

Review Article

Current status of laparoscopic transhiatal esophagectomy for esophageal cancer patients: a systematic review of the literature

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SUMMARY. Minimally invasive techniques in transhiatal esophagectomy (THE) were introduced to reduce morbidity and enhance postoperative recovery. Aim of this study was to systematically review the current status and possible beneficial effects of the minimally invasive approach in THE. A systematic search was performed in PubMed, the Cochrane Library, and Embase to identify English articles published on laparoscopic THE. Comparative cohort studies were included for critical appraisal. Data describing perioperative and oncological outcomes were analyzed. A total of four comparative cohort studies that compared laparoscopic THE ($n = 122$) with open THE ($n = 144$) and four noncomparative cohort studies reporting on laparoscopic THE ($n = 212$) were included in this review. Median blood loss was significantly lower in the laparoscopic group in all studies (100–500 vs. 526–900 mL). Length of hospital stay was also significantly shorter for the laparoscopic approach in all studies (9–13 vs. 12–16 days). One study reported less major postoperative complications after laparoscopic THE (12 vs. 23%), in the other studies no differences were found. Also no differences were found with regard to operating time, postoperative morbidity, radicality, and lymph node retrieval. Based on these pioneer studies, laparoscopic THE was demonstrated to be safe and feasible with evidence of reduced blood loss and shorter hospital stays. However, level 1 evidence is lacking and further research is warranted to confirm these findings and also to evaluate long-term oncologic outcomes.

KEY WORDS: esophageal cancer, transhiatal esophagectomy, minimal invasive esophagectomy, laparoscopic surgery.

INTRODUCTION

Esophagectomy is the key element in the curative treatment of patients with esophageal cancer. However, the type of approach and extent of lymphadenectomy that is necessary for esophageal cancer patients remains controversial.^{1,2} Transthoracic esophagectomy (TTE), is advocated because of its extended mediastinal lymph node dissection and improved locoregional control.^{3,4} Others have advocated the transhiatal esophagectomy (THE) for distal esophageal cancer offering decreased postoperative morbidity with supposedly no compromise in cancer recurrence or survival.⁵ Regardless of the type of approach, both procedures still have high

complication rates, varying between 40 and 80%.⁶ This has encouraged the search for alternative techniques that achieves similar oncological outcomes but with less morbidity and faster recovery times. With this objective in mind, minimally invasive techniques in esophagectomy were introduced for TTE by Cuschieri and coworkers⁷ in 1992 and for THE by Depaula and coworkers⁸ in 1995. A recent meta-analysis showed that minimally invasive esophagectomy (MIE) reduces overall morbidity and pulmonary complications and could lead to a shorter hospital stay.⁹ This was, however, only reported for the transthoracic approach. By avoiding a thoracotomy, it seems obvious that pulmonary complications can be reduced. However, in a laparoscopic approach these benefits are less obvious. To date, no systematic review or meta-analysis has been reported comparing laparoscopic versus open THE. Hence, this systematic review was conducted to elucidate the current status and possible beneficial effect of the minimally invasive approach in THE.

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PATIENTS AND METHODS

The present review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁰

Search strategy

A systematic search was performed in PubMed, the Cochrane Library and Embase (January 1985–January 2015). The search included three different domains and the medical subject headings (MeSH) terms and keywords between the domains were combined with “AND.” Within the domains, the terms were combined with “OR.” The first domain contained terms related to “esophagus” and “gastro-esophageal junction,” the second domain contained terms related to “cancer,” and the third domain contained terms related to treatment (i.e. open or laparoscopic THE). The terms were restricted to title and abstract. A full description of the search strategy is available in Supporting Information Appendix S1. Only original studies on humans and written in English were considered for inclusion. Duplicate publications were excluded. To enhance the search sensitivity, a manual hand-search was performed using cross referencing of included studies. The last search was performed on October 17, 2015.

Study selection

All eligible studies were retrieved and studies that seemed unrelated to the study aims were excluded based on single author title review. For the remaining studies all abstracts were independently assessed for eligibility by two authors (KP and JR). Full papers were retrieved for all abstracts deemed potentially eligible. Full papers underwent dual author review and were assessed against inclusion/exclusion criteria. In case of discrepancies between the two authors regarding eligibility, a consensus was reached through discussion.

