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Management and Survival of Pleural Mesothelioma: A Record Linkage Study

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Keywords
Pleural neoplasm · Mesothelioma · Survival · Cohort study · Management

Abstract
Background: Pleural mesothelioma (PM) is a rare, highly lethal tumor. A definite consensus on its management has yet to be established. ***Objectives:*** To assess management, overall survival (OS), and their predictors in a cohort of patients from Lombardy, the largest Italian region (about 10 million inhabitants). ***Methods:*** Through a record linkage between Lombardy health care administrative databases, we identified patients diagnosed with PM in 2006–2011 without history of cancer, evaluating their management. OS from PM diagnosis was estimated using the Kaplan-Meier method. Predictors of OS and of treatment were assessed using Cox regression models with time-dependent covariates when appropriate. ***Results:*** Out of 1,326 patients, 754 (56.9%) received treatment for PM: 205 (15.5%) underwent surgery, and 696 (52.5%) used chemotherapy. Surgery was spread across several hospitals, and most patients diagnosed in nonspecialized centers (70%) underwent surgery in the same centers. Age at diagnosis was a strong inverse determinant of surgery. Determinants of receiving chemotherapy were younger age, a more recent first diagnosis, and first diagnosis in a specialized center. OS was 45.4% at 1 year, 24.8% at 2 years, and 9.6% at 5 years (median 11 months). OS decreased with age, and was higher for those who underwent surgery, but not for those treated with chemotherapy. ***Conclusions:*** Management of PM varied widely in clinical practice, and significant predictors of treatment were younger age and recent diagnosis, though a high proportion of patients were not treated. Patients were treated in various hospitals, indicating the importance of concentrating serious rare neoplasms in Comprehensive Cancer Centers (as recognized by the Italian Health Ministry).

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Introduction

Pleural mesothelioma (PM) is a rare, devastating tumor, strongly related to asbestos exposure. The incidence of PM worldwide mostly reflects asbestos utilization and exposure. Due to the extremely long latency period between first exposure and disease occurrence, epidemiological projections of PM incidence in Western Europe indicate a peak around 2020, and a trend towards reduction only afterwards [1]. The latest age-specific mortality rates revealed a median increase of 3% per year over the last 15 years in the age group 65–74 years in most high-income countries, except for the USA (in reduction), the Netherlands (in reduction) and Australia (stable), but a decrease in the younger age groups (35–54 and 55–64 years), owing to reduced asbestos exposure of those generations [2].

The prognosis of PM is extremely poor, with 5-years survival around 10% [3–7]. Available data from clinical trials are limited and controversial, and, to date, there is no consensus on its management [8, 9]. The current treatment approaches include chemotherapy, with antifolates (pemetrexed or raltitrexed) and platinum-based agents as the only approved drugs, radiotherapy, and surgery, either in combination or as single treatment [6, 10, 11].

Following the heterogeneous management of PM, in the present work we analyzed data on treatment and prognosis of PM in a large real-world cohort of patients from Lombardy, the largest Italian region (about 10 million inhabitants).

Material and Methods

Data Sources

In order to select a cohort of PM patients resident in Lombardy between 2006 and 2011, we retrieved data from three regional health care administrative databases.

The first source of data was the regional hospital discharge forms (Scheda di Dimissione Ospedaliera, SDO) database (2001–2012). This reports integral parts of medical records and contains detailed clinical information about patients and their hospitalizations, either ordinary or day hospitals. Every record refers to a single hospitalization. These data include demographic characteristics, admission and discharge dates, the main diagnosis and five secondary diagnoses (coded according to the International Classification of Disease, 9th revision, clinical modification, ICD9-CM [12]), date and type of up to five interventions and hospitalization-related costs (coded according to the national Diagnosis Related-Group (DRG) system [13]).

