LONG-TERM RESULTS OF LUNG METASTASECTOMY: PROGNOSTIC ANALYSES BASED ON 5206 CASES

The International Registry of Lung Metastases*
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Objectives: **The International Registry of Lung Metastases was established in 1991 to assess the long-term results of pulmonary metastasectomy.** ***Methods:*** **The Registry has accrued 5206 cases of lung metastasectomy, from 18 departments of thoracic surgery in Europe (*n* = 13), the United States (*n* = 4) and Canada (*n* = 1). Of these patients, 4572 (88%) underwent complete surgical resection. The primary tumor was epithelial in 2260 cases, sarcoma in 2173, germ cell in 363, and melanoma in 328. The disease-free interval was 0 to 11 months in 2199 cases, 12 to 35 months in 1857, and more than 36 months in 1620. Single metastases accounted for 2383 cases and multiple lesions for 2726. Mean follow-up was 46 months. Analysis was performed by Kaplan-Meier estimates of survival, relative risks of death, and multivariate Cox model.** ***Results:*** **The actuarial survival after complete metastasectomy was 36% at 5 years, 26% at 10 years, and 22% at 15 years (median 35 months); the corresponding values for incomplete resection were 13% at 5 years and 7% at 10 years (median 15 months). Among complete resections, the 5-year survival was 33% for patients with a disease-free interval of 0 to 11 months and 45% for those with a disease-free interval of more than 36 months; 43% for single lesions and 27% for four or more lesions. Multivariate analysis showed a better prognosis for patients with germ cell tumors, disease-free intervals of 36 months or more, and single metastases.** ***Conclusions:*** **These results confirm that lung metastasectomy is a safe and potentially curative procedure. Resectability, disease-free interval, and number of metastases enabled us to design a simple system of classification valid for different tumor types. (J Thorac Cardiovasc Surg 1997;113:37-49)**

Surgical resection of pulmonary metastases is now considered a standard therapeutic procedure in properly selected cases and is routinely performed in many departments of thoracic surgery. In fact, many tumors may involve the lung as the unique site of distant spread. Complete surgical excision of all pulmonary deposits is often technically feasible with low morbidity and mortality.[1-3]

However, the curative potential of metastasectomy had been recognized slowly. Pulmonary metastasectomy has been gradually accepted as a surgical procedure of proved therapeutic value in selected cases. Several years after the first resection of a single lung metastasis, discovered during the excision of a chest wall sarcoma,[4] elective surgery has been occasionally offered to selected patients[5] with single pulmonary metastases or a long disease-free interval (DFI).[6] In only a few selected centers has metastasectomy been applied systematically to multiple or bilateral lesions, with the hope of improving long-term survival.[7, 8] In addition, adjuvant chemotherapy has also been used to facilitate surgical resection.

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Although the criteria of eligibility have been progressively expanded, it is difficult to assess the real proportion of patients with isolated lung metastases who are candidates for salvage surgery, because the denominator cannot be properly defined in most clinical conditions. In some tumors, such as sarcomas, germ cell tumors, or pediatric malignant tumors, a high proportion (>50%) of all patients with lung metastases may be candidates for metastasectomy.[9] However, in most epithelial cancers only a small minority of patients with distant disease may be considered.

The data so far available suggest that lung metastasectomy is able to improve significantly the overall and disease-free survival with a limited morbidity and mortality. The overall 5-year survival ranges between 20% and 40% when all the primary sites are combined,[1, 2] much higher than expected after chemotherapy or radiotherapy alone.[10-12]

Unfortunately, the majority of the experiences reported in the literature are affected by small numbers and limited follow-up. Even in the largest series it is difficult to adjust properly for the heterogeneity of patients in terms of age, sex, primary tumor type, extent of metastatic spread, surgical techniques, and concurrent medical treatments.[13-16]

Major areas of controversy remain with respect to the following aspects: selection of patients (i.e., maximum number of resectable metastases), bilateral surgical staging, adjuvant chemotherapy, and prognostic factors for each primary tumor site.[8, 14, 17]

For all these reasons it appeared reasonable to try to overcome the limits of present knowledge by a cooperative multicentric clinical study. The International Registry of Lung Metastases was launched in 1990 with a few clear objectives: set up a common database through the major centers of thoracic surgery in Europe and the United States to facilitate the exchange of information; perform a more homogeneous evaluation of the results for the various primary tumors; define prognostic factors by multivariate analysis; propose a novel system of stage grouping; and define areas of uncertainty concerning surgery and other therapeutic modalities to be explored by prospective randomized trials.

This article is the first analysis of the data collected by the International Registry.

Patients and methods

Structure of the database. A new comprehensive database was designed at the Istituto Nazionale Tumori of Milan to provide a simple and flexible instrument for the Registry. This included a single record form for each patient, divided into four different sections: identification of patients, description of the primary neoplasm (time, site, histology, type of therapy), description of every metastasectomy performed (date, number and size of deposits, type of operation, and combined therapies), and the updated follow-up (pulmonary recurrence, relapse in other organs, treatment, and outcome). All data (except identification of patients) were precoded; in addition, extended description was requested for the primary site, histologic type, and concurrent nonpulmonary resections. Patients who underwent planned sequential or staged thoracotomies were considered to have had one single metastasectomy and not redo surgery. All major centers of thoracic surgery with a specific experience in the surgical management of lung metastases were contacted and offered the opportunity to join the Registry. Specific software programs were designed to retrieve the information already available in the various centers, by computerized recoding and import in the new database, and to update the patients' follow-up.

Accrual of patients. All patients who underwent resection of lung metastases (metastasectomy) with curative intent were considered eligible for the Registry. Incomplete ablation of pulmonary metastases, although not necessarily a reason for exclusion, had to be unequivocally identified. Eradication of the primary tumor and absence or effective treatment of metastases in other organs, before or concurrent with pulmonary metastasectomy, were considered mandatory for inclusion in the Registry.

The accrual of patients in the database was activated in 1991. A pilot study was performed with the use of the data available at the Istituto Nazionale Tumori of Milan and at the Royal Brompton Hospital of London. All records derived from the other centers were subsequently merged by means of purpose-designed recodification systems for each original source of data. For those centers in which a local database was not available, a copy of the Registry database was delivered to allow the input of data on site.