Inclusion and exclusion criteria

Primary endpoints included were morbidity and duration of hospital stay. Secondary endpoints were blood loss, duration of the surgical procedure, and oncological outcomes (resection margin and lymph node retrieval). Reporting of at least one of these outcomes for laparoscopic THE was considered sufficient for inclusion. Comparative cohort studies between laparoscopic and open THE were included if they had a sample size >10 per treatment group. Studies were excluded if they were review articles, meta-analyses, experimental studies or noncomparative cohort studies with a sample size ≤30. In case of duplicate publications reported by the same author

with overlapping or similar patient outcomes, only the study with the best quality or the most complete data was considered.

Quality assessment

The methodological quality of the included comparative studies were critically appraised according to the Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence.¹¹ The risk of bias was assessed using a standardized list of ten potential risk factors of bias, based on the Oxford CEBM Critical Appraisal Skills Programme appraisal sheet for observational cohort studies.^{12,13}

Statistical analysis

Outcomes were expressed as reported originally. Due to the heterogeneity between the studies, no formal meta-analysis could be performed. Some studies reported medians with range and some studies reported means with standard deviation. It was, therefore, not possible to calculate weighted means.

RESULTS

Eligible studies

A flowchart of the literature search process is shown in Figure 1. The initial search identified 6309 unique records from the electronic databases. Of these, 5804 records were excluded after initial screening of titles and another 434 records were excluded after screening of abstracts. In total 71 articles were included for full-text review, after which 63 were excluded based on no full text available, not written in English, reporting of duplicate patient populations, intervention was not laparoscopic THE, usage of novel techniques in THE or poorly reported results. In total 8 studies remained available for analysis, of which 4 were comparative cohort studies^{14–17} and 4 were noncomparative cohort studies.^{18–21} The results of the critical appraisal to assess the methodological quality of the comparative studies are shown in Table 1. None of the included studies performed a prospective calculation of the sample size nor were patients randomized. The level of evidence for the studies ranges between 3 and 4. Baseline characteristics of the included studies are outlined in Table 2. In total 266 patients were involved in the comparative studies, of which 122 underwent laparoscopic and 145 open THE. Mean age ranged between 61 and 76 years. In one study,¹⁵ patients treated with the laparoscopic approach were significantly older (69 vs. 61y, $P = 0.003$) with a lower BMI (28 vs. 32, $P = 0.030$). In another study,¹⁷ the male gender percentage was significantly higher in the open group (85 vs. 67%, $P = 0.003$).

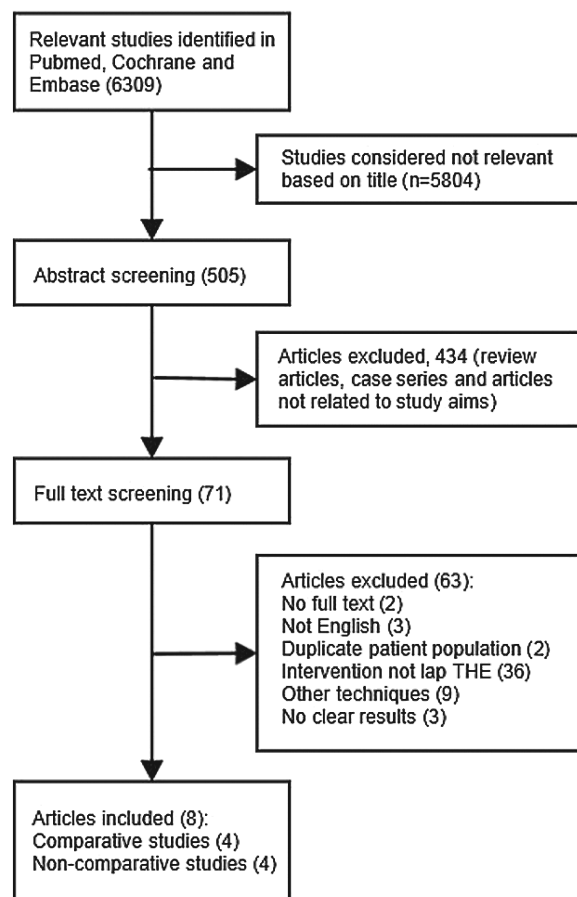


Fig. 1 Flowchart of the search strategy. Lap THE = laparoscopic transhiatal esophagectomy.