We first selected from the SDO database all subjects with a pleural cancer diagnosis (ICD9-CM codes: 1630-1, 1638-9) between 2006 and 2011, without any SDO reporting a pleural cancer prior to 2006. We defined the pleural cancer diagnosis date as the date of the first SDO reporting this condition. The ICD9 code "163" does not allow distinguishing between PM and other pleural cancers. In order to select a cohort of cases with a high probability of PM, we excluded all subjects whose characteristics were more compatible with a pleural extension of a tumor arising in the lung or another organ. In particular, we excluded (i) subjects with any diagnosis of lung or other primary cancers in the whole period 2001–2011 (either as main or secondary diagnosis), (ii) patients with metastases at any site other than the lung or thoracic lymph nodes (i.e., ICD code: 1970-3 and 1961), and (iii) patients who underwent surgery not compatible with mesothelioma. Through the SDO database, we also investigated whether patients underwent the palliative procedure of pleurodesis (ICD code: 349.2).

The second database was the File F registry (2004–2012), including all drug and selected novel high-cost drug prescriptions administered both in the outpatient setting and in day hospital, and reimbursed by the National Health Service (NHS) [14]. Each record includes information about the market authorization code of the drug package (Autorizzazione all'Immissione in Commercio, AIC), the date and dosage of drug administration, and information about the hospital and the physician administering the drug.

We retrieved pleural cancer-related interventions (surgery, chemotherapy, and pleurodesis) from the SDO database and the File F registry. Using the SDO database, we evaluated whether patients underwent pleurectomy/decortication (P/D) (ICD code: 345, 345.1, 345.9) or extrapleural pneumonectomy (EPP) (ICD code: 325, 326). If both interventions were reported, we classified surgery as EPP. We evaluated whether patients underwent oncologic drug treatment after mesothelioma diagnosis by searching for an SDO reporting a diagnosis of chemotherapy (ICD code: V581, V581.1) or an SDO reporting an intervention of infusion of chemotherapy (ICD code: 992.5). In addition, we searched in the File F registry for prescriptions of oncologic drugs for mesothelioma treatment (pemetrexed, cisplatin, carboplatin, gemcitabine, doxorubicin, vinorelbine, and mitomycin). In the case of surgery, we also evaluated whether the drug was utilized as adjuvant or neoadjuvant treatment.

The third source of data was the Registry Office database of Lombardy, updated to November 2012, which includes information on vital status and (in cases of death) on dates of death of Lombardy residents.

Each of these databases contains a personal identification code, which identifies the NHS beneficiary in a unique and anonymous way. The investigation did not involve any human contact, but only anonymous record linkage analysis of administrative health care databases.

Data Analysis

Each subject was followed up from the first date of diagnosis of pleural cancer to December 31, 2012, thus having a minimum follow-up of 1 year and a maximum of 7 years. Age of patients was considered at the date of mesothelioma diagnosis.

We computed the Charlson comorbidity score index [15] using diagnostic SDO information preceding the date of mesothelioma diagnosis. We categorized this index into three classes (2/3/4 or more comorbidities). We classified hospitals as "specialized" centers if they treated at least 50 PM in 2006–2011 or are recognized as IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) for

oncology by the Italian Ministry of Health. We also conducted a validation study of our selection algorithm at the "Ospedali Riuniti" hospital, Bergamo.

To investigate determinants of medical interventions (surgery or chemotherapy), we fitted Cox proportional hazards models in which the independent variables were year of diagnosis of mesothelioma (2006–2007, 2008–2009, 2010–2011), age (≤50, 51–60, 61–70, 71–80, and >80 years), gender, the Charlson comorbidity score index (2, 3, ≥4), and the hospital of first diagnosis (specialized, nonspecialized). The effect of these covariates was expressed as hazard ratio (HR) and its 95% confidence interval (CI).

In order to estimate overall survival (OS), we retrieved vital status in the Registry Office database of Lombardy. This information was not available in this registry for 57 patients. For them, we considered the last contact with the NHS reported in the other two databases: if the last SDO ended in death we retrieved the date of death from the discharge date, otherwise we used the discharge date as the censoring date. Thus, for OS, individuals accumulated person-years of follow-up from the first mesothelioma diagnosis date until the occurrence of death from any cause, the end of December 2012, or the censoring date. We used the Kaplan-Meyer method to compute OS estimates, also stratifying by age. Differences in survival estimates among strata were assessed by the log-rank test.

