



The evolution of fast track protocols after oesophagectomy

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Abstract: Fast track is a standardised goal directed patient's care pathway that aims to facilitate recovery following surgery. Currently, there are large variations in the fast track protocols used in oesophagectomy due to the complexity of the procedure. The objective of this systematic review is to assess the evolution of fast track protocols following oesophagectomy since its implementation and the resulting effect on postoperative outcomes. Relevant electronic databases were searched for studies assessing the clinical outcome from fast track in oesophagectomy and also those assessing the effects of the individual key components in fast track protocols. The search yielded twenty-three publications regarding fast track implementation in oesophagectomy. A pattern of consistent evolution in fast-track protocols was clearly demonstrated and these have shown variations in the core-identified components across the studies. However, evolution in fast track protocols over time showed, an overall improvement in length of stay, anastomotic leak, pulmonary complications and mortality over time. Thirty publications were included that evaluated specific components of fast track protocols, with an increasing trend towards addressing the nutritional aspect in oesophagectomy care in more recent years. The variations in the key components of fast track protocol of care identify the need for continued assessment and identification for areas of improvement. In the future incremental gains through focused improvements in key components will lend itself to even better postoperative outcomes and patient experience during oesophageal cancer treatment.

Keywords: Fast track; enhanced recovery programme; oesophagectomy

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Introduction

Fast track is a multimodal approach aimed at reducing the surgical stress response and improving postoperative recovery and return of functional status. Fast track protocols involve key elements aimed at optimization of crucial components in pre-, peri- and post-operative period (*Figure 1*).

The concept of fast track post-operative protocols for surgery was initially introduced by Kehlet in 1997 in which he described the risk factors associated with postoperative morbidity and duration of hospital stay (1). This led to the introduction of this multimodality system in colonic surgery

in 1999. Several studies have shown improvements in clinical outcomes with the utilisation of fast track protocols in colonic surgery. It has been directly linked to decreasing length of stay (2,3) and reductions in the incidence and severity of postoperative complications (4,5). This led the ERAS (enhanced recovery after surgery) study group to publish a consensus statement in 2005 regarding a unified protocol for colonic surgery. Since then enhanced recovery has been applied in several subspecialties and guidelines have been published for colorectal surgery (6), gastrectomy (7), bariatric surgery (8), liver surgery (9) and gynaecologic oncology (10,11).

Surgical resection is the mainstay of treatment for

Pre operatively	Pre operative counselling
	Carbohydrate loading
Peri-operatively	Goal directed fluid therapy
	Maintaining normothermia
	Preemptive analgesia with epidural
	Surgical technique
Post operatively	Limitation of drains, lines and catheter use
	Early enteral feeding
	Adequate pain management
	Early mobilization

Figure 1 This figure illustrated the main fast track components.

locoregional oesophageal cancer (12) and is associated with high levels of mortality (30-day 2.4% and 90-day of 4.5%) and morbidity rate varying between 40–80% (13). The implementation of fast track protocols after oesophagectomy has been limited due to the high complexity of the procedure and the huge technical variations involved. Further some aspects are highly controversial for example one of main key components of ERAS is early feeding, which contradicts the traditional surgical concerns regarding early feeding leading to anastomotic leak. Fast track in the setting of oesophageal surgery was first introduced in 2004 (14), and since then several studies have investigated the effect of ERAS in this patient cohort. There are varieties in the ERAS protocols used and the ERAS society has recently published recommendations regarding fast track with oesophagectomy in the aim of a standardising the protocol for oesophagectomy which can be routinely applied and audited to improve patients' outcomes (15).

The objective of this present review is to identify from the published literature, the evolution of fast track protocols for oesophagectomy over time and the changes in the key components that have led to a measurable improvement in postoperative outcomes. A systematic literature search was performed up until September 2018 using MEDLINE, Embase, Web of Science and the Cochrane Library databases. *Figure 2* shows the PRISMA chart of the literature search.

Evolution of fast track protocols in oesophagectomy

Both Comparative and non-comparative Cohort studies and randomised trials investigating the effect of ERAS with

a clearly documented fast track pathway were included. Articles assessing the effect of one component of fast track were excluded from this section. A total of twenty-two publications were included in the analysis of ERAS pathway evolution. Of these, seven prospective cohort studies (16–22), eleven retrospective cohort studies (23–33), 1 study that used a combination of prospective and retrospective methods (34), two randomized control trials (35,36) and three non-comparative studies (14,37,38) were identified. *Table S1* shows the key components in fast track protocol and the variation in the protocol used regarding those components. *Figure 3* showing the timeline of the studies included in the fast track protocol development. The primary outcome measure was the length of hospital stay (defined at the time from surgery to discharge from hospital). Secondary outcome measures in-hospital mortality and postoperative complications, specifically anastomotic leak, and pulmonary complications (including pneumonia, persistent pneumothorax, and acute respiratory distress syndrome).

