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ORIGINAL RESEARCH

Laparoscopic esophageal myotomy versus pneumatic dilation in the treatment of idiopathic achalasia: a meta-analysis of randomized controlled trials

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Background: Achalasia is a primary esophageal motility disorder of unknown etiology associated with abnormalities in peristalsis and lower esophageal sphincter relaxation. The disease is incurable; however, definitive treatment procedures like pneumatic dilation (PD)/balloon dilation and laparoscopic esophageal myotomy (LEM) are performed to relieve dysphagia and related symptoms. Currently, there is paucity of data comparing the outcomes of these procedures. The aim of this meta-analysis is to compare the short- and long-term success rates of PD and LEM.
Methods: A thorough systematic search of PubMed, Scopus, clinicaltrials.gov, and Cochrane library was conducted for randomized controlled trials (RCTs) comparing the outcomes of PD versus LEM in the treatment of achalasia. The Mantel-Haenszel method and random effect model were used to analyze the data. RCTs with outcome data at 3-month, 1-year, and 5-year intervals were analyzed.
Results: A total of 437,378 and 254 patients at 3-month, 1-year, and 5-year intervals were analyzed for outcome data. At 3 months and 1 year, PD was not as effective as LEM (odds ratio [OR]: 0.50; confidence interval [CI] 0.31–0.82; $P = 0.009$ and OR: 0.47; CI 0.22–0.99; $P = 0.21$) but at 5 years, one procedure was non-inferior to the other (OR: 0.62; 0.33–1.19; $P = 0.34$).
Conclusion: PD was as effective as LEM in relieving symptoms of achalasia in the long-term.
Keywords: achalasia, balloon dilation, pneumatic dilation, laparoscopic myotomy, Heller's myotomy

Introduction

Achalasia is an incurable primary progressive motility disorder of the esophagus where inhibitory ganglionic cells in the myenteric plexus of the lower esophageal sphincter (LES) are irreversibly lost. This leads to impaired relaxation of the LES after swallowing, causing functional obstruction.[1–6] The most common symptoms of achalasia are dysphagia, heartburn, regurgitation, aspiration, and weight loss leading to impaired quality of life.[7–9] This clinical diagnosis is enhanced by barium swallow studies and endoscopy, and confirmed by manometry.[10] Although there is no curative treatment of achalasia, various therapies have been tried in the past without much success.[10–15] New options for achalasia peroral endoscopic myotomy (POEM), self-expanding metal stents, endoscopic sclerotherapy have shown promising results but there are only a few prospective observational studies to support their efficacy.[15–23] Current standard of care for achalasia includes forceful pneumatic dilation/balloon dilatation (PD/BD) and laparoscopic (Heller's) esophageal myotomy (LEM) with or without an anti-reflux procedure.[15] There are some randomized controlled trials (RCTs)

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comparing the success rate (improvement of dysphagia) of these procedures at short-term follow-up,[8,24–26] but there are only 3 RCTs comparing the long-term outcomes at 5 years published till date.[27–29] Although there are systematic reviews and meta-analyses on prospective studies and non-RCTs,[30] there is only one meta-analysis of RCTs comparing the outcomes of these two procedures in the short-term.[31] Herein, we analyzed the published RCTs to study the short- and long-term success rates of these procedures in order to shed light on this controversial issue.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement for reporting meta-analysis and systemic reviews[32] as recommended by the Cochrane Collaboration was used for this meta-analysis (Figure 1). A comprehensive electronic literature search was conducted for all the clinical trials on treatment of esophageal achalasia between the years 2000 and 2016 on PubMed, Embase, Scopus, Cochrane Library, clinicaltrials.gov, Ovid Medline, and Google scholar using the all-field "Achalasia, Esophageal", all-fields "Balloon dilation" or "Pneumatic dilation, and all-fields "Myotomy" or " Laparoscopic Heller's Myotomy" or "Laparoscopic esophageal myotomy"; all three search headings were connected with Boolean operator "AND". The eligibility criteria for the included studies relied on previously published guidelines for systematic reviews and were based on the PICO framework: P (Population: patients with idiopathic primary achalasia diagnosed with the help of clinical, endoscopic and manometric, and radiographic evidence), I (Intervention: repeated BD/PD), C (Comparative intervention/control group: LEM/Heller's myotomy), and O (Outcomes: improvement in dysphagia score). Only RCTs published in English were included. Patients were randomly assigned to PD or LEM group. Studies with at-least 3-month follow-up were included. Two reviewers (RB and SU) independently assessed the eligibility and validity of each study. Any disagreements were resolved with discussion with the

