Nonseminomatous germ cell tumors: Assessing the need for postchemotherapy contralateral pulmonary resection in patients with ipsilateral complete necrosis

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Objectives: Our objective was to explore the pathologic components of residual masses after primary chemotherapy in patients with metastatic nonseminomatous germ cell tumors.

Methods: A multicenter retrospective study was conducted of 71 patients with thoracic residual masses (39 patients had bilateral lung metastasis) after first-line cisplatin-based chemotherapy for disseminated nonseminomatous germ cell tumors. Among the 71 patients, 52 also had a retroperitoneal lymph node dissection.

Results: Pathologic findings in postchemotherapy residual masses included complete necrosis, teratoma, and viable cancer in 31%, 55%, and 14% of patients, respectively. Discordant pathologic findings were evidenced between retroperitoneal lymph node and thoracic (lung or mediastinal lymph nodes) residual masses in 27% of patients. When a bilateral pulmonary resection was performed, only 2 (5%) of 39 patients had discordant histologic findings between the two lungs. Among patients who had necrosis only in residual masses from their first lung (n = 20), 19 (95%) also had necrosis only in contralateral lesions. A single patient had necrosis only in the first lung and some teratoma in the contralateral lung.

Conclusions: This report shows a high rate (95%) of pathologic concordance between the two lungs. Avoiding contralateral lung surgery could therefore be considered when complete necrosis is found in the first lung after induction chemotherapy for nonseminomatous germ cell tumor.

Multimodality treatments combining cisplatin-based chemotherapy and surgery cure about 80% of patients with advanced nonseminomatous germ cell tumor (NSGCT).¹ Guidelines promote tailoring induction chemotherapy to the prognostic groups identified in the International Germ Cell Consensus Classification (IGCCCG) and using serum tumor markers to monitor its efficacy.^{2,3} At normalization of serum tumor markers after chemotherapy, about one third to one half of patients have residual masses at radiologic assessment. The largest surgical studies have shown that residual masses contain viable tumor cells and teratoma in 12% to 15% and 34% to 42% of cases, respectively.⁴⁻¹³ Moreover, comparative pathologic analysis of retroperitoneal lymph node dissection (RPLND) specimens and lung metastases has unveiled a discordance in lesion components in 28% to 36% of cases.^{8,11,13,14} Complete necrosis is found in residual lung masses in a relatively high proportion of

patients, ranging from 54% to 71%, after normalization of serum tumor markers after chemotherapy.^{8,11,13,14} Extensive resection of all residual masses is therefore currently recommended by most authors. However, in this setting, surgical complications range from 6% for an isolated lung metastasis and 8% for an isolated RPLND to 13% for mediastinal resection or 35% for a sequential RPLND and thoracic resection.¹⁵⁻¹⁸ use and the cumulative dose of bleomycin were shown to be correlated with increased lung surgery-related morbidity and mortality, particularly in patients requiring major pulmonary resections.¹⁹

This prompted our decision to conduct this retrospective study of patients with metastatic NSGCT after normalization of tumor markers to (1) confirm the discrepancy of histologic findings between thoracic and retroperitoneal residual masses, (2) correlate histologic findings in mediastinal lesions with those found in retroperitoneal or lung lesions, due to the lack of published data,¹⁴ and (3) compare histologic findings between ipsilateral and contralateral lung lesions to determine whether contralateral lung surgery is necessary when necrosis only is found in postchemotherapy residual lung masses.

METHODS AND PATIENTS

This is a French multicenter retrospective study. Eligibility criteria included the following: male patients treated consecutively from January 1980 to January 2003, histologically proven metastatic NSGCT (or the diagnosis based on elevated serum markers and a presentation compatible with a metastatic germ cell tumor [GCT]), first-line cisplatin-based chemotherapy, and evidence of residual masses after first-line chemotherapy: (1)