Perioperative protocols

No specific guidelines were followed regarding fluid management in the majority of the studies. In general all seven studies incorporating goal directed fluid management in their protocol, aimed at avoidance of fluid overload. In 2009 Munitiz *et al.* (23) aimed for a negative fluid balance four days postoperatively, whilst a 2015 cohort study targeted at an obtainment of an even balance without applying a restricted regimen (20). A 2017 study combining both pro- and retrospective study design defined a protocol with a negative fluid balance in the first days postoperatively and obtainment of an even balance on subsequent days (32). Most studies compared fast track protocols in patients undergoing open oesophagectomy. The first study incorporating patients treated with minimally invasive oesophagectomy (MIO) in the fast track protocol was by Li *et al.* Minimally invasive oesophagectomy was not integrated as an element of the fast track protocol as patients treated with MIO were included in both fast track and conventional care group (16).

A 2014 prospective cohort study made a comparison between patients undergoing open and laparoscopically assisted Ivor Lewis oesophagectomy. Fast track protocol was applied for both surgical approaches. However, the conventional group not following fast track consisted only

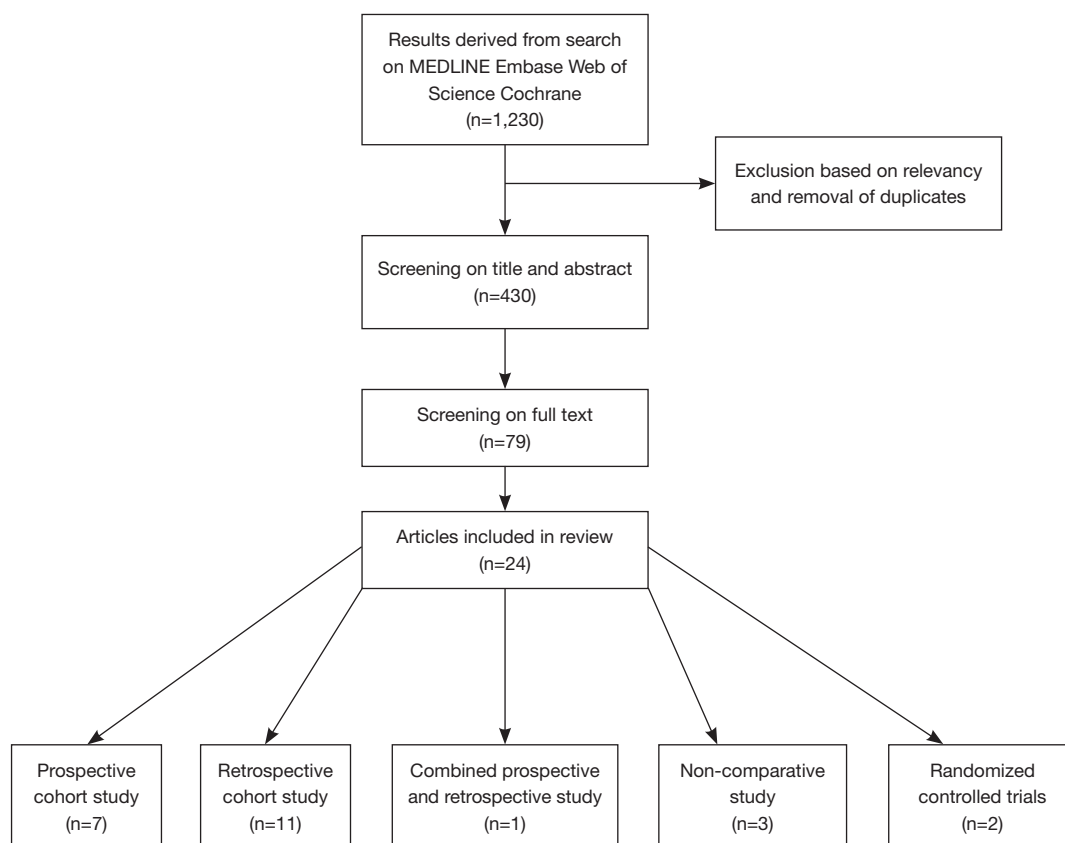


Figure 2 Prisma flowchart process showing search results and study selection.

of patients receiving open surgery. A significant reduction in the median postoperative length of hospital stay was achieved in the fast track group (10 days) in comparison with the conventional group (13 days). Nevertheless, no difference could be demonstrated between both surgical treatments within the fast track group. The authors could therefore not conclude that the reduction in length of hospital stay in the fast track group could be based on the surgical technique. (19) The only study assessing fast track in patients treated with MIO only was conducted by Pan *et al.* (28).

Postoperative management

The majority of the studies implemented immediate extubation in their fast track protocol. This was not applied in the first fast track study following oesophagectomy in 2004, yet intensive care unit (ICU) stay could also be avoided in the majority of these patients. Recent studies aimed at immediate extubation following surgery.

Since fast track protocol first used, there appears to be uniformity in the epidural removal within first five days and early mobilization. Additionally, no noticeable difference could be observed in the protocols regarding early chest tube removal. However, feeding in terms of early oral intake or jejunostomy feeding showed variation over the years, but most of the recent studies showed discharge on jejunostomy feeding. There also appears to be less use of gastrografin to assess the anastomosis and nasogastric tube removal.

Outcome measures

A total 22 publications were included in this section. *Table S1* showing the studies included and a summary of the outcomes of interest. Overall, fast track had positive effect on patient outcomes. Anastomotic leak rate (*Figure 4*) was persistently lower in the ERAS group in comparison to the non-ERAS. Higher rate of anastomotic leaks in 2015 in comparison to other fast track studies could be explained due inclusion of clinically non-significant leaks

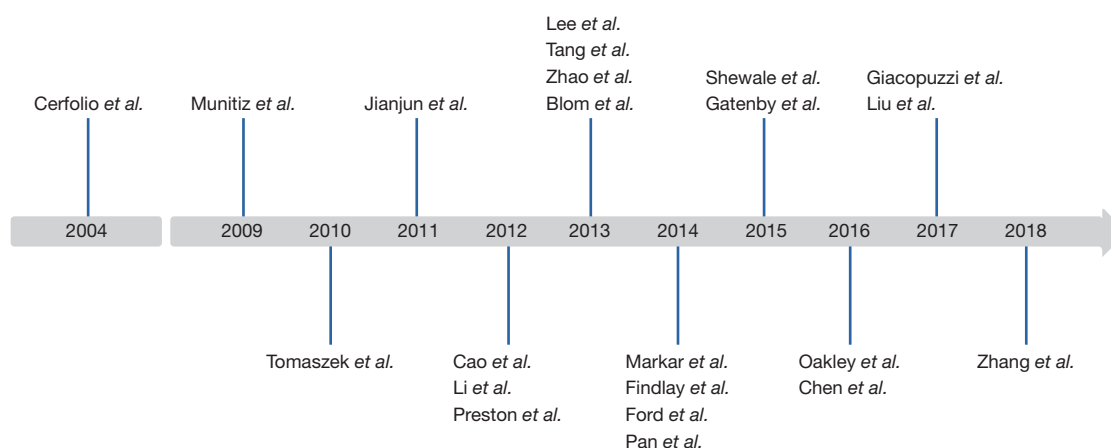


Figure 3 Figure showing the chronological order of the studies investigating fast track protocol in oesophagectomy.

