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Surgical Resection of Residual Tumor after Chemotherapy in Non-seminomatous Testicular Cancer*

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Abstract—*Fifteen patients with disseminated non-seminomatous testicular cancer, 13 of whom had advanced disease, underwent surgery for residual tumor after induction chemotherapy. Complete remissions were achieved in 7 of 9 patients with mediastinal or pulmonary metastases and in 2 of 6 patients with retroperitoneal metastases. Patients with alpha-fetoprotein (AFP) levels over* 10^4 ng/ml *at diagnosis and/or a positive AFP preoperatively failed to achieve complete remission. Complete remissions were obtained in all 8 patients who had resection of necrosis, mature teratoma, immature teratoma or mature teratoma with malignant foci, but in only 1 of 7 patients who had resection of embryonal carcinoma or yolk sac tumor with other components. Of 9 patients with complete remission, 8 have remained free of disease after a median follow-up time of 29 months (range 6–66 months) and one had a contralateral non-seminomatous testicular cancer removed after 60 months. In addition to being therapeutically successful, the combined use of chemotherapy followed by surgery for residual tumor may lead to a better understanding of the influence of chemotherapy on the biology of testicular carcinoma.*

INTRODUCTION

THE MAJORITY of patients with disseminated non-seminomatous testicular cancer can hope to be cured by chemotherapy today. With combination chemotherapy including bleomycin, vinblastine and cisplatinum, complete remissions can be expected in 60–70% of cases [1–3], the relapse rate approaching less than 10% [4]. This represents a substantial improvement since the introduction of combination chemotherapy for this disease in 1960 [5]. The initial tumor burden was found to be a major prognostic factor. Complete remissions with chemotherapy have been achieved in over 90% of patients with minimal disease but in only 35–50% of patients with advanced disease [1, 6]. With the recognition that in some patients with imcomplete remission the residual tumor consisted of mature teratoma only [7], an increasing number of patients underwent surgery for residual disease after chemotherapy (postinductive surgery). The experience gained in the meantime shows that an additional 20% of patients will achieve complete remission by postinductive surgery [1, 8]. It is predominantly the group of patients with advanced disease that benefits from such a combined modality approach [8]. In this report we present the results of postinductive surgery in disseminated non-seminomatous testicular cancer at the University Hospital of Zürich.

MATERIALS AND METHODS

Between September 1976 and October 1981 15 patients with disseminated non-seminomatous testicular cancer who had been treated at the Division of Oncology, University Hospital of Zürich, were referred for surgical resection of residual tumor following chemotherapy. The median age at diagnosis was 26 yr, ranging from

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16 to 34 yr. All patients had had a high orchiectomy, followed by retroperitoneal lymphadenectomy in 8. Four patients were treated with infradiophragmatic radiotherapy after orchiectomy or retroperitoneal lymphadenectomy for proven or suspected retroperitoneal metastases. The extent of disease before chemotherapy was determined according to the clinical and radiological criteria generally used [9]. Where available the pathological findings of the initial retroperitoneal lymphadenectomy were included and involvement of over 5 lymph nodes or a diameter of the metastasis over 2 cm was classified as advanced disease [10]. Five patients had advanced pulmonary disease, 2 patients had minimal abdominal and pulmonary disease, 2 had advanced abdominal disease and 6 advanced abdominal and pulmonary disease. In all patients induction treatment consisted of combination chemotherapy including bleomycin, vinblastine and cisplatinum according to the Einhorn and Donohue regimen [11], or of a regimen including adriamycin according to a Swiss protocol [12]. The indications for postinductive surgery were persistent tumor masses after chemotherapy, either following first induction (12 patients) or following relapse (3 patients).

The median time from the onset of initial chemotherapy or chemotherapy of a relapse to surgery was 6 months, with a range of 3–27 months. Eleven patients were treated with a single induction regimen, while the others had two or more different regimens before surgery. All patients had serial determinations of AFP (RIA, ABBOTT or monorocket immune diffusion by the method of Laurell) and 13 had serial determinations of beta-HCG (RIA, Radium-Chemie) throughout their course, especially within one month before and after postinductive surgery.

