Prospective Study on Functional Results After Lung-Sparing Radical Pleurectomy in the Management of Malignant Pleural Mesothelioma

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Introduction: Malignant pleural mesothelioma (MPM) can reduce lung function by entrapping lung parenchyma via a rind of tumor with or without concurrent effusion. Radical pleurectomy (RP) allows expansion of the trapped lung. The purpose of this study was to investigate changes in pulmonary function and lung perfusion in patients undergoing RP.

Methods: In a prospective, nonrandomized study, all patients with histologically proven MPM were evaluated from January to December 2010 for trimodality therapy including RP as surgical procedure. Pulmonary-function tests and perfusion scans were obtained before and 2 months after RP. Primary end points were pulmonary function (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1]) and ipsilateral lung perfusion.

Results: Sixteen out of 25 consecutive patients (age 68.8±8.9 years) were enrolled in the study. Macroscopic complete resection could be achieved in 13 patients (81.3%). Diaphragm resection was necessary in 5 patients. Significant postsurgical improvement of pulmonary function at 2 months was observed for FVC and FEV1 (both absolute and percentage of predicted values) and ipsilateral perfusion ($p < 0.001$). Avoidance of diaphragm resection was associated with greater increase in FVC (+34.6±17.0% versus +13.5±5.4%; $p = 0.002$) and FEV1 (+29.2±18.1% versus +12.1±6.4%; $p = 0.015$), respectively.

Conclusions: Lung-sparing RP leads to significant improvement of pulmonary function and perfusion after a recovery time of 2 months. Functional results are better after preservation of the diaphragm. Preservation of physiological reserve via lung-sparing RP might allow patients with MPM to be eligible for further therapeutic options in the long term.

Key Words: Mesothelioma, Pleurectomy, Decortication, Perfusion, Pulmonary function.

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Malignant pleural mesothelioma (MPM) is an aggressive and rapidly fatal malignancy of the pleura. MPM can reduce lung function by entrapping lung parenchyma via a rind of tumor with or without concurrent effusion.

Originally, pleurectomy/decortication (P/D) was a palliative option to control MPM-related pleural effusions.[1] However P/D or radical pleurectomy (RP) within a multimodality therapy concept seems to be an alternative for patients with MPM unsuitable or unwilling to undergo extrapleural pneumonectomy (EPP).[2,3] RP is lung sparing and allows for re-expansion of trapped lung. Thus RP, as a surgical strategy within a multimodality therapy concept for patients with MPM, could be associated with the preservation or improvement of physiological reserve and thus allow patients to be eligible for multimodality approaches.[2]

There are several studies reporting on the changes of pulmonary function before and after lung decortication for chronic empyema.[4,5] In general, studies demonstrated improvement in pulmonary function after surgery. In contrast, there is, to the best of our knowledge, no data on the effects of RP or P/D for MPM on lung function. The purpose of this study was to investigate the effects of RP on the objective measures of pulmonary function and lung perfusion in patients with MPM.

PATIENTS AND METHODS

At a single tertiary referral center, all patients with nonspecific unilateral pleural effusion underwent videothoracoscopic evaluation including pleural-fluid evacuation and biopsy of the pleura. In patients with histologically proven MPM the drainage was removed without pleurodesis. All patients with MPM were evaluated for trimodality therapy with curative intent, as described previously.[2] In brief, the multimodality therapy included RP followed by four cycles of cisplatin/pemetrexed and radiation of the chest wall. Inclusion criteria were as follows:

- Histologically confirmed diagnosis of MPM.
- Clinical T1-3, N0-2, M0 disease.
- No prior treatment for MPM.
- Adequate cardio-pulmonary reserve.
- Adequate renal and liver function.

Within this patient cohort, pulmonary-function tests (PFTs) and perfusion scans were obtained before and 2 months after RP in a prospective, nonrandomized study over a 1-year-period from January to December 2010. The primary end points in the present study were the effects on lung-function parameters measured by bodyplethysmography (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], FEV1/FVC ratio) and ipsilateral lung perfusion. The bodyplethysmographic measurements were performed between the videothoracoscopy and RP (pre PFTs) and 2 months after RP (post PFTs) according to the American Thoracic Society criteria and established standards.[6] The secondary outcomes included improvement of 10% or more in FEV1 (% predicted), and operative morbidity and mortality.