One or more site visits were necessary in some centers to help with the data collection, retrieve missing information, and update the follow-up. The medical research fellows participating in the data management visited eight centers in five countries, spending a total of 14 man-months abroad.

From 1991 to 1995, 5290 patients were enrolled in the International Database, covering a period of more than four decades. In fact, the first metastasectomy was performed in 1945. Adequate information was available for the vast majority of these patients. Only 84 (1.6%) were excluded from the present analysis because of missing crucial information such as age, sex, site of primary tumor, type of primary tumor, or number of resected metastases. A further small group of 46 patients were not included in the multivariate analysis of complete resections because of other missing information.

The distribution of the 5206 eligible patients among the 18 members of the Registry is illustrated in the appendix.

Analysis. The data were analyzed by an independent agency (Institute of Drug Development, or ID2, Brussels) using the SAS Statistical Analysis System under license from the SAS Institute (Cary, N.C.).

The following variables were tested: sex, age, number of resected as well as pathologically proved metastases, DFI, and histologic type and site of the primary tumor. For the multivariate analysis, primary histology codes were grouped as follows: breast, lung, bowel, kidney, uterus, and head and neck cancer, osteosarcoma, other bone sarcomas, histiocytoma, leiomyosarcoma, synovial sarcoma, other soft tissue sarcomas, Wilms' tumor, teratoma, embryonal carcinoma, other germ cell tumors, and any other tumors.

Survival was calculated from the time of first metastasectomy to the last date of follow-up by means of the Kaplan-Meier estimate and the log-rank test.

So that variables could be screened for their potential prognostic value, the patients in each level of a variable were contrasted with the rest of the patient population. The hazard rate for each level of the variable relative to the rest of the population (called for simplicity the "relative risk of death") was estimated, together with its 95% confidence limits, via a Cox proportional hazard model. A relative risk of death smaller than 1 indicated a better than average prognosis. All variables with significant prognostic impact on survival were submitted simultaneously to a Cox regression model.

Results

Patients' features. A total of 5206 cases of lung metastasectomy were included in the present analysis, of which 4572 (88%) involved complete surgical resection. Metastasectomy was considered incomplete in 634 patients (12%) because of microscopic (n = 127) or macroscopic (n = 507) residual disease.

Main patient features are shown in Table I according to the completeness of resection. Overall, 2932 (56%) were male and mean age was 44 years (median 46 years, range 2 to 93 years).

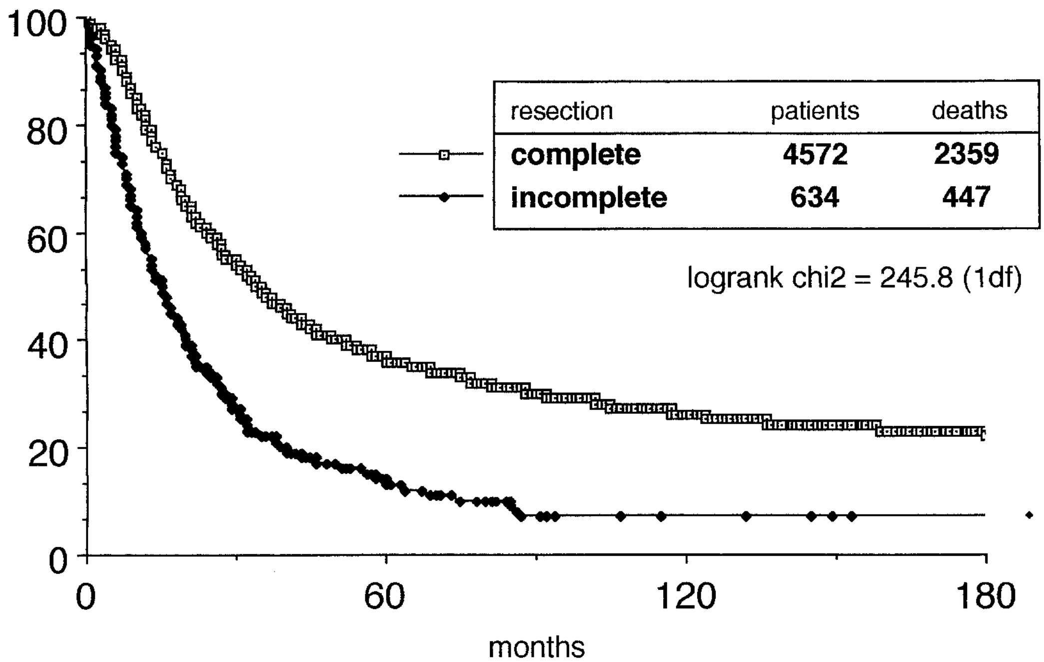
In 43% of patients lung metastases were from an epithelial tumor, in 42% from sarcomas, in 7% from germ cell tumors, in 6% from melanomas, and in 2% from other types, including 30 cases of Wilms' tumors. In the whole series, 31% of patients had a DFI of 0 to 11 months, including 11% who had synchronous metastases; 36% had a DFI of 12 to 35 months and 31% of 36 months or more. Median DFI was 19 months. In most patients (64%) with germ cell tumors the DFI was less than 12 months; the corresponding value was 39% for sarcomas, 21% for epithelial tumors, and 17% for melanomas. In 126 (2%) patients the DFI was not specified.

The surgical approach was monolateral thoracotomy in 58% of patients, bilateral synchronous or staged thoracotomy in 11%, median sternotomy in 27%, and thoracoscopy in only 2%. For the large majority of patients the maximum resection volume was sublobar, including 67% wedge resections, 9% segmentectomies, 21% lobectomies or bilobectomies, and 3% pneumonectomies. Two hundred three lobectomies and six pneumonectomies were performed through median sternotomies. Surgical resection included other sites, such as chest wall, diaphragm, pleura, lymph nodes, mediastinal organs, or liver in 9% of patients.

On the basis of pathologic assessment, single metastases accounted for 46% and multiple metastases 52%. Overall, 26% had four or more metastases, 9% (n = 457) ten or more, and 3% (n = 165)

Table I. *Patients' features*

	Complete	*Incomplete*	*Total*
Age (yr):			
Mean (range)	44 (2-93)	43 (2-79)	44 (2-93)
Sex			
Male	2587	345	2932
Female	1984	289	2273
Type			
Epithelial	1984	276	2260
Sarcoma	1917	256	2173
Germ cell	318	45	363
Melanoma	282	46	328
Other	70	11	81
Free interval			
0	469	87	556
1-11 mo	915	132	1047
12-35 mo	1662	195	1857
36+ mo	1416	204	1620
Approach			
Monolateral thoracotomy	2770	341	3111
Bilateral thoracotomy	534	42	576
Sternotomy	1179	236	1415
Thoracoscopy	84	9	93
Resection			
Wedge	3012	461	3473
Segment	409	40	449
Lobe	1014	95	1109
Pneumonectomy	112	21	133
Other resections	344	102	446
Number			
1	2169	214	2383
2-3	1226	147	1373
4+	1123	230	1353
Diseased nodes (N1-2)	174	65	239
Chemotherapy			
Preoperative	932	213	1145
Postoperative	698	143	841
Redo surgery			
2 operations	732	54	786
≥ 3 operations	243	13	256
Total	4572	634	5206



Patients at risk:

complete	809	254	78
incomplete	35	5	1

Fig. 1. Overall actuarial survival after lung metastasectomy: complete resection versus incomplete resection. The number of patients at risk at 5, 10, and 15 years is reported at the bottom of the curve.

twenty or more; the maximum number of lesions resected was 154. Multiple metastases were resected in 64% of sarcomas, 57% of germ cell tumors, 43% of epithelial tumors, and 39% of melanomas.

In a total of 97 (2%) patients, and in 54 (1%) of those who underwent complete metastasectomy, pathologic examination did not reveal any viable tumor. Such cases were not included in the analyses concerning the number of metastases.

Metastases to hilar or mediastinal nodes were found in 5% of cases, corresponding to 11% of germ cell tumors, 8% of melanomas, 6% of epithelial metastases, and only 2% of sarcomas.

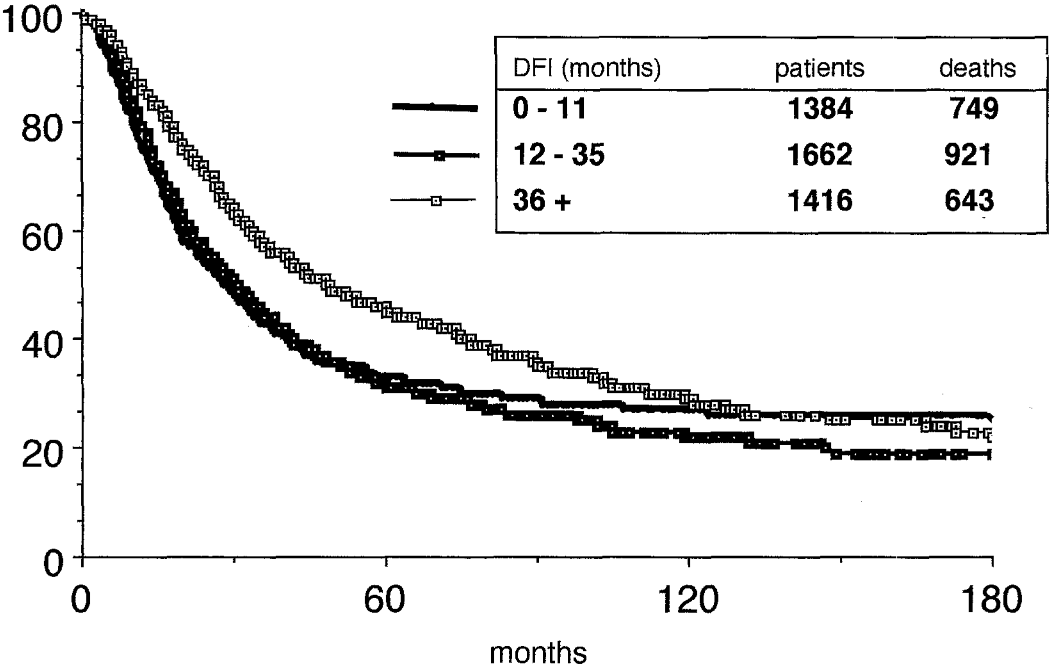
Chemotherapy was administered at the time of occurrence of lung metastases in 38% of patients; in 22% before metastasectomy and in the remaining 16% only after lung resection. The proportion of patients receiving chemotherapy was slightly higher (56%) in the group having incomplete resections and in patients with multiple metastases (45% vs 29% with single metastases).

One fifth of patients underwent multiple metastasectomies (redo surgery): 15% had two metastasectomies, 4% (183) three operations, and 1% (73) four or more; the maximum number of metastasectomies performed on a single patient was seven.

The likelihood of incomplete metastasectomy was higher in patients with nodal metastases (27% vs 11%), as well as in patients with other resections (23% vs 11%).

The information on the number of lesions detectable at radiologic staging was available only for 3498 (67%) patients: 86% of these lesions were completely resected and 14% were unresectable; 51% of the patients had a single radiologic lesion and 49% multiple lesions. The probability of incomplete resection was higher in patients with multiple lesions (23% vs 9%).