The histology of all primary testicular tumors and all specimens resected after chemotherapy was reviewed and classified according to the systems of the WHO [13] and the Testicular Tumor Panel and Registry of Great Britain [14]. The questions involved in classifying testicular neoplasms according to either system, as well as the advantages of their combined use, have been discussed elsewhere [15]. As the separate listing of neoplastic components is of primary importance in the morphologic part of the present paper, the WHO classification takes precedence here, albeit with the following annotations: teratoma with malignant foci corresponds to the WHO's teratoma with malignant transformation and refers to a well-differentiated teratoma harboring within its organoid formation one or several foci of malignant-appearing cells or cell groups, mostly carcinoma. Yolk sac tumor was diagnosed on the basis of the morphologic pattern, histochemical criteria not being available in every case. The one case of choriocarcinoma in our series displayed a typical villous pattern, equivalent to the British panel's teratoma trophoblastic. The diagnostic entities and abbreviations used in the text and the translation between the two systems of classification are given in Table 1.

RESULTS

Surgery

Nine patients underwent thoracic surgery for persistent pulmonary or mediastinal metastases (Table 2, patients 1–9). In 7 patients all gross tumor was resected and postoperative markers were negative. Patient 6 had progressive pulmonary lesions during induction therapy; his pulmonary metastases consisted of immature teratoma. In patient 8, who had residual pulmonary and abdominal disease, no further surgery was attempted because all metastases removed by unilateral thoracotomy consisted of embryonal carcinoma. No surgical mortality or major morbidity was observed.

Six patients underwent retroperitoneal surgery (Table 2, patients 10–15). In 2 all gross tumor was resected and postoperative markers were negative. In patient 11 a retroperitoneal tumor was detected while he was on maintenance chemotherapy with methotrexate, vinblastine, and CCNU 26 months after the onset of chemotherapy and 14 months after being considered in complete clinical remission. Histology revealed mature teratoma with malignant foci. Patient 12 had a progressing tumor after a second induction regimen. For the removal of all gross tumor his left kidney had to be sacrificed. Similarly, in patient 13 a polar artery to the right kidney was ligated resulting in necrosis of the lower pole of the kidney and the formation of a spontaneous urinary fistula. No surgical mortality or other morbidity was observed.

Tumor markers

Beta-HCG in the serum was elevated in 3 of 13 patients at diagnosis, but was normal in all at surgery. The levels of AFP at diagnosis and at surgery are depicted in Fig. 1. An AFP level of over 10^4 ng/ml at diagnosis and an elevated AFP level preoperatively were associated with failure to obtain complete remission through chemotherapy followed by surgery. At the onset of chemotherapy 4 patients had AFP levels over 10^4 ng/ml. All 4 patients with such high levels of AFP before chemotherapy, but only 2 of 11 patients with lower levels of AFP at that time failed to achieve complete remission ($P = 0.05$,

Table 1. Diagnostic entities and their abbreviations as used in the text

WHO classification	British Testicular Tumor Panel classification
Embryonal carcinoma (EC)	Malignant teratoma undifferentiated
Teratocarcinoma (TC)	Malignant teratoma intermediate
Teratoma immature (TI)	
Teratoma with malignant foci (TMF)	
Teratoma mature (TM)	Teratoma differentiated
Yolk sac tumor (YST)	Yolk sac tumor
Choriocarcinoma (CC)	Malignant teratoma trophoblastic