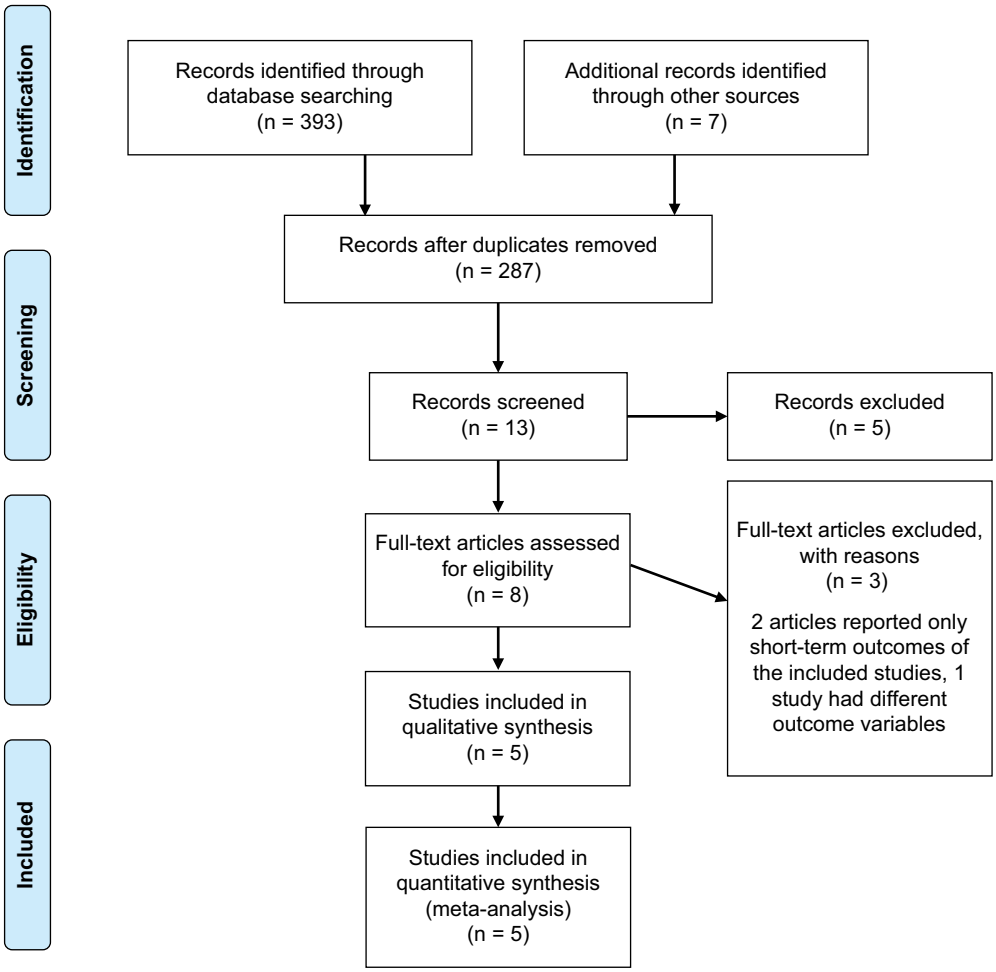

Figure 1 PRISMA statement of the study.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

third and fourth authors (JK and SKS). The fifth, sixth, and seventh authors (TSM, BKG, and GB) evaluated the quality of the studies independently and any disagreement was resolved via discussions among all the reviewers, ultimately reaching to an agreement by consensus. This search parameter yielded 393 articles. Case reports, retrospective studies, letters, comments, and studies without the availability of the data were excluded. Only human studies were included. A total of 5 RCTs met the aforementioned criteria. Quality of the included studies was assessed with the Delphi Consensus criteria for RCTs (Table 1).[33]