Within the subset of 2988 patients who had both preoperative radiologic and postoperative pathologic assessment of the number of lesions with complete metastasectomy, it was possible to estimate the accuracy of clinical staging. Overall, the radiologic assessment of the number of lung metastases was accurate in 61% (n = 1812) of patients, underestimated in 25% (n = 746), and overesti-



Patients at risk:

0 - 11	239	90	31
12 - 35	249	77	20
36 +	310	84	26

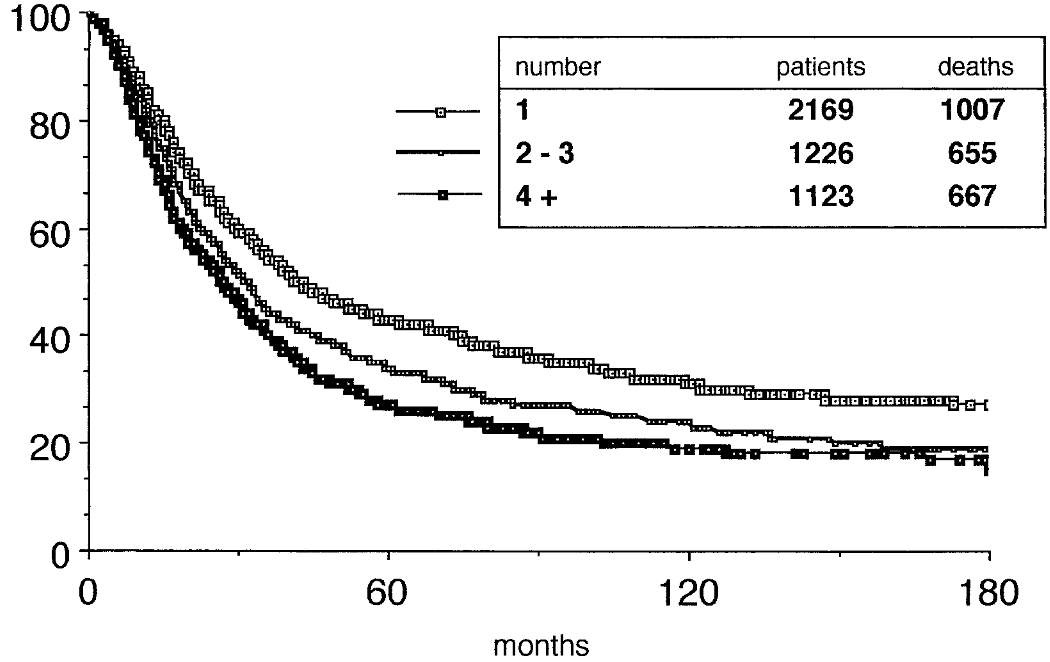
Fig. 2. Survival of patients having complete resections according to the DFI: 0 to 11 months, 12 to 35 months, and 36 or more months.

mated in 14%. In the group of 1854 patients who underwent monolateral thoracotomy, the radiologic accuracy was 75%, underestimation 16% and overestimation in only 8%. However, in the group of 1134 patients who had median sternotomy or bilateral thoracotomy, the number of radiologic metastases was accurate in only 37%, underestimated in 39% and overestimated in 25%. These data underline the importance of bilateral surgical staging in lung metastasectomy.

Survival. The total number of perioperative deaths was 51, corresponding to an overall operative mortality of 1.0%. This figure was 2.4% (n = 15) after incomplete resections and 0.8% (n = 36) after complete metastasectomy. In the group of patients with resectable lesions, the mortality varied according to the maximum resection volume, being 0.6% (n = 20) for sublobar resections, 1.2% (n = 12) for lobectomies and bilobectomies, and 3.6% (n = 4) for pneumonectomies. By adding to the reported surgical deaths 18 patients who died within 30 days of metastasectomy, the overall mortality was 1.3% and the corresponding figure for complete resections, 1.0%.

Fig. 1 illustrates the overall actuarial survival up to 15 years (180 months) for complete and incomplete metastasectomies. The survival after complete metastasectomy was 36% at 5 years, 26% at 10 years, and 22% at 15 years, with a median survival of 35 months; the number of patients alive at these intervals was 809, 254, and 78, respectively. The corresponding survivals for incomplete resections were 13% at 5 years and 7% at 10 and 15 years, with a median of 15 months. In this group 35 patients were alive at 5 years, five at 10 years, and only one at 15 years. The difference was highly significant with a log-rank χ^2 of 245.8 (1 *df*).

Fig. 2 illustrates the actuarial survival of complete resections according to the DFI. For patients with a DFI of 0 to 11 months, the survival was 33% at 5 years and 27% at 10 years, with a median of 29 months. For a DFI of 12 to 35 months, the corre-



Patients at risk:

1	445	150	53
2 - 3	212	65	14
4 +	152	39	11

Fig. 3. Survival of patients having complete resections according to the number of pathologically proved metastases: single lesions, two to three lesions, and four or more lesions.

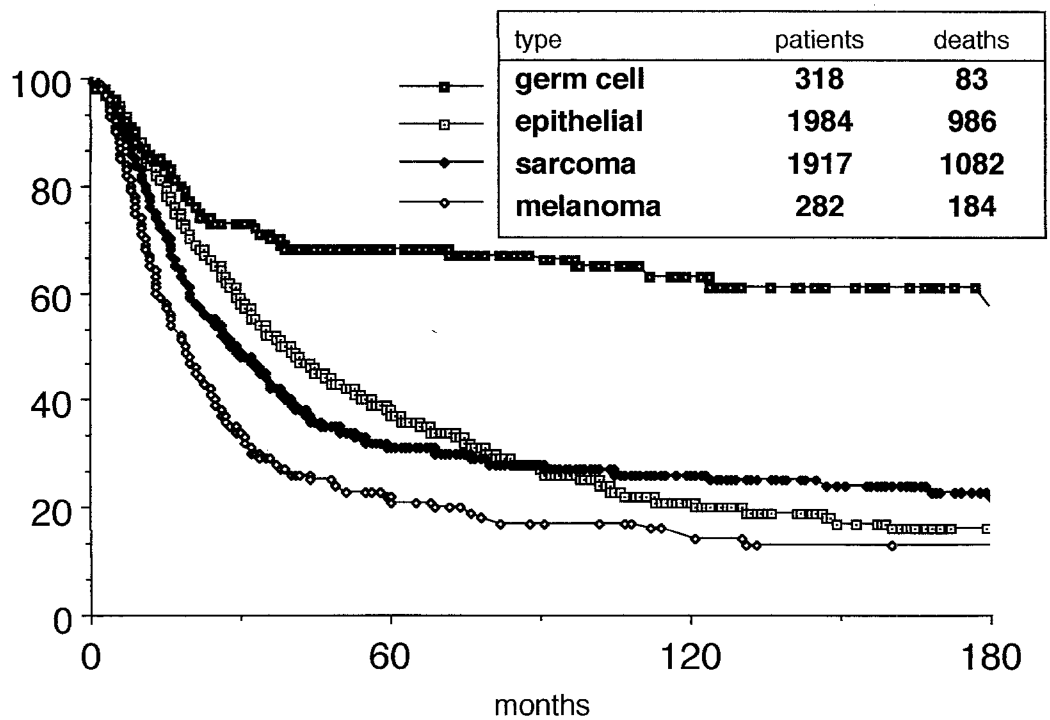
sponding values were 31%, 22%, and 30 months; for a DFI of 36 months or longer, survivals were 45%, 29%, and 49 months, respectively.