Table 2. Surgery for residual tumor after chemotherapy

Patient No.	Months after onset of chemotherapy	Preoperative AFP, ng/ml	Site of resection	Histology of resected tumor	Result of surgery	Months of follow-up	Current status, comments
1	6	<5	L lung	necrosis			
	10	<5	R lung	necrosis	CR	6	NED
2	4	<5	mediastinum	TM	CR	29	NED
3	9	<5	L lung	TM	CR	24	NED
4	6	<5	R lung	TM	CR	28	NED
5	5	<5	L lung, L azilla	TM	CR	62	60 months after surgery YST + TC in the contralateral testis
6	4	<5	R and L lung	TI	CR	64	NED
7	3	<5	L lung*	EC			
	9	<5	R lung	EC	CR	66	NED
8	7	<5	L lung	EC	IR	14	LWD
9	5	<78	L lung*	YST + TC	↑AFP postop	7	DD
10	3	<5	retroperitoneal	TM	CR†	60	persistent but unchanged mediastinal tumor
11	27	<5	retroperitoneal	TMF	CR	26	NED
12	14	<5	retroperitoneal	YST + EC	↑βHCG postop	3	DD
13	4	180	retroperitoneal	YST + TC	IR	11	DD
14	5	1300	retroperitoneal	YST + EC	↑AFP postop	12	
	13	4925	retroperitoneal	YST + EC	↑AFP postop		DD
15	5	<5	retroperitoneal	necrosis	IR		
	20	220	retroperitoneal	YST + EC	↑AFP postop	5	DD

*Resection and cryosurgery.

†Patient declined surgery for mediastinal tumor.

CR = complete remission, IR = incomplete resection, NED = no evidence of disease, LWD = living with disease, DD = died of disseminated testicular cancer.

Fisher's test). At the time of postinductive surgery 4 patients had persistent elevation of AFP, including 3 patients with initial levels of over 10^4 ng/ml. Complete remission by postinductive surgery was achieved in none of these 4 patients, but in 9 of 11 patients with negative preoperative AFP ($P = 0.05$, Fisher's test). Persistent malignant tumor was found in all patients with elevated and in 4 of 11 patients with negative preoperative AFP.

Histology

The histology of the primary testicular tumor and of the metastases resected after chemotherapy is depicted in Fig. 2. In one patient the resected tumor consisted of necrosis only. In 7 patients the metastases revealed a more differentiated histology (5 TM, 1 TI, 1 TMF) than the primary tumor; all of them obtained complete remission by postinductive surgery. Of the 4 patients whose metastases had the same histology as the primary tumor (1 EC, 1 YST + TC, 2 YST + EC) only one had a complete surgical remission. In 3 patients with a differentiated primary testicular tumor (2 TM, 1 TMF) the resected metastases consisted of less-differentiated components only (1 EC, 1 YST + TC, 1 YST + EC). All three had AFP levels over 10^4 ng/ml before chemotherapy and none achieved complete remission. In all patients with an elevated preoperative AFP the metastases revealed yolk sac components. Seminomatous elements were present in 6 primary testicular tumors and absent in all metastases.

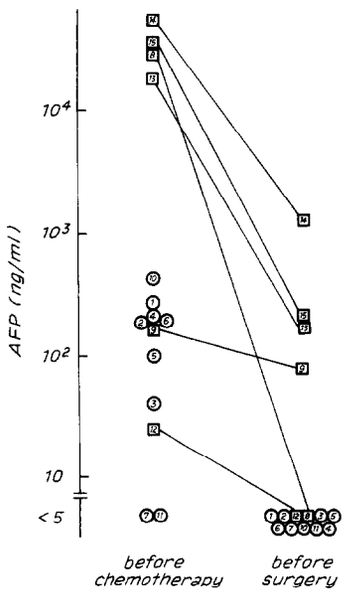

Fig. 1. Level of AFP at the onset of chemotherapy and before surgery in patients with (○) and without (□——□) complete remission by postinductive surgery (patient No. refers to Table 2).

