Survival results in biphasic malignant pleural mesothelioma patients: A multicentric analysis

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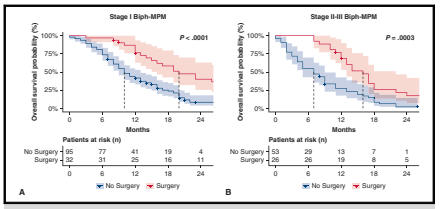
ABSTRACT

Objective: The best strategy of care for biphasic malignant pleural mesothelioma (Biph-MPM) is controversial. In this study, a large dataset of Biph-MPM cases was reviewed to identify prognostic factors and to evaluate the role of a multimodal approach, including cancer-directed surgery.

Methods: A total of 213 patients with Biph-MPM treated at 4 tertiary centers who experienced MPM from January 2009 to December 2016 were selected, and clinical, pathologic, and surgical information was retrieved. A Cox regression model was used to identify predictors of survival, and the Kaplan–Meier method was used to summarize overall survival.

Results: The mean age and the male/female ratio were 68.4 ± 9.5 years and 5:1, respectively. Tumors were assigned to stages I (127, 59.6%), II (3, 1.4%), III (76, 35.4%), and IV (7, 3.3%) according to the Eighth Tumor, Node, Metastasis (TNM) edition. A multimodal treatment including pleurectomy/decortication was performed in 58 patients (27.2%), chemotherapy alone in 99 patients (46.5%), and best supportive care in 56 (26.3%). The median overall survival was 11 months. A univariate analysis revealed that survival was significantly associated with the percentage forced expiratory volume in 1 second ($P < .0001$), performance status ($P = .0002$), multimodal treatment including surgery ($P < .0001$), and TNM stage ($P = .011$). A multivariable analysis confirmed performance status, percentage forced expiratory volume in 1 second, TNM, and a multimodal approach as independent variables affecting long-term survival.

Conclusions: Despite the overall poor prognosis of biphasic histology, a multimodal approach, including cancer-directed surgery, is associated with improved long-term results in very selected patients with Biph-MPM. (J Thorac Cardiovasc Surg 2020;159:1584-93)



Long-term survival function in Biph-MPM stage I (A) and in stage II-III (B).

Central Message

Long-term survival may be expected in selected patients with Biph-MPM after a multimodal approach including cancer-directed surgery. This approach should not be denied to a part of these patients.

Perspective

By reporting encouraging results after a multimodal approach including cancer-directed in selected patients with Biph-MPM, we have provided a proof of principle to include this subset of patients in future clinical trials investigating the role of multimodality therapy. Further investigations (ie, MARS2-trial) could definitely clarify the real benefit of cancer-directed surgery in these patients.

See Commentaries on pages 1594 and 1596.

Malignant pleural mesothelioma (MPM) is a very aggressive and often-fatal malignancy with a median overall survival of approximately 1 year.[1] The decision to select a treatment modality is currently determined by the disease stage, histologic type and subtype, and the patient's performance status.[2] We assume that patients with clinical

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This study was supported by "5 per Mille-Year 2014" funding, assigned to IRCCS-Reggio Emilia.

Received for publication Dec 3, 2018; revisions received July 20, 2019; accepted for publication Aug 3, 2019; available ahead of print Oct 5, 2019.

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0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.08.027

Abbreviations and Acronyms

Biph = biphasic
BSC = best supportive care
CI = confidence interval
CT = computed tomography
FEV1 = forced expiratory volume in 1 second
HR = hazard ratio
MCR = macroscopic complete resection
MPM = malignant pleural mesothelioma
P/D = pleurectomy/decortication
%EpC = percentage of epithelioid differentiation
TNM = Tumor, Node, Metastasis

stage I to III epithelioid–MPM who are judged medically operable and surgically resectable can undergo multimodal therapy, including surgery,[1] whereas clinical stage IV or sarcomatoid MPMs (regardless of the Eighth Tumor, Node, Metastasis [TNM] stage) are treated with systemic chemotherapy and/or best supportive care (BSC). The management of biphasic pleural mesothelioma (Biph-MPM, representing about 30% of mesotheliomas[3]) remains extremely controversial. Indeed, although the National Comprehensive Cancer Network guidelines (version 3.2016[4]) previously suggested managing Biph-MPM as for an epithelioid tumor, the subsequent National Comprehensive Cancer Network guidelines (version 2.2018[5]) recommended treating it like sarcomatoid MPM, thus excluding them from a multimodal therapy that includes surgery. In contrast, the European Respiratory Society/European Society of Thoracic Surgery guidelines for managing and treating MPM,[6] and more recently the American Society of Clinical Oncology guidelines,[7] do not preclude the use of cancer-directed surgery in the multimodal approach to Biph-MPMs.

The discrepancy between guidelines is probably due to the lack of robust literature. In fact, only a few large datasets are available on this specific population, and even when extrapolating information on the role of cancer-directed surgery in Biph-MPM from large MPM series,[8] the confounding biases of selection (different type of surgical approaches with different intents) lead to further controversy in the results analysis.[8-10] Therefore, the role of cancer-directed surgery in the setting of a multidisciplinary strategy for patients with Biph-MPM and its effect on survival is not well-defined in the literature.

We established a multi-institutional collaborative group among 4 tertiary thoracic surgery centers experienced in MPM to identify prognostic factors in patients with Biph-MPM and to explore the long-term results of a multimodal strategy, including cancer-directed surgery (pleurectomy/decortication).