Fig. 3 shows the actuarial survival of complete resections according to the number of pathologically proved metastases. Patients with single metastases had a survival of 43% at 5 years and 31% at 10 years, with a median of 43 months. In the group of patients with two or three metastases, the survival was 34% at 5 years and 24% at 10 years, with a median of 31 months. Patients with four or more metastases had a lower survival: 27% at 5 years and 19% at 10 years, with a median of 27 months. However, even in the group of patients who had 10 or more metastases resected (n = 342), the survival reached 26% at 5 years and 17% at 10 years, with a median of 26 months.

Fig. 4 illustrates the actuarial survival of complete resections according to the four major primary tumors types. Patients with germ cell tumors had by far the best survival (68% at 5 years and 63% at 10 years) and melanoma the worst (21% at 5 years and 14% at 10 years, median 19 months). The survivals of patients with epithelial tumors (37% at 5 years and 21% at 10 years, median 40 months) and sarcomas (31% at 5 years and 26% at 10 years, median 29 months) did not differ significantly when these two large groups were compared. However, there were significant differences among the specific histologic types of sarcoma and the various sites of epithelial cancer (discussed later). The survival of all tumor types combined (other than germ cell and Wilms' tumors) was 34% at 5 years and 23% at 10 years, with a median of 33 months (not shown).

Patients with prior or concurrent extrapulmonary resections had a marginally lower survival than patients with only pulmonary resections (29% vs 36% at 5 years and 21% vs 27% at 10 years; not shown).

Recurrence. A recurrence of the disease was documented in 53% of patients who underwent complete lung metastasectomy (Table II). Median time



Patients at risk:

germ cell	100	33	6
epithelial	338	81	21
sarcoma	316	116	40
melanoma	29	10	5

Fig. 4. Survival of patients having complete resections according to the four major primary tumors types: epithelial, sarcoma, germ cell, and melanoma.

Table II. *Relapse after metastasectomy*

	Epithelial		*Sarcoma*		*Germ cell*		*Melanoma*	
Relapse	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
All sites	917		1218		84		180	
Single intrathoracic	111	12	191	16	18	21	14	8
Multiple intrathoracic	291	32	607	50	30	36	34	19
Extrathoracic	515	56	420	34	36	43	132	73
Second metastasectomy	260	28	642	53	34	40	28	16

to recurrence was 10 months. The probability of relapse was higher for sarcomas and melanoma (64%) than for epithelial (46%) or germ cell (26%) tumors. However, the site of relapse was significantly different among the four types. In sarcomas, intrathoracic relapse accounted for 66% of all recurrences, whereas in melanoma 73% of relapses involved extrathoracic organs. Epithelial and germ cell tumors showed an intermediate pattern. Median time to recurrence was shorter in sarcomas than in epithelial tumors (8 vs 12 months).

In accordance with the relapse pattern, the proportion of patients who underwent a second metastasectomy was higher in recurrent metastatic sarcomas (53%) than in any other type. Median interval between the first and second metastasectomy ranged between 10 months for sarcomas and 17 months for epithelial tumors.

Table III. *Adjusted relative risks of death**

	No.	*Relative risk (RRD)*	*95% Confidence interval*
DFI			
Synchronous	474	0.952	(0.820, 1.104)
1-11 mo	909	1.401	(1.263, 1.555)
12-23 mo	1040	1.217	(1.104, 1.343)
24-35 mo	622	1.007	(0.892, 1.136)
36+ mo	1416	0.637	(0.575, 0.705)
Number			
0	47	1.034	(0.678, 1.575)
1	2169	0.764	(0.681, 0.818)
2	738	1.070	(0.953, 1.200)
3	487	1.021	(0.885, 1.178)
4	235	1.316	(1.091, 1.587)
5	214	1.183	(0.971, 1.442)
6	125	1.328	(1.029, 1.715)
7	88	1.251	(0.947, 1.652)
8-9	118	1.206	(0.932, 1.561)
10	73	1.677	(1.262, 2.229)
11-19	179	1.083	(0.880, 1.334)
20+	90	1.270	(0.935, 1.725)
Tumor type			
Teratoma	203	0.373	(0.272, 0.510)
Wilms'	25	0.503	(0.232, 1.088)
Embryonal	92	0.571	(0.373, 0.829)
Uterus	83	0.796	(0.555, 1.142)
Bowel	645	0.831	(0.721, 0.959)
Other bone sarcoma	223	0.965	(0.789, 1.180)
Breast	396	1.117	(0.945, 1.320)
Head and neck	247	0.898	(0.735, 1.096)
Kidney	372	0.928	(0.790, 1.091)
Osteosarcoma	734	0.990	(0.863, 1.136)
Synovial sarcoma	174	1.026	(0.833, 1.264)
Leiomyosarcoma	156	1.098	(0.878, 1.374)
Other epithelial	184	1.120	(0.900, 1.393)
Other soft sarcoma	421	1.238	(1.078, 1.422)
Histiocytoma	186	1.150	(0.937, 1.412)
Lung	53	1.374	(0.913, 2.067)
Melanoma	282	2.034	(1.728, 2.394)

*Adjusted by sex, age, DFI, number of metastases, and tumor type. *RRD*, Relative risk of death.