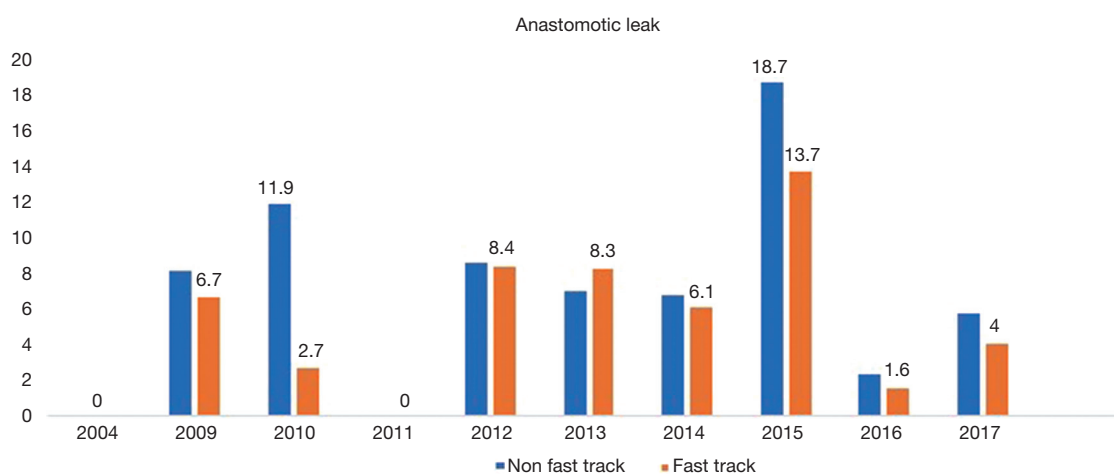


Figure 4 Figure showing the percentage of anastomotic leak in both fast track and non fast track patients since fast track introduction.

in the study by Shewale *et al.* (29). Reduction in pulmonary complications and length of stay in the ERAS group (Figures 5 and 6). Also, the rate of anastomotic leak and pneumonia varied across the years which may reflect variation in the criteria used to define those outcomes. Mean length of stay did not exceed 12 days in the fast track groups, whilst this could extend up to a mean length of stay of 19 days in the conventional care groups. The mortality rate followed the same pattern and fast track led to reduction in mortality rate in comparison to traditional care (Figure 7).

Evolution of the individual fast track components

A total of 218 studies included were those investigating

specific ERAS component, pre-rehabilitation, Surgical technique, Fluid therapy, preemptive analgesia, Peri-anastomotic drain use, NG tube decompression, chest drains, nutrition, early mobilisation and Post-operative Analgesia. Articles included in the fast track protocol evolution mentioned above were excluded in this section. The aim is to assess the frequency that have described that particular component, taking the year of publication into account. This will allow an overview understanding of the evolution of the importance of each component and its impact on recovery. Figure 8 shows the fast track components evolution, highlighting the aspects that has been mostly investigated have been surgical technique changes in the field of minimally invasive oesophagectomy as well as nutritional development. This goes hand in hand

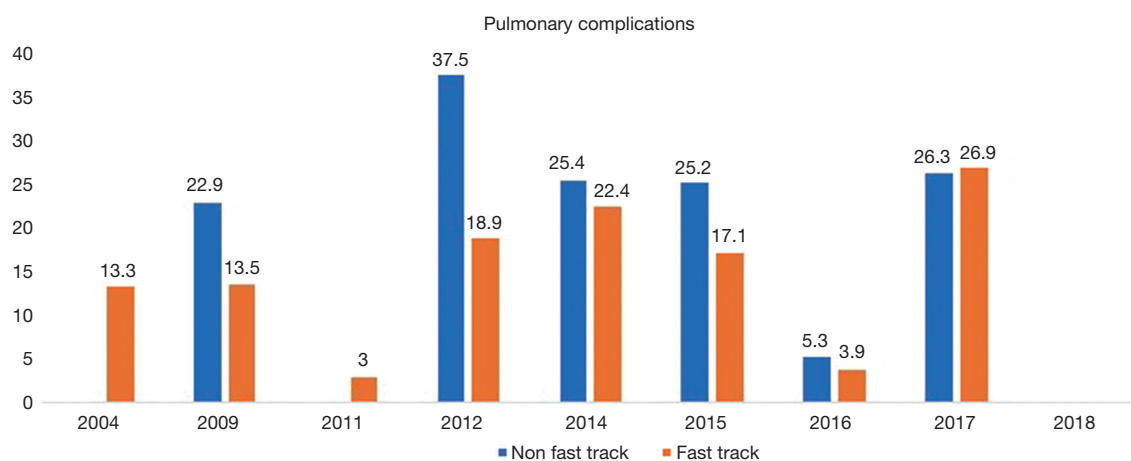


Figure 5 Figure showing the percentage of pulmonary complications in both fast track and non fast track patients since fast track introduction.