The definition of P/D or RP remains variable. The International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group defined P/D as a surgical procedure to remove all macroscopic tumor involving the parietal and visceral pleura. The term "extended" P/D is implemented when the diaphragm or pericardium is resected.[7] On the contrary, we define RP as a surgical approach that involves resection of the visceral and parietal pleura while preserving the lung. We always try to resect the visceral pleura even if there are no visible tumor spots. However, wedge resections are carried out in the event of deep infiltration of the lung parenchyma. We aim to preserve the phrenic nerve, pericardium, and diaphragm as maximally possible from oncological point of view. Generally, we resect the diaphragmatic pleura leaving only the bare muscle fibers. Furthermore, the pericardium is split and only the fibrous part is resected whereas the serous part is left intact. Nonetheless, partial or total resection and reconstruction of the diaphragm and pericardium can be performed depending on the intraoperative findings.

Nicotine cessation was a precondition for surgery. Intensive chest physiotherapy program was administered, including deep-breathing exercises and incentive spirometry using a volume-oriented device (Voldyne 5000 Volumetric Exerciser, Teleflex Medical GmbH, Kernen, Germany) at least six times a day for 10 minutes each time during the hospitalization. The patients had to become acquainted with the mechanism of active cycle of breathing, forced cough, and expiratory techniques, respectively. The learning of these techniques was controlled in the pulmonary rehabilitation group daily session under the supervision of a respiratory therapist. Aerosol therapy was performed at least twice-daily. In addition, mucus clearance was facilitated by a flutter valve device (VRP1 Flutter, Tyco Healthcare Deutschland GmbH, Neustadt/Donau, Germany). The exercise compliance was enforced both by nurses and surgeons/physicians, respectively. Furthermore, patients had to continue their exercise regimen after discharge from the hospital.

Institutional review board approval was obtained for this study. The trimodality treatment was registered with ClinicalTrials.gov (identifier NCT01343264). Written consent was obtained from each study patient. The study was conducted according to the revised Declaration of Helsinki and the requirements of good clinical practice.

Means and standard deviations are used for description of continuous measures. Descriptive statistics for discrete variables are presented as frequencies and percentages. The outcomes were assessed using Student's *t* tests or Fisher's exact tests as appropriate. We used descriptive statistics to investigate possible treatment effects because of the small sample size in this pilot study. We used two approaches to analyze treatment effects descriptively. We evaluated Cohen's d (effect-size estimates) using change values in outcome measures. Depending on the effect size, the effect was considered "small effect" (Cohen's d of 0.2), "medium effect" (Cohen's d of 0.5), and "large effect" (Cohen's d of 0.8), respectively. Linear regression analysis was performed to analyze the relation between preoperative and postoperative pulmonary-function data. A p value less than 0.05 dividing with the number of factors examined (Bonferroni adjustment), was considered statistically significant. Data were stored using Excel (Microsoft, Seattle, WA). SPSS 15.0 software (SPSS Inc., Chicago, IL) was used to analyze the data.

RESULTS

During the study period, 25 patients with histologically confirmed MPM were referred to our Department of Thoracic Surgery for cardio-pulmonary evaluation before RP. Of these evaluated patients, 16 study subjects (age 68.8 ± 8.9 years, 14 men, Table 1) were eligible for RP and entered the study.

The reasons for the exclusion were as follows:

- Metastatic disease (n = 1).
- Ongoing palliative chemotherapy (n = 1).
- Complete remission after induction chemotherapy (n = 1).
- Rapid progressive disease (n = 1).
- Diffuse chest wall infiltration (n = 2).
- Impaired cardio-pulmonary reserve (n = 3).

Surgical morbidity was 43.8 % (7 of 16). The complications included tachyarrhythmia (n = 3), reoperation for bleeding (n = 1), pneumonia (n = 1), prolonged air leak (n = 1) and chylothorax (n = 1), respectively. No mortality occurred. Macroscopic complete resection could be achieved in 13 patients (81.3%). Resection of the diaphragm was necessary in 5 patients (31.3%). Twelve patients had advanced disease at International Mesothelioma Interest Group (IMIG) stages III/IV (75%). Primary histology was epithelial (87.5%).

