Quality of life after surgery for pleural malignant mesothelioma – methodological considerations

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Background There is a dearth of literature on patient quality of life (QoL) after treatment for malignant pleural mesothelioma (MPM).
Objectives To review the literature on QoL after surgery for MPM and assess differences in quality of life between patients who have extrapleural pneumonectomy (EPP) and those who have pleurectomy and decortication (P-D).
Methods We retrieved and reviewed original research studies on quality of life after mesothelioma surgery. They had been published from January 1990 through June 2016, and included 15 articles and 12 datasets for a total of 523 patients.
Results QoL data was available for 102 EPP patients and 296 P-D patients. Two studies directly compared QoL outcomes between the 2 techniques. Symptoms, lung function parameters, and physical and social functioning were still compromised 6 months after surgery. However, P-D patients fared better than did EPP patients across QoL measures.
Limitations The amount of available literature is small, and the studies are heterogeneous.
Conclusions QoL is better for a longer period of time in patients who undergo P-D, compared with those who have EPP. Given the need for multimodality therapy for MPM and the aggressive nature of the disease, QoL outcomes should be strongly considered when choosing type of surgery for mesothelioma.

Malignant pleural mesothelioma (MPM) is an often fatal cancer associated with past exposure to asbestos, either in the occupational or environmental setting. Despite treatment with multimodal therapies that include platinum-based chemotherapy, tyrosine-kinase inhibitors, surgery and radiation, the average survival after diagnosis is 15 months in US.[1] Most patients present with advanced-stage disease and have comorbidities that prevent aggressive treatment and are therefore offered palliative care. The primary goal is often to control symptoms and improve quality of life (QoL) during a relatively short life expectancy.

Surgical treatment has been found to be an independent predictor of extended survival in an analysis of data from the Surveillance, Epidemiology, and End Results (SEER) database,[1] and is currently performed in 22% of MPM patients.[2] Two procedures are available – extrapleural pneumonectomy (EPP), and pleurectomy and decortication (P-D) – and the debate around which offers better results in terms of complications from surgery and survival persists. Based on our review of the literature, we suggest that the differences in survival between the two procedures are modest, but favor P-D in both short- and long-term survival.[3] Given the morbidity and mortality associated with surgical resection for MPM, it is important to assess whether QoL is equally affected by EPP and P-D to inform patients and guide treatment choices. In the current study, we compare published QoL results for patients undergoing EPP or P-D for malignant pleural mesothelioma.

Material and methods

We performed a Medline search in PubMed and Embase databases using the key words and phrase combination of *quality of life* AND *mesothelioma* AND *surgery*. In addition, we also searched meta-analyses on mesothelioma surgical outcomes,[4-6] as well as a review on quality of life after mesothelioma treatment,[7] and data on QoL after surgical resection

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TABLE Description of studies presenting QoL in MPM patients treated with surgery