Outcome parameters

Postoperative complications

The overall morbidity for the laparoscopic treated patients ranged between 9 and 62% with reoperation rates varying between 0 and 10% (Table 3). In the comparative studies, the overall morbidity rate was reported in 3 studies.^{15–17} In those studies, the morbidity rate decreased with 20% for the laparoscopic approach, however this was not significant in any of the studies. In two studies, the morbidity was further specified as minor and major complications.^{15,17} Minor complications were those that did not require any interventional procedures or reoperations. There were no differences between laparoscopic and open THE regarding minor complications, however in the study by Cash and colleagues,¹⁷ major complications occurred more often in the open group (12 vs. 23%, $P = 0.04$). The reoperation rate was reported in 2 studies and this did not differ between both techniques.^{16,17}

Pulmonary complications

Patients treated with the laparoscopic approach developed pulmonary complications in 15–24% (Table 3). These included pneumonia, pneumothorax, pleural

Table 1 Critical appraisal of the included studies reporting on open versus laparoscopic transhiatal esophagectomy.

Reference	Level of evidence*	Study design	Clear inclusion and exclusion criteria	Similar groups	Standardized treatment	Same follow-up and data collection	Missing data verified	Analysis	Risk of selection bias	Measurement bias	Confounding factor
Bernabe <i>et al.</i> (2005)	4	Retrospective	+	+	+	n.a.	n.r.	+	+	+	+
Perry <i>et al.</i> (2009)	3	Retrospective	+	+	+	+	n.r.	+	+	+	+
Maas <i>et al.</i> (2012)	3	Retrospective	+	+	+	+	n.r.	+	+	+	+
Cash <i>et al.</i> (2013)	3	Retrospective	+	+	+	+	n.r.	+	+	+	+

* According to the Oxford Centre for Evidence-Based Medicine levels of evidence.

Table 2 Baseline characteristics of the includes studies.

	Study	Study design	Approach	Sample size	Gender (M/F)	Age (median, range)
Comparative cohorts	Bernabe <i>et al.</i> (2005)	Retrospective	LTH	17	16/1	64 ± 14 [†]
			OTH	14	11/3	64 ± 10 [†]
	Perry <i>et al.</i> (2009)	Retrospective	LIE	21	18/3	69 ± 8 [†]
			OTH	21	17/21	61 ± 9 [†]
	Maas <i>et al.</i> (2012)	Retrospective	LTH	50	41/9	63 (57–69)
			OTH	50	33/17	65 (57–69)
	Cash <i>et al.</i> (2013)	Retrospective	LTH	33	22/11	72 (50–83)
			OTH	60	51/9	76 (70–80)
Noncomparative cohorts	Palanivelu <i>et al.</i> (2007)	Prospective	LTH	32	22/10	62 (39–72)
	Tinoco <i>et al.</i> (2007)	Retrospective	LTH	68	50/18	56 (28–73)
	Montenovo <i>et al.</i> (2011)	Retrospective	LTH	72	58/14	64 (42–83)
	Dunn <i>et al.</i> (2013)	Retrospective	RATH	40	32/8	65 (36–84)

[†]mean ± standard deviation, LTH = laparoscopic transhiatal esophagectomy, OTH = open transhiatal esophagectomy, LIE = laparoscopic inversion esophagectomy, RATH = robot-assisted transhiatal esophagectomy, NR = Not reported.

effusion, and acute respiratory distress syndrome. In the comparative studies, pulmonary complications were reported in 2 studies and in both studies no difference was found between both techniques.^{15,16} In the first study¹⁵ pulmonary complications occurred in 24% of the laparoscopic and 29% of the open group, while in the other study,¹⁶ this was 18% for laparoscopic and 26% for open THE.

Anastomotic leakage

The anastomotic leakage rate ranged between 3 and 25% for laparoscopic treated patients (table 3). Only two comparative studies reported on anastomotic leakage and in both studies no significant difference was found.^{15,17} In the study by Perry *et al.*¹⁵ anastomotic leakage was found in 19% of the patients treated laparoscopically versus 29% in the open group. In the study by Cash and colleagues¹⁷ this was respectively 9% versus 13%.

ICU and hospital stay

Median ICU stay ranged between 1 and 3 days for patients treated with the laparoscopic approach (Table 3). Two comparative studies reported on ICU stay and in the study by Maas and colleagues¹⁶ this was significantly shorter for the laparoscopic group (1 vs. 3 days, $P < 0.001$). In the study by Perry *et al.*,¹⁵ also a shorter ICU stay for the laparoscopic group was found, however not significantly (2 vs. 3 days, $P = 0.150$). Regarding the length of hospital stay, 7–13 days were reported for laparoscopic treated patients. In all of the comparative studies, the median length of hospital stay was significantly shorter for the laparoscopic group (9–13 vs. 12–16 days). The difference in hospital stay between the laparoscopic and open approach ranged between 2 and 4 days.

Operating time

The median operating time for laparoscopic THE ranged between 200 and 399 minutes (Table 4). There

were no differences found between the laparoscopic and the open group. Bernabe *et al.*¹⁴ reported a sub analysis of the last 6 laparoscopic versus 6 open THE and found a shorter operating time for the laparoscopic approach (311 vs. 388 minutes, $P = 0.010$).

Blood loss

Median blood loss ranged between 100 and 500 mL for laparoscopic treated patients (Table 4). In all of the comparative studies that reported on blood loss, the laparoscopic approach had significantly less compared to the open approach. In the open groups, median blood loss ranged from 526 to 900 mL. One study did not mention blood loss, but instead reported on the necessity of perioperative blood transfusion.¹⁷ This was significantly lower for the laparoscopic group at 0, compared with 2.5 in the open group.

Oncological outcomes

Radical resection margins for the laparoscopic approach ranged between 82 and 100% (table 4). Two comparative studies reported on the resection margins and had comparable rates for both techniques.^{15,16} The number of removed lymph nodes ranged between 3 and 24 for the laparoscopic approach. In the comparative studies, the numbers varied between the studies. In two studies, no difference was found between the laparoscopic and open technique.^{14,16} However, in one study the number of resected lymph nodes was significantly lower for the laparoscopic group (24 vs. 36, $P < 0.001$),¹⁷ whereas in another study this was significantly higher for the laparoscopic group (10 vs. 3, $P = 0.005$).¹⁵ Only two studies reported survival data and in both studies no significant differences were found. In the study by Maas *et al.*,¹⁶ the 5-year survival for laparoscopic and open THE were respectively, 29% versus 26%. In the study by Cash *et al.*,¹⁷ 2-year survival was 70% for laparoscopic and 65% for open THE.

Table 3 Postoperative course.

	Study	Approach	Morbidity	Pulmonary	Anastomotic leakage	Re-operation	ICU stay (median, range)	Hospital stay (median, range)	In hospital mortality
Comparative cohorts	Bernabe <i>et al.</i> (2005)	LTH (<i>n</i> = 17)	NR	NR	NR	NR	NR	9 ± 3 [†]	0
		OTH (<i>n</i> = 14)	NR	NR	NR	NR	NR	12 ± 3 [†]	0
	Perry <i>et al.</i> (2009)	LIE (<i>n</i> = 21)	13 (62%)	5 (24%)	4 (19%)	NR	2 (2-4)	10 (8-14)	0
		OTH (<i>n</i> = 21)	17 (81%)	6 (29%)	6 (29%)	NR	3 (2-10)	14 (10-19)	1 (5%)
	Maas <i>et al.</i> (2012)	LTH (<i>n</i> = 50)	21 (42%)	9 (18%)	NR	2 (4%)	1 (1-2)	13 (11-16)	0
Noncomparative cohorts		OTH (<i>n</i> = 50)	33 (66%)	13 (26%)	NR	3 (6%)	3 (2-4)	16 (14-20)	1 (2%)
	Cash <i>et al.</i> (2013)	LTH (<i>n</i> = 33)	13 (39%)	NR	3 (9%)	0	NR	10	0
		OTH (<i>n</i> = 60)	37 (61%)	NR	8 (13%)	6 (10%)	NR	13	1 (2%)
	Palanivelu <i>et al.</i> (2007)	LTH (<i>n</i> = 32)	3 (9%)	NR	1 (3%)	NR	1 (1-28)	7 (5-42)	0
	Tinoco <i>et al.</i> (2007)	LTH (<i>n</i> = 68)	32 (47%)	13 (19%)	10 (15%)	NR	NR	7	4 (6%)
Dunn <i>et al.</i> (2013)	Montenovo <i>et al.</i> (2011)	LTH (<i>n</i> = 72)	37 (51%)	11 (15%)	14 (19%)	2 (3%)	1 (1-35)	9 (7-58)	1 (1%)
		RATH (<i>n</i> = 40)	NR	8 (20%)	10 (25%)	0	1 (0-21)	9 (6-36)	1 (3%)

[†]mean ± standard deviation, LTH = laparoscopic transhiatal esophagectomy, OTH = open transhiatal esophagectomy, LIE = laparoscopic inversion esophagectomy, RATH = robot-assisted transhiatal esophagectomy, NR = Not reported.