From all the selected studies, we extracted the baseline study details (Table 2): total number of patient enrolled, number of patients in each arm, mean age, sex ratio, inclusion and exclusion criteria, procedure detail (Tables 3 and 4), randomization process, definition of success or failure, adverse events, and quality of life score. Success rate was measured at 3 months, 1 year, and 5 years. The outcomes were calculated with RevMan, version 5.2 for Windows (Cochrane Collaboration, Oxford, UK). Analysis was performed by Mantel-Haenszel test. Odds ratio (OR) was calculated using confidence interval (CI) of 95%. Heterogeneity was

Table 1 Results of quality assessment by Delphi consensus criteria

Items	Persson et al[27]	Moonen et al[28]	Hamdy et al[26]	Borges et al[37]	Novais and Lemme[25]
1. Treatment allocation					
a) Was a method of randomization performed?	Yes	Yes	Yes	Yes	Yes
b) Was the treatment allocation concealed?	No	No	No	No	No
2. Were the groups similar at baseline regarding the most important prognostic indicators?	Yes	Yes	Yes	Unknown	Yes
3. Were the eligibility criteria specified?	Yes	Yes	Yes	Yes	Yes
4. Was the outcome assessor blinded?	No	No	No	No	No
5. Was the care provider blinded?	No	No	No	No	No
6. Was the patient blinded?	No	No	No	No	No
7. Were point estimates and measures of variability presented for the primary outcome measures?	Yes	Yes	Yes	Yes	Yes
8. Did the analysis include an intention-to-treat analysis?	Yes	No	No	No	No

Table 2 Baseline characteristics and results of the included studies

PD vs LEM	Persson et al[27]	Moonen et al[28]	Hamdy et al[26]	Borges et al[37]	Novais and Lemme[25]
Study design, location, and duration	Prospective, randomized, single-center study (Sweden) – minimum of 60 months	Prospective, randomized, multicenter, multinational study (Europe) – minimum of 5 years	Prospective, randomized, single-center study (Egypt) – median of 4 years	Prospective, randomized, single-center study (Brazil) – 5 years	Prospective, randomized, single-center study (Brazil) – 5 years
Total number of patients enrolled	28 vs 25	96 vs 105	25 vs 25	48 vs 44	47 vs 47
Mean age (years)	46 vs 43	46.4 vs 45.7	30.8 vs 32	52.8 vs 45.8	52.3 vs 46.5
Male (%)	43 vs 44	64 vs 53	25 vs 47	52 vs 36.4	53 vs 38
Follow-up (years)	6.9 vs 6.7 (median)	6.0 vs 6.6 (median)	4.0 (median)	2.0	3 months
Therapeutic success at 3 months	–	76 vs 91	19 vs 24	35 vs 37	31 vs 38
Therapeutic success at 1 year	22 vs 96	90 vs 93 (median %)	14 vs 22	28 vs 29	–
Success at 2 years	–	86 vs 90 (median %)	–	21 vs 21	–
Success at 3 years	19 vs 24	–	–	–	–
Success at 5 years	18 vs 23	82 vs 84 (median %)	–	–	–
Health economy	$5,558 vs $13,421	Not available	$228 vs $580	Not available	Not available
Baseline LESP before treatment	Not available	Not available	37.4 vs 39.8	27.8 mmHg vs 29.9 mmHg	28.3 ± 13.7 vs 30.3 ± 12.2
Complications (perforation, mucosal tears, reflux)	Perforation: 2 vs 0	Perforation: 5 vs 0 Mucosal tears: 0 vs 13	Perforation: 2 vs 1 Mucosal tears: 0 vs 3 Reflux: PD-28%, LEM-16%	Perforation: 2 vs 0 Reflux: 13 vs 2	Perforation: 2 vs 0 Reflux: 13 vs 2

Note: All data given in numbers unless otherwise specified, data are given in pneumatic dilation/laparoscopic esophageal myotomy format.
Abbreviations: PD, pneumatic dilation; LEM, laparoscopic esophageal myotomy; LESP, lower esophageal sphincter pressure.