Source (study period)	Design	N	Case selection	Treatment	QoL measurements	QoL measurement taken					Recurrence (R) or survival (S) after surgery
						Baseline	0-4 mo	5-9 mo	12-18 mo	>2 y	
EPP											
Weder,[9] Ribi,[10] (2000-2003)	O	45	Clinical T1-3, N0-2, M0, any histology	Neoadjuvant, EPP, radiotx	RSCL, SEIQoL	Y	1, 3	6	12	–	Median R 13.5 mo
Ambrogi[11,12] (1997-2007)	O	29	None	Adjuvant, EPP, radiotx	SF-36, SGRQ, symptoms, lung function, 6-min walk, cardiac EF, KPS	Y	3	6	12	2, 3	Median R 19.5 mo
Alvarez[13] (2004-2007)	O	16 (18 no EPP)	Stage I or II, epithelioid, <70 y	EPP, chemotx, radiotx	ECOG, KPS	ECOG 0	–	6	12	–	R 18% at 6 mo
Treasure[14] (2005-2008)	RCT	12 (19 no EPP)	T1-3, N0-1, M0, any histology	Chemotx, EPP, radiotx	EORTC QLQ-C30 and -LC13	Y	6 wk, 3	6, 9	12, 18	2	R 75% at 6 mo
P-D											
Burkholder[15] Mollberg[16] (2010-)	O	36	Epithelioid, biphasic WHO PS 0-2	EPD (some talc, some adjuvant)	EORTC QLQ-C30, lung function	Y	4	5, 7, 8	–	–	NA
Sauter[17] (1988-1992)	O	20	None	Partial P (some chemotx, some radiotx)	Dyspnea, pain	Y	–	6	–	–	Median R 10 mo
Soysal[18] (1974-1992)	O	100	None	56 P-D, 44 partial pleurectomy	Dyspnea, pain, cough		3	6	–	–	Median S 17 mo
Martin-Ucar[19] (1997-2001)	O	51	Exclude early stage	P-D palliative	Symptoms	Y	6 wk	6	12	–	R 53% at 6 mo
Bolukbas[20] (2010)	O	16	None	Radical P, chemotx, radiotx	Lung function	Y	2	–	–		NA
Rintoul[21] (2003-2012)	RCT	73	None	73 partial P, 78 talc	EORTC QLQ-C30 and -LC13, EQ-5D, lung function	Y	1, 3	6	12	–	Median S 13 mo
P-D Vs Epp											
Ploenes[22]	O	48	None	25 EPP; 23 P-D	Lung function	Y	–	6	12	Median survival, 22 and 29 mo	–
Rena[23] (1998-2009)	O	77	Stage I or II	40 EPP, 37 P-D (chemotx and radiotx)	EORTC QLQ-C30	Y	–	6	12	–	Median S 14 and 11 mo

Chemotx, chemotherapy; ECOG, Eastern Cooperative Oncology Group Performance Status; EF, ejection fraction; EORTC QLQ-C30, 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EPD, enzyme potentiated desensitization; EPP, extrapleural pneumonectomy; EQ-5D, EuroQol Group; KPS, Karnofsky Performance Status Scale; O, observational; P-D, pleurectomy and decortication; radiotx, radiotherapy; RCT, randomized, controlled trial; RSCL, Rotterdam Symptom Checklist; SEIQoL, Schedule for the Evaluation of Individual Quality of Life; SF-36, 36-item Short-Form Health Survey; SGRQ, St George's Respiratory Questionnaire; Y, yes; WHO PS, World Health Organization Performance Status (aka, ECOG)

for MPM were extracted. Data published from January 1990 through June 2016 were included. The inclusion criteria were that the studies had to: report on cohort or randomized, controlled trials; have used standardized instruments for measuring QoL; report on QoL measurement after surgery; describe the type of surgery performed (EPP or P-D); and be written in English.

The search yielded 94 publications for possible consideration. We reviewed the abstracts, and 78 were excluded because the publication was a case report (n = 2), review/commentary (n = 25), did not include mesothelioma cases (n = 25) or QoL data (n = 14), or reported on cases not treated with surgery (n = 12). The 16 remaining articles were reviewed in detail, and 1 more was excluded because it was not written in English.[8] That left 15 articles and 12 distinct datasets for a total of 523 pleural mesothelioma patients with QoL information (Table) for us to review. Data was extracted independently by two reviewers (ET, AW). In cases of discordance between the reviewers, they reviewed the articles again, and the final decision was reached by discussing the issue with a third reviewer (RS).

Results

QoL after EPP

There were 4 datasets that included QoL after EPP – 3 observational trials and 1 randomized, controlled trial – for a total of 102 patients. A study by Weder and colleagues reported on QoL measured with the Rotterdam Symptom Checklist, a cancer-specific questionnaire measuring physical and psychological distress, in 45 patients treated with neoadjuvant chemotherapy, EPP and then possible adjuvant radiation.[9] QoL was assessed before surgery and after surgery at 1, 3, 6, and 12 months. Psychological distress returned to values similar to baseline at 6 months. Physical symptoms worsened at 1 month (-16.7 from baseline measure), but improved at 6 months (-4.3). Overall QoL did not reach baseline levels after 6 months (-8.3). Among the additional symptoms they were asked about, tiredness, shortness of breath, and chest pain were worse at 1 month, and returned to baseline at 6 months.[9] These same patients were also administered the Schedule for the Evaluation of Quality of Life-Direct Weighting (SEIQoL-DW), which is an individually driven QoL measure in which the patient determines the five QoL domains that are most important to him/her and then rates those 5 domains. Overall QoL scores as measured by the SEIQoL-DW decreased after surgery, returned to baseline at 3 months, but then worsened again at 6 months.[10]