MATERIALS AND METHODS

The clinical, pathologic, and surgical information from 213 patients with Biph-MPM who were diagnosed and treated from September 2009 to December 2016 at 4 tertiary centers experienced in MPM was retrospectively reviewed. The Promoting Center (IRCCS-Arcispedale Santa Maria Nuova-Reggio Emilia) selected the other institutions, considering their high volume and long experience managing MPM and a certain homogeneity of treatments between centers that substantially agreed with the management policy for this pathology. The Consolidated Standards of Reporting Trials diagram (Figure 1) shows the flow chart of the treatments performed in our cohort, and the selection criteria are as follows. Inclusion criteria: (1) histologic diagnosis of Biph-MPM; and (2) exclusion criteria: (1) uncertain histologic or cytological diagnosis of Biph-MPM; (2) records missing data on stage or treatment; and (3) Patients who underwent extrapleural pneumonectomy as part of their strategy of care.

Before undertaking the data analysis, we obtained institutional review board approval (protocol number 2017/0013216; May 23, 2017) for research use of the retrospectively collected data (observational) stemming from standard clinical practice.

Data related to age, sex, comorbidities, baseline, performance status, and forced expiratory volume in 1 second (FEV1) values, radiologic evaluation, TNM, percentage of epithelioid differentiation (%EpC), type of treatment, surgical notes, and pathologic features were reviewed and recorded (Table 1).

Preoperative Evaluation

Despite the differences between centers, the preoperative evaluation was essentially the same. The diagnosis of Biph-MPM was made by video-assisted thoracoscopic pleural biopsy in most patients (203 cases, 95.3%), whereas in clinically unfit patients it was made by computed tomography (CT)-guided or ultrasound-guided needle biopsy (10 cases, 4.7%). Preoperative staging included video-assisted cervical mediastinoscopy, laparoscopy, and 18F-fluorodeoxyglucose-positron emission tomography/CT scans only in selected cases,[7] according to local practices and the decision of the multidisciplinary tumor board. Mediastinoscopy and laparoscopy were performed only in selected cases with a suspicious radiologic result and when the pathologic confirmation of T4/N2/M1 disease could potentially change the strategy of care. A positron emission tomography/CT scan was performed (when available) in selected cases as reported previously,[7] particularly when radiometabolic results could be useful in the multidisciplinary evaluation of a multimodal approach.

Preserved pulmonary function was defined when baseline FEV1 values were >80% of the theoretical value according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.

Strategy of Care

All Biph-MPM cases were referred to a thoracic surgeon after a case-by-case discussion by the multidisciplinary tumor board. Despite some disagreements between the different tumor boards, the overall policy of treatment was essentially similar: cancer-directed surgery was performed in patients with radiologically and thoracoscopically resectable disease and considered fit for surgery as a first treatment or following neoadjuvant chemotherapy. All cases were debated by a multidisciplinary team to decide the best therapy for the patient (including the opportunity to perform neoadjuvant therapy), according to the disease stage, histology, and baseline performance status. Although it is extremely difficult to retrospectively reconstruct the decision-making process, we assumed that induction therapy could more likely have been scheduled in patients with good performance status and preserved pulmonary function (in line with the American Society of Clinical Oncology guidelines[7]), even though this does not exclude a priori the possibility that a patient with these same characteristics could go directly to surgery.

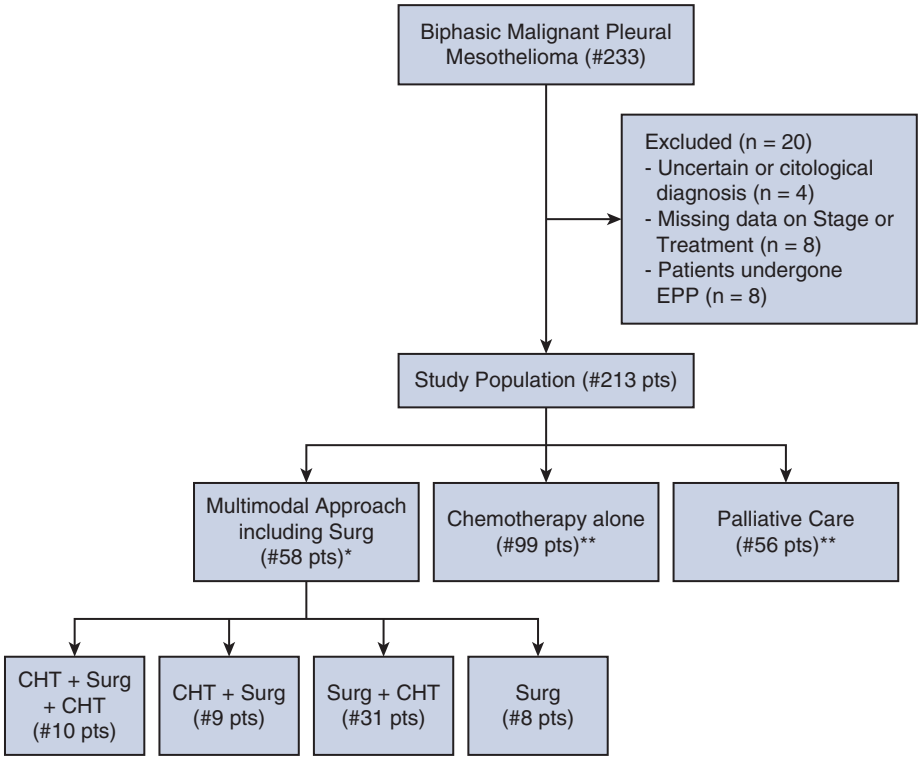

FIGURE 1. Flow chart of the study. *EPP*, Extrapleural pneumonectomy; *CHT*, chemotherapy.

Surgical Technique

The objective of cancer-directed surgery was to achieve macroscopic complete resection (MCR), defined as removal of all visible or palpable tumor tissues in the thoracic cavity.[4] A complete parietal, diaphragmatic, mediastinal, and visceral pleurectomy was performed through a posterolateral thoracotomy through the fifth/sixth intercostal space, following the principles reported by Batirel and colleagues.[11] If MCR was achieved without removing the diaphragm and/or pericardium, this was accepted as pleurectomy/decortication (P/D), whereas if a grossly visible or palpable tumor (whatever the size) was left behind, the method was recorded as partial P/D (extensive debulking procedure). Patients undergoing only a pleural biopsy or talc poudrage with purely palliative intent were not included in the surgical group.