Table 3 Pneumatic dilation/balloon dilation procedure of included studies

RCT	Procedure
Persson et al[27]	Anesthesia: conscious sedation with midazolam and pethidine or under general anesthesia. Procedure: graded 30–40 mm PD balloons insufflated to 10 psi for 60 seconds over the gastroesophageal junction under fluoroscopic guidance using predefined staged dilatation protocol; 30 mm dilation in female and 35 mm dilation in male. If suboptimal results, further dilatation with 35 mm balloon for female and 40 for male within 10 days.
Hamdy et al[26]	Anesthesia: conscious sedation. Procedure: the non-compliant pneumatic balloon is inflated up to a pressure of 15 psi for 60–90 seconds. Graded dilation by 3, 3.5, and 4 cm diameter balloons unless mucosal ulceration occurs.
Moonen et al[28]	Anesthesia: not available. Procedure: a two-stage pneumatic dilation balloon was performed with 30 mm balloon, followed by 35 mm balloon within 2 weeks.
Borges et al[37]	Anesthesia: conscious sedation. Procedure: non-compliant 30 mm pneumatic balloon positioned in the cardia and inflated at a pressure of 10 psi for 1 minute. Graded dilation in the same session if no laceration or shallow lacerations.
Novais and Lemme[25]	Anesthesia: not available. Procedure: graded dilation with 30, 35 and 40 mm polyethylene balloons inflated for 1 minute at 10 psi pressure starting with low caliber to produce optimum laceration.

Abbreviations: RCT, randomized controlled trial; PD, pneumatic dilation.

Table 4 Laparoscopic surgical procedure of included studies

RCT	Procedure
Persson et al[27]	Myotomy (involving division of the entire muscle layer down to the mucosa about 5 cm above the gastroesophageal junction and 2–3 cm in the proximal stomach) plus toupet (partial) fundoplication to prevent reflux.
Hamdy et al[26]	Myotomy starting just above the point of apparent constriction until the place between the muscle and the mucosa identified. Myotomy extended 6 cm in the lower esophagus and 2 cm in the proximal stomach. Dor's fundoplication to prevent reflux.
Moonen et al[28]	Myotomy performed extending at least 6 cm above the gastroesophageal junction and up to 1.5 cm on proximal stomach followed by anterior 180 degree Dor's fundoplication.
Borges et al[37]	Heller laparoscopic myotomy performed with circular and longitudinal myotomy of 6 cm extending to distal esophagus and 2 cm into proximal stomach.
Novais and Lemme[25]	Anesthesia: general anesthesia. Procedure: sectioning the longitudinal and circular muscular muscle layer involving distal 6 cm of esophagus and 2 cm proximal stomach followed by 180 degree anterior fundoplication.

Abbreviation: RCT, randomized controlled trial.

calculated using I^2. A randomized model was used because of the low heterogeneity from the low number of studies. A P-value of <0.05 was considered significant. The primary analysis focused on symptom resolution as the outcome of interest. This was based on various dysphagia scores in each study. Success rate was evaluated by using improvement validated tools like Watson dysphagia score[34] by Persson et al,[27] Eckardt score[35] by Moonen et al,[28] Demeester's grading of dysphagia[5] by Hamdy et al,[26] and Vantrappen and Hellemans score[36] by Borges et al[37] and Novais and Lemme[25] (Table 5).

Results

A total of 437 patients at 3-month interval, 378 patients at 1-year interval, and 254 patients at 5-year interval were analyzed for success rate of the procedure, namely the improvement in the dysphagia score. At 3 months, success rate was significantly lower in patients with BD (OR: 0.50; CI 0.31–0.82; $P = 0.02$). At 1 year, success rate was still significantly lower in BD (OR: 0.47; CI 0.22–0.99; $P = 0.99$) but nearing non-inferior levels. At 5 years, BD was non-inferior to myotomy (OR: 62; CI 0.33–1.19; $P = 0.15$) (Figure 2). In an RCT, not included in our study, by Chrystoja et al,[29] no significant difference was found in the improvement of achalasia severity questionnaire at 1 year (score difference: 7.3; CI −4.7 to 19.3; $P = 0.23$ at 1 year) and 5 years (score difference: 0.5; CI −13.5 to 14.4; $P = 0.95$).