Preoperative spirometry showed a mean FVC (% predicted) of 54.7±9.9 %, a mean FEV1 (% predicted) of 60.2%±10.3 % and a mean FEV1/FVC-ratio 0.82±0.08, reflective of a moderate restrictive ventilatory defect. Ipsilateral perfusion was reduced to 29.2%±6.5%. Significant postsurgical improvement of pulmonary function was observed for FVC (L), FVC (%), FEV1 (L) FEV1 (%), and ipsilateral perfusion (Table 2, Figs. 1 and 2). The effect size was high in all measurements. The average increases were in post–pre-FVC +28.0% (+3.5% to +59.0%), post–pre-FEV1 + 23.9% (+1.5% to +61.5%) and post–pre-perfusion + 37.8% (+8.7% to +150.0%), respectively. The postoperative FVC (% predicted) of 68.9%±9.1 %, mean FEV1 (% predicted) of 73.6%±11.4 % and a mean FEV1/FVC-ratio 0.80±0.06 demonstrated the improvement to a mild restrictive ventilatory defect 2 months after RP. Thirteen patients (81.3%) had an improvement of 10% or more in FEV1 (% predicted). No significant changes were observed with regard

TABLE 1. Patients' Demographics

#	Patients' Age	Sex	Laterality	Histology	IMIG Stage	Resection of Diaphragm	Macroscopic Completeness of Resection
1	70	Male	Right	Sarcomatoid	III (pT3N0)	No	Yes
2	79	Male	Left	Epitheloid	I (pT1bN0)	No	Yes
3	68	Male	Left	Epitheloid	III (pT3N2)	No	Yes
4	75	Male	Right	Epitheloid	III (pT3N0)	Yes	Yes
5	57	Female	Left	Epitheloid	IV (pT4N2)	Yes	No
6	59	Male	Right	Epitheloid	IV (pT4N2)	No	No
7	58	Male	Left	Epitheloid	III (pT3pN0)	No	Yes
8	51	Female	Left	Sarcomatoid	I (pT1bN0)	No	No
9	63	Male	Right	Epitheloid	IV (pT2N3)	Yes	Yes
10	74	Male	Right	Epitheloid	III (pT3N1)	Yes	Yes
11	71	Male	Right	Epitheloid	II (pT2N0)	No	Yes
12	82	Male	Right	Epitheloid	III (pT3N0)	No	Yes
13	69	Male	Right	Epitheloid	III (pT3N0)	Yes	Yes
14	71	Male	Left	Epitheloid	III (pT3N1)	No	Yes
15	76	Male	Right	Epitheloid	II (pT2N0)	No	Yes
16	77	Male	Left	Epitheloid	III (pT3N0)	No	Yes

to the blood gas analysis. Laterality of the disease, completeness of resection and histology had no significant impact on pulmonary function or perfusion scan, respectively.

Avoidance of the diaphragm resection was associated with greater increase in FVC (=Post–pre-FVC (%) + 34.6%±17.0% versus +13.5%±5.4%; $p = 0.002$) and FEV1 (=Post–pre-FEV1 (%) +29.2%±18.1% versus + 12.1±6.4%; $p = 0.015$), respectively. The presence of the diaphragm resection had no significant effect on the lung perfusion.

In a linear regression analysis a lower preoperative FVC (% predicted) or FEV1 (% predicted) was associated with higher relative increases in FVC or FEV1 after RP ($p < 0.02$ for both, Fig. 3). A higher preoperative FEV1/FVC-ratio was associated with a greater relative increase in FVC than in FEV1, whereas a lower preoperative FEV1/FVC-ratio was associated with a greater relative increase in FEV1 then in FVC ($p = 0.01$, correlation coefficient r = 0.65, Fig. 4).

DISCUSSION

To our knowledge, this is the first study reporting on the effects of RP or P/D on objective measures of pulmonary function and ipsilateral lung perfusion. We found that lung-sparing RP leads to significant improvement of pulmonary function and perfusion after a recovery time of 2 months. Functional results are better after preservation of the diaphragm. This is important information for the clinician evaluating a patient regarding candidacy for RP.