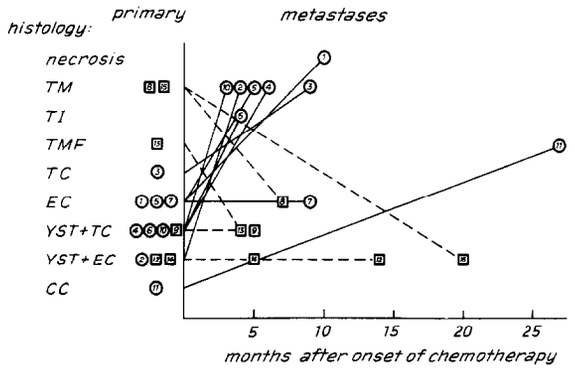

Fig. 2. Histology of the resected metastatic tumor in relation to the primary testicular tumor and time interval between the onset of chemotherapy and surgery in patients with (○——○) and without (□----□) complete remission by postinductive surgery (patient No. refers to Table 2).

Follow-up

Of 9 patients who achieved complete remission by postinductive surgery as judged by resectability of all gross tumor and negative postoperative markers, 8 remained free of disease during a median follow-up time of 29 months, ranging from 6 to 66 months (Table 2). Five of these patients received no further treatment postoperatively (2 TM, 1 TI, 1 TMF, 1 EC). Two patients who received postoperative radiotherapy to the involved field according to treatment protocol [12] had mature teratoma. Patient 10 had a persistent mediastinal mass that was treated according to protocol [12] with mediastinal radiotherapy and an additional 12 months of chemotherapy following retroperitoneal resection of a mature teratoma. The patient declined further interventions and the mediastinal mass has remained unchanged 60 months after surgery. Patient 5, who had undergone thoracotomy for a mature teratoma, was treated with two additional cycles of chemotherapy due to a questionable small pulmonary lesion. A subsequent needle aspirate did not reveal malignant cells and the lesion disappeared on follow-up X-rays. Sixty months after surgery and 72 months after initial orchiectomy a contralateral testicular tumor was removed. The histological examination revealed yolk sac tumor and teratocarcinoma.

Of the 6 patients in whom postinductive surgery failed to achieve complete remission, 5 died within one year and one is alive with disease 14 months postoperatively.

DISCUSSION

Combination chemotherapy including bleomycin, vinblastine and cisplatinum (with or without other agents) will induce complete remission in 60–70% of patients with dis-

seminated non-seminomatous testicular cancer [1–3]. The prognosis is related to the tumor burden, complete remissions being observed in over 90% of patients with minimal disease but only in 35–50% of patients with advanced disease [1, 6]. In approximately 20% of the latter patients complete remissions will be achieved by surgical resection of residual tumor after chemotherapy [1, 8]. Results of such a combined modality treatment have been published [16–18].

Of our 15 patients with disseminated non-seminomatous testicular cancer who underwent surgery for residual disease after chemotherapy, 9 had complete remissions as judged by resection of all gross tumor and negative markers post-operatively. Eight of these 9 patients have remained disease-free during a median follow-up time of 29 months, ranging from 6 to 66 months. In one patient a contralateral non-seminomatous testicular carcinoma was diagnosed 5 yr after complete remission by postinductive surgery. Since virtually all relapses following complete remission by chemotherapy occur within one year [8, 19], it may be assumed that our 7 patients who have remained in complete remission for over 2 yr are cured of their disease. This represents an encouraging result of chemotherapy followed by surgery for residual tumor in a group of patients with mostly advanced disease. However, as one of our patients exemplifies, there may be a risk of developing a sequential contralateral neoplasm, most likely representing a second primary tumor [20]. Prior to the use of combination chemotherapy, the incidence of a sequential contralateral germ cell cancer was reported to be in the order of 1.2–1.4% [14, 21]. When pure seminomas are excluded the incidence of a contralateral sequential non-seminomatous testicular cancer calculated from the data of the British Testicular Tumor Panel is 0.5% [14]. As observed by others [17], the importance of a complete remission by postinductive surgery is emphasized by the poor prognosis of the 6 patients in whom all gross tumor could not be resected or who had elevated tumor markers within one month postoperatively. Five died within one year and one is alive with disease 14 months after postinductive surgery.