Chemotherapy and Radiotherapy

The chemotherapy regimen consisted of 1 of the following schemes: pemetrexed–cisplatin (generally adopted in the neoadjuvant setting), gemcitabine–cisplatin, cisplatin–adriamycin, or single-agent gemcitabine. Postoperative radiotherapy was performed only in selected cases using either intensity-modulated radiotherapy of the hemi-thorax (at least 45 Gy) or low-dose (usually 25 Gy) radiation therapy of the macroscopic neoplastic residual tissue and/or of the surgical field.

Pathologic Diagnosis and Histologic Classification

A revision of the pleural specimens was performed by a designated expert thoracic pathologist at each institution to confirm the final diagnosis of Biph-MPM. A further centralized revision was done by a specialized pulmonary pathologist (S.P.) with experience in MPM. According to the World Health Organization recommendation, tumors containing at least 10% of each component (epithelioid or sarcomatoid) are classified as having biphasic histology.[12] The surgical-pathologic stage was (re)assigned according to the Eighth TNM classification system as defined previously.[13] The TNM stage was assessed based on the pathologic results or using radiologic/radiometabolic information when pathologic results were not available.

Statistical Analysis

Descriptive statistics were performed to investigate the sample characteristics. Mean ± standard deviation was chosen to summarize continuous variables, and absolute and relative frequencies (n, %) were used for categorical variables. Differences in the means of continuous variables between groups were assessed by the linear model, whereas the Fisher test was used for analysis of the distribution of the categorical variables in different population subgroups. The variable distributions were compared between patients who had <4 months survival (“poor survivors,” defined as survivors with less than 3 times the median survival of the overall population) and patients who had >36 months survival (“long survivors,” defined as survivors with more than 3 times the median survival of the overall population).

The threshold for statistical significance was set at $P < .05$. R (v. 3.4.2; R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses. A survival analysis was performed by applying the Kaplan–Meier and Cox methods.

RESULTS

The mean age and the male/female ratio were 68.4 ± 9.5 years and 5:1, respectively. The main characteristics of our population are summarized in

TABLE 1. Clinical, pathologic, and surgical findings of the population

Variables	No. patients (%)
Age, y, mean (range)	69 (35-88)
Sex	
Female	39 (18.3)
Male	174 (81.7)
Symptoms*	
No	3 (1.4)
Yes	206 (98.6)
FEV1 %*,†	
30-80	95 (55.6)
>80	76 (44.4)
Performance status	
0-1	148 (69.5)
>1	65 (30.5)
Comorbidity*	
No	81 (38.6)
Yes	129 (61.4)
Surgery	
No	155 (72.8)
Yes	58 (27.2)
Macroscopic complete resection†	
No	35 (60.4)
Yes	23 (39.6)
Epithelioid differentiation*	
<50%	88 (50.6)
≥50%	86 (49.4)
TNM	
I	127 (59.6)
II	3 (1.4)
III	76 (35.7)
IV	7 (3.3)
T	
1	29 (13.6)
2	76 (35.7)
3	74 (34.7)
4	34 (16.0)
N*	
0	142 (70.6)
1	10 (5.0)
2	49 (24.4)
M	
0	204 (95.8)
1	9 (4.2)
Neoadjuvant therapy†	
No	39 (67.2)
Yes	19 (32.8)
Treatment	
Best supportive care	56 (26.3)
CHT only	99 (46.5)
Surgery +/– (neo)adjuvant CHT	58 (27.2)
Adjuvant CHT*,†	
No	14 (25.5)
Yes	41 (74.5)

FEV1, Forced expiratory volume in 1 second; *TNM*, Tumor, Node, Metastasis; *CHT*, chemotherapy. *Missing data. †Only in the surgical group.

Table 1. The most common comorbidity was hypertension (132 patients), followed by diabetes (76 patients) and cardiovascular disease (53 patients). A multimodal treatment, including cancer-directed surgery, was performed in 58 patients (27.2%), chemotherapy alone was performed in 99 patients (46.5%), and BSC was used in 56 patients (26.3%). Among the surgical cases, MCR was obtained in 40% of the cases. Most tumors were stage I (127 patients, 59.6%), with T1/T2 tumors accounting for 50% of cases. Lymph node involvement was observed in about 30% of cases. The mean epithelioid component was 37.4 ± 25.2%. Biphasic histology was established postoperatively in 12 cases (20.6%), as the initial biopsy was interpreted as epithelioid–MPM.

When exploring the distribution of the main clinical and pathologic variables in the surgical group and nonsurgical group, we observed no significant differences in terms of comorbidities at diagnosis (Table E1). The performance status and FEV1% differed significantly between the 3 groups, and the age was significantly greater in the nonsurgical group.

Survival Data

The median, 1-year, and 3-year overall survival rates in the study population were 11% (range 0%-70%) months, 43%, and 5%, respectively. A univariate analysis (Table 2 and Figure 2) showed that survival was significantly influenced by the FEV1% ($P < .0001$, evaluated both as a continuous and categorical variable), performance status ($P = .0002$), TNM stage (I vs II-III-IV, $P = .011$), and a multimodal approach including cancer-directed surgery ($P < .001$).

A multivariable analysis confirmed the baseline performance status (hazard ratio [HR], 1.38; 95% confidence interval [CI], 1.04-1.83; $P = .025$), FEV1% as a categorical variable (HR, 0.31; 95% CI, 0.22-0.45; $P < .0001$), TNM as a categorical variable (HR, 1.70; 95% CI, 1.21-2.39; $P = .002$), and a multimodal approach including cancer-directed surgery (HR, 0.55; 95% CI, 0.35-0.86; $P = .009$) as independent variables affecting long-term survival (Table 3). The univariate (Table 4) and multivariable analyses (HR, 0.55; 95% CI, 0.35-0.86; $P = .009$, Table E2) showed a positive prognostic impact of the multimodal approach including surgery even after excluding patients receiving BSC.

When stratifying by stage, we observed that patients with Biph–MPM who underwent a multimodal approach including cancer-directed surgery presented a better median survival compared with patients treated with chemotherapy only when analyzing patients with stage I (20 vs 10 months; HR, 0.32; 95% CI, 0.19-0.53; $P < .0001$) and stage II to III tumors (16 vs 7 months; HR, 0.38; 95% CI, 0.22-0.65; $P = .0003$), as shown in Figure 3. Moreover, a survival analysis performed on the surgical group only (58 cases) revealed that a better outcome (HR, 0.33; 95% CI,

THOR

TABLE 2. Univariate survival analysis on total population

Total population	No. patients	Median survival, mo	Hazard ratio	*P* value	95% CI
Age			1.02	**.008**	1.01-1.04
Sex					
Female	39	12			
Male	174	11	1.34	.135	0.91-1.98
Symptoms*					
No	3	15.5			
Yes	206	12.0	1.32	.693	0.33-5.35
FEV1% (categorical)*					
30-80	95	9			
>80	76	18	0.33	<**.0001**	0.24-0.47
FEV1% (continuous)*			0.96	<**.0001**	0.96-0.97
Performance status					
0-1	148	13			
>1	65	8	1.81	**.0002**	1.32-2.48
Surgery					
No	155	9			
Yes	58	17	0.35	<**.0001**	0.24-0.51
Macroscopic complete resection†					
No	35	17			
Yes	23	16.5	0.77	.399	0.42-1.41
Epithelioid differentiation*					
<50%	88	12			
≥50%	86	10	1.08	.625	0.79-1.48
TNM					
I	127	13			
II	3	9	2.93	.069	0.92-9.30
III	76	10	1.37	**.044**	1.01-1.85
IV	7	9	2.46	**.023**	1.13-5.32
T					
1	29	13			
2	76	11	1.26	.355	0.78-2.03
3	74	12	1.07	.798	0.66-1.73
4	34	7	1.92	**.019**	1.11-3.31
N*					
0-1	152	12			
2	49	12	1.16	.391	0.82-1.64
M					
0	204	12			
1	9	9	1.92	.074	0.94-3.94
Neoadjuvant therapy†					
No	39	17			
Yes	19	19	0.88	.676	0.48-1.61
Treatment					
Best supportive care	56	5			
CHT only	99	13	0.38	<**.0001**	0.11-0.27
Surgery +/–(neo)adjuvant CHT	58	17	0.17	<**.0001**	0.27-0.53
Multimodal approach					
Surgery only	8	16			
CHT + surgery	9	19	0.78	.641	0.27-2.25
Surgery + CHT	31	17	0.85	.735	0.34-2.13
CHT + surgery + CHT	10	19.5	0.77	.630	0.27-2.19

(Continued)

TABLE 2. Continued

Total population	No. patients	Median survival, mo	Hazard ratio	*P* value	95% CI
Adjuvant CHT†					
No	17	18			
Yes	41	17	1.05	.895	0.52-2.11

Bold indicates $P < .05$. *CI*, Confidence interval; *FEV1*, forced expiratory volume in 1 second; *TNM*, Tumor, Node, Metastasis; *CHT*, chemotherapy. *Missing data. †Only surgical patients.

0.13-0.86; $P = .019$) was predicted in patients with preserved respiratory function (FEV1 >80%), whereas other factors (MCR and (neo)adjuvant therapy) did not significantly influence long-term survival. Moreover, the %EpC was not associated with long-term survival when tested as either a continuous ($P = .391$) or a categorical variable (median survival in prevalent epithelioid tumor 18 vs 14 months in patients with prevalent sarcomatoid tumors; $P = .158$).

We also compared (Table E3) the clinical and pathologic features of poor survivors with those of long survivors. Poor