The effect of potential predictors on OS was estimated by the Cox proportional hazards model and expressed as HR and its 95% CI. The model included terms for age (≤50, 51–60, 61–70, 71–80, and >80 years), gender, the Charlson comorbidity score index (2, 3, ≥4), time-dependent terms for surgery (yes, no), oncologic drug administration (yes, no), and the hospital of first diagnosis (specialized, nonspecialized).

Results

We identified 3,709 subjects with pleural cancer diagnosis between 2006 and 2011. Of these, 2,852 were Lombardy residents without prior diagnosis of pleural cancer. We further excluded patients for whom we found at least an SDO record reporting a diagnosis of other primary tumors – 1,257 subjects – (for this step we considered the main diagnosis and the secondary five diagnoses). We also excluded patients with metastases other than those to the lung – 193 subjects – (we included patients who only had thoracic lymph node metastases, or of the lung, or both). Patients who had a history inconsistent with mesothelioma – 53 subjects – or underwent surgery incompatible with this neoplasm – 16 subjects – were also excluded. We further excluded 7 patients with inconsistent data. The final cohort, thus, consisted of 1,326 Lombardy residents with pleural cancer diagnosed between 2006 and 2011 (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000486578).

Table 1 gives the baseline characteristics and selected treatments performed during follow-up by the identified sample. There was a slight increase in the number of diagnoses in 2010 and 2011 compared to previous years. Median age at diagnosis was 73 years, and 61.2% were males. Two comorbidities were reported by 64.0%, 20.4%

Table 1. Baseline characteristics and treatments during follow-up of 1,326 patients with mesothelioma enrolled between 2006 and 2011, in Lombardy, Italy.

Characteristics at baseline	
Year of first diagnosis	
2006	197 (14.9)
2007	227 (17.1)
2008	189 (14.3)
2009	212 (15.9)
2010	256 (19.3)
2011	245 (18.5)
Age[a]	
≤50 years	50 (3.8)
51–60 years	127 (9.6)
61–70 years	367 (27.7)
71–80 years	489 (36.8)
>80 years	293 (22.1)
Gender	
Male	811 (61.2)
Female	515 (38.8)
Charlson comorbidity score index[b]	
2	848 (64.0)
3	271 (20.4)
≥4	207 (15.6)
Treatments during follow-up	
Surgery	
No	1,121 (84.5)
Yes	205 (15.5)
Pleurectomy/decortications	144
Radical pneumonectomy	61
Chemotherapy	
None	630 (47.5)
Pemetrexed	548 (41.3)
Other[c]	148 (11.2)
Combination of chemotherapy and surgery	
None	572 (43.1)
Chemotherapy only	549 (41.4)
Surgery only	58 (4.4)
Chemotherapy and surgery	147 (11.1)
Neoadjuvant treatment	52
Adjuvant treatment	95
Pleurodesis	
No	860 (64.9)
Yes	466 (35.1)

Values are *n* (%). [a] Age at first diagnosis of mesothelioma reported in regional hospital discharge form database. [b] Charlson comorbidity score index, adapted from Deyo et al. [15]. [c] Cisplatin, carboplatin, gemcitabine, doxorubicin, vinorelbine, and chemotherapy from SDO database.