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Abbreviations and Acronyms

CI	= confidence interval
GCT	= germ cell tumor
IGCCCG	= International Germ Cell Consensus Classification
NSGCT	= nonseminomatous germ cell tumor
OS	= overall survival
PFS	= progression-free survival
RPLND	= retroperitoneal lymph node dissection

thoracic (either lung or mediastinal lymph node metastases) and retroperitoneal masses or (2) bilateral thoracic lesions. Patients with metastatic primary mediastinal tumors were not included. In addition, normalized serum tumor markers, including alfa-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) in all cases, were required at the time of postchemotherapy surgery. Surgical management could include partial or complete excision of residual masses and, if reoperation was performed, the interval between the two operations had to be less than 4 months. No additional chemotherapy was allowed between the first and last resections. Patients with residual viable NSGCT containing malignant non-GCT neoplasms such as sarcoma and adenocarcinoma, usually called “teratoma with malignant transformation,”²⁰ were included in this study. Investigators were asked to provide pathologic data on the primary tumor, the prognostic group according to the IGCCCG classification,²¹ the type of first-line chemotherapy, postchemotherapy normalization of serum tumor markers, sites concerned by postchemotherapy surgery, pathologic analysis of residual masses, surgery-related mortality, follow-up information including data on relapse and survival, and the incidence of the growing teratoma syndrome.²² Data collection was finalized in July 2004. Shrinkage was calculated as the percentage of change in the maximum diameter of a mass. The model developed by Steyerberg and associates,¹¹ which identifies subgroups of patients with a high probability of necrosis, was applied in this series. Progression-free survival (PFS) was defined as the time from randomization until objective tumor progression or death. PFS and overall survival (OS) rates were estimated by the Kaplan–Meier method. For the analysis of survival, follow-up started on the date of postchemotherapy surgery. This research was conducted within the framework of the Internal Review Board (Commission Scientifique des Essais Thérapeutiques de l’Institut Gustave Roussy).

RESULTS

Patient Characteristics and Treatment

Five institutions participated in the study. Seventy-one patients fulfilling study criteria were recruited over a 23-year period. Patient characteristics and first-line chemotherapy regimens are listed in Table 1. The median number of chemotherapy cycles was 4 (range 3–12). Tumor markers had normalized after the first regimen in 57 (80%) patients. The first surgical resection of residual masses was performed after a median period of 44 days after chemotherapy (range 10–121 days). Fifty (70%) and 11 (15%) patients underwent a second and a third resection after a median period of 47 and 41 days, respectively. Surgical procedures are summarized in Figure 1. Fifty-two (73%) patients underwent both RPLND and a thoracotomy, including 29 who had a resection of pulmonary metastases, 16 who had a resec-

TABLE 1. Patient characteristics

Characteristics	Patients (n = 71)	
	No.	%
Age, y		
Median	26.8	
Range	17–43	
Primary tumor site		
Testis	67	94
Retroperitoneum	4	6
Pathologic components in the primary tumor		
Seminoma	7	10
Embryonal carcinoma	45	63
Yolk sac tumor	30	42
Choriocarcinoma	26	37
Teratoma	37	52
Immature teratoma	21	30
Other	1	1
Serum markers prior to initial chemotherapy		
HCG, IU/L		
Median	277.5	
Range	0–1,000,000	
Missing values	6	8
AFP, ng/mL		
Median	106	
Range	0–40,927	
Missing values	4	6
LDH, IU/L		
Median	1.88 N	
Range	0–26 N	
Missing values	18	25
IGCCCG		
Favorable	17	30
Intermediate	15	27
Poor	24	43
Missing data	15	
First-line chemotherapy regimen		
BEP	48	67
EP	7	10
Other	16	23

AFP, Alfa-fetoprotein; BEP, etoposide, cisplatin, bleomycin; EP, etoposide, cisplatin; HCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Consensus Classification; LDH, lactate dehydrogenase.

tion of mediastinal lymph nodes, and 7 who had both operations. Resection of bilateral lung lesions and mediastinal lymph node metastases was achieved in 39 and 28 patients, respectively. Bilateral lung surgery was performed by sternotomy in 4 patients and bilateral thoracotomies in 34 patients (missing data for 1 patient). Bilateral thoracotomies were sequential in 25 patients (median time between operations was 13 days), whereas it was performed during the same procedure in 9 patients.