Ambrogi and colleagues evaluated 29 consecutive patients who underwent adjuvant chemotherapy, EPP, and adjuvant radiation.[11,12] An extensive list of QoL measurements were reported at baseline and after surgery for up to 3 years of follow-up. Lung and cardiac function were

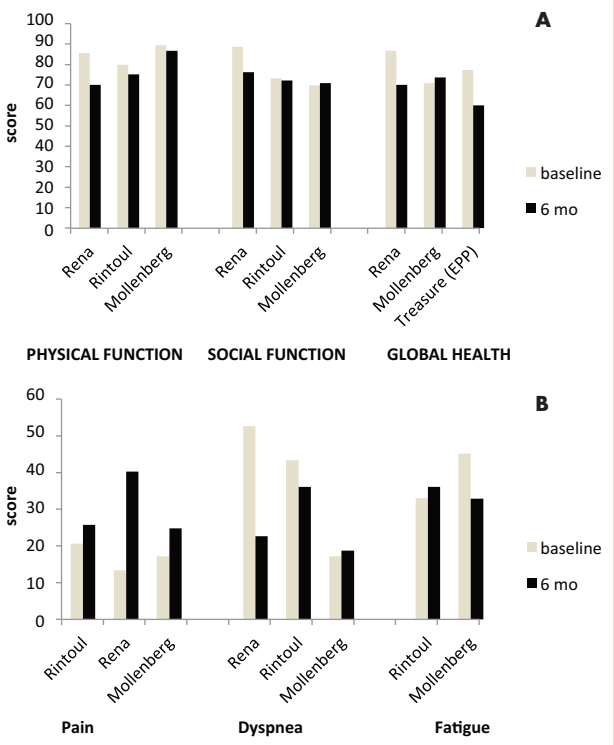

FIGURE 1 Quality of life (A) and symptom scores (B) from the EORTC questionnaire[a]

EORTC, European Organization for Research and Treatment of Cancer

[a]EORTC QLQ-30 (v3.0) score ranges from 0-100, with the highest score represent a better state of the patient.

stable at 6 months but had significantly deteriorated at 12 months. Pain, dyspnea, cough, and fever improved at 3 months but deteriorated again at 12 months, as did the scores for the Karnofsky Performance Status index, a 100-point measure of performance status (100, normal with no evidence of disease; 0, dead). The SF-36, a 36-item survey of mental and health QoL summary measures, showed improvement in all domains at 3 months, but at 12 months only the physical QoL domains remained above baseline and at 24 months, both scores were below baseline. Similar results were obtained by the St George's Respiratory Questionnaire.

Two studies compared QoL after EPP with no surgery; one study was observational and the other was a randomized, controlled trial. Alvarez and colleagues[13] studied 16 patients with stage I or II epithelioid mesothelioma who had an ECOG (Eastern Cooperative Oncology Group) performance status score of 0 (range, 0-5; 0 is asymptomatic, 5 indicates death), aged younger than 70 years, and were treated with EPP followed by chemo- and radiotherapy.

ECOG (also known as the WHO score) and Karnofsky scores were measured at 6 months and 1 year after surgery,