Table 2. Determinants of different clinical procedures for mesothelioma

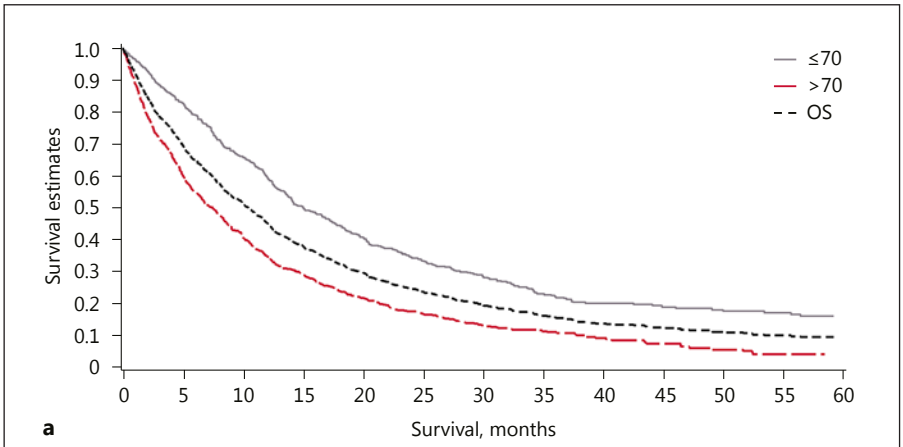
Characteristics	Surgery (n = 205)		Chemotherapy (n = 696)	
	n (%[a])	HR[b] (95% CI)	n (%[a])	HR[b] (95% CI)
Year of first diagnosis				
2006–2007	69 (16.3)	1[c]	195 (46.0)	1[c]
2008–2009	66 (16.5)	0.99 (0.71–1.40)	219 (54.6)	1.27 (1.05–1.55)
2010–2011	70 (14.0)	0.91 (0.65–1.28)	282 (56.3)	1.46 (1.22–1.76)
per 1-year increase[d]		*1.00 (0.92–1.08)*		*1.10 (1.05–1.15)*
Age[e]				
≤50 years	22 (44.0)	2.30 (1.41–3.73)	39 (78.0)	0.78 (0.55–1.10)
51–60 years	47 (37.0)	1.91 (1.32–2.77)	97 (76.4)	0.83 (0.66–1.05)
61–70 years	71 (19.4)	1[c]	286 (77.9)	1[c]
71–80 years	51 (10.4)	0.57 (0.39–0.82)	251 (51.3)	0.53 (0.44–0.63)
>80 years	14 (4.8)	0.32 (0.18–0.56)	23 (7.9)	0.08 (0.05–0.13)
per 1-year increase[f]		*0.96 (0.95–0.97)*		*0.96 (0.96–0.97)*
Gender				
Female	63 (12.2)	1[c]	229 (44.5)	1[c]
Male	142 (17.5)	1.17 (0.87–1.58)	467 (57.6)	1.15 (0.98–1.34)
Comorbidity score index[g]				
2	148 (17.5)	1[c]	520 (61.3)	1[c]
3	40 (14.8)	1.08 (0.76–1.53)	128 (47.2)	0.89 (0.73–1.08)
≥4	17 (8.2)	0.77 (0.46–1.29)	48 (23.2)	0.40 (0.30–0.55)
Hospital of first diagnosis				
Specialized	101 (19.9)	1.27 (0.96–1.67)	329 (64.8)	1.45 (1.24–1.68)
Nonspecialized	104 (12.7)	1[c]	367 (44.9)	1[c]

Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for surgery and for chemotherapy according to selected baseline characteristics among 1,326 patients with mesothelioma enrolled between 2006 and 2011, in Lombardy, Italy.

[a] Percentages are based on the total number of subjects in the same category. [b] Estimated through Cox model including terms for year of first diagnosis (2006–2007/2008–2009/2010–2011), age (≤50/51–60/61-70/71–80/>80 years), gender (female/male), and comorbidity score index (2/3/≥4). [c] Reference category. [d] Obtained by substituting in the model, in place of year of first diagnosis variable in categorical form, the same variable coded as continuous. [e] Age at first diagnosis of mesothelioma reported in regional hospital discharge form database. [f] Obtained by substituting in the model, in place of age variable in categorical form, the same variable coded as continuous. [g] Charlson comorbidity score index, adapted from Deyo et al. [15].