Table 4 Perioperative outcomes.

	Study	Approach	Operating time in minutes (median, range)	Blood loss (mL) (median, range)	Conversion	Lymph nodes (median, range)	Radical resection	Stage
Comparative cohorts	Bernabe <i>et al.</i> (2005)	LTH (<i>n</i> = 17)	336 ± 102 [†]	331 ± 220 [†]	0	9	NR	0-I
		OTH (<i>n</i> = 14)	388 ± 53 [†]	542 ± 212 [†]		10	NR	0-I
	Perry <i>et al.</i> (2009)	LIE (<i>n</i> = 21)	399 ± 86 [†]	168 ± 149 [†]	0	10 (4-12)	21 (100%)	0-II
		OTH (<i>n</i> = 21)	408 ± 127 [†]	526 ± 289 [†]		3 (0-7)	21 (100%)	0-II
	Maas <i>et al.</i> (2012)	LTH (<i>n</i> = 50)	300 (265-320)	500 (400-650)	9 (18%)	14 (10-19)	41 (82%)	I-III
Noncomparative cohorts		OTH (<i>n</i> = 50)	280 (250-320)	900 (650-1400)		11 (8-15)	37 (74%)	I-III
	Cash <i>et al.</i> (2013)	LTH (<i>n</i> = 33)	274	NR	2 (6%)	24	NR	I-III
		OTH (<i>n</i> = 60)	276	NR		36	NR	I-III
	Palanivelu <i>et al.</i> (2007)	LTH (<i>n</i> = 32)	200 (180-310)	150 (50-700)	0	15 (9-32)	32 (100%)	I-III
	Tinoco <i>et al.</i> (2007)	LTH (<i>n</i> = 68)	153 (lap component)	NR	5 (7%)	NR	NR	I-IV
Dunn <i>et al.</i> (2013)	Montenovo <i>et al.</i> (2011)	LTH (<i>n</i> = 72)	299 (212-700)	300 (75-1700)	0	11 (2-32)	72 (100%)	I-III
		RATH (<i>n</i> = 40)	311 (226-491)	100 (25-300)	5 (12.5%)	20 (3-38)	37 (95%)	0-IV

[†]mean ± standard deviation, LTH = laparoscopic transhiatal esophagectomy, OTH = open transhiatal esophagectomy, LIE = laparoscopic inversion esophagectomy, RATH = robot-assisted transhiatal esophagectomy, NR = Not reported.

DISCUSSION

This is the first systematic review evaluating laparoscopic versus open THE. Thus far, no randomized controlled trial evaluating these techniques has been conducted and after a literature search, only 4 comparative cohort studies were identified. Based on these pioneer studies, it was demonstrated that laparoscopic THE is a safe and feasible alternative to the open approach, with evidence of reduced blood loss and a shorter hospital stay. The laparoscopic approach may also decrease short-term morbidity with comparable operating times and oncological outcomes. Long term overall survival data were not yet reported adequately.

Minimal invasive techniques in esophageal surgery were introduced to decrease postoperative morbidity by reducing the surgical trauma. In the current review, three studies reported on overall morbidity and demonstrated a decrease of 20% in patients treated with a laparoscopic approach. However in all of these studies the difference was not significant.^{15–17} Only one study reported significantly less major complications that required an intervention or reoperation in the laparoscopic group.¹⁷ Regarding pulmonary complications and anastomotic leakage, also no differences were observed. In TTE, the benefit of a MI approach in reducing morbidity was evident as there was a 50% decrease in total morbidity and significantly fewer pulmonary complications in the MI approach.^{9,22} In THE, the supposed differences might be smaller because of the avoidance of a thoracic phase. In addition, all comparative studies in this review were relatively small, i.e., the largest laparoscopic cohort included 50 patients which makes it difficult to gain significant power. Also, the results may reflect the early experience of the authors with this technique. The overall morbidity rate for the laparoscopic approach ranged from 9 to 61% and is comparable to large open THE series.^{5,23–25} This wide range is probably due to variations in the definition of complications. For example, in some centers pulmonary complications were defined as any unexpected pulmonary event (atelectasis, pleural effusion etc.) whereas in other centers only the most severe pulmonary complications were addressed (ARDS, need for tracheostoma).

