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Clinical and Radiological Correlation of Retroperitoneal Metastasis from Nonseminomatous Testicular Cancer Treated with Chemotherapy

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Abstract—*Forty patients with retroperitoneal metastasis from nonseminomatous testicular cancer treated with chemotherapy were retrospectively studied to* (1) *evaluate the predictive value of mass size as detected by computerized tomography (CT) as an indicator for postchemotherapy surgery and* (2) *determine the factors that influence relapse. Patients received two further courses of chemotherapy after their serum biomarkers became normal and computed tomography indicated a complete response or presence of a residual but stable mass. We found that patients with initial metastases less than* 2 cm *had a low frequency* (14%) *of residual masses after chemotherapy,* vs. 59% *for those with masses of* 2–5 cm *and* 75% *for those with masses of greater than* 5 cm (P = 0.03). *Of* 22 *patients with primary embryonal carcinoma, three of seven* (43%) *with residual masses after chemotherapy had mature teratoma at surgery. Six patients had small* (1–2 cm) *residual abnormalities that were not removed, and three of these patients relapsed. In conclusion, increasing size of retroperitoneal metastasis by CT scan predicts for increased likelihood of a residual mass after chemotherapy; patients who have a residual mass greater than or equal to* 1 cm *require retroperitoneal lymphadenectomy after chemotherapy, whether the tumor histology is embryonal carcinoma or teratoma. The role of surgery for patients who have residual retroperitoneal masses less than* 1 cm *after chemotherapy could not be determined from our study.*

INTRODUCTION

PATIENTS with metastasis from nonseminomatous germ cell tumors of the testis (NSGCTT) can frequently be cured with chemotherapy, with surgery reserved for patients who have residual masses [1]. At The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, we have recently treated patients who have stage II tumors with primary chemotherapy in an attempt to avoid double therapy (surgery and chemotherapy) and preserve ejaculatory function. Among 50 patients so treated, 78% achieved complete remission with chemotherapy and were spared a retroperitoneal lymph node dissection [2].

The present study was undertaken to determine if the appearance or size of the retroperitoneal nodal metastasis, as visualized by a computerized tomography (CT) scan, correlated with the subsequent need for surgical exploration after chemotherapy. Our study included patients, some of them included in previous reports, with stage II or stage III NSGCTT, who had CT scan evidence of retroperitoneal metastasis by CT scan, and who were managed by primary chemotherapy.

MATERIALS AND METHODS

For this retrospective study, we selected for review 28 patients with stage II nonseminomatous germ cell tumors of the testes who had been treated with primary chemotherapy, had evidence of retroperitoneal metastasis as indicated by a CT scan, and had adequate follow-up CT studies during chemotherapy. In addition, 12 patients with stage III disease who had retroperitoneal metastasis, monitored by CT scan during chemotherapy, are included in this report. All patients were derived from three clinical studies done between 1980 and 1987 [1–3]. Patient characteristics are described in Table 1.

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Table 1. *Patient and treatment characteristics* (n = 40)

Characteristics	No.
Stage of patients with CT-documented retroperitoneal metastasis	
II (≤10 cm)	28
III (>10 cm or <10 plus extranodal involvement)	12
Histology	
Embryonal (± seminoma ± EST ± choriocarcinoma)	22
Teratocarcinoma (± other elements)	17
Seminoma with elevated AFP	1

Abbreviations: EST, endodermal sinus tumor; AFP, alpha-fetoprotein.

Three chemotherapy protocols were used, and these have been previously described [1–3]. Twenty-eight patients received $CISCA_{II}/VB_4$ (cyclophosphamide, doxorubicin and cisplatin alternating with vinblastine and bleomycin). Twelve patients received cyclophosphamide, etoposide and cisplatin; or vincristine, bleomycin and cisplatin alternating with etoposide and cisplatin. Two courses of chemotherapy were administered after biomarkers reached normal levels and the CT scan indicated either a complete response or a residual but stable mass. This was accomplished in 36 of the 40 patients. The other four patients received only one course of chemotherapy after serum biomarker levels became normal.

The histology of the testicular tumor and lymph node dissections was reviewed by a member of the Department of Pathology at M. D. Anderson Hospital accustomed to evaluate germ cell tumors. Testicular tumors were classified as: (1) embryonal carcinoma with or without elements of seminoma, endodermal sinus tumor or choriocarcinoma; (2) teratoma with either mature or immature elements with or without other elements; and (3) seminoma accompanied by an elevated alpha-fetoprotein level. Surgical specimens were classified after retroperitoneal lymphadenectomy, as necrosis-fibrosis, mature teratoma or viable carcinoma.