of patients had 3 comorbidities, and about 16% had 4 or more comorbidities. Pleural surgery was performed on 205 (15.5%) patients, partial surgery (P/D) being more frequent than radical surgery (EPP): 144 (10.9%) patients underwent P/D and 61 (4.6%) EPP. About 52.5% of the patients had at least one record from the File F or SDO database reporting administration of oncologic drugs: 548 (41.3%) had pemetrexed prescriptions and, in some cases, the prescription of other chemotherapies, such as cisplatin, carboplatin, gemcitabine, doxorubicin, or vinorelbine, while 148 (11.2%) used chemotherapy agents other than pemetrexed. As regards the combination of chemotherapy and surgery, 41.4% of the sample received oncologic drugs only, 4.4% had surgery only, and about 11.1% had both chemotherapy and surgery. Of the latter, 35.4% received chemotherapy as neoadjuvant treatment and 64.6% in an adjuvant setting. Pleurodesis intervention was performed on 35.1% of the patients.

Table 2 reports the HRs and the corresponding 95% CIs of surgery or chemotherapy according to selected covariates. The HR of surgery was not influenced by calendar year of first diagnosis. Compared to subjects aged 61–70 years, the HR of surgery was above unity in younger patients and below unity in older ones. The HR per 1-year increase in age was 0.96 (95% CI 0.95–0.97). Surgery was not influenced by sex and comorbidities. The HR for patients first diagnosed in specialized centers, compared to those diagnosed in nonspecialized centers, was 1.27 (95%



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	Years from pleural cancer diagnosis				
	1 year	2 years	3 years	4 years	5 years
OS					
Survival	45.4	24.8	15.9	11.7	9.6
Cumulative events	702	939	1,018	1,044	1,053
Number at risk	579	246	119	57	29
≤70 years (*n* = 544)					
Survival	60.0	34.7	22.4	18.7	16.2
Cumulative events	213	335	382	393	398
Number at risk	317	147	75	44	24
>70 years (*n* = 782)					
Survival	35.1	17.7	11.2	6.2	4.2
Cumulative events	489	604	636	651	655
Number at risk	262	99	44	13	5

b

Fig. 1. Kaplan-Meier estimates of overall survival (OS) for the entire cohort and in strata of age (≤70/>70 years) (**a**), with the numbers at risk and the numbers of cumulative events by year of follow-up (**b**), among 1,326 mesothelioma patients enrolled between 2006 and 2011 in Lombardy, Italy.

CI 0.96–1.67). The HR of using oncologic drug treatment significantly increased by 10% (95% CI 5–15) per calendar year of diagnosis. Compared to patients aged 61–70 years, patients aged 71–80 years had an HR of 0.53 (95% CI 0.44–0.63), and patients aged >80 years had an HR of 0.08 (95% CI 0.05–0.13). The HR per 1-year increase in age was 0.96 (95% CI 0.96–0.97). The HR of receiving an oncologic drug was 0.89 for those with 3 comorbidities compared to 2 comorbidities, and 0.40 (95% CI of 0.30–0.55) for those with 4 or more comorbidities. Compared to those diagnosed in nonspecialized centers, patients first diagnosed in specialized centers had an HR of 1.45 (95% CI 1.24–1.68).

Overall, there were 1,058 deaths. Median survival was 11 months. Figure 1 shows OS for the entire cohort and in strata of age (≤70/>70 years), with the numbers at risk and the numbers of cumulative events by year of follow-up. The OS was 45.4% at the first, 24.8% at the second, 15.9% at the third, 11.7% at the fourth, and 9.6% at the fifth year. After 5 years, the OS was 16.2% in subjects aged ≤70 years, and 4.2% in those aged >70 years ($p < 0.0001$). Median survival for patients who underwent P/D was 17.8 months, and 25.4 months for those who underwent EPP. The 2- and 5-year survival rates were 37.9 and 19.9%, respectively, in those receiving P/D, and 53.8 and 24.8% in those receiving EPP.