Although differences in morbidity rates between the laparoscopic and open approach were not significant, all comparative studies reported a significantly shorter hospital stay for the laparoscopic approach, with differences ranging between 2 and 4 days. This advantage of minimal invasive techniques regarding postoperative recovery was demonstrated before in the transthoracic approach. In a recent meta-analysis, the ICU and hospital stay were both significantly reduced if patients were treated with MIE as compared to the standard open transthoracic approach.⁹ In the only randomized controlled trial reported thus far,

the hospital stay significantly decreased from 14 days in the open transthoracic group to 11 days in the MIE group.²² The decreased hospital stay for the MI techniques in both TTE and THE may be related to the reduced operative trauma and subsequently reduced inflammation which allows for a more adequate pain control and improved patient mobilization, and thereby facilitating recovery. This highlights the advantage of the minimally invasive approach in THE.

The laparoscopic technique had raised some concerns regarding oncological outcomes. At first glance, there were no differences between resection margins and lymph node retrieval between laparoscopic and open THE. However, it needs to be stressed that the number of studies was small, one study only included limited disease, three studies also included Stage 0 disease, and not all studies reported on these outcomes. It is therefore not possible to draw any conclusions from these studies, and the short-term oncological outcomes should be interpreted with caution. Also regarding the long-term oncological outcome, results were inadequately documented. A recent meta-analysis²⁶ that had focused purely on the oncological merits of MIE techniques versus conventional open esophagectomy demonstrated that MIE provides for a more complete lymph node clearance as compared to the open approach (16 vs. 10, $P = 0.03$) with no differences in regard to tumor stage. Also comparable survival rates were reported, which has showed that MIE is equivalent to standard open esophagectomy in achieving similar oncological outcomes. However, the studies in this meta-analysis were all comparative cohort studies and most of the included patients were treated via the transthoracic approach. Further research is needed to provide evidence of similar oncological results between laparoscopic and open THE.

Several limitations of the current systematic review must be taken into account when considering its results. First, the overall quality of the comparative studies is moderate. All studies were nonrandomized, nonblinded, comparative cohort studies, or case-control studies with a limited number of patients, which inevitably introduces selection bias. To provide a reliable indication of the quality of the included studies, a critical appraisal was performed and CEBM levels were assigned. Second, there was a variation in inclusion criteria between the studies including limited disease, operative technique, and variations in the reporting on outcomes. Due to the obvious heterogeneity between the studies we could not perform a formal meta-analysis. Finally, the sample size in the studies was relatively small and it was not clear whether the laparoscopic treated patients resembled the author's first experience with this technique. It is not completely elucidated what a reasonable learning curve is in laparoscopic THE. In transthoracic MIE and laparoscopic total gastrectomy some

studies reported improved operative and perioperative parameters after 35–40 patients.^{27,28} Hence, the results of the included studies in the current systematic review may reflect the adaptation phase of the laparoscopic approach. To overcome the limitations of the included studies and to provide for a higher level of evidence, a prospective randomized controlled trial is warranted. However, there are several challenges in setting up such a trial including learning curve, credentialing of surgeons and standardization of coding of complications. Preferably, this trial should be set up in high-volume Upper-GI centers with surgeons experienced in both laparoscopic and open THE and with an experienced multidisciplinary team for the postoperative care. The primary focus of the trial should be on reducing the hospital stay and postoperative morbidity with laparoscopic THE.

In conclusion, results from pioneer comparative cohort studies showed that a laparoscopic approach for THE is a feasible and safe alternative to the open approach. The laparoscopic approach leads to reduced perioperative blood loss and a shorter hospital stay. Furthermore, laparoscopic THE may lead to decreased short-term morbidity. However, evidence is lacking and further research, preferably a prospective randomized controlled trial, is warranted to confirm these findings and also to evaluate long-term oncologic outcomes.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1: Search strategy