CHIRURGIA SI O CHIRURGIA NO: IL PARERE DEI CHIRURGHI

M. PACI

S.C. CHIRURGIA TORACICA

AUSL-IRCCS DI REGGIO EMILIA

RUOLO DELLA CHIRURGIA NEL MESOTELIOMA BIFASICO

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

Filippo Lococo, MD,[1] Federica Torricelli, PhD,[2] Loic Lang-Lazdunski, PhD,[3] Giulia Veronesi, PhD,[4] Ottavio Rena, PhD,[5] Massimiliano Paci, MD,[1] Caterina Casadio, MD,[1] Simonetta Piana, MD,[1] Pierluigi Novellis, MD,[4] Teresa Severina Di Stefano, MD,[1] Alessia Ciarrocchi, PhD,[2] and Andrea Rilli, PhD[2]

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;159:1564-93)

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.[1] We assume that patients with clinical

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

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Long-term survival function in Biph-MPM stage I-II and ii-stage II-III

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 via MARO-trial could definitely clarify the real benefit of cancer-directed surgery in these patients.

See Commentaries on pages 1594 and 1596.

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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.

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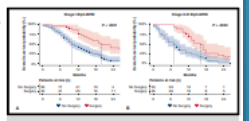

Long-term survival function in Biph-MPM stage I (A) and in stage II-III (B).

Central Message

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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.

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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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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).

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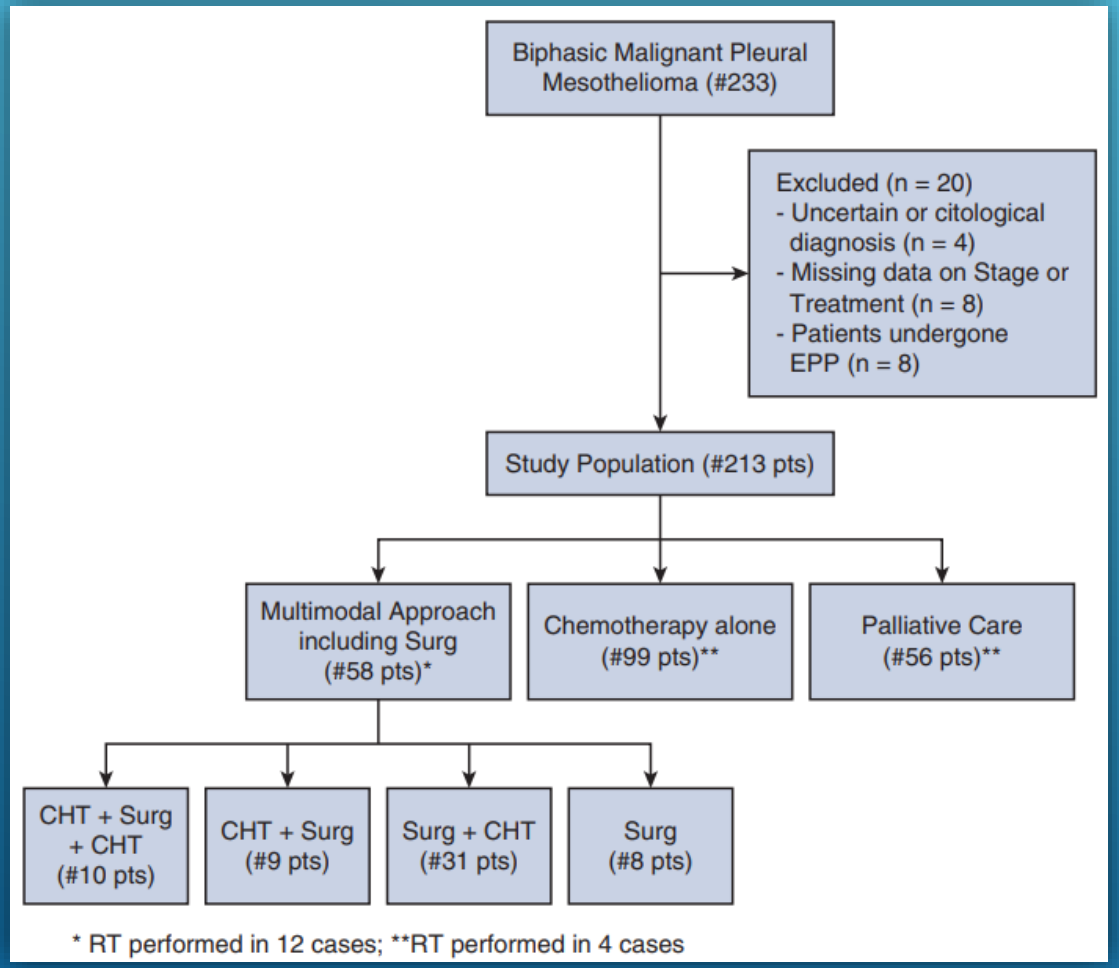

The clinical, pathologic, and surgical information from 213 patients with Biph-MPM who were diagnosed and treated from September 2009 to December 2016 at 4 tertiary centers experienced in MPM was retrospectively reviewed. The Promoting Center (IRCCS-Arcispedale Santa Maria Nuova-Reggio Emilia) selected 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.