Generally, studies reporting on the changes of pulmonary function before and after lung decortication for chronic empyema have shown improvements of FEV1 and FVC in the range of +18.6% to +30.5% and +19.2% to +28.8%,

TABLE 2. Changes in Pulmonary Function and Ipsilateral Perfusion

	Preoperative Value [range]	Postoperative Value [range]	*p* Value	Cohen's *d*	Effect Size
FVC (Liter)	2.18±0.49 [1.30–3.11]	2.73±0.55 [1.89–3.77]	< 0.001*	1.06	Large
FVC (%)	54.7±9.9 [39–69]	68.9±9.1 [53–83]	< 0.001*	1.49	Large
FEV1 (Liter)	1.79±0.45 [1.05–2.91]	2.18±0.50 [1.49–3.65]	< 0.001*	0.81	Large
FEV1 (%)	60.2±10.3 [40–79]	73.6±11.4 [58–91]	< 0.001*	1.23	Large
FEV1 / FVC	0.82±0.08 [0.72–1.00]	0.80±0.06 [0.72–0.97]	0.12	0.44	Medium
Ipsilateral Perfusion (%)	29.2±6.5 [16–37]	38.5±3.5 [25–43]	< 0.001*	1.78	Large

* Significant, $p < 0.05/6$ (Bonferroni adjustment).
FVC, forced vital capacity; FEV1, forced expiratory volume.

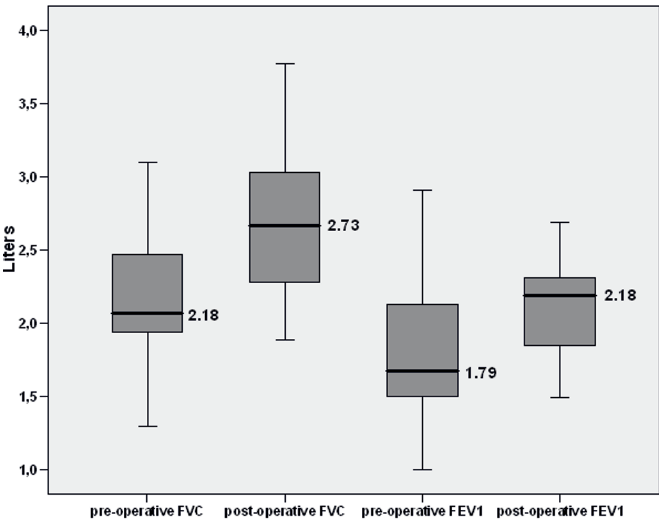

FIGURE 1. Box plot of changes in pulmonary function. FVC, forced vital capacity; FEV1, forced expiratory volume.

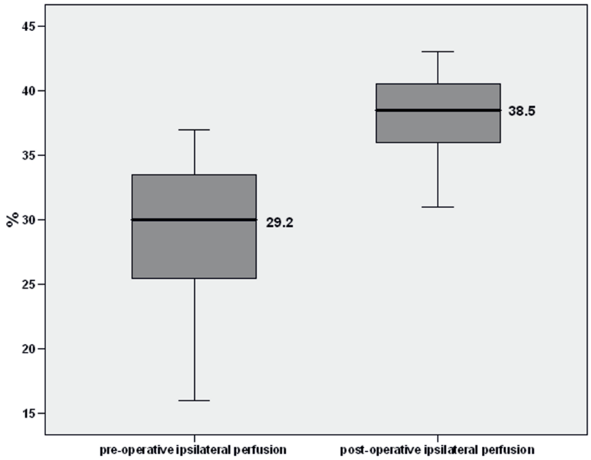

FIGURE 2. Box plot of changes in ipsilateral perfusion scans.

respectively.[4,5] The mean increase of FEV1 and FVC in the present study was +23.9% and +28.0%, respectively. An on-average moderate restrictive ventilatory defect was present preoperatively. However, an improvement to an-only mild restrictive ventilatory defect at 2 months after RP was realized. Whether the improvements in pulmonary function after RP persist in the long-term is, however, not answered by this investigation. We studied the restoration of the respiratory function 2 months after surgery. Long-term comparisons of the pulmonary function in the rapidly fatal disease of MPM are difficult because the 1-year overall survival rate in general is 55%.[8] Nevertheless, quantitative measurement of lung reexpansion in MPM patients undergoing P/D showed that there are no statistically significant changes in ipsilateral lung volume between 1- and 4-month-postsurgical computer tomography scans.[9] This suggests that improvements in lung function persist beyond 2 months after surgery.[9]

The most significant respiratory muscle is the diaphragm. Resection of the diaphragm, phrenic nerve injury, or sacrifice of the phrenic nerve causes the loss of diaphragmatic function. In otherwise healthy patients, unilateral diaphragm paralysis results in the loss of FVC and FEV1 of approximately 25% and 30%, respectively.[10] MPM might involve the diaphragm by direct extension. The RP technique usually allows the isolated resection of the diaphragmatic pleura without impairment of the diaphragm function. If the tumor extension involves the diaphragm muscle, diaphragm resection and reconstruction might be necessary. The sacrifice of the phrenic nerve might be indicated in case of phrenic nerve extension of the tumor bulk. In our study, preservation of diaphragm function was associated with greater increase in FVC and FEV1 of approximately 23.1% and 17.1%, respectively. Thus, the preservation of the diaphragm should be attempted whenever technically and oncologically feasible.

In general, approximately 85% of the patients die within the first 3 months in event of the recurrence of MPM.[11] However, several phase-III trials demonstrated that second-line chemotherapy is associated with significantly prolonged

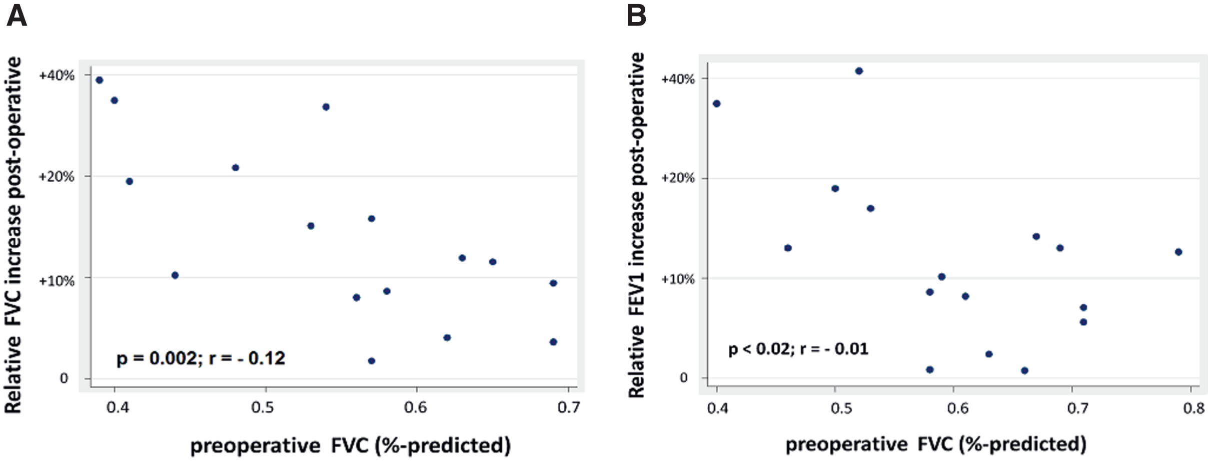

FIGURE 3. Scatter plot of preoperative FVC (%-predicted) against relative increase in FVC after RP and preoperative FEV1 (%-predicted) against relative increase in FEV1 after RP (r = correlation coefficient). FVC, forced vital capacity; FEV1, forced expiratory volume; RP, radical pleurectomy.

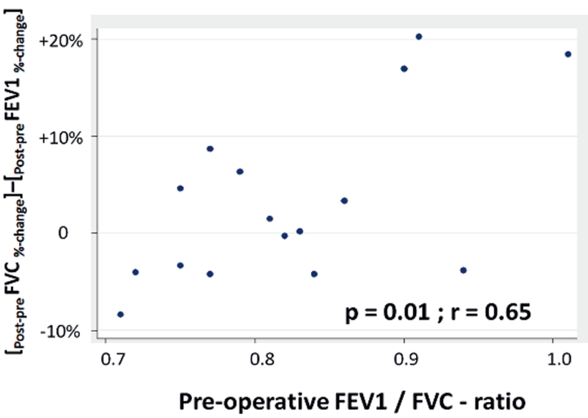

FIGURE 4. Scatter plot of (relative change in FVC-relative change in FEV1) against preoperative FEV1/FVC-ratio (r = correlation coefficient). FVC, forced vital capacity; FEV1, forced expiratory volume.