The long-term outcome of patients who were treated by a second metastasectomy was remarkably good: a 44% survival at 5 years and 29% at 10 years, compared with 34% and 25%, respectively, for patients having had one single operation. This is not surprising in the short term, inasmuch as redo surgery is generally offered to patients with limited pulmonary relapse and good general condition. However, the favorable long-term results suggest a real curative benefit of repeated salvage operations, rather than a simple selection effect.

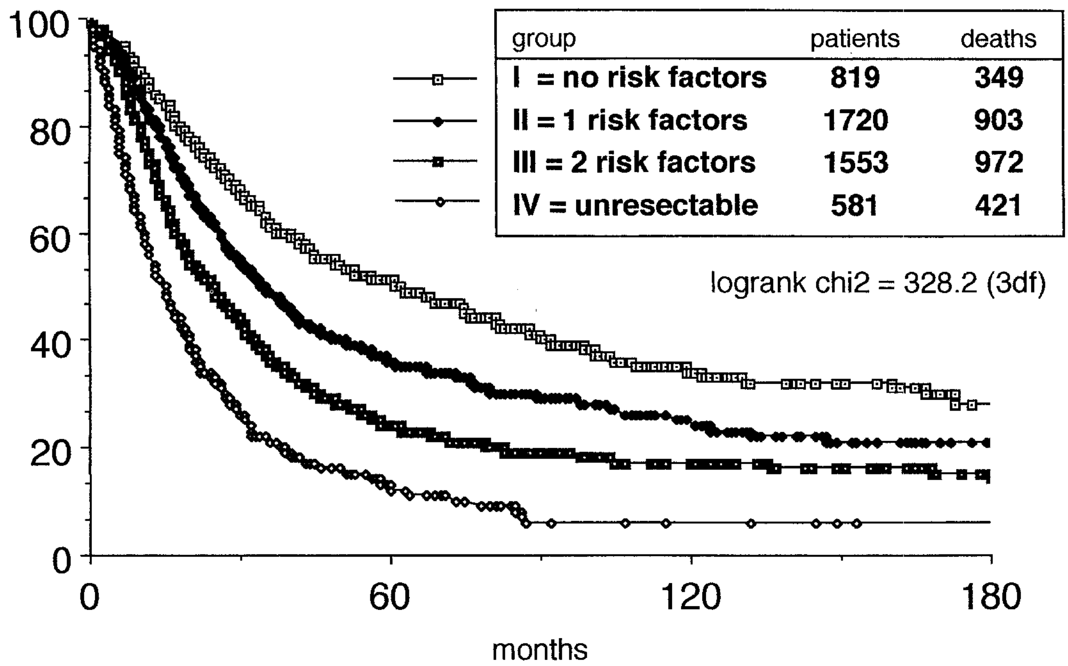
Relative risks of death and multivariate analysis. Relative risks of death and multivariate analysis were calculated on patients who had a complete metastasectomy. When considered separately, DFI, number of metastases, and tumor type were highly significant prognostic variables; age was only marginally significant, and sex was not significant.

Table III illustrates the relative risks of death, that is, the hazard rates for each level of the variable relative to the rest of the population, as well as 95% confidence limits estimated by the Cox proportional hazard model. The relative risks of death for each variable are adjusted for all the other variables of interest: sex, age, DFI, number of metastases, and tumor type. There was a trend to poorer prognosis (relative risk of death > 1) associated with shorter DFI and greater number of metastases. As expected, the best prognosis was observed for DFIs of 36 months or more, single metastases, germ cell tumors, and Wilms' tumors. As far as tumor type was concerned, melanoma had clearly the worst prognosis.

When considered simultaneously, primary tumor type, DFI, and number of metastases emerged as highly significant prognostic factors. In particular, germ cell and Wilms' tumors showed the best prognosis (relative risk [RR] = 0.4) and melanoma the worst prognosis (RR = 2.1); the value of 36 months or more seemed to be the best DFI cutoff to identify a large group of patients with a clearly better prognosis (RR = 0.6). Similarly, single versus multiple metastases seemed to be the best way to group the number of lesions without losing too much information, single metastases having a clearly better prognosis (RR = 0.7).

Prognostic grouping. This model was used to construct a system of prognostic groupings that could take into account all the relevant prognostic factors simultaneously. Germ cell and Wilms' tumors were not included in this system of prognostic grouping because of their peculiar clinical features and, particularly, the different role of metastasectomy after effective chemotherapy.

To build a prognostic grouping that would be simple, discriminant, and valid in different tumor types (other than germ cell and Wilms' tumors), we used three parameters of prognostic significance: resectability, DFI, and number of metastases. Among patients with resectable lesions, a DFI of less than 36 months and multiple metastases were seen to be independent risk factors. Four clearly



Patients at risk:

I	198	65	20
II	296	85	30
III	189	60	18
IV	31	5	1

Fig. 5. Survival of the four prognostic groups: resectable, no risk factors (DFI ≥ 36 months and single metastasis); resectable, one risk factor (DFI < 36 months or multiple metastases); resectable, two risk factors (DFI < 36 months and multiple metastases), and unresectable. Germ cell and Wilms' tumors were excluded.

distinct prognostic groups could thus be identified:

Group I: Resectable, no risk factors (DFI ≥ 36 months, and single metastasis)
Group II: Resectable, one risk factor (DFI < 36 months or multiple metastases)
Group III: Resectable, two risk factors (DFI < 36 months and multiple metastases)
Group IV: Unresectable

Fig. 5 shows the actuarial survival of the four prognostic groups. The difference among the curves was massively significant with a log-rank χ^2 of 328.2 (3 *df*). Median survival was 61 months for group I, 34 months for group II, 24 months for group III, and 14 months for group IV.

The discriminant power of this prognostic grouping was tested on different primary tumors (curves not shown) and proved to be highly significant in each specific tumor type. The log-rank χ^2 (3 *df*) was 131.8 for epithelial tumors, 118.8 for bone sarcomas, 77.4 for soft tissue sarcomas, and 29.6 for melanomas.