A high level of AFP at diagnosis as seen in 4 of our patients with levels of over 10^4 ng/ml indicates a group of tumors resistant to complete eradication by the chemotherapy and post-inductive surgery currently used. In none of our 4 patients was complete remission achieved; two of them had persistent AFP postoperatively despite surgical resection of all gross tumor, and a rapidly growing tumor was again evident within a few months after surgery. A similar fatal clinical course after surgery has been observed in other patients [22], the majority of whom had AFP levels over 10^3 ng/ml at diagnosis. One report found such high levels to be predictive of a poor prognosis [23]. A high level of AFP is characteristic of yolk sac tumor [24, 25] and might in part reflect the tumor burden [24]. We think that it is indicative of a kind of tumor that requires a new therapeutic approach.

All 4 patients with an elevated AFP at surgery had components of yolk sac tumor and none achieved complete remission. The poor outcome in patients with an elevated tumor marker at the time of surgery has been observed by others [17]. In view of these findings, we would favor, whenever possible, a prolongation of the initial chemotherapy or the use of an alternative regimen in such patients before considering surgical resection. For patients with negative markers after induction chemotherapy the optimal time for surgery of residual disease remains to be defined. In order to avoid the toxicity and late sequelae of prolonged chemotherapy, it seems preferable to resect residual tumor after 3–5 cycles of induction chemotherapy if markers are negative at that time.

Since the introduction of combination chemotherapy the correlation between histology of the primary tumor and prognosis in patients with disseminated testicular cancer [14, 26] has decreased in bearing [8]. This does not come as a surprise, given the discrepancy between the morphology of the primary lesion and of the residual tumor after chemotherapy. In 5 of our patients whose primary tumor consisted of embryonal carcinoma or teratocarcinoma with or without yolk sac components, metastases consisted of mature teratoma only, the earliest having been removed after 3 months of chemotherapy. The mechanism of such a transformation is still unknown, but may well be related in some way to chemotherapy [7] since such observations were rarely made in the past [27, 28]. It is possible that chemotherapy destroys the poorly differentiated tissue only, leaving more differentiated components unharmed, and may even enhance differentiation of the tumor. The biological behavior of an unresected adult teratoma is uncertain. There have been reports, however, of lesions growing despite chemotherapy, that at resection were shown to consist of a mature teratoma only [29]. In 3 of our patients the resected tumour had been growing under chemotherapy (1 TI, 1 TMF, 1 EC + YST). In the two patients with immature teratoma and mature teratoma with malignant foci complete remission was achieved by postinductive surgery. Post-operative treatment was given in neither and no relapse occurred. A similar favorable prognosis

for patients with immature teratoma has been observed by others [16].

Postinductive surgery is a diagnostic as well as a therapeutic tool. The histology of the resected tumor will help to guide further treatment. Most authors [16, 17] think that in the absence of postoperative markers further treatment is not indicated after complete resection of necrotic tissue, scar tissue or mature teratoma, but that patients with less-differentiated tumors should receive further chemotherapy because of their unfavorable prognosis.

Patients with disseminated non-seminomatous testicular cancer should have residual tumor resected after induction chemotherapy if tumor markers are negative at that time. A very high level of AFP at the time of diagnosis may indicate a tumor that is relatively resistant to complete eradication by the currently used approach. A persistent elevation of AFP always indicates malignant disease, and it may be preferable to continue with alternative chemotherapy in such patients before considering surgical resection. Lesions progressing under chemotherapy with negative markers may be due to mature teratoma, immature teratoma or mature teratoma with malignant foci and should be resected.

The combined modality approach of chemotherapy followed by surgery for residual tumor is a successful therapeutic concept in non-seminomatous testicular cancer. Analysis of the results including tumor markers and histology offers the oncologist guidance for management decisions and will hopefully lead to a better understanding of the influence of chemotherapy on the biology of this disease.

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