Table 3 shows mortality HRs by selected baseline characteristics, surgery, and chemotherapy. The HR increased with increasing age, from 0.68 (95% CI 0.47–0.98) in patients aged ≤50 years to 2.51 (95% CI 2.10–3.00) in patients aged >80 years, as compared to those aged 61–70 years. Sex was not associated with OS: males had an HR of 0.95 (95% CI 0.84–1.08) compared to females. Compared to those with 2 comorbidities, patients with 3 comorbidities had an HR 1.14 (95% CI 0.97–1.32), and patients with 4 or more had an HR of 1.18 (95% CI 0.99–1.40). The HR of death in those receiving surgery was 0.76 (95% CI 0.59–0.97), while HR for chemotherapy was 1.25 (95% CI 1.00–1.58). Being first diagnosed in specialized centers did not affect the HR of death.

Table 3. Total mortality hazard ratios (HR) according to selected baseline characteristics, surgery, and chemotherapy

Characteristics	Deaths, n (%[a]) (n = 1,058)	Adjusted HR[b] (95% CI)
Age[c]		
≤50 years	31 (62.0)	0.68 (0.47–0.98)
51–60 years	95 (74.8)	0.88 (0.70–1.11)
61–70 years	275 (74.9)	1[d]
71–80 years	403 (82.4)	1.34 (1.15–1.57)
>80 years	254 (86.7)	2.51 (2.10–3.00)
Gender		
Male	647 (79.8)	0.95 (0.84–1.08)
Female	411 (79.8)	1[d]
Comorbidity score index[e]		
2	659 (77.7)	1[d]
3	223 (82.3)	1.14 (0.97–1.32)
≥4	176 (85.0)	1.18 (0.99–1.40)
Surgery		
Yes	142 (69.3)	0.76 (0.59–0.97)
No	916 (81.7)	1[d]
Chemotherapy		
Yes	537 (77.2)	1.25 (1.00–1.58)
No	521 (82.7)	1[d]
Hospital of first diagnosis		
Specialized	401 (78.9)	0.91 (0.80–1.04)
Nonspecialized	657 (80.3)	1[d]

[a] Percentages are based on the total number subjects in the same category. [b] Estimated through Cox model including terms for age (≤50/51–60/61–70/71–80/>80 years), gender (female/male), comorbidity score index (2/3/≥4), surgery (time-dependent: yes/no) and chemotherapy (time-dependent: yes/no). [c] Age at first diagnosis of mesothelioma reported in regional hospital discharge form database. [d] Reference category. [e] Charlson comorbidity score index, adapted from Deyo et al. [15].

Surgery for mesothelioma was performed in a large number of different hospitals. Of the 104 patients diagnosed in a nonspecialized center who received surgery, 73.1% did so in a nonspecialized center (online suppl. Table 1).

Online supplementary Table 2 shows the validation study of our selection algorithm on 68 subjects for whom we could check and validate the diagnosis through immunohistochemical pathology report [16] at the "Ospedali Riuniti" hospital, Bergamo. Of the 38 (56%) patients included in our cohort, 36 (95%) were confirmed mesothelioma cases. Of the 30 patients excluded by our selection algorithm, 20 (67%) were mesothelioma cases, all of whom had previous history of other primary cancers, which was the reason for their exclusion.

Discussion

This study describes the management and survival of 1,326 mesothelioma patients in real-world clinical settings in Lombardy. Out of the total cohort, 754 (56.9%) subjects received surgery and/or chemotherapy: 15.5% underwent surgery, and 52.5% used oncologic drugs (of these, 78.7% used pemetrexed). Among patients for whom we did not retrieve any surgery or chemotherapy treatment data, 83.2% were aged over 70 years. Sex was not associated with the choice of treatment. Age at pleural cancer diagnosis was a significant determinant of undergoing surgery; age and calendar year at pleural cancer diagnosis and being diagnosed in specialized centers were significant determinants of using chemotherapy. The median OS of our cohort was 11 months. This estimate is consistent with a median survival of 12 months from a review published in 2005 [5], denoting little progress over the last decades.

This study provides important information on clinicians' practices, in the absence of clear indicators from guidelines or scientific evidence. The assessment of PM management in clinical practice revealed a heterogeneous approach, with a substantial proportion of patients who did not receive either surgery or chemotherapy. In the presence of rapid disease progression, bad prognosis, and advanced age, considerations on the risk-benefit profile of interventions often lead to the use of palliative treatment. In particular, younger age at diagnosis was a significant determinant of treatment choice in our cohort, possibly reflecting better general health conditions and the fact that even a modest gain in life expectancy is perceived as more valuable in younger patients. Similar attitudes have been described in other European countries, as reported from a population-based study on treatment patterns of 9,014 patients with PM, assessed by combining analyses from health care databases of Belgium, the Netherlands, and England [17]. The use of chemotherapy was more frequent in Belgium, and decreased with increasing age in all three countries. Overall, chemotherapy rates in patients aged 70–79 years were 55, 36, and 34%, respectively, in Belgium, the Netherlands, and England, while more than half of patients aged <70 years were treated in these three countries. So far, although international guidelines [18] agree on an added benefit of chemotherapy in PM management, they state that treatment choice should depend on the performance status of patients, and should be discussed with them and their relatives on a case-by-case basis. Given the growing evidence of different approaches to PM according to age in current

practice, and the likely increase in age at PM diagnosis due to heavier asbestos exposures of older generations, less toxic therapeutic options for more frail patients are needed.

Our OS estimate is in between those of two previous Italian studies. In a population-based study of 4,100 Italian PM patients diagnosed between 1990 and 2001 and followed up to 2005 [19], median survival was 9.8 months (95% CI 9.4–10.1), and in a retrospective analysis of 1,365 mesothelioma patients from various Italian centers it was 14.5 months [7]. In that study, patients who underwent P/D had a median survival of 20.5 months (similar to our estimate of 17.8) and 2- and 5-year survival rates of 40 and 10%, respectively. Patients who underwent EPP had a median survival of 18.8 months. Corresponding estimates in our cohort were more favorable, with a median survival of 25.4 and 2- and 5-year survival rates of 53.8 and 24.8%, respectively. In the initial analysis of the IASLC (International Association for the Study of Lung Cancer Mesothelioma Databases), a survival advantage was reported in patients undergoing EPP compared to P/D: stage I tumors resected by EPP were associated with a median survival of 40 months, whereas those managed by P/D had a median survival of 23 months. No differences in survival between EPP and P/D were identified in patients with higher-stage disease [20]. In the study of Bovolato et al. [7], factors that predicted a better prognosis, at univariate analysis, were age, histology, chemotherapy, and surgical treatment. The univariate HRs for surgery were similar to our estimates: 0.58 (95% CI 0.50–0.67) for EPP surgery and 0.57 (95% CI 0.47–0.69) for P/D surgery, compared to no surgery. In a multivariate analysis, they found that age, histology, and surgical treatment were independent prognostic factors associated with survival. Moreover, surgical patients had a better prognosis than patients who underwent palliative treatment or chemotherapy alone. However, the better survival in patients receiving surgery was accounted for by selection bias [7]. In the Surveillance, Epidemiology, and End Results (SEER) database [21], surgery was related to better prognosis in patients with epithelioid, but not in those with sarcomatoid mesothelioma. We were unable to distinguish the two histotypes.

More recent studies on immune checkpoint inhibition [22] also showed progress in median disease-free (5.4 months) and OS (18 months) rates. Chemotherapy has been shown to improve – though modestly – survival for PM. Targeted therapy anti-VEGF may also play some role, though still undefined [6].

When comparing patients who underwent surgery or chemotherapy to those who did not, two potential sources of bias must be considered. One is immortal time bias, i.e., the fact that for treated patients an event could not occur before the date of surgery/treatment, and time-dependent analysis was performed to overcome this problem [23]. A second source of bias is confounding by indication, i.e., the fact that subjects undergoing surgery/treatment may have a different prognosis. The surgical approach may in fact select cases with a better baseline prognosis [7].

A prospective clinical trial, the Mesothelioma and Radical Surgery (MARS) trial [24], analyzed the benefit of performing EPP after chemotherapy compared with chemotherapy alone, and found no survival benefit. However, that study was not originally designed to assess the survival benefit of EPP, included a small number of patients ($n = 50$), and reported an operative mortality higher than that of other studies [7, 20, 25]. Despite the modest impact, multidisciplinary treatment is now advocated for PM, whenever possible [8, 9, 11, 26].

