 with viable cancer.

The histological diagnosis of the testicular cancer was made according to the British classification [16].

Mature teratoma

Of the 26 patients with mature teratoma the primary tumour was diagnosed as malignant teratoma intermediate (MTI) in 11 (42%), undifferentiated (MTU) in 13 (50%) and trophoblastic (MTT) in 2 patients (8%), similar to the distribution in the whole study population of 239 patients.

Of these 26 patients, 24 underwent resection of retroperitoneal masses (Table 1) and 2 were operated to remove tumour from lung, mediastinum and liver. Of the 24 laparotomised patients, 4 also underwent a supraclavicular lymph-node resection and 3 other patients had additional tumour resections from lung and inguinal region. The tumour mass could not be completely removed from the retroperitoneum in 7 patients. Immature teratoma was found in 1 patient. In none of the patients were tumour types other than germ cell found.

3 patients (12%) developed progression of disease. The first patient relapsed 4 months after a right retroperitoneal lymph-node dissection (RPLND). Histological examination showed a small area of mature teratoma, necrosis and fibrosis. At relapse he showed rising markers (HCG and AFP). He received salvage chemotherapy with 3 cycles of cisplatin and etoposide, followed by a left-sided RPLND. Histology showed only necrosis and normal tissue. 3 months later he relapsed again. Despite multiple chemotherapy regimens including ablative chemotherapy and autologous bone marrow reinfusion, he died 9 months after the second relapse.

The second patient had residual masses retroperitoneally, in the upper mediastinum and in the left supraclavicular region. A left supraclavicular lymph-node resection and a bilateral RPLND were performed. Histological examination showed mature teratoma and necrosis. 4 months later a residual mass was removed from the mediastinum, which also contained mature teratoma only. 33 months after the RPLND a growing mature teratoma was resected from the right retroperitoneum. The patient remains disease free 56 months after the second laparotomy.

The third patient presented with a large mediastinal mass, a big metastasis occupying the lower lobe of the right lung and a liver metastasis involving half of the right lobe of the liver. After completion of induction chemotherapy he underwent a right lower lobectomy, together with a resection of the mediastinal mass and a right hemihepatectomy. All three tumour masses contained mature teratoma. 3 months later the patient noticed a small tumour on the dorsal side of the right forearm, about 2 cm above the wrist. When he first mentioned this to his physician, it was considered to be a ganglion. The tumour grew very slowly and in December 1985 an incisional biopsy was done, which showed mature teratoma. After additional examinations with nuclear magnetic resonance imaging (NMR) (Fig. 1) the tumour was completely removed in April 1986. The mass consisted solely of mature teratoma (Fig. 2). The patient is still free of disease (May 1991).

Of the remaining 23 patients, 2 were lost to follow-up due to emigration after 53 and 55 months. The remaining 21 patients are free of disease for a median follow-up of 92 months (range 60–110 months).

Carcinoma

Of the 22 patients with residual viable cancer, 16 underwent resection of retroperitoneal masses, including 2 patients who also had resection of a supraclavicular mass and a thoracotomy for resection of bilateral lung metastases, respectively. 6 other

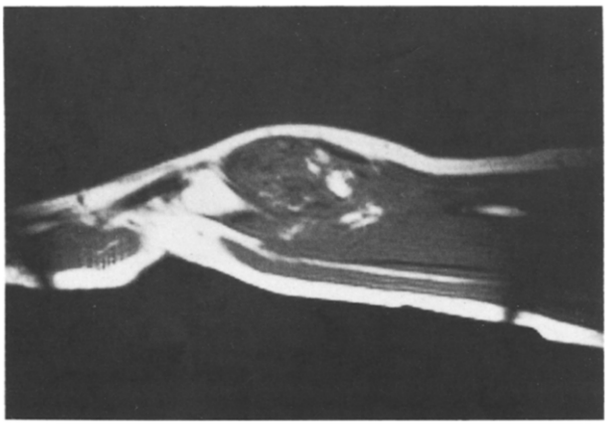

Fig. 1. NMR image of mature teratoma of the right forearm.

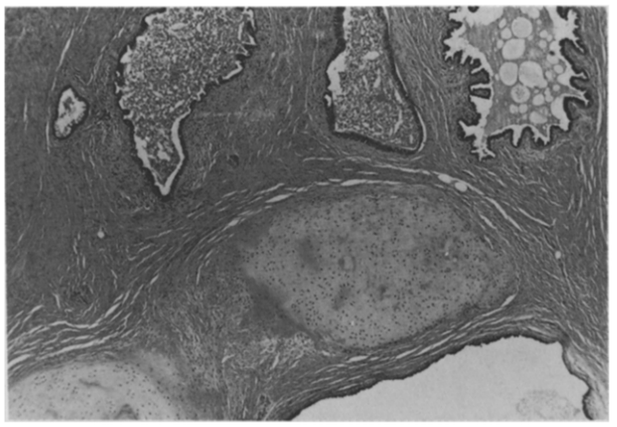

Fig. 2. Histological view of mature teratoma of the right forearm.

Table 3. Consolidation therapy following surgery in patients with residual carcinoma, related to completeness of surgery and survival

Further therapy	No. of patients	Surgery	Alive	Dead
Chemotherapy alone	15	Complete	7*	1
		Incomplete	3	5
Chemotherapy and radiotherapy	1	Complete	0	1
		Incomplete	0	0
Radiotherapy alone	2	Complete	1	0
		Incomplete	0	1
None	3	Complete	3	0
		Incomplete	0	0

*Including 1 patient lost to follow-up after 25 months.

patients underwent complete resections of lung metastases and a supraclavicular mass. Table 2 shows that 8 patients with retroperitoneal surgery had macroscopically incomplete resections.