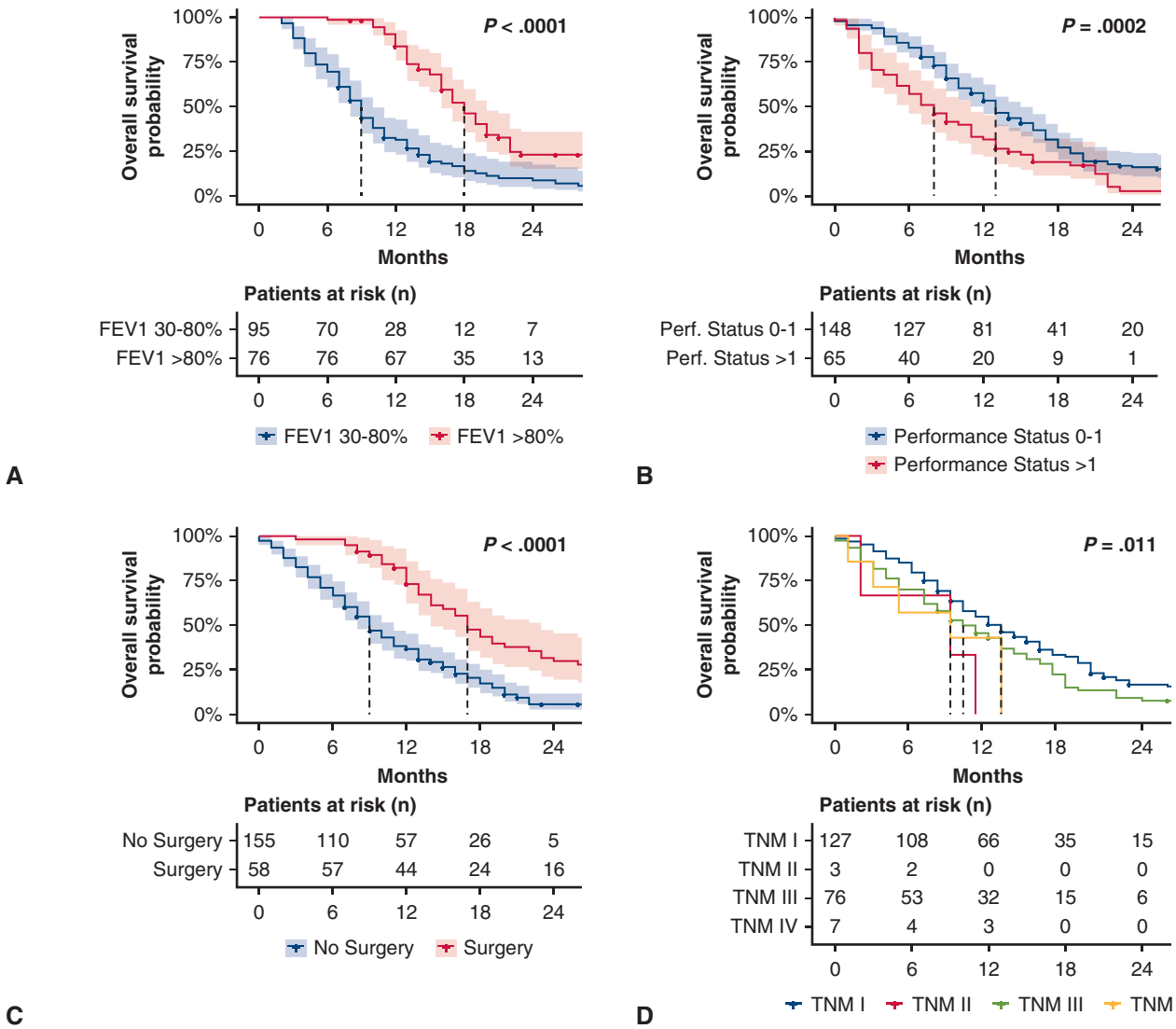

FIGURE 2. Long-term survival function according with FEV1% (A), performance status (B), cancer-directed surgery (C), TNM staging (D), and strategy of care (E-F). Confidence Intervals are reported as a *colored, shaded area* apart from D and F (see Table 2). All curves were truncated when 10% of the original cohort was no longer available. *FEV1*, Forced expiratory volume in 1 second; *TNM*, Tumor, Node, Metastasis; *CHT*, chemotherapy; *NAD*, neoadjuvant therapy.

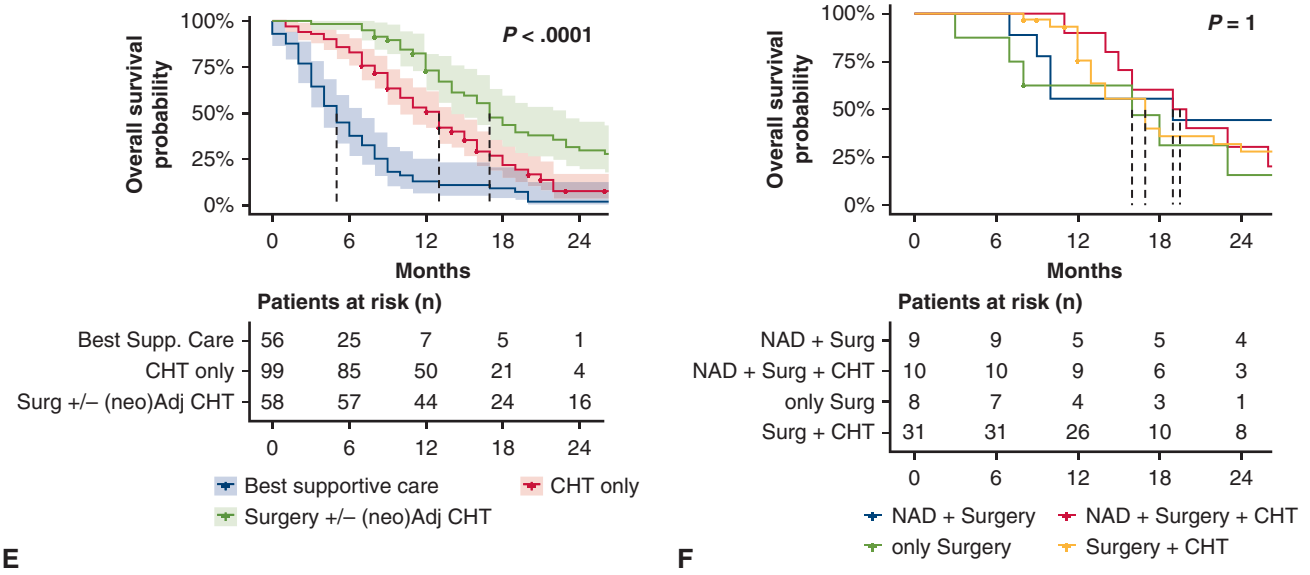

FIGURE 2. (*continued*).

survivors were older and presented with a worse performance status and compromised pulmonary function at diagnosis; most received only BSC or palliative chemotherapy. As expected, long survivors were young with preserved performance status, and all were surgically treated as part of a multimodal therapy scheme.

DISCUSSION

A robust body of evidence clearly indicates that patients with epithelioid MPM have a better prognosis than those with the sarcomatoid type,[14] and the prognosis of biphasic MPM has been compared both with the epithelioid and sarcomatoid types[15] as carrying a prognosis intermediate between those of the other types.[8] Thus, surgical indications for this MPM histotype are controversial. However, because of limited sampling during thoracoscopic procedures or needle biopsy, it is not rare to miss a significant spindle cell component in the tumor,[14] and therefore, biphasic histology is often a postoperative histologic diagnosis (approximately 20% of surgically treated patients in the present series).