Pathology

Pathologic findings in residual lesions included complete necrosis, teratoma, immature teratoma, and viable cancer in 31%, 39%, 16%, and 14% of patients, respectively. The

GTS

FIGURE 1. Distribution of surgical procedures among the 71 pts included.

pathologic discordance are listed in Table 2 and the pathological discordances are summarized in Figure 2. The overall rate of pathologic discordance (complete necrosis vs teratoma vs viable cancer) between retroperitoneal lymph node and thoracic (lung or mediastinal lymph nodes) residual masses was 27% ($n = 14/52$). In patients who had both a resection of lung metastases and RPLND ($n = 36$), the discordance rate was 33% ($n = 12$). The more aggressive pathologic component was found in the retroperitoneal lymph nodes in 9 (25%) patients and in the lung in 3 (8%) patients. Among 15 patients who had complete necrosis in retroperitoneal lymph nodes, pathologic findings in their lung metastases were as follows: complete necrosis ($n = 12$, 80%), teratoma ($n = 2$), and cancer cells ($n = 1$). In patients who underwent resection of both mediastinal and retroperitoneal lymph nodes ($n = 23$), the discordance rate was 17% ($n = 4$); the more aggressive pathologic component was found in the retroperitoneal lymph nodes in 3 patients. Pathologic findings were discordant in 4 (33%) of 12 patients who underwent resection of both mediastinal lymph nodes and pulmonary metastases.

In contrast, only 2 (5%) of the 39 patients who underwent a resection of ipsilateral and contralateral pulmonary metastases had discordant pathologic findings between the two lungs. The first of these 2 patients was classified in the good prognostic group according to IGCCCG and was treated with 4 cycles of cisplatin and etoposide. Metastases from both lungs contained teratoma, but only pulmonary metastases located in the right lung also contained yolk sac tumor. The second patient was treated with 4 cycles of cisplatin, bleomycin, and etoposide followed by high-dose chemotherapy for an intermediate prognosis NSGCT. The pathologic examination of residual masses found complete necrosis in retroperitoneal and mediastinal lymph nodes and also in the pulmonary metastases located in the right lung, whereas the contralateral lung also contained some teratoma. Among 20 patients who had complete necrosis in the residual masses in the first operated lung, 19 (95%) also had complete necrosis in the residual masses from the contralateral lung.

TABLE 2. Tumor characteristics and pathologic analyses of residual pulmonary masses

	Necrosis		Teratoma		Cancer		Total	
	No.	%	No.	%	No.	%	No.	%
Primary tumor histology								
Teratoma negative	9	36	12	48	4	16	25	50
Teratoma positive	17	68	4	16	4	16	25	50
Prechemotherapy AFP (ng/mL)								
Normal	5	50	3	30	2	20	10	24
Elevated	16	50	9	28	7	22	32	76
Prechemotherapy HCG (IU/L)								
<1,000	13	45	11	38	5	17	29	61
1,000–10,000	2	40	1	20	2	40	5	10
>10,000	14	100	0	0	0	0	14	29
IGCCCG								
Good	3	23	8	62	2	15	13	33
Intermediate	6	67	2	22	1	11	9	22
Poor	16	84	1	5	2	11	19	45
Steierberg score								
>95% necrosis	13	100	0	0	0	0	13	24
Histology at RPLND								
Necrosis	12	80	2	13	1	7	15	47
Teratoma	5	42	7	58	0	0	12	38
Cancer	4	44	2	22	3	33	9	28
Histology at contralateral lung resection								
Necrosis	19	95	1	5	0	0	20	51
Teratoma	0	0	12	100	0	0	12	31
Cancer	0	0	1	14	6	86	7	18
Shrinkage								
Retroperitoneal lymph nodes								
≥50 %	8	80	2	20	0	0	10	59
<50 %	8	47	6	35	3	18	17	41
Lung metastasis								
≥50 %	7	44	7	44	2	12	16	48
<50 %	7	41	4	23	6	36	17	52

AFP, Alfa-fetoprotein; HCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Consensus Classification; RPLND, retroperitoneal lymph node dissection.