CT examinations of the abdomen and pelvis were performed after the administration of oral, rectal and intravenous contrast by using 8- or 10-mm slice thickness determined by the scanning device and at equivalent intervals. Retroperitoneal metastases were retrospectively classified radiologically on the basis of original size and appearance on CT scan. The longest diameter of the largest mass determined the size category (<2 cm, 2–5 cm and >5 cm). The mass was categorized as solid (psoas density), cystic (uniform low attenuation) and mixed (low attenuation with solid components). Complete response to chemotherapy was defined as the absence of a residual abnormality in the retroperitoneum. If a residual retroperitoneal mass was identified, a retroperitoneal lymph node dissection was generally recommended.

The initial testicular histology was correlated with the prechemotherapy size and appearance of the retroperitoneal mass on the CT scan and with the frequency of residual radiologic abnormalities after chemotherapy. The CT scans after chemotherapy were correlated with surgical findings, and factors were identified that possibly influenced relapse.

The chi-square test for a linear trend was used to correlate the size of the initial retroperitoneal mass with the incidence of residual masses after chemotherapy. Fischer's exact test was used to compare relapse rates.

RESULTS

We found no correlation between the histology of the testicular tumor and the initial size and appearance of retroperitoneal metastasis visible on CT scan (Table 2). Twenty-one patients (53%) had residual CT scan identified abnormalities after chemotherapy (Table 3). The initial size of retroperitoneal metastasis correlated with the incidence of residual abnormalities after chemotherapy: abnormalities became more frequent as the initial size increased (<2 cm, 14%; vs. 2–5 cm, 59%; vs. >5 cm, 75%, $P = 0.03$). Initial appearance (solid vs. cystic or mixed) did not correlate with the frequency of residual abnormalities after chemotherapy, although the combination of embryonal and solid appearance had a lower incidence of residual abnormalities (2 of 9, 22%) vs. the other groups combined (19 of 31, 61%) ($P = 0.04$).

After chemotherapy, CT scans indicated that the retroperitoneal masses disappeared completely in 16 patients. Three patients had residual discrete masses less than 1 cm. Twenty-one patients had residual abnormalities greater than or equal to 1 cm and lymphadenectomy was performed in 16 of these 21 patients (Table 4). No relationship could be demonstrated between the appearance of the residual retroperitoneal abnormalities on CT scan and their histologic types found at surgery (Table 5). None of the three patients with residual masses less than 1 cm has relapsed or developed progressive disease. One patient deserves special mention. Cystic masses in the retroperitoneum were removed after chemotherapy, but a 1.5-cm cystic retrocrural mass, which had not been recognized on the preoperative CT scan, was left in place. Five years later, this mass had grown slightly, accompanied by a rise in the serum alpha-fetoprotein level. When this mass was then removed, only mature teratoma was revealed, but surprisingly, this patient's alpha-fetoprotein level later normalized, and he remains without evidence of recurrence.

Table 2. Relationship between testicular tumor type and initial size and appearance of retroperitoneal metastasis

Testicular tumor type	Metastases identified by CT						
	Size (cm)			Appearance			
	<2	2–5	>5	Solid	Cystic	Mixed	Total
Embryonal	3	16	3	9	1	12	22
Teratocarcinoma	4	12	1	8	1	8	17
Seminoma + AFP	0	1	0	1	0	0	1
Total	7	29	4	18	2	20	40

Abbreviation: AFP, alpha-fetoprotein.

Table 3. Relationship between initial size and appearance of metastasis and frequency of residual masses after chemotherapy

Original metastasis		Residual mass ≥1 cm	
Characteristic	No.	No.	%
Total	40	21	(53%)
Size*			
<2 cm	7	1	(14%)
2–5 cm	29	17	(59%)
>5 cm	4	3	(75%)
Histology and appearance†			
Embryonal and solid	9	2	(22%)
Other	31	19	(61%)

*$P = 0.03$.
†$P = 0.04$.