TABLE 3. Multivariate survival analysis on total population

	Hazard ratio	*P* value	95% CI
Age	1.0	.583	0.99-1.03
Sex (male)	0.92	.734	0.57-1.49
Performance status	1.38	**.025**	1.04-1.83
FEV1% (categorical)	0.31	**<.0001**	0.22-0.45
Surgery	0.55	**.009**	0.35-0.86
TNM (I vs II-III-IV)	1.70	**.002**	1.21-2.39

Bold indicates $P < .05$. *CI*, Confidence interval; *FEV1*, forced expiratory volume in 1 second; *TNM*, Tumor, Node, Metastasis.

In the present study, we better clarified the long-term results after a surgical approach in patients with Biph-MPM. Notably, only 27.2% of the population underwent a multimodal approach including cancer-directed surgery, suggesting a cautious policy in the management of such aggressive disease (rigorous selection of patients). The experience of Balduyck and colleagues[14] confirmed as surgery with radical intent was performed less often in the biphasic group than in the epithelioid groups ($P < .001$). In our series, the median survival was 11 months, and the 1- and 3-year survival rates were 43% and 5%, respectively. Patients with Biph-MPM who underwent a multimodal approach including cancer-directed surgery had a median survival of 17 months, slightly better than the survival of surgically treated patients with Biph-MPM extrapolated from other series.[16-18] A median survival of 14.5 months for 34 surgically treated patients with Biph-MPM was reported by Batirel and colleagues.[18] Balduyck and colleagues[14] observed a median survival of 10 months in 66 surgically treated patients with Biph-MPM, but the surgical procedures with upfront palliative intent (33% of cases) were also included in the analysis. Finally, the positive prognostic impact of cancer-directed surgery in non-epithelioid MPM has recently reported by Kim and colleagues.[19] These authors explored the outcomes of non-epithelioid stage I to II MPM from the National Cancer Database, reporting significantly better survival in patients with Biph-MPM who underwent cancer-directed surgery in the context of multimodal treatment when compared with the others (median survival, 15.8 vs 9 months). These results are substantially in line with those reported in the present study (stage I median survival, 20 vs 10 months).

TABLE 4. Univariate survival analysis (excluding patients who underwent BSC only)

	No. patients	Median survival, mo	Hazard ratio	*P* value	95% CI
Age			1.01	.179	0.99-1.03
Sex					
Female	35	13			
Male	122	15	1.19	.428	0.78-1.82
Symptoms*					
No	2	11			
Yes	153	14	0.62	.633	0.09-4.47
Smoking habit*					
never	49	15			
smoker	34	13	1.12	.640	0.69-1.84
Ex-smoker	57	14	1.20	.402	0.78-1.84
FEV1 % (categorical)*					
30-80	65	11			
>80	69	18	0.40	**<.0001**	0.27-0.59
FEV1 % (continuous)*			0.97	**<.0001**	0.96-0.98
Performance status					
0-1	118	15			
>1	39	12	1.52	**.043**	1.01-2.27
Surgery					
No	99	13			
Yes	58	17	0.44	**<.0001**	0.30-0.65
Macroscopic complete resection†					
No	35	17			
Yes	23	16.5	0.77	.399	0.42-1.41
Epithelioid differentiation*					
<50%	62	15			
≥50%	65	12	1.26	.232	0.86-1.83
TNM					
I	99	14			
II	2	6.5	4.9	**.028**	1.18-20.3
III	53	14	1.2	.396	0.81-1.69
IV	3	13	2.2	.174	0.70-7.20
T					
1	26	15			
2	51	14	1.09	.744	0.64-1.88
3	60	14	0.92	.758	0.54-1.57
4	20	13	1.32	.394	0.69-2.52
N*					
0-1	118	13			
2	36	15	1.05	.814	0.70-1.58
M					
0	153	14			
1	4	13	1.70	.367	0.54-5.42
Treatment					
CHT only	99	13	0.38	**<.0001**	0.11-0.27
Surgery +/–(neo)adjuvant CHT	58	17	0.17	**<.0001**	0.27-0.53

Bold indicates $P < .05$. *CI*, Confidence interval; *FEV1*, forced expiratory volume in 1 second; *TNM*, Tumor, Node, Metastasis; *CHT*, chemotherapy. *Data missing. †Only surgical patients.

With the aim to help physicians identify the subgroup of patients who may benefit from multimodal treatment, we observed the prognostic impact of performance status and FEV1% in our cohort of patients with Biph-MPM, suggesting the relevance of the clinical selection of MPM cases. A good performance status and a preserved pulmonary function at the time of diagnosis are predictors of long-term survival and the best candidates for a

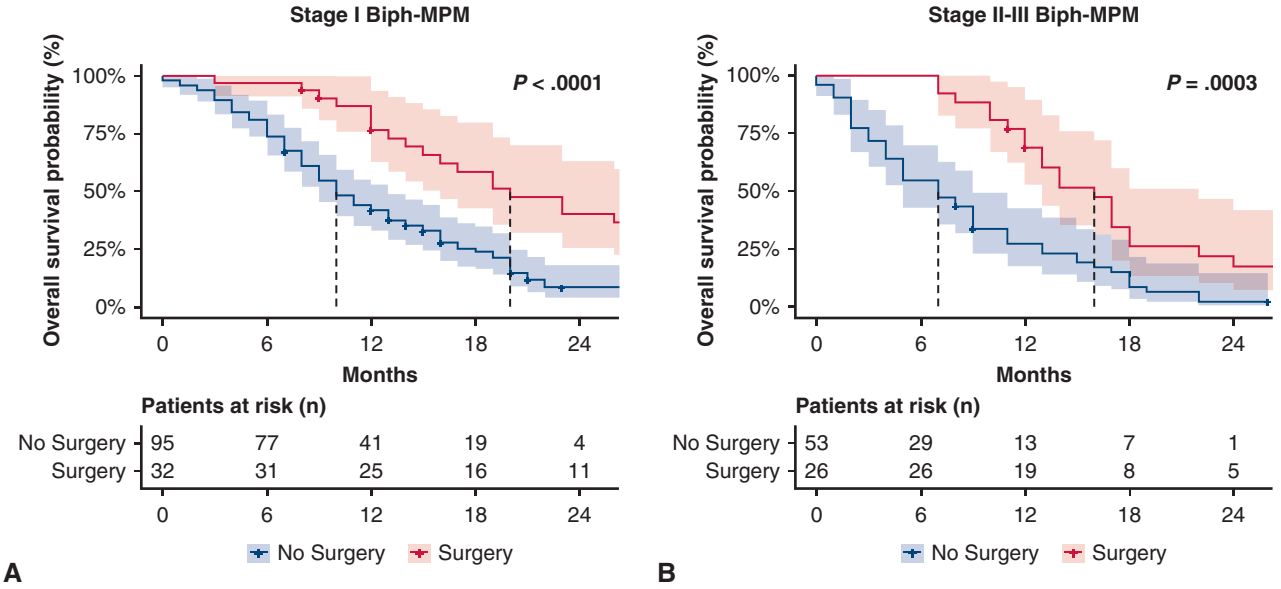

FIGURE 3. Long-term survival function in stage-I (A) and in stage II to III (B). Confidence Intervals are reported as a *colored, shaded* area. All curves were truncated when 10% of the original cohort was no longer available. *Biph-MPM*, Biphasic malignant pleural mesothelioma.

multimodal approach including surgery. In this setting, a case-by-case multidisciplinary discussion performed by a panel of experts played a crucial role.

Our analysis showed that the disease stage was significantly correlated with long-term survival in patients with Biph-MPM. This result is in line with those of several previous studies[16,20] but in contrast with others.[8] The N status seems to have no influence on the prognosis, even though this result needs to be carefully interpreted.

Vigneswaran and colleagues[21] reported the outcomes of patients with Biph-MPM who underwent P/D, observing different median survival rates according to %EpC, with a better outcome (~12 months) in tumors consisting of prevalent epithelioid features. In our analysis, %EpC was not confirmed as a prognostic factor even after it was analyzed as either a continuous or a categorical variable; this result could be related to a technical limit in our measurements, and this issue needs to be further evaluated in other studies.

In the present analysis, MCR after cancer-directed surgery was achieved in 40% of cases. This result appears to be in line with the experience recently reported by Batirel and colleagues[18] on a series of 154 surgically treated patients with MPM, in which MCR was achieved in 49% of the cases (47% in Biph-MPM). The results in terms of completeness of resection were strongly correlated with our conservative policy adopted during surgery. Indeed, considering the aggressiveness of the disease and the importance of preserving a satisfying postoperative quality of life, surgeons preferred not to perform an extended P/D (especially hemidiaphragmatic resection and grafting). We agree with the principle that achieving MCR remains the main objective of a surgical procedure with curative intent. When this can be obtained only by performing a more extensive resection (diaphragmatic and pericardial resection/reconstruction), it may be reasonable to give more weight to the preservation of a good quality of life rather than to the completeness of the resection in Biph-MPM. Moreover, Batirel and colleagues did not observe differences in the median survival of patients with MPM with and without MCR ($P = .6$). This result was also observed in the present analysis, in which MCR was not associated with improved survival (Table 2). Although the limited number of surgical cases could be a reason to justify this result, only further analyses on large surgical cohorts can confirm this point. We reiterate how the primary goal of cancer-directed surgery should be to obtain an MCR.

We observed that patients with Biph-MPM subjected to chemotherapy alone experienced improved survival compared with patients undergoing BSC only (13 vs 5 months, $P < .001$). Nevertheless, we failed to demonstrate a clear positive impact of (neo)adjuvant chemotherapy in the present study because of the limited number of patients (8 cases) who underwent surgery as an exclusive treatment. Finally, concerning the role of radiotherapy in MPM (extremely controversial in the literature[22]), we have inadequate information to express an opinion.

Limitations and Strengths

This study had several limitations and some strengths. This was a retrospective, multi-institutional study with clinical data missing in a small part of the sample. Moreover, the comparison between the surgical and nonsurgical groups could have been potentially influenced by a significant bias of age, fitness, or staging at presentation (Table E1). Indeed, the TNM staging of

surgical patients may be more accurate in comparison with the TNM stage assessed in nonsurgical patients who undergo thoracoscopy, as reported in the International Association for the Study of Lung Cancer study.[17] Therefore, we cannot exclude that staging of nonsurgical patients was underestimated and influenced the survival analysis between the surgical and nonsurgical groups, especially when this was stratified for stage. In addition, in the absence of a control group, we cannot exclude that patients selected for surgery may have been poised to have a better outcome even without cancer-directed surgery.

Moreover, to evaluate the baseline performance of the patients with MPM, we have adopted the Eastern Cooperative Oncology Group score but we have not included in the analysis a proper comorbidity index, this representing a minor but further limitation that deserves to be enunciated. Finally, the results of inference observed when comparing poor survivors and long survivors were not supported by a robust methodology, and these should be evaluated as purely observational results. Therefore, in light of all of the aforementioned limitations, readers should interpret our results with caution, as multiple biases exist.

However, the present study has the merit of focusing on a specific population of MPM patients (Biph-MPM) and collecting a large dataset, which is the main strength. We also identified prognostic factors in our cohort of patients that could be considered in further trials on this topic. Lastly, we provided a proof of principle to include Biph-MPM in future clinical trials investigating the role of cancer-directed surgery in MPM multimodal therapy, which was the original purpose of our study.

Further investigations should clarify the role of surgery in Biph-MPM. In this framework, the forthcoming MARS2 trial (including patients with Biph-MPM) might provide answers to a few of these questions.