survival in the management of MPM.[12,13] No more than 25% of the patients receive additional chemotherapy after EPP and multimodality treatments.[14] On contrary, 64% of the patients with MPM recurrence after RP were found to be eligible for further therapy options after RP.[2] Patients managed with RP and first-line chemotherapy are commonly still in good performance status when radiological progression of MPM is documented. Clinical benefit from further therapy might be seen in 65% of patients with MPM recurrence.[15] Thus, preservation of the cardio-pulmonary reserve might be a precondition to being eligible for further therapy options such as second-line and third-line therapies, and novel cytostatic drugs or vaccines currently under investigation.[16]

Another important issue is quality of life (QOL) after possible surgery. Even if we did not evaluate the QOL in the present study, physical functioning and dyspnea status play a major role in the evaluation of QOL.[17] Reduced pulmonary-function status after surgery is associated with decrements in QOL in thoracic malignancies.[18] Furthermore, FVC was correlated with patient-reported disease-related symptoms and health-related QOL (HRQOL) using the Lung Cancer Symptom Score-Mesothelioma.[19]A higher baseline FVC was associated with higher baseline Karnofsky Performance Status and correlated with normal activity scores, as well. These functional factors can be significantly influenced by the type of resection. We have shown that parenchyma-saving RP is associated with the improvement of lung function. The available data and the results of the present study would suggest that a surgical strategy of limiting loss of lung function may result in a better preservation of QOL. Nonetheless, pulmonary-function tests alone cannot substitute QOL- or subjective dyspnea-scoring evaluations.[20] Thus, QOL- and dyspnea-scoring assessments are planned for future trials at our institution.

In general, mortality rates for RP are in the range of 2% to 5.8%.[2,21] We observed no surgical mortality. Surgical morbidity was 43.8 % and the complications were not life-threatening. However, preoperative impaired FEV1 and predicted postoperative FEV1 are associated with morbidity and mortality after thoracic surgery.[22] Numerous large studies documented the association of reduced pulmonary function with enhanced mortality in many different patient population.[23,24] Furthermore, the most frequently used parameters for the presurgical evaluation of thoracic-surgery candidates are FEV1 and the predicted postoperative FEV1.[25] However, we have shown that there is no loss of pulmonary function post surgery. The average increase of FEV1 was +23.9% postsurgically. Furthermore, in a linear regression analysis the lower the preoperative FVC (%-predicted) or FEV1 (%-predicted) was, the higher the relative increase in FVC or FEV1 after RP was ($p < 0.02$ for both). Therefore, it seems that preoperative FEV1 is not the best predictor of complications after RP, and might in isolation not be useful to guide the selection of surgical candidates for RP. In non–small-cell lung cancer surgery, the Charlson comorbidity index was predictive of major postoperative complications.[26] Thus, we plan to evaluate the Charlson comorbidity index as a possible reliable predictor for patient selection.

Because of the small number of patients, the differences in the analyses could be attributable to chance even if Bonferroni adjustment and effect-size calculation were applied. The results of this study should be confirmed in a study with larger sample size. We observed a rapid reaccumulation of the pleural fluid between thoracoscopy and RP irrespective of the underlying reason (entrapment or fluid accumulation). There was reaccumulation of pleural fluid at different levels in all patients. There might be a bias because of the rapidness of pleural-fluid accumulation and the influence on changes in pulmonary function and perfusion. Pulmonary therapists helped patients undergoing RP to strengthen the pulmonary function in the preoperative and postoperative management. These multiple components included smoking cessation, intensive chest physiotherapy, maximal inspiratory maneuvers, and use of a flutter valve to facilitate mucus clearance. These confounding factors might have influenced the results. These aspects should be considered when the results of the present study are interpreted.

CONCLUSIONS

Lung-sparing RP leads to significant improvement of pulmonary function and perfusion after a recovery time of 2 months. Functional results are better after preservation of the diaphragm. Preservation of physiological reserve via lung-sparing RP might allow patients with MPM to be eligible for further therapeutic options in the long term.

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