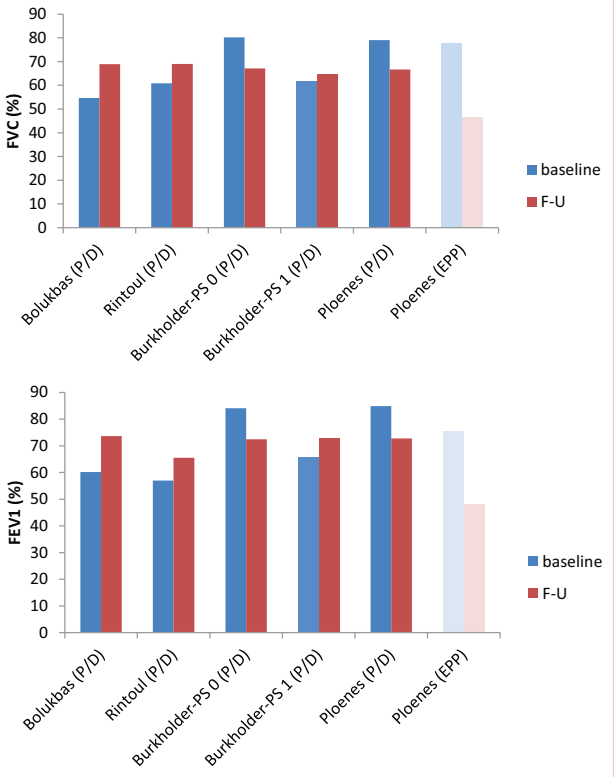

FIGURE 2 Lung function after extrapleural pneumonectomy and pleurectomy and decortication

FEV, forced expiratory volume; FVC, forced vital capacity

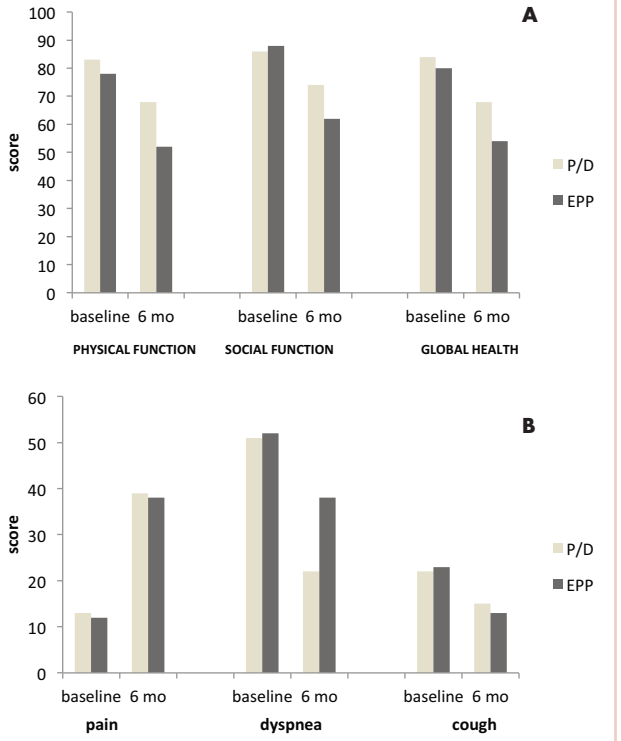

FIGURE 3 Comparison of EORTC quality of life (A) and symptoms (B) for extrapleural pneumonectomy and pleurectomy and decortication[ab]

EORTC, European Organization for Research and Treatment of Cancer

[a]Rena (2012). [b]EORTC QLQ-30 (v3.0) score ranges from 0-100, with the highest score represent a better state of the patient.

with no baseline measurements available. Mean ECOG scores at 6 months and 1 year were 1 and 0.8, respectively, while the Karnofsky index scores for the same intervals were 74 and 82, respectively. By comparison, patients who did not undergo surgery (n = 18) demonstrated a stable mean ECOG of 1.7 and Karnofsky of 46 at both 6 and 12 months. Treasure and colleagues[14] conducted a feasibility trial in which patients were randomized EPP or no surgery. In that study, 12 patients underwent induction chemotherapy, EPP, and adjuvant radiation. QoL was measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-30 version 3.0; range, 0-100, with highest score representing a better state of the patient) and the EORTC lung cancer-specific quality of life questionnaire, EORTC QLQ-LC13, which has an additional 13 items that are specific to lung cancer (range, 13-52, with higher scores indicating greater lung cancer-related symptomatology. Results were compared with the control group undergoing chemotherapy only. Median QoL scores were lower in the EPP group compared with those in the no-surgery group at all time points, but particularly at 6 weeks (score, 33.3 vs 75, respectively). However, none of the group differences were statistically significant.

QoL after P-D

There were 6 studies with a total 296 patients evaluating QoL after P-D. Burkholder and colleagues[15,16] reported on 36 patients who completed the EORTC QLQ-30 questionnaire at baseline and up to 8 months after surgery. In some patients, neoadjuvant chemotherapy was given and/or pleurodesis was also performed. Among patients with WHO/ECOG performance status (PS) of 0, baseline QoL scores were significantly higher compared with those with a score of 1. Among the PS 0 patients, no postoperative change was observed in global health or function and symptoms scores, except for emotional function, which improved significantly during follow-up. Patients with PS 1 or PS 2 demonstrated improvement at 4 -5 months with further improvement at 7-8 months in all QoL and symptom domains. The PS 0 patients demonstrated a significant decrease in all lung function parameters, whereas no change was observed in PS 1 and 2 patients.