Discussion

The project of the International Registry of Lung Metastases had identified in the initial research protocol a few clear objectives: to gather the experience of leading centers of thoracic surgery in the world with outstanding tradition in cancer research, to perform a homogeneous evaluation of the results of lung metastasectomy with multifactorial analysis and proper adjustment for relevant clinical features, to set up the basis for a system of classification and staging of lung metastases applicable to the various histologic types, and to promote prospective clinical trials on specific areas of uncertainty (optimal surgery, neoadjuvant and adjuvant chemotherapy) for the various diseases. Most of these targets have been reached.

The excellence of surgical centers participating in this project has made it possible not only to collect a large number of cases and the broadest spectrum of primary diseases, but also to provide an extensive period of observation. In fact, our analyses of survival and long-term prognosis are based on a considerable number of patients alive at 10 to 15 years.

The results of this International Registry of Lung Metastases confirm that metastasectomy is a potentially curative treatment that can be administered safely with low mortality. In keeping with general principles of surgical oncology, complete removal of all metastatic deposits is associated with long-term survival. Our data suggest that radiologic staging is inaccurate in a large proportion of cases and that intraoperative exploration by an experienced surgeon is required to optimize resection of all metastases.[18-22] Thorough intraoperative staging is therefore required to identify and resect all metastases.[23-26] In this respect, video-assisted thoracoscopy cannot provide optimal intraoperative identification of pulmonary metastases, particularly when more than one lesion is identified in the preoperative period. Our results also suggest that multiple metastasectomies may be required to achieve permanent cure, and that repeated salvage surgery can be safe and effective over the long term.[27, 28]

The role of lung metastasectomy is less clear in tumors such as breast cancer and melanoma and needs to be better defined by future prospective studies. Other areas of uncertainty that may require prospective randomized trials are the efficacy of surgical screening of occult contralateral metastases by median sternotomy (or bilateral thoracotomy) in tumors other than sarcomas, as well as the contribution of induction/adjuvant chemotherapy in specific tumor types.

The present proposal of four prognostic groups, based on three easily available clinical parameters, represents a preliminary attempt at achieving a simple system of classification. Our present data indicate that this system is discriminant in very different tumor types, but further analyses of the Registry data are planned to confirm its validity. On the other hand, the Registry could not assess the role of potential tumor-specific prognostic factors such as estrogen receptors in breast cancer, histologic grading in sarcomas,[29] or carcinoembryonic antigen in colorectal cancer.[30]

An important problem that remains completely undefined is the applicability of salvage surgery in the various diseases. In fact, the proportion of all cases of lung metastases that are amenable to salvage surgery with curative intent varies enormously among the different tumors, ranging from over 50% in osteosarcomas[9] and other pediatric tumors to far less than 1% in most epithelial cancers.

Such questions could not be addressed within the present project because it was impossible to identify a proper denominator, but they may be considered in future developments of the Registry.

The present database is available and running in the various centers for the purposes of updating and follow-up of retrospective cases. In the meantime, a new version of the database is being developed to improve the scientific quality of data in the future, to facilitate prospective accrual of new cases, and to promote the expansion of the International Registry to new members.

Members of the International Registry of Lung Metastases

England: Peter Goldstraw and Ugo Pastorino, Royal Brompton Hospital, London; *France:* Jacques Cerrina, Alain Chapelier, and Philippe Dartevelle, Centre Chirurgical Marie Lannelongue, Paris; Pierre Baldeyrou, Philippe Girard, and Dominique Grunenwald, Hopital Porte de Choisy, Paris; *Germany:* Heinrich Bulzebruck, Joachim Schirren, and Ingholf Vogt-Moykopf, Thoraxklinic, Heidelberg-Rohrbach; Godehard Friedel and Heikki Toomes, Thoraxchirurgie Clinic Scillerhohe, Gerlingen; *The Netherlands:* Albert N. van Geel, Dr. Daniel den Hoed Cancer Center, Rotterdam; *Belgium:* Matteo Cappello and Pierre Rocmans, Hôpital Erasme, Brussels; *Poland:* Andrezej Pietraszek and Maria Sklodowska, Warsaw; *Italy:* Stefano Andreani, Matteo Incarbone, Gianni Ravasi, and Luca Tavecchio, Istituto Nazionale Tumori, Milano; Vincenzo Ambrogi and Costante Ricci, Università La Sapienza; Tommaso Mineo, Università Tor Vergata, Roma; Giuliano Maggi, Ospedale Le Molinette Università di Torino; Antonio Briccoli, Roberta Gelmini, and Afsmin Heidari, Patologia Chirurgica Università di Modena; Natalino Guernelli, Ospedale S. Orsola, Bologna; Vanni Beltrami, Università "G. D'Annunzio," Chieti; *United States:* Manjit S. Bains, Michael E. Burt, Robert J. Ginsberg, Nael Martini, Patricia M. McCormack, and Valerie W. Rusch, Memorial Sloan Kettering, New York; Joe B. Putnam, Jr., and Jack Roth, The University of Texas M. D. Anderson Cancer Center, Houston; Carmack Holmes, University of California (UCLA), Los Angeles; Harvey Pass and Barbara Temeck, National Cancer Institute, Bethesda; *Canada:* Michael Johnston, Mount Sinai Hospital, Toronto.

Statistical analysis. Marc Buyse and Pascal Marchand, Institute for Drug Development (ID2), Brussels, Belgium.

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Discussion

Dr. Valerie W. Rusch *(New York, N.Y.).* The benefit of pulmonary metastasectomy is still questioned by some physicians, particularly nonsurgeons, because patients are frequently offered this treatment on a highly individualized basis, and the prognosis of such patients without surgical resection is still not fully known. Although it is unlikely that the benefit of surgical resection compared with supportive care alone could ever be defined in a randomized manner prospectively, analysis of this large, carefully developed multiinstitutional registry confirms that patients whose tumors are unlikely to respond to systemic therapy often survive long term after pulmonary metastasectomy.

Several important features of this study include the confirmation of the prognostic importance of the number of metastases, the DFI, tumor histologic type, complete resection, and especially the documentation of long-term survival at 10 and even 15 years after resection. It is striking that long-term survival was seen in a small proportion of patients to whom we often hesitate to offer resection, those who have four or even as many as ten metastases.