Table 4. Relationship between testicular tumor type and residual masses ≥1 cm in 21 patients after chemotherapy

Testicular tumor		Residual mass							
Histologic type	No.	Appearance on CT					Histologic surgery type		
		No.	Solid	Cyst.	Mixed	No. excised	Fibrosis	Mature teratoma	Carcinoma
Embryonal	22	9	3*	2†	4	7	3	3	1†
Teratocarcinoma	17	12	5‡	4§	3‖	9	1	7	1§
Seminoma + AFP	1	0	0	0	0	0	0	0	0
Totals	40	21	8	6	7	16	4	10	2

Abbreviation: AFP, alpha-fetoprotein.
*One patient had an irregular 1.7-cm mass, not operated on; tumor later recurred. Another patient had a 1.2-cm mass that resolved gradually.
†One patient had mature teratoma and focal areas of endodermal sinus tumor; currently disease-free.
‡One patient had a 1-cm mass that has not been operated on, and remains without clinical evidence of active disease after 4 years.
§One patient had incomplete removal of mature teratoma and embryonal carcinoma in the retrocrural areas; disease progressed there 5 years later.
‖One patient had a mixed 1-cm mass, not operated on, that later recurred; one patient with a 1.5 × 1 cm retrocrural mass has not been operated on.

Table 5. Relationship between the radiographic appearance of residual masses after chemotherapy and their histologic type at surgery

Radiographic appearance (No.)		Histologic type		
		Necrosis-fibrosis	Mature teratoma	Viable carcinoma
Solid	(4)	2	2	0
Cystic	(6)	0	4	2
Mixed	(6)	2	4	0
Total	(16)	4	10	2

Five of the patients with residual abnormalities did not undergo lymphadenectomy. One of these had an irregular 1.7-cm mass that was interpreted as 'fibrosis'; however, 6 months later, a CT scan indicated the mass grew, and surgery confirmed it was viable carcinoma (Fig. 1). A second patient had a 1.0-cm residual mass with a cystic component that later grew, accompanied by a rise in serum biomarker levels. The third patient had brain metastasis and extensive chest surgery for a mature teratoma; a 1.5 × 1-cm mass remained in the retrocrural area; this patient's mass had not enlarged as of 17 months after chemotherapy. The fourth patient had a residual 1.2-cm mass that resolved gradually and the fifth patient had a 1.0-cm residual mass that remained stable after 4 years; both of these patients are without evidence of active disease.

Of the 22 patients with embryonal carcinoma, we identified a 41% incidence of residual abnormalities after chemotherapy, as compared with a 71% incidence among 17 patients with teratoma elements (Table 4). However, mature teratoma was found in the residual retroperitoneal mass in three of seven patients (43%) whose testicular primary tumor contained only embryonal carcinoma without teratoma elements.

The median duration of follow-up for all 40 patients was 31 months (range, 7–82 months). Disease progressed in five patients (Table 6). Of note is that two of these five patients had small residual masses and were not operated on; a third is the patient described above whose residual cystic masses were incompletely removed. Therefore, three of six patients with residual masses between 1 and 2 cm relapsed, as compared with two of 34 patients whose residual lymph node masses were less than 1 cm or had complete removal of retroperitoneal masses ($P = 0.02$). In addition, two of the five patients who relapsed had received only one course of chemotherapy after marker normalization. One of these had a residual mass between 1 and 2 cm. Therefore, only one of 33 patients who had complete excision or residual masses of less than 1 cm and two courses of chemotherapy beyond marker normalization progressed or relapsed (as compared with four of seven patients with either residual masses of more than 1 cm or only one course of chemotherapy beyond marker normalization ($P < 0.01$)).

Table 6. Characteristics of patients that relapsed (n = 5)

Tumor	Metastases				
	Initial CT appearance and size (cm)	Chemotherapy	Courses after marker normalization	Residual mass in place	Outcome
T + E	Cystic, 3 × 2	$CISCA_{II}/VB_4$	2	1 cm	Dead of disease
E + S	Mixed, 10 × 8	$CISCA_{II}/VB_4$	2	1.7 cm	Dead of disease
T + EST + E	Solid, 8 × 7	Alternate*	1	Incomplete removal; 1.5 × 1 cm left behind	Salvaged with further chemotherapy and surgery
E + S	Mixed, 5 × 4	Alternate*	1	No	Alive with disease
E	Mixed, 2.5 × 2.5	$CISCA_{II}/VB_4$	2	No	Salvaged with further chemotherapy; died of an unrelated cause

*Alternate: vincristine, bleomycin, cisplatin alternating with etoposide and cisplatin.
Abbreviations: T, teratoma; E, embryonal; S, seminoma; EST, endodermal sinus tumor; $CISCA_{II}/VB_4$, cyclophosphamide, doxorubicin, cisplatin alternating with vinblastine and bleomycin.