Survival and Factors Predictive of Necrosis in Lung Lesions

Survival. After a median follow-up of 5.6 years (range 0.6–19.7), the 5-year PFS was 65% (95% confidence interval [CI], 59%–72%) and the 5-year OS was 94% (95% CI, 91%–97%). Eleven (15%) and 11 (15%) patients had a recurrent malignant NSGCT and growing teratoma syndrome, respectively. Among the 39 patients with bilateral lung resection, 9 had recurrence including 4 with growing teratoma syndrome; site of recurrence was only lung in 3 patients, lung and other site in 3 patients, and others site in 2 patients (missing data for 1 patient). Of 16 patients with unilateral lung resection, none had contralateral residual nodules, 1 has a mediastinal recurrence, and 3 extrathoracic

FIGURE 2. Pathological discordance rate among the residual sites. *RPLN*, Retroperitoneal lymph nodes; *MED.*, mediastinal lesions.

recurrences were observed. Four patients died, all of disease progression.

Shrinkage. Shrinkage was not correlated with OS or PFS. However, shrinkage was well correlated with the percentage of complete necrosis in retroperitoneal lymph nodes but not in lung metastases (Table 2).

Predictive model of complete necrosis. Among the 13 (24%) patients who fit Steyerberg’s subgroup criteria indicating a likelihood of complete necrosis in excess of 90% according to this model, complete necrosis was found in lung metastases in all cases (Table 2).

DISCUSSION

The discrepancy in pathologic findings between postchemotherapy residual retroperitoneal and pulmonary masses in patients with disseminated NSGCT has been extensively reported, and our results (a concordance rate of only 67%) are consistent with previously published data.^{8,11,13,14} Although the numbers are too small to allow firm conclusions, postchemotherapy residual mediastinal lymph node masses seem to be quite similar to residual retroperitoneal masses with a pathologic concordance rate of 83% (95% CI, 61%–95%), which contrasts with a pathologic concordance rate of only 67% (95% CI, 35%–90%) for residual pulmonary masses. The similarity in pathologic findings between residual retroperitoneal and mediastinal masses is likely to be explained by the route of lymphatic drainage from the retroperitoneum directly into the visceral mediastinum via the thoracic duct. Although data in the literature are scarce and limited regarding pathologic findings between residual mediastinal and pulmonary masses,^{14,20,23} the discrepancy we found has previously been suggested.¹⁴

To our knowledge, no published study has focused specifically on the pathologic analysis of residual ipsilateral and contralateral lung masses; hitherto, only anecdotal cases have been reported.^{7,14} The high rate (95% CI, 83%–99%, $n = 39$) of pathologic concordance between residual masses from the two lungs found in this study is potentially an important finding given the alleged paucity of reports on the subject. Of 20 patients with complete necrosis in residual

masses in the first lung, 19 (95%) also had complete necrosis in residual masses in the contralateral lung. The practical consequences may include surveillance of the contralateral lung in such patients, rather than resection of contralateral masses, thus avoiding significant morbidity and allowing substantial cost savings.

Unfortunately, the models currently available to predict complete necrosis in residual lesions are not considered accurate enough. In a multicentric series of 215 patients with disseminated NSGCT and postchemotherapy residual masses, Steyerberg and associates¹¹ identified subgroups of patients with a high likelihood of necrosis at thoracotomy. However, an attempt to validate this predictive model failed; only a 76% complete necrosis rate was obtained in a series of 70 patients in whom the predicted probability of complete necrosis in residual pulmonary masses was 93%.⁸ New methods are being investigated to predict pathologic findings in residual masses. The use of positron emission tomography with 2-(fluorine-18)-fluoro-2-deoxy-D-glucose has been investigated. Unfortunately, the absence of tracer uptake did not correlate with complete necrosis in 37% to 58% of cases in NSGCT.^{23,24} Gene expression profiling in NSGCT may be a useful tool for the selection of chemosensitive tumors, but it has not been validated in postchemotherapy residual masses.²⁵

In conclusion, we found a 95% rate of pathologic concordance between residual ipsilateral and contralateral pulmonary masses after chemotherapy in patients with metastatic NSGCT. This result raises the question of surveillance alone, rather than a contralateral thoracotomy in patients in whom complete necrosis is found in residual masses from the first lung, to avoid unnecessary morbidity. We proposed a renewed algorithm for the surgical management of patients with metastatic NSGCT (Figure 3).

FIGURE 3. Proposed algorithm for residual lung lesions.

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