We defined specialized centers either as recognized Comprehensive Cancer Centers by the Italian Health Ministry, or based on the concept that "volume makes quality." In fact, morbidity and mortality of surgical treatment were lower in more experienced centers [11]. In our cohort, 73.1% of surgically treated patients first diagnosed in nonspecialized centers did not migrate to a specialized one to undergo surgery. There were some indications that patients first diagnosed in specialized centers received surgery and chemotherapy more often, and that their survival was 10% better, although results were significant for chemotherapy only.

A major difficulty of our record linkage study consisted in selecting a cohort of cases with a high probability of being PM, since a valid diagnosis of PM is complex [9, 10, 20, 27, 28]. The main problem was to distinguish mesothelioma from cancer of the lung invading the pleura or from pleural metastases of other primary tumors. Out of 2,852 pleural cancer cases identified, 1,588 (56%) were excluded from our cohort. It is also likely that, particularly for older or terminal patients, the complex diagnostic procedures needed to diagnose a mesothelioma were not performed.

It is known that classification of mesothelioma cases based on ICD9 code is open to methodological issues even in occupational cohort studies of workers exposed to asbestos [29]. This applies to record linkage studies as well. It is possible that misdiagnosis of mesothelioma has occurred if no immunohistochemical verification, re-

quested for diagnosis confirmation, was performed [10, 16]. The present study is based on the Lombardy region health care administrative databases. This is the largest Italian region, with about 10 million inhabitants, and its administrative databases have been used and validated in a large numbers of studies [30–32]. In addition, our validation study at the Bergamo "Ospedali Riuniti" hospital, using up-to-date histopathological techniques, showed that almost 95% of included patients were confirmed mesothelioma cases. However, a proportion of mesothelioma patients were excluded because of history of another primary tumor. The decision to exclude these cases by design was part of a "conservative" strategy. Pleural involvement in this context could be either the expression of secondary localization from a different primitive cancer or a mesothelioma, and, thus, we decided to reduce the potential risk of including nonmesothelioma patients. Thus, our results refer to mesothelioma cases without history of other cancers.

Another limitation of the present study, and in general of research based on the use of administrative health care databases, refers to the lack of information on a number of covariates [33]. In fact, we had no access to information about relevant tumor characteristics, such as stage and grade, asbestos exposure, lifestyle habits, comorbidities, and family history of diseases. Data on immunohistochemistry [10] were also not available in our study. We were also unable to distinguish between epithelioid and other mesothelioma subtypes, and it is known that the former had better survival. Even if the completeness and accuracy of the medical information reported in our databases improved over the last few years, the administrative purpose for which these datasets were primarily built may lead to inaccuracies in the results [34]. The main advantage of these data is the representativeness of routine clinical practice, since they refer to all medical interventions reimbursed by the NHS, which covers all residents. The complete coverage, in fact, is an essential requirement in order to provide a complete picture of real-world management of PM. Other strengths of this study include the large number in our cohort and the length of follow-up.

In conclusion, our study investigates the choices performed in clinical practice on a controversial topic, where guidelines did not provide clear indications. Surgery and/or chemotherapy were more frequent in younger pleural cancer patients diagnosed in more recent periods, but a large number of patients did not receive either. Moreover, our data showed that patients were treated in a large number of hospitals, several of which performed only a few surgical procedures (P/D or EPP), thus indicating the importance of concentrating serious rare neoplasms in Comprehensive Cancer Centers.

Financial Disclosure and Conflicts of Interest

Dr. Corrao reports grants from Novartis, GSK, Roche, Amgen, BMS, the European Community (EC), the Italian Agency of Drugs, and the Italian Ministry for University and Research (MIUR) outside the submitted work. Dr. La Vecchia reports expert opinions for Edison, Enel, Michelin, and Pirelli outside the submitted work. None of the other authors have potential conflicts of interest.

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