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Perspective

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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.

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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.

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vascular 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 $37.4 \pm 25.2\%$. Biphasic histology was established postoperatively in 12 cases (20.6%), as the initial biopsy was interpreted as epithelioid–MPM.

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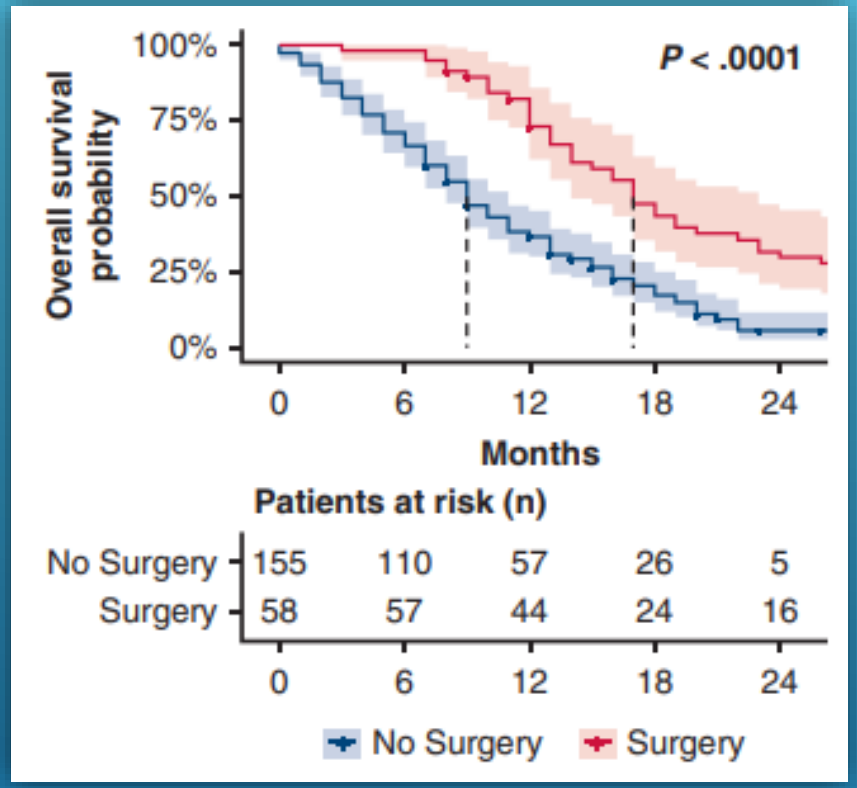
The median, 1-year, and 3-year overall survival rates in the study population were 11% (range 0%-70%) months, 43%, and 5%, respectively. A univariate analysis (Table 2 and Figure 2) showed that survival was significantly influenced by the FEV1% ($P < .0001$, evaluated both as a continuous and categorical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



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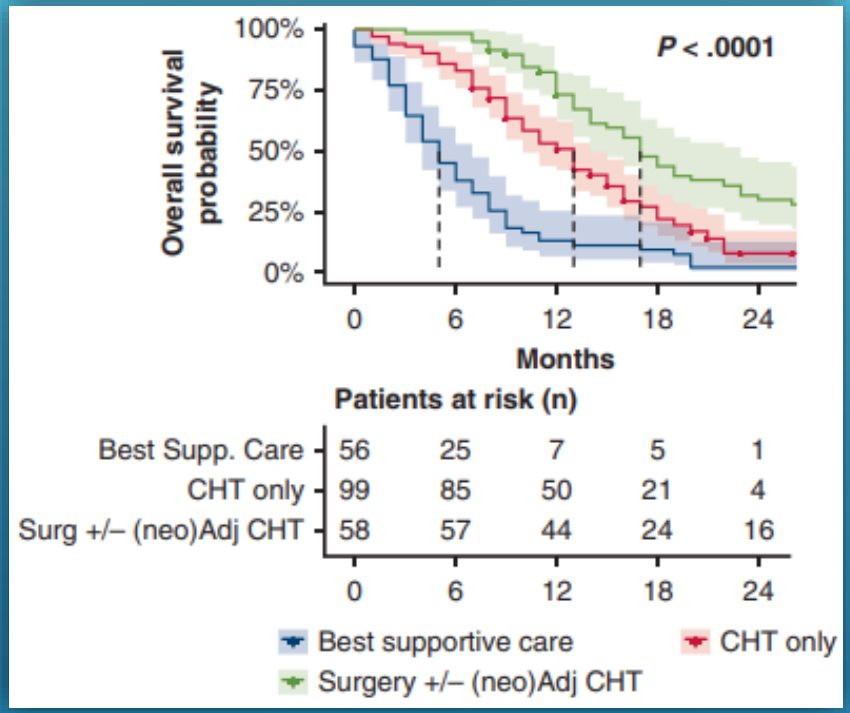

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A multivariable analysis confirmed the baseline performance status (hazard ratio [HR], 1.38; 95% confidence interval [CI], 1.04-1.83; $P = .025$), FEV1% as a categorical variable (HR, 0.31; 95% CI, 0.22-0.45; $P < .0001$), TNM as a categorical variable (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.

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.

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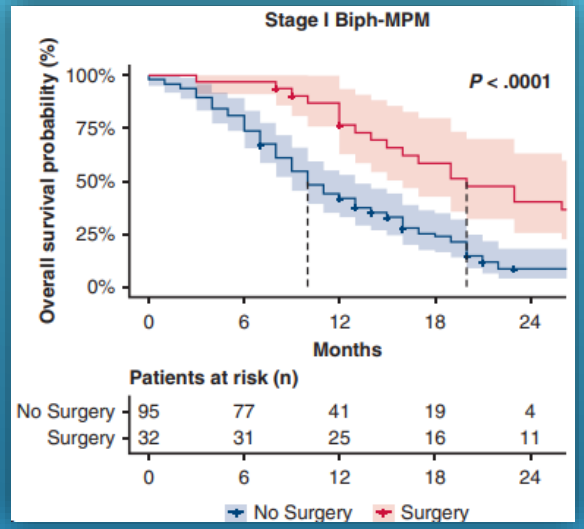
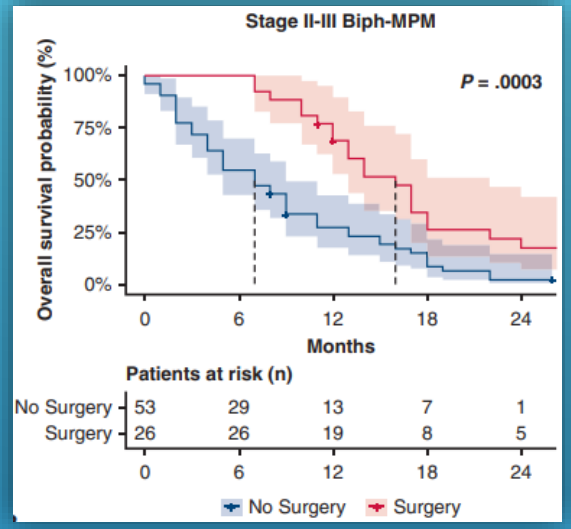
When stratifying by stage, we observed that patients with Biph–MPM who underwent a multimodal approach including cancer-directed surgery presented a better median survival compared with patients treated with chemotherapy only when analyzing patients with stage I (20 vs 10 months; HR, 0.32; 95% CI, 0.19-0.53; $P < .0001$) 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





RUOLO DELLA CHIRURGIA NEL MESOTELIOMA BIFASICO

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

Filippo Lococo, MD,[1] Federica Torricelli, PhD,[2] Loic Lang-Lazdunski, PhD,[3] Giulia Veronesi, PhD,[4] Ottavio Rena, PhD,[5] Massimiliano Paci, MD,[1] Caterina Casadio, MD,[1] Simonetta Piana, MD,[1] Pierluigi Novellis, MD,[4] Teresa Severina Di Stefano, MD,[1] Alessia Ciarrocchi, PhD,[2] and Andrea Rilli, PhD[2]

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)

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

respiratory function (FEV1 >80%), whereas other factors (MCR and (neo)adjuvant therapy) did not significantly influence long-term survival. Moreover, the %EpC was not asso-

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

N*					
0-1	118	13			
2	36	15	1.05	.814	0.70-1.58

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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

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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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.

MPM. Emerging evidence also suggests that the percentage of epithelioid differentiation is an independent predictor of survival in patients with biphasic MPM.[78] Patients with epithelioid differentiation of 100%, 51% to 99%, and < 50% had median overall survivals of 20.1, 11.8, and 6.62 months, respectively ($P < .001$) in a 144-patient series.[78] A systematic

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Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline

Epithelioid differentiation*					
<50%	88	12			
≥50%	86	10	1.08	.625	0.79-1.48

Epithelioid differentiation*					
<50%	62	15			
≥50%	65	12	1.26	.232	0.86-1.83

RUOLO DELLA CHIRURGIA NEL MESOTELIOMA BIFASICO

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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-II and in stage I-II-III.

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 via MARGO trials could definitely clarify the real benefit of cancer-directed surgery in these patients.

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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.