CONCLUSIONS

A multimodal approach seems to be a reasonable option in selected cases despite the poor prognosis of biphasic histology in tertiary centers experienced in MPM. As the limitations of the present study make it challenging to demonstrate the prognostic impact of a multimodal approach including cancer-directed surgery in this patient population, we advocate that patients with Biph-MPM should be included in future clinical trials evaluating multimodal therapeutic strategies.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

We thank Dr Wen (London), Prof Boldorini (Novara), and Dr Bossi (Milan) for their precious support in pathological evaluation and Dr Pagano Maria (Oncology Unit, Reggio Emilia).

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Key Words: malignant pleural mesothelioma, pleurectomy, decortication, pleural tumor, surgery

TABLE E1. Distribution of clinical and pathologic features between surgical and nonsurgical patients

Total population	No surgery	Surgery	*P* value
	155	58	
Age	70.6 ± 8.8	62.9 ± 8.9	**<.0001**
Sex			**.001**
Female	20 (51.3)	19 (48.7)	
Male	135 (77.6)	39 (22.4)	
Smoking habit*			.088
Never	45 (72.6)	17 (27.4)	
Smoker	28 (62.2)	17 (37.8)	
Ex-smoker	66 (80.5)	16 (19.5)	
Symptoms*			.564
No	3 (100)	0 (0)	
Yes	149 (72.3)	57 (27.7)	
Comorbidity*			.431
No	56 (69.1)	25 (30.9)	
Yes	96 (74.4)	33 (25.6)	
FEV1 % (categorical)*			**<.0001**
30-80	76 (80.0)	19 (20.0)	
>80	39 (51.3)	37 (48.8)	
FEV1 % (continuous)*			**.0002**
	70.2 ± 17.4	81.1 ± 17.6	
Performance status			**<.0001**
0	17 (65.4)	9 (34.6)	
1	75 (61.5)	47 (38.5)	
2	61 (96.8)	2 (3.2)	
3	2 (100)	0 (0.0)	
Epithelioid differentiation*			.297
<50%	69 (71.9)	27 (28.1)	
≥50%	61 (66.3)	31 (33.7)	
TNM			.197
I	95 (74.8)	32 (25.2)	
II	2 (66.7)	1 (33.3)	
III	51 (67.1)	25 (32.9)	
IV	7 (100.0)	0 (0)	
T			**.006**
1	23 (79.3)	6 (20.7)	
2	64 (84.2)	12 (15.8)	
3	44 (59.5)	30 (40.5)	
4	24 (70.6)	10 (29.4)	
N*			.204
0-1	112 (73.7)	40 (26.3)	
2	31 (63.3)	18 (36.7)	
M			.118
0	146 (71.6)	58 (28.4)	
1	9 (100.0)	0 (0.0)	

Bold indicates $P < .05$. *FEV1*, Forced expiratory volume in 1 second; *TNM*, Tumor, Node, Metastasis. *Data missing.

TABLE E2. Multivariable survival analysis (excluding patients who underwent BSC only)

Multivariate Cox analysis	Hazard ratio	*P* value	95% CI
Age	1.00	.914	0.98-1.02
Sex (male)	0.86	.565	0.52-1.44
FEV1% (categorical)	0.39	**<.0001**	0.26-0.58
Surgery	0.55	**.010**	0.35-0.87
TNM	1.27	**.013**	1.05-1.53

Bold indicates $P < .05$. *CI*, Confidence interval; *FEV1*, forced expiratory volume in 1 second; *TNM*, Tumor, Node, Metastasis.

TABLE E3. Clinical and pathologic features distribution between "short survivors" and "long survivors"

	Survival ≤4 mo	Survival ≥36 mo	*P* value
	34	10	
Age	73.8 ± 7.9	63.2 ± 7.2	**.0005**
Sex			**.032**
F	5 (50.0)	5 (50.0)	
M	29 (85.3)	5 (14.7)	
Smoking habit*			.432
Never	11 (64.7)	6 (35.3)	
Smoker	8 (80.0)	2 (20.0)	
Ex-smoker	12 (85.7)	2 (14.3)	
FEV*			**<.0001**
30%-80%	19 (95.0)	1 (5.0)	
>80%	0 (0.0)	8 (100.0)	
FEV*	52.4 ± 10.3	93.1 ± 15.0	**<.0001**
Performance status			**.001**
0	1 (25.0)	3 (75.0)	
1	13 (65.0)	7 (35.0)	
2	19 (100.0)	0 (0)	
3	1 (100.0)	0 (0)	
Surgery			**<.0001**
No	33 (100.0)	0 (0.0)	
Yes	1 (9.1)	10 (90.9)	
Epithelioid differentiation*			1
<50%	16 (84.2)	3 (15.8)	
≥50%	13 (81.3)	3 (18.7)	
Stage			.529
I	15 (68.2)	7 (31.8)	
II	1 (100.0)	0 (0.0)	
III	16 (84.2)	3 (15.8)	
IV	2 (100.0)	0 (0.0)	
T			.083
1	2 (66.7)	1 (33.3)	
2	12 (92.3)	1 (7.7)	
3	7 (53.8)	6 (46.2)	
4	13 (86.7)	2 (13.3)	
N			.650
0-1	22 (71.0)	9 (29.0)	
2	6 (85.7)	1 (14.3)	
M			1
0	32 (76.2)	10 (23.8)	
1	2 (100.0)	0 (0.0)	
Surgery and therapy combination			**<.0001**
Best supportive care	23 (0.0)	0 (0.0)	
Only CHT	10 (100.0)	0 (0.0)	
Surgery +/– (neo)adjuvant CHT	1 (9.1)	10 (90.9)	

Bold indicates $P < .05$. *FEV1*, Forced expiratory volume in 1 second; *CHT*, chemotherapy. *Data missing.