Discussion

Achalasia is a primary motor disorder of the esophagus that is chronic and incurable. Although LEM and PD are the mainstays of treatment, the best modality remains controversial.[4] Both treatment approaches carry a variable risk of recurrence of symptoms, perforation, and gastrointestinal reflux.[38] Therefore, it is imperative to identify the best method for the

Table 5 Outcome measure or primary endpoint for included studies

RCT	Dysphagia score	Outcome measure (definition of failure)
Persson et al[27]	Watson dysphagia score	1. Incomplete symptom control or symptom relapse requiring more than three additional treatments other than those given initially (surgery or one to two dilations at 10-day interval). 2. Relapse requiring treatment occurring within 3 months after the initial treatment series.
Hamdy et al[26]	Demeester's grading of dysphagia assessing successful symptomatic relief.	1. Recurrent symptoms after surgery was considered failure. 2. Pneumatic dilation was considered failure if more than 3 sets of dilations was needed.
Moonen et al[28] The European Achalasia trial	Therapeutic success based on presence of Eckardt score ≤3.	1. If Eckardt score remained >3 at 4 weeks after the index dilation. 2. Redilation allowed twice (second and third series) but the third dilation allowed for recurrence after 2 years only. If third dilation required before 2 years, then it was considered a failure. 3. For laparoscopic myotomy, Eckardt score >3 was considered a failure.
Borges et al[37]	Clinical improvement based on Vantrappen and Hellemans score for dysphagia.	1. Poor responder defined under fair results (dysphagia for one or two times/week, associated with food regurgitation, without weight loss) and poor results (dysphagia over twice a week, regurgitation and weight loss).
Novias and Lemme[25]	Vantrappen and Hellemans criteria for dysphagia response.	1. Excellent result: absence of dysphagia. 2. Good: occasional dysphagia, less than once a week. 3. Fair: dysphagia more than once a week, associated with regurgitation. 4. Poor: dysphagia more than once a week, associated with regurgitation and weight loss. 5. Considered failure if fair or poor response.

Abbreviation: RCT, randomized controlled trial.