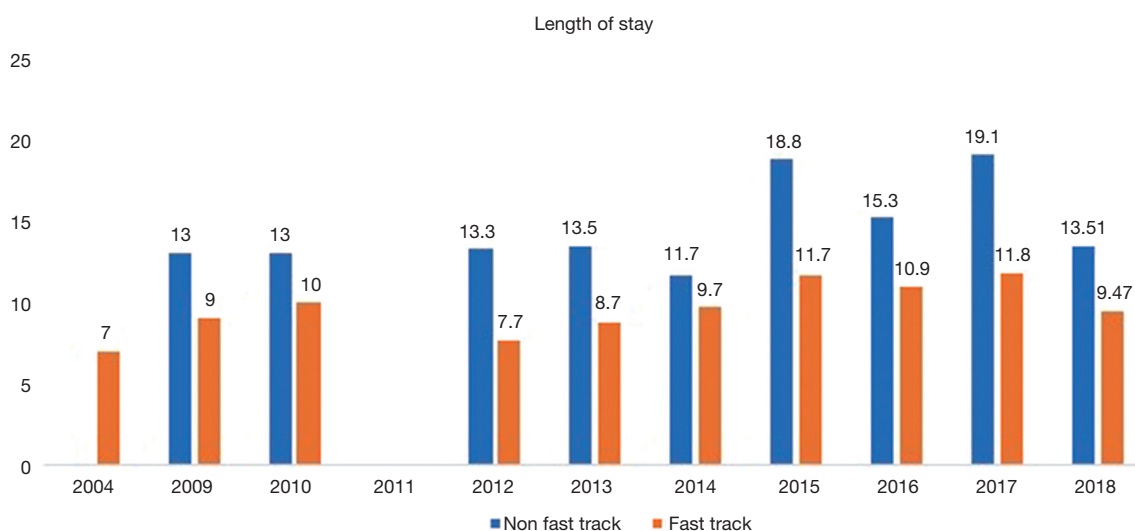


Figure 6 Figure showing the length of stay in both fast track and non fast track patients since fast track introduction.

with the variation in practice that has been seen in *Table S2*.

Discussion

The evolution of fast track protocols for oesophagectomy demonstrates a continuous commitment to evaluation of service that has used more commonly in the recent years. This can be explained by studies utilising fast track guidelines adapted from other current approved protocols approved by ERAS study group and not specifically designed to be address the unique nature of the care needed with oesophageal resection; given it is the only general

surgical operation which has a thoracic component.

Restrictive perioperative fluid therapy showed a reduction in complications after colonic surgery (39). A retrospective cohort study examined fluid management after oesophagectomy and found a strong correlation between postoperative fluid overload and increased postoperative morbidity (40). Goal directed fluid therapy has been reported in less than half of the studies utilising fast track protocols in the context of oesophagectomy. Goal directed fluid therapy to avoid hypervolemia is advocated, as fluid overload has been shown to be associated with higher rates of anastomotic leak, pneumonia (41).

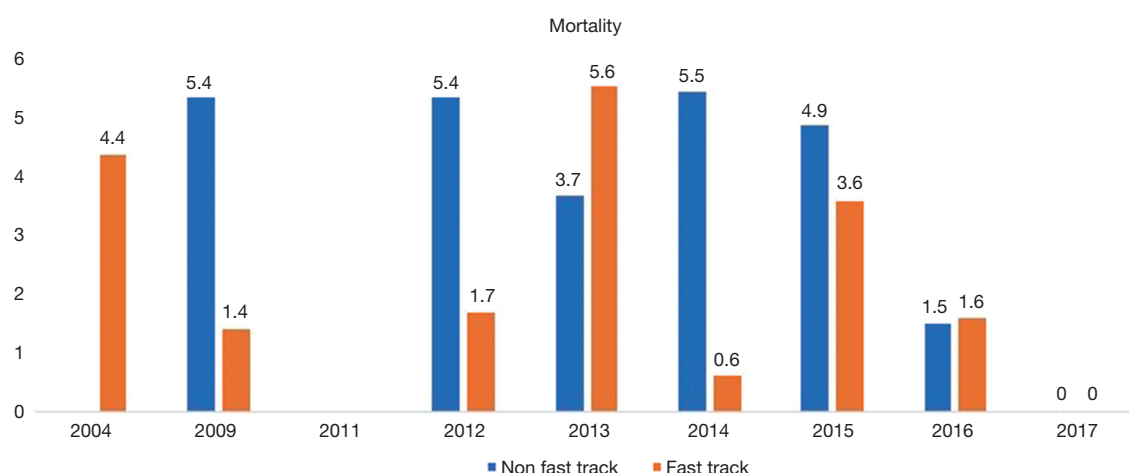


Figure 7 Figure showing the percentage of mortality in both fast track and non fast track patients since fast track introduction.