I have a few questions for Dr. Pastorino. A total of 239 patients were reported as having diseased N1 or N2 nodes. Could you tell us how many patients actually had complete nodal sampling and what percentage of these do the 239 patients represent? Is sufficient information available to make a statistically valid statement about the prognostic importance of nodal disease?

Second, you suggested that all patients should have both lungs surgically examined because of the diagnostic inaccuracy of current imaging techniques. However, the data suggest that the diagnostic accuracy of computed tomography is especially poor in patients who are already known to have multiple bilateral metastases, and certainly bilateral exploration in all patients is not standard care in many centers. One way to clarify this issue would be to analyze the patients who underwent unilateral thoracotomy and to tell us how many of those have a quick relapse, say, within 6 to 12 months, in the contralateral lung.

Third, a particular dilemma is when to perform redo operations for recurrent metastases. How many of the patients who had multiple metastasectomies survived 5 and 10 years? Is there a point at which redo operations become inappropriate?

Fourth, in the manuscript the discriminant power of the algorithm for prognostic grouping, which you noted at the end of the presentation, is noted to be lowest for melanoma. Could you comment on this? Are there prognostic groups for which the survivals either for melanoma or other histologic types are so poor that pulmonary metastasectomy is simply not worth considering?

Finally, you note in the manuscript that patients with prior or concurrent resection of extrapulmonary metastases had a marginally lower survival. How many patients were actually in this category? Are there circumstances in which prior or concurrent resections, say, a liver resection, then a lung resection, are either clearly appropriate or of no benefit?

Dr. Pastorino. Thank you, Dr. Rusch, for these very important questions.

Nodal disease was documented in about 5% of our patients, but we could not discriminate between patients having had a full nodal dissection and patients who had just a sampling or diagnostic assessment. We can try to estimate this value in terms of percent of patients reported as having complete resection and assume that under these circumstances the positive nodal status was based on complete dissection. However, nodal dissection in metastatic disease is only applied at the discretion of the surgeon, and we cannot provide this information reliably. What I can tell you is that in the whole series the difference in long-term survival was not significant. However, the relevance of nodal metastases has to be explored within each separate cell type. In fact, the prognosis of diseased lymph nodes is completely different for germ cell tumors than for melanomas. I suspect that when we adjust for the primary tumor this factor may become significant.

It is difficult to assess the value of bilateral surgical screening with a retrospective analysis. We will certainly try to evaluate the frequency of early relapses in patients who underwent sternotomy compared with those treated by thoracotomy. However, I believe that this question should be addressed by a prospective randomized trial in properly selected patients.

The group of patients with multiple metastasectomies in our experience had a very good survival. The 5-year survival was actually higher in patients having undergone redo surgery: 44% compared with 34% for patients who had only one metastasectomy. This is due in part to the patient selection, because to get the second metastasectomy, the patient has to have a limited recurrence, have good performance status, and probably be comparatively young. However, I must reiterate that those patients who received a second metastasectomy had a good long-term survival.

The prognosis of melanoma is dismal, but there are patients who can be cured. I could not show these data, but within our system of prognostic grouping, none of the patients classified in group III or IV survived. Patients classified in group I had significantly better survival statistics than patients in group II, but both groups had long-term survivors. So there is a curative space for metastasectomy in melanoma, but patients who have two concurrent risk factors probably should be excluded.

As far as other resections are concerned, we could not demonstrate a prognostic impact of such condition in the whole population. However, nodal status has to be examined within each individual tumor because the biology of the various tumors is different. For example, in colon cancer the association of liver metastasis, provided that the resection of all metastatic deposits in the liver is complete, does not confer a poorer life expectancy. By contrast, inasmuch as liver metastasis tends to occur earlier, patients with previous liver metastasis are more selected, and when they require lung metastasectomy they usually have a good prognosis. Again, this will be the subject of further analyses.

Dr. Stefano Nazari *(Pavia, Italy).* I wonder whether the good results in this field could allow us to change our minds about the treatment of primary cancer with lung metastasis at the time of the primary cure. For example, may surgery be an option in a patient with lung cancer and contralateral metastasis, who now is considered not suitable for surgery?

Dr. Pastorino. For certain primary tumors, this is certainly true. In sarcomas, particularly osteosarcoma, metastasectomy for patients with synchronous metastases has probably the same chance of success as for patients with a long disease-free survival. In other words, synchronous metastases in sarcomas may not represent a more aggressive disease and certainly are suitable for curative metastasectomy, provided that the other criteria are satisfied. This is not true for other tumors. Particularly in lung cancer, I do not see any place for curative resection of synchronous metastases and primary tumors. I could not provide the data for each primary tumor, but in this series metastasectomy for lung cancer has a poor prognosis, similar to that of melanoma. It may be applicable to a tiny minority of patients, if any. Furthermore, in this subset there is a big problem of bias and confusion between new primary cancer and metastases. In other words, you never know when you resect one single pulmonary lesion whether you are really dealing with a metastasis or a new primary tumor of the lung.

Appendix 1. *Number of cases by center*

Country	*Hospital*	*No. of patients*
England	Royal Brompton Hospital (RBH), London	289
France	Centre Marie Lannelongue (CCML), Paris	184
	Hopital Porte de Choisy, Paris	561
Germany	Rohrbach Clinic, Heidelberg	152
	Thoraxchirurgie, Gerlingen	528
The Netherlands	Daniel den Hoed Cancer Center, Rotterdam	89
Belgium	Hopital Erasme, ULB, Brussels	41
Poland	Maria Sklodowska, Warsaw	125
Italy	Istituto Nazionale Tumori (INT), Milano	548
	Università La Sapienza and Tor Vergata, Roma	119
	Ospedale Le Molinette Università di Torino	136
	Patologia Chirurgica di Modena and Ospedale S. Orsola, Bologna	302
	Università "G. D'Annunzio", Chieti	62
United States	Memorial Sloan Kettering Cancer Center (MSKCC), New York	1075
	The University of Texas M. D. Anderson Cancer Center (MDACC), Houston	469
	University of California (UCLA), Los Angeles	86
	National Cancer Institute (NCI), Bethesda	338
Canada	Mount Sinai Hospital, Toronto	102