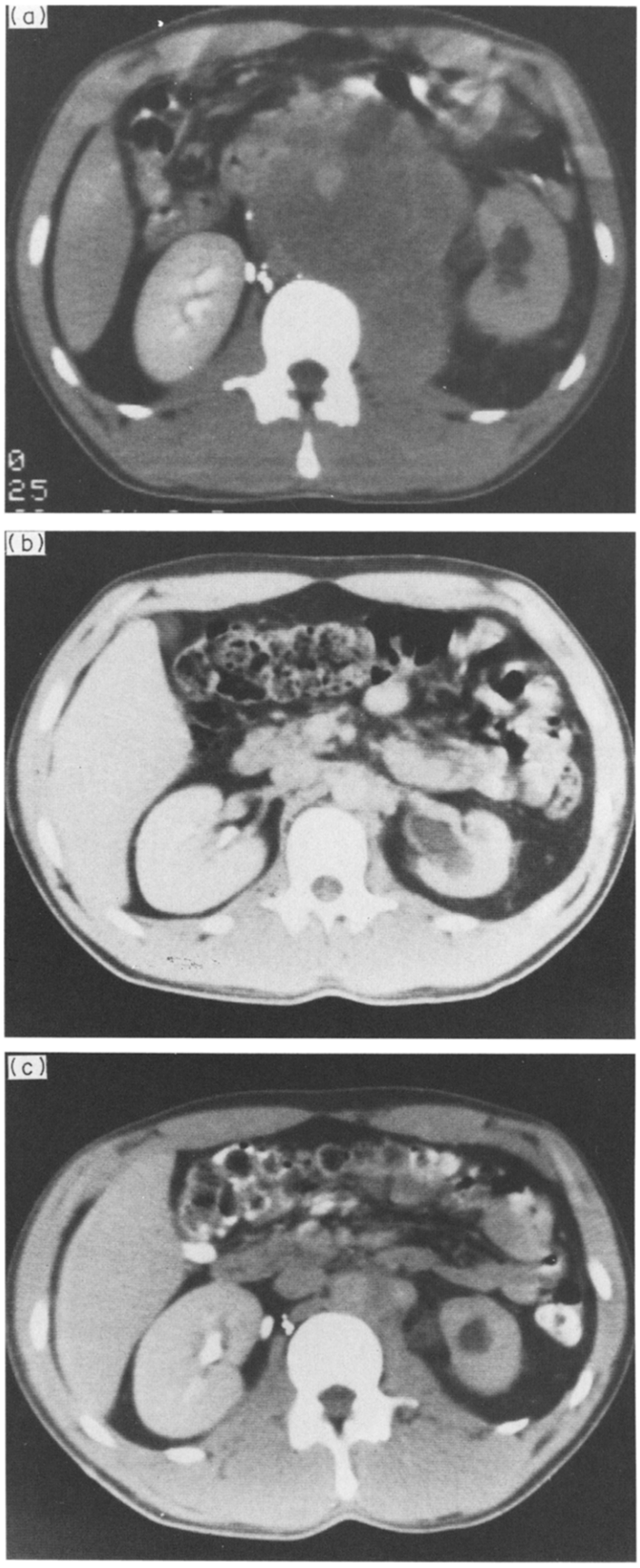

Fig. 1. Twenty-six year old male with metastatic embryonal carcinoma and seminoma of the testes to the retroperitoneum.(a) Prior to chemotherapy (a, aorta). (b) Postchemotherapy solid residual 1.7 cm *abnormality in left paraaortic area, interpreted as 'fibrosis' radiographically. (c) Progression of residual abnormality to a* 2.5 cm *mass* 6 *months later.*

DISCUSSION

The patients for this study were selected retrospectively because they had initial CT-scan evidence of retroperitoneal metastasis and their initial and follow-up CT studies were available for review. Within the limitations of a retrospective study and our patient selection criteria, we noted that the increased incidence of residual abnormalities after chemotherapy correlated with the size of initial retroperitoneal metastasis. These data support previous reports correlating bulk of disease with need for surgery after chemotherapy [1, 4, 5]. However, in our previous study of primary chemotherapy for patients with clinical stage II nonseminomatous testicular cancer [2], we documented that in 50 consecutive patients the most important predictor of the need for surgery after chemotherapy was the presence of teratomatous elements in the testicular tumor. This is also apparent in the present study, where 71% of patients with testicular teratoma elements required surgery as compared with 41% of those with embryonal tumors only. The higher frequency of surgery for patients with embryonal carcinoma in the present study (it was 8% in the previous study) probably reflects the inclusion of patients with higher volume and stage III disease.