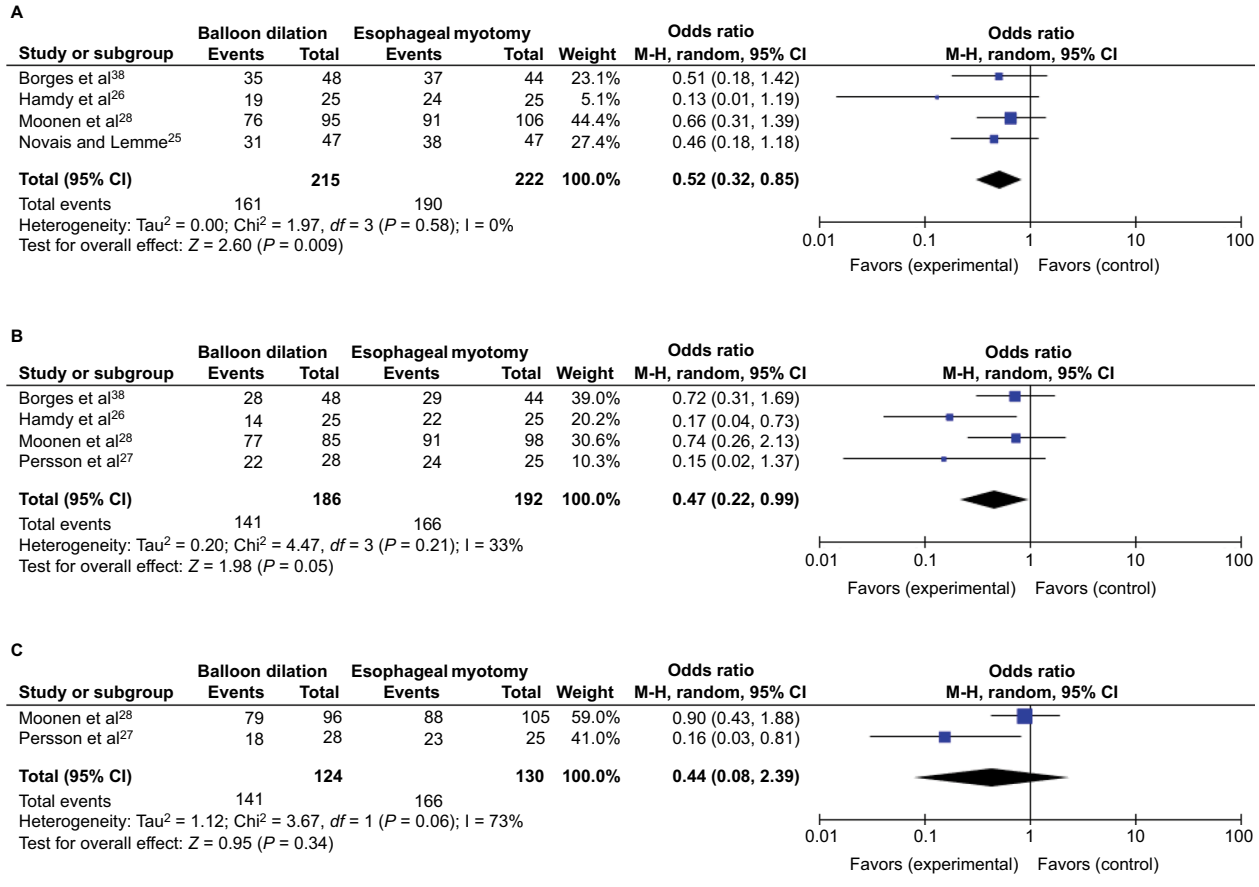

Figure 2 Forest plot of response rate at (**A**) 3 months, (**B**) 1 year, and (**C**) 5 years.
Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

short- and long-term symptom relief with due consideration of complications. Our study compared the short- and long-term outcomes of the two procedures based on symptom relief at 3 different intervals. Our analysis shows that LEM is better at 3 months and at 1 year (with increasing confidence interval), while PD becomes non-inferior to LEM at 5 years. These results indicate that both treatment approaches lead to comparable outcomes in the long run.

In contrast to LEM, one major advantage of PD is that it can be performed safely in the outpatient setting without need for general anesthesia. However, more patients in single PD group require re-intervention compared to those treated with LEM.[39] Although the remission rate is higher with graded dilation approach,[40–43] it is associated with higher rates of perforation and complex surgery[44] LEM, on the other hand, has the major risk of mucosal tear, and leads to abdominal wall trauma requiring longer recovery time.

In a meta-analysis by Yaghoobi et al,[31] LEM provided greater relief of symptoms compared to graded dilation. The main limitation of the study was the lack of long-term follow-up and a small number of included studies. The network meta-analysis by Schoenberg et al[45] corroborated these findings. The study did not include long-term follow-up and included indirect comparison. In another meta-analysis by Campos et al,[30] LEM was found to be more effective and long lasting compared to BD or botulin toxin injection. However, the complication rate was higher in the surgical group due to the invasiveness of the procedure. In this regard, PD was deemed more suited for frail patients who are poor surgical candidates, or for those patients who fail surgery. However, the results of these studies have to be interpreted with caution as these studies often use variable and subjective definitions of success rate. Furthermore, some of the studies included in the analysis used data from single dilations, while it is well known that it is a multistage procedure with graded dilation.[46] In lieu of the largest RCT, the European Achalasia Trial,[28] the present meta-analysis is the only one of its kind to include this in the analysis.

The other consideration for this study is the evolving technique of the procedure. The technique of dilation has evolved from rigid dilators to hydrostatic balloon. This allows achievement of maximum controlled volume with low pressure, which improves efficacy and prevents perforation.[47] The hypothesis that BD causes the disruption of muscular layer has been challenged by the study by Borhan-Manesh et al.[48] The finding shows that PD works by circumferential stretching of the LES. This has resulted in modification of the current method of dilation by slowing the rate of inflation, leading to increased remission rate of BD. POEM is a newer technique that is being used to perform myotomy of the LES. Long-term data from RCTs comparing POEM with conventional treatment methods are lacking. This procedure is still evolving and its role in management of achalasia is not clearly outlined.[49] Further studies comparing conventional treatment with POEM with a longer follow-up will be needed for change in practice. Thus, PD or LEM continues to remain the standard of care for achalasia with comparable outcome in the long-term.

Conclusion

Taken together, the data presented here provide evidence that both treatments have similar success rate at 5 years. So, eligible patients should be given the option of PD or LEM at this time.

Disclosure

The authors report no conflicts of interest in this work.

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