The therapy after surgery was left to the discretion of the physician. 3 patients with complete resections did not receive further therapy. They all survived disease free. 19 patients received consolidation therapy, consisting of chemotherapy alone in 16 patients, chemotherapy combined with radiotherapy in 1 patient and radiotherapy alone in 2 patients (Table 3). Of these 19 patients 10 relapsed during or after consolidation therapy. 1 patient relapsed with a mature teratoma, which was resected. 1 other patient was successfully treated with salvage chemotherapy for lung metastases, 18 months after surgery. In the other 8 patients salvage therapy (chemotherapy in 6, surgery in 5 and radiotherapy in 4 patients) was unsuccessful. Of note, 5 of 7 relapsing patients with incomplete retroperitoneal surgery also developed metastases at sites other than the retroperitoneum.

In sum, 8 of the 22 patients (36%) have died of progressive disease at a median of 21 months after postchemotherapy surgery (range 9–88 months). 1 patient was lost to follow-up 25 months after surgery because of emigration. Thus, 13 of 22 patients (59%) are alive and disease free after a median follow-up of 95 months (range 74–112 months).

In these 22 patients the primary tumour was MTI in 9 patients (41%), MTT in 8 (36%) and MTU in 5 patients (23%). There was no correlation between these histologies and the completeness of surgery and survival.

The relationship between the initial tumour mass before first chemotherapy and survival was also analysed. 9 of the 22 patients started with low volume metastases (defined as lymph-node metastases <5 cm and/or lung metastases <2 cm); 7 (78%) are alive and disease free. Only 6 of 13 patients (46%) with high volume are alive and disease free ($P = 0.14$) (χ^2 test).

There was a clear relationship between prognosis and completeness of surgery: 11 of 13 patients (85%) with complete resections and 3 of 9 (33%) with incomplete resections are alive and disease free ($P = 0.01$). Initial tumour mass was also correlated with the completeness of surgery as 8 of 9 patients (89%) with low volume had complete resections in contrast to 5 of 13 patients (38%) with high volume metastases ($P = 0.02$).

In 7 patients only a "small area" of residual cancer was found; 3 of them had macroscopically incomplete resections. These 7 patients (100%) are alive and disease free, compared with 7 of 15 (47%) in which this was not the case ($P = 0.02$).

Table 2. Type and macroscopic completeness of retroperitoneal surgery in 16 patients with carcinoma

	RPLND		Biopsy	
	Bilateral	Unilateral	Excisional	Incisional
Surgery				
Complete	5	1	2	—
Incomplete	3	0	2	3

DISCUSSION

In this study the survival of patients with residual mature teratoma is 96%. Only 3 of 26 patients relapsed, 2 with mature teratoma, 1 with cancer. The latter patient died. Median follow-up in this group is 92 months. This result was obtained despite the fact that 7 patients had macroscopically incomplete resections. In a study from the Royal Marsden Hospital concerning 32 patients with residual mature teratoma, survival was 84% at a median follow-up of 37 months, and the risk of relapse was clearly correlated with the completeness of surgery. In the Royal Marsden series and in an analysis from the University of Groningen [6, 17], the finding of postchemotherapy mature teratoma was correlated with the diagnosis of MTI in the primary tumour. This could not be confirmed by a study from Memorial Sloan-Kettering Hospital [10] or by our observations reported here.

Investigators from Indiana University have reported on a poor outcome in 51 patients who had postchemotherapy resections of residual teratoma in the presence of normal serum markers [8]. 20 of these patients (39%) relapsed with either teratoma (10 patients) or carcinoma (10 patients) and 9 patients died. Univariate factors that predicted relapse were initial tumour burden, immature teratoma with non-germ cell elements in the resected specimens, and the site of residual disease (mediastinum). This unexpectedly high relapse rate may partly be explained by patient selection, since 25% of patients were treated with multiple chemotherapy regimens before surgery.

The case of a growing mature teratoma in an extremity, as described here, has to our knowledge not been reported before.

In conclusion, patients with mature teratoma in the resected specimens have an excellent prognosis and need no further therapy.

The 59% survival rate of patients with residual carcinoma in this study is comparable with the outcome in other studies [6, 13, 14]. The South-Eastern Cancer Study Group [14] has reported a study of 27 patients with residual viable cancer. Complete resection of tumour could be performed in 18 patients. 7 of these (40%) died of malignant disease as compared with 7 of 9 (78%) incompletely resected patients. In our study 2 of 13 patients (15%) with complete and 6 of 9 (67%) with incomplete resections died because of progressive disease. When these data are taken together, 22 of 31 patients (71%) with complete resections survived as compared to 5 of 18 patients (28%) with incomplete resections. Since incomplete resection is highly correlated with bulky disease at the start of chemotherapy, it is likely that the poor prognosis of these patients is due to chemotherapy resistance, rather than to surgical technicalities. This assumption is further supported by the fact that 5 of the 7 patients with incomplete retroperitoneal resections developed progression at sites other than the retroperitoneum, and that further chemotherapy failed in 4 of these 7 patients.

The role of additional treatments after surgical resection is difficult to assess [6, 12–14]. Our patients did not receive one consistent type of consolidation therapy, but it is interesting to observe that 3 patients survive disease free without further treatment. Several groups of investigators have attempted to define radiological and clinical criteria to predict which patients still harbour (malignant) teratoma or fibronecrotic tissue [6–8, 10, 13, 17–20]. In the opinion of the EORTC investigators complete surgical resection of residual masses in the presence of normal serum tumour markers remains indicated.

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Acknowledgements—We wish to thank Mrs C. Blok-Kort for preparing the manuscript and P.I.M. Schmitz for the statistical calculations.