In another study, Sauter and collegeagues included 36 patients treated with partial pleurectomy in various combinations with chemotherapy and radiation.[17] Symptoms were collected at baseline and during follow-up using the five grades (0-4) of pulmonary symptoms listed in the

National Cancer Institute Common Toxicity Criteria. Dyspnea improved in 47% of patients after surgery, whereas pain improved in only 21%. However, no follow-up time frame is given in the article regarding the assessment of symptoms and pain. Soysal and colleagues reported a retrospective analysis of 100 consecutive patients who underwent P-D or partial pleurectomy.[18] Symptoms were measured at baseline and during 6 months follow-up. Chest pain decreased in 71% of the patients, cough in 40%, dyspnea in 37%, and chest constriction in 30%.

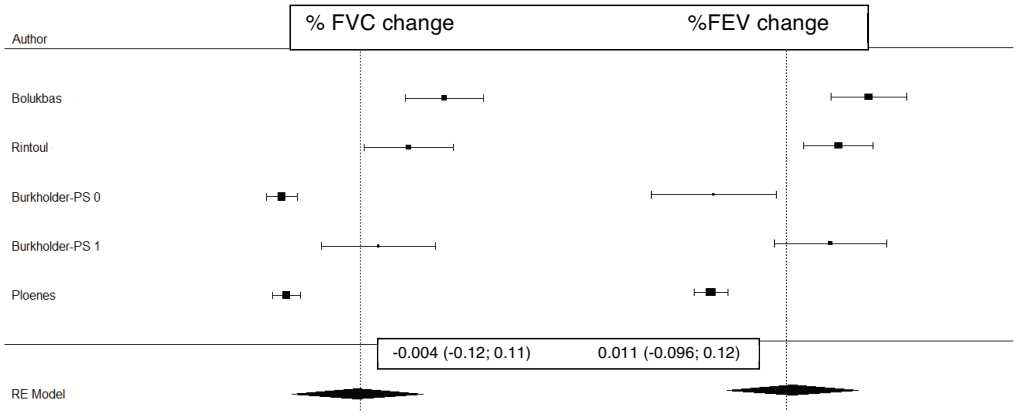

FIGURE 4 Change in lung function after pleurectomy and decortication

FEV, forced expiratory volume; FVC, forced vital capacity

Martin-Ucar and colleagues reported on symptoms after P-D in 51 consecutive patients, excluding those with early stage disease who underwent EPP.[19] The Medical Research Council (MRC) Dyspnoea Scale was used and pleuritic chest pain was assessed on a 4-point scale (range, 1-4: 1, not at all; 2, a little; 3, moderate; 4, severe). Significant improvement in dyspnea and pain scores was observed at 6 weeks and 3 months. Bolukbas and colleagues included 16 patients treated with radical pleurectomy followed by chemotherapy and radiation.[20] Lung function was measured at baseline and 2 months after treatment completion. All functional parameters improved from baseline to follow-up. Rintoul and colleagues completed an RCT comparing partial pleurectomy with talc pleurodesis in 151 patients, of whom 73 underwent surgery.[21] EORTC QLQ-C30, EuroQoL-5D (EQ-5D), and EORTC QLQ-LC13 questionnaires were used to assess QoL at baseline and up to 1 year after surgery. The EQ-5D data showed a significant decrease in QoL at 1 month after surgery, with a return to baseline values at 3 months, and improvement at 12 months. The EORTC physical, cognitive, and role function scales were lower at 1 month after surgery, but then returned to pre-surgery levels at 3, 6, and 12 months. Emotional and social function scales and global health were better at 1 year compared with before surgery, whereas symptoms were worse at 6 months and 1 year. Lung function improved 1 month after surgery, and the improvement persisted throughout follow-up.

A comparison across studies that measured QoL components and symptoms before and after surgery for the studies that used the EORTC questionnaire showed that at 6 months after surgery, physical and social functions, and global health were not yet back to pre-surgery values, and pain was still the main symptom reported, while dyspnea scores were improved compared with before surgery (Figure 1).