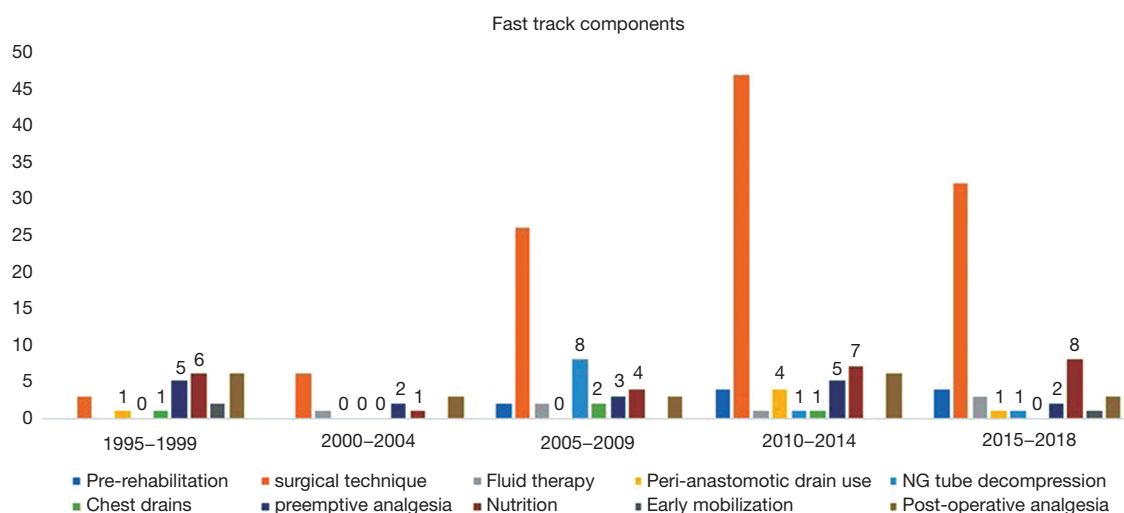


Figure 8 This figure illustrates the evolution of each fast track component in terms of frequency each component is investigated in literature in a chronological order.

Immediate postoperative extubation demonstrated its beneficial effect in other types of surgery regarding the length of ICU stay (42,43). However, no difference was found for the fast track post-oesophagectomy studies not implementing this in their protocol. Early mobilisation was used in almost all the studies with fast track in oesophagectomy. It has been shown early postoperative mobilization improves cardiovascular and pulmonary functioning and reduces the risk of thromboembolic complications (1). It also has longer term benefits after discharge of showed significant improvement in such parameters as fatigue, sleep, return to leisure activity and

activities of daily living (44). Taniguchi *et al.* (45) found that goal directed fluid therapy enhanced postoperative gastrointestinal recovery and mobilisation, as well as postoperative nutritional status and protein synthesis. The program did not affect either postoperative LOS or the incidence of complications.

Almost all studies commonly placed NG tube during the surgery and most are removed within 5 days with or without gastrografin study prior to removal. Only three studies did not use NG tube routinely (25,27,35). There is current evidence that NG tubes can increase the risk of postoperative respiratory tract infection (46). In addition,

it was shown that NG tube post oesophagectomy led to significant higher rate of anastomotic leak as well as leading to longer length of stay and an increase in pulmonary complications (47).

Feeding has been a source of discrepancy between studies, this is due to the thought that early feeding can lead to anastomotic leak and aspiration. Martos-Benítez *et al.* (48) showed that early enteral feeding in gastrointestinal surgery led to a significant reduction in major complications, respiratory complications, and gastrointestinal complications specifically anastomotic leak. There was also reduction in length of hospital stay. Specifically, in relation to oesophageal surgery, Cao *et al.* (25) showed no significant differences in anastomotic leak rate in their study with initiation of jejunostomy feed on day 1 as well as oral intake on day 4. Early enteral feeding is an important part of any fast track program. Enteral feeding via feeding tube was shown to reduce anastomotic leak, wound and other infections, pneumonia, and mortality. There is also an associated reduction of length of stay (49).

Chest tube is believed to allow for early detection and management of anastomotic leakage. Cao *et al.* (25) showed that anastomotic leak rate was not significantly different between early removal of chest tube in fast track and late removal. However, early removal of chest tube was one of several factors that shortens length of hospital stay.

Postoperative pain is a major factor in the recovery of patients after esophageal surgery and adequate pain control is believed to decrease cardiopulmonary complications, length of hospital-stay, and mortality. Epidural analgesia has been the choice of analgesia post oesophagectomy due to the reduction in cardiopulmonary complications and length of stay. However, anastomotic leak was not statistically different with the use of epidural (50). Later studies, Li *et al.* (51) in a cohort of 587 patients have shown that the use of epidural in oesophagectomy has led to significantly reduced rate of pneumonia from 32% to 19.7% and anastomotic leak 23.0% to 14.0%. Michelet *et al.* (52) have also shown that that epidural analgesia is associated with a decreased incidence of anastomotic leak.