There was no correlation between radiologic appearance of metastasis as detected by CT after chemotherapy and histologic type determined after lymphadenectomy, although the number of patients was small. Two of six patients with a residual cystic mass had upon histologic examination viable carcinoma elements in a mass composed mostly of mature teratoma. The other four patients had mature teratoma only. This agrees with the report of Scatarige *et al.*, who found that two of three patients with low-attenuation residual masses had persistent tumor [6]. However, the studies of Stomper *et al.* and Husband *et al.* identified no malignancy in residual masses that had low attenuation [7, 8].

Of interest is that of seven patients with testicular embryonal carcinoma without teratoma elements who had residual abnormalities after chemotherapy and had surgery, three (43%) had mature teratoma in the residual retroperitoneal masses. The frequency of finding teratoma after chemotherapy in patients without teratoma elements in the testis has ranged between 0% and 29% in several studies [9–13]. The finding of teratoma in the retroperitoneal nodes of patients without teratoma elements in the testis is unexplained. Perhaps a small focus of teratoma was not detected in the pathologic examination of the testicular tumor, or differentiation of the undifferentiated malignant histologic types to mature teratoma occurred in the metastasis. Complete removal of teratoma is recommended. Tait *et al.* documented a 44% relapse rate (four of nine) if mature teratoma was not removed completely [14].

As reported in the literature, the accuracy of CT in distinguishing retroperitoneal node metastases from nonseminomatous germ cell tumors ranges between 68% and 87% [15–20]. These studies were performed with untreated patients and cannot be extrapolated to patients who have received chemotherapy, since other factors such as fibrosis or necrosis can enlarge lymph nodes. After chemotherapy, six of our patients had residual abnormalities that measured between 1 and 2 cm that were not removed. Three of these patients have shown disease progression in the same area, so we recommend retroperitoneal lymph node dissections in patients who have residual masses measuring 1 cm or more. For residual masses that are smaller than 1 cm and for patients who have no residual abnormalities, the role of surgery cannot be determined from our study. Two of the patients that relapsed had no residual abnormalities remaining in the retroperitoneum (one received two courses and the other received one course of chemotherapy beyond complete response).

We believe that, although all residual abnormalities measuring 1 cm or more (perhaps also masses that are <1 cm) should be removed, the most important contributor to a high cure rate and freedom from relapse is the type of chemotherapy used. In our previous study of 100 consecutive patients with advanced germinal tumors, we documented a 91% complete remission rate with only a 2% relapse using $CISCA_{II}/VB_4$ [1]. In this present retrospective study, 12 patients received chemotherapy other than $CISCA_{II}/VB_4$; as a result, we can draw no conclusions about the role of a particular chemotherapy combination in the relapse of the five patients. We have, however, recently completed a prospective randomized study that has documented clearly the superiority of $CISCA_{II}/VB_4$ [3].

Donohue *et al.* recently reported a study correlating clinical–radiological evidence of retroperitoneal metastasis with their subsequent findings after surgery [13]. They do not recommend retroperitoneal node dissection in patients with no initial teratoma elements if the CT scan indicates a greater than 90% reduction in the volume of retroperitoneal metastasis after chemotherapy. In our opinion, their study, which used a complex formula for calculating volume of metastasis, was based on the assumption that metastases were ellipsoid, uniform and cigar-shaped, and that CT could reliably measure their length. Any variation in those assumptions could introduce error into the calculations. In addition, in our study, two of the three patients with embryonal carcinoma without teratoma who relapsed had a

greater than 95% reduction in tumor volume (Table 6), and relapse occurred in the retroperitoneum in the area of previous disease.

At M. D. Anderson Hospital, patients with NSGCTT generally receive an individualized number of courses of chemotherapy. We aim to deliver two further courses of chemotherapy after the markers return to normal and a CT scan demonstrates a complete response or a residual mass documented to be stable for two courses. With less aggressive chemotherapy, the percentage of viable carcinoma found at surgery for a residual mass increases substantially, and in those situations relapse will frequently occur despite further chemotherapy [21, 22]. Even in patients who have only mature teratoma after chemotherapy with cisplatin, vinblastine and bleomycin there is a 40% chance of relapse of teratoma or carcinoma [23].

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