QoL comparison between EPP and P-D

Two studies directly compared QoL after EPP and P-D. Ploenes and colleagues analyzed lung function at baseline and at another time point between 6 and 12 months after surgery in 25 patients who underwent EPP and 23 who underwent P-D (Figure 2),[22] and found that EPP patients had a significantly reduced pulmonary function compared with P-D patients.

Rena and colleagues studied 77 patients with stage I or II mesothelioma, 40 of whom underwent EPP and 37 P-D.[23] The EORTC questionnaire was administered at baseline and at 6 and 12 months after surgery. Both procedures caused a significant impairment of all EORTC QLQ-C30 variables at 6 months. The severity of QoL impairment was worse in EPP patients (Figure 3), and only P-D patients returned to baseline levels at 12 months.

In the five studies that reported on changes in lung function after PD, the change in overall percentage forced vital capacity (%FVC) was close to 0 and the percentage forced expiratory volume (%FEV) change was 1% (Figure 4), compared with changes of -31% in %FVC and -27% in %FEV in the single study reporting on lung function after EPP.

Discussion

The review of the current literature on QoL after surgical resection for MPM suggests that symptoms, lung function parameters, and physical and social functions are compromised for 6 months after surgery. However, when comparing the two surgical procedures, P-D patients consistently fared better in QoL measures than did EPP patients. This may reflect the increased morbidity of EPP compared with P-D, and the higher rate of disease recurrence and progression in the first months after treatment (Table). Most studies in the literature are retrospective, so it is possible that patients in each cohort were treated with one or the other

procedure based on clinical indications and/or comorbidities, and those same factors may independently have had an impact on QoL. This type of selection bias would be accounted for in a randomized, controlled trial that compared the two procedures. In one of the two studies that compared the two procedures in an observational retrospective design,[22] lung function was comparable at baseline, but was significantly worse at 6 months among EPP patients compared with P-D patients. In the second study,[23] lung function in P-D and EPP patients was very similar at baseline, but the physical function, social function, and global health measures were worse after EPP compared with P-D. Therefore, even when one considers how the selection bias might affect the results of retrospective studies, the conclusions still favor P-D. In fact, comorbidities that have an impact on the choice of surgical resection for an MPM patient tend to associate sicker patients with compromised lung function with P-D as they would not likely tolerate EPP, and any impact of these comorbidities on QoL should favor EPP. With regard to extent of disease, critics of P-D may suggest that patients undergoing EPP have higher tumor burden that might affect QoL, but most studies in the review stratified by stage or otherwise excluded patients with advanced disease.

This review highlights several gaps and limitations in the existing literature. The number of datasets that included QoL measures was relatively small (12 datasets), especially given the extensive literature on MPM surgery. In addition, each study involved a small number of patients, from 12 to 100. The instruments used to measure QoL were also highly variable and often not comparable with each other, thus making it difficult to quantify the effect of each surgical approach on QoL. Another source of variability was that QoL measurement was often performed at baseline and then after surgery at different time points, from 1 to 6 months, and occasionally at 1 year. Other treatments, such as chemotherapy and radiation, were often administered, but their effect on QoL was not accounted for in the publications. Patients included in the QoL studies were very heterogeneous in age, stage, and comorbidities.

Most radical resections are performed by thoracotomy, but it is also possible that video-assisted thoracoscopy approaches were used. That may have had a differential impact on QoL, but the details were missing in the publications. There were more QoL data on patients who underwent P-D than EPP, and it is possible that if more EPP patients had been included, the results might differ. Furthermore, whenever QoL questionnaires are used, one must consider that the subset of patients who respond may exclude the most ill patients (those with the lowest QoL), who are unable to respond, or those with a better performance status who prefer to continue with their daily activities rather than remain involved in clinical studies. Accounting for the net direction of these biases would allow for a more accurate quantification of change in QoL after MPM surgery. Future studies on MPM treatment and outcomes should include QoL measurements that have been obtained at baseline and at multiple time intervals after surgery, and stratified according to treatment, including multimodal therapies. QoL results are needed to inform patients and treating clinicians to guide treatment choices in MPM.

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