The surgical technique in the form of minimally invasive oesophagectomy has been a major advancement in the field. Minimally invasive oesophagectomy was first introduced in 1992 (53). There has been two randomised controlled trials (54,55) which have revealed the feasibility of a minimally invasive technique with evidence of short term benefits as

well as a comparable lymph node yield in comparison to open surgery which mounts to good oncological resection. Despite this the majority of resections carried out through an open technique (56), and there are currently ongoing trials to delineate the advantages of minimally invasive versus open such The ROMIO (Randomized Oesophagectomy: Minimally Invasive or Open) trial (57), The ROBOT trial (58). Recently, a propensity-matched population-based study from the Dutch Esophagectomy revealed that the pulmonary complication rate and mortality for minimally invasive surgery were similar to open technique. However, anastomotic leaks and the need for re-interventions were more significant in minimally invasive surgery. The length of stay was shorter in minimally invasive group (59). This will have a further positive effect on enhancing the recovery of such complex patients. To date no studies have been conducted comparing MIO as an element of fast track program to conventional care with an open surgical approach. Early studies regarding fast track after oesophagectomy have been assessing protocols for open surgery alone. The first study to incorporate MIO was done by Li *et al.* in 2012 (16). Later studies also made a comparison of fast track programs versus conventional care in which patients treated with MIO were included in both study groups. Therefore, impact of a minimally invasive approach as part of a fast track protocol on recovery could not be assessed.

In summary, Fast track protocols in oesophagectomy shows variations in practice due to the complexity of the procedure. Fast track has been shown to reduce hospital stay and morbidity following oesophagectomy. It has been advocated that early mobilisation, early enteral feeding, early removal of chest tube, limiting the use of nasogastric decompression and optimizing the use of epidural anaesthesia or analgesia facilitates early discharge of patients. Recommendations for standardised pathway post oesophagectomy has been recently published by ERAS study group, this will allow the outcomes to be assessed in a unified manner as well as allowing the auditing of fast track pathway.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Table S1 Table Illustrating fast track studies and the components used in a chronological order, highlighting the evolution of the protocols

Studies	Year in order	Goal directed fluid management	Immediate extubation	ICU step down <2	Mobilisation POD <1	No routine NG	Removal of urinary catheter <3	Nasogastric removal <5	Epidural removal <5	Sips POD <1	Enteral diet with jeje/gas <1	Normal diet <7	Gastrografin swallow <5	Chest drain removal <200 mL/ POD3	NG tube decompression	No Perianastomotic drain	Discharge soft diet	Discharge Jej feeds
Cerfolio	2004				✓		✓	✓	✓		✓	✓	✓	✓	✓			
Munitiz	2009	✓	✓		✓			✓	✓				✓				✓	
Tomaszek	2010										✓		✓					
Jianjun	2011				✓		✓	✓		✓				✓		✓	✓	
Cao	2012				✓	✓	✓		✓	✓	✓		✓			✓	✓	
Li	2012		✓		✓		✓	✓	✓		✓	✓		✓	✓		✓	
Preston	2012		✓	✓	✓			✓	✓		✓		✓	✓	✓	✓		✓
Lee	2013	✓	✓		✓	✓			✓				✓	✓			✓	
Tang	2013		✓		✓			✓	✓			✓	✓	✓	✓		✓	
Zhao	2013		✓								✓					✓		
Blom	2013	✓	✓	✓	✓			✓	✓	✓	✓	✓		✓	✓			
Markar	2014				✓				✓		✓	✓	✓	✓	✓			✓
Findlay	2014	✓	✓	✓	✓			✓	✓	✓	✓	✓		✓			✓	
Ford	2014				✓		✓	✓	✓		✓	✓		✓		✓	✓	✓
Pan	2014	✓			✓		✓		✓		✓	✓				✓		✓
Shewale	2015		✓		✓		✓	✓	✓									✓
Gatenby	2015				✓			✓	✓					✓	✓			
Oakley	2016		✓		✓				✓			✓		✓	✓		✓	
Chen	2016				✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	
Giacopuzzi	2017	✓	✓		✓			✓	✓	✓	✓	✓		✓	✓			
Liu	2017	✓	✓		✓			✓						✓				✓
Zhang	2018						✓				✓			✓				

Table S2 Table showing the percentage of main outcomes of the studies involved

Studies	Year	Type of study	Study groups	No. group 1	No. group 2	Mean age 1	Mean age 2	Open surgery	MIO	Overall morbidity 1 (%)	Overall morbidity 2 (%)	Pulmonary complications 1 (%)	Pulmonary complications 2 (%)	Anastomotic leak 1 (%)	Anastomotic leak 2 (%)	LOS 1 (days)	LOS 2 (days)	Mortality 1 (%)	Mortality 2 (%)
Cerfolio	2004	Non-comparative	ERAS	–	90	–	63	90	–	–	16	–	12	–	0		7	–	4
Munitiz	2009	Retrospective cohort	ERAS vs. non-ERAS	74	74	60.5	59	148	–	28	23	17	10	6	5	13	9	4	1
Tomaszek	2010	Retrospective cohort	ERAS vs. non-ERAS	276	110	54	–	386	–	–	–	–	–	33	3	13	10	–	–
Jianjun	2011	Non-comparative	ERAS	–	80	–	62	80	–	–	–	–	3	–	0			–	0
Cao	2012	Retrospective cohort	ERAS vs. non-ERAS	55	57	55.6	55.5	112	–	16	27	11	6	6	4	14.8	7.7	3	1
Li	2012	Prospective cohort	ERAS vs. non-ERAS	47	59	65	64	83	23	29	35	16	13	5	8	10	8	0	1
Preston	2012	Retrospective cohort	ERAS vs. non-ERAS	24	86	68.5	65	110	–	18	39	14	21	1	4	15	7.5	–	–
Lee	2013	Retrospective cohort	ERAS vs. non-ERAS	47	59	–	–	181	–	–	–	–	–	–	–	10	8	–	–
Tang	2013	Retrospective and prospective cohort	ERAS vs. non-ERAS	27	36	68.5	64	82	24	7	6	–	–	3	3	15	11	1	2
Zhao	2013	Prospective RCT	ERAS vs. non-ERAS	34	34	57.86	55.14	19	44	4	2	–	–	1	0	12.52	7.15	–	–
Blom	2013	Prospective cohort	ERAS vs. non-ERAS	78	103	64	65	–	80	53	73	18	15	18	15	1	4	–	–
Markar	2014	Prospective cohort	ERAS vs. non-ERAS	92	183	66	64	68	–	–	–	–	–	3	12	10	8	0	1
Findlay	2014	Prospective cohort	ERAS vs. non-ERAS	55	77	66	64	275	–	47	38	21	21	4	5	12	14	3	1
Ford	2014	Prospective cohort	ERAS vs. non-ERAS	121	80	–	–	132	–	–	–	–	–	12	3	13	10	–	–
Pan	2014	Retrospective cohort—MIO	ERAS vs. non-ERAS	40	40	62.5	66	100	96	31	23	5	7	3	3	12	7	0	0
Shewale	2015	Retrospective cohort	ERAS vs. non-ERAS	322	386	61	61	584	124	–	–	88	76	45	49	12	8	16	14
Gatenby	2015	Retrospective cohort	ERAS vs. non-ERAS	16	9	–	–	62	–	–	–	–	–	–	–	20.5	17	–	–
Oakley	2016	Retrospective cohort	ERAS vs. non-ERAS	81	66	78.8	78.8	147	–	–	–	–	–	–	–	18	14	–	–
Chen	2016	Randomised controlled Trial	ERAS vs. non-ERAS	132	128	55.72	56.43	128	132	16	11	7	5	3	2	12.56	7.62	2	2
Giacopuzzi	2017	Retrospective cohort	ERAS vs. non-ERAS	17	22	66	61	30	9	–	–	–	–			10	9	–	–
Akiyama	2017	Prospective cohort	ERAS vs. non-ERAS	21	33	64.9	64.7	–	–	–	–	8	14	0	0	32.7	19.6	0	–
Liu	2017	Retrospective cohort	ERAS vs. non-ERAS	69	64	55.1	53.8	88	45	24	11	10	4	4	2	14.6	9.5	0	0
Underwood	2017	Non-comparative	ERAS	–	81	–	66	–	–	–	9	–	26	–	4		9	–	0
Zhang	2018	Randomised controlled trial	ERAS vs. non-ERAS	57	57	67.01	66.89	144	–	16	6	–	–	–	–	13.51	9.47	–	–
Total				1,685	1,924	63.2	62.7	–	–	24.1	23.3	19.5	17	9.2	6.8	13.6	9.8	2.6	1.9

ERAS, enhanced recovery after surgery; MIO, minimally invasive oesophagectom .