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A comparative study of survival after minimally invasive and open oesophagectomy

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Abstract
Background Oesophageal cancer is increasing in incidence worldwide. Minimally invasive techniques have been used to perform oesophagectomy, but concerns regarding these techniques remain. Since its description by Cuschieri in 1992, the use of minimally invasive oesophagectomy (MIO) has increased, but still only used in a minority of resections in the UK in 2009. In particular, there has been reluctance to use minimally invasive (thoracoscopic and laparoscopic) techniques in more advanced cancers for fears regarding the adequacy of the oncological resection. In order to identify any factors that could affect survival, we undertook a retrospective analysis on all patients who underwent surgery in our department over an 8-year period.
Methods A retrospective data analysis was undertaken on all patients who underwent oesophagectomy in a tertiary upper gastrointestinal surgery unit, from 2005 to 2012 inclusive. Data were collected from the departmental database and case note review, with follow-up and survival data to time of data collection. The survival data were analysed using univariate and multivariate Cox proportional hazard regression models to determine which variables affected survival. Variables examined included age, tumour position, tumour stage (T0, 1, 2 vs T3, 4), nodal stage (N0 vs N1), tumour histology, completeness of resection (R0 vs R1), use of neoadjuvant chemotherapy and operative technique (thoracoscopic/laparoscopic (MIO) vs laparoscopic abdomen/open chest (Lap assisted) vs Open.
Results 334 patients underwent oesophagectomy between 2005 and 2012. Male to female ratio was 3.75:1, with a mean age of 64 years (range 36–87). There were 83 open oesophagectomies, 187 laparoscopically assisted oesophagectomies and 64 minimally invasive oesophagectomies. Following univariate regression analysis the following factors were found to be correlated to survival: use of neoadjuvant chemotherapy (Hazard Ratio 2.889, 95 % CI 1.737–4.806), T stage 3 or 4 (3.749, 2.475–5.72), Node positive (5.225, 3.561–7.665), R1 resection (2.182, 1.425–3.341), type of operation (MIO compared to open oesophagectomy) (0.293, 0.158–0.541). There was no significant relationship between age, tumour position or tumour histology and length of survival. When these factors were entered into a multivariate model, the independently significant factors correlated to survival were found to be T stage 3 or 4 (HR 1.969, 1.248–3.105), Node positive (3.833, 2.548–5.766) and type of operation (MIO compared to open) (0.5186, 0.277–0.972).
Conclusion Multiple small studies have found reduced pulmonary complication rates and duration of hospital stay when using a minimally invasive approach compared to open. Concerns in the literature over long-term outcomes, however, have led to limited utilisation of this method, especially in advanced disease. The data from this large study show significantly better survival following operations performed using minimally invasive techniques

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compared to open, however, we have not adjusted for some known or unknown confounding factors. International and national RCTs, however, will provide more information in due course.

Keywords Oesophageal · General oesophageal · Surgical · Thoracoscopy

The incidence of oesophageal cancer worldwide has increased dramatically over the last two decades making it the 8th most common cancer [1, 2]. In the west, the incidence of oesophageal adenocarcinoma has almost doubled in this time which has been attributed to changing social and dietary habits [3, 4]. It is well established in the literature that surgical resection is the only viable cure for oesophageal adenocarcinoma [5, 6]. However, oesophagectomy is associated with mortality rates of 5–10 % even in specialist tertiary centres [7–9]. Bailey et al. [9] 2003 found that 50 % of their 1777 patient series developed one or more of 20 predefined complications. Due to the extensive surgery required, at least half of patients who undergo an open oesophagectomy through right thoracotomy and laparotomy are at risk of significant morbidity from pulmonary sequelae [10].

High mortality and morbidity rates are thought to be due to the invasive nature of such extensive open surgery. As with many other surgical procedures, efforts have been made to reduce the inflammatory response, post-operative pain and slow mobilisation seen in large open procedures, by increasing the use of minimally invasive techniques [11, 12]. However, since the description of minimally invasive oesophagectomy by Cuschieri in 1992 [13], many surgeons have held concerns over the complexity of the procedure; adequacy of resection and nodal clearance in upper third tumours; and the use of MIO in patients who have had chemoradiotherapy [14, 15]. Many case series have demonstrated that the procedure is safe and comparable to the open operations, but there has been little conclusive outcome data to support the theoretical benefits [15]. Some studies have shown a reduction in operative and short-term outcomes, such as estimated blood loss and length of intensive care and inpatient stays. However, the results were mixed, analysing small patient numbers or using historical data as a control [8, 9, 11, 16]. Recent meta-analysis and systematic reviews, including Dantoc et al.'s recent review of 17 case–control studies and Verhage's yield of 494 tans hiatal or transthoracic surgeries against 616 patients that received some form of MIO, were hindered by heterogeneous data, publication bias and patient selection bias. The latter may be due to advanced tumours or adjuvant therapy being considered contraindications to MIO by surgeons [14, 17].

The first randomised control trial comparing MIO and open oesophagectomy was published in 2013 and included 59 patients undergoing MIO and 56 undergoing open surgery. Statistical significance was found for improved outcome in patients undergoing MIO [7, 15]. Their primary endpoint was pulmonary complications and further short-term secondary endpoints, such as post-operative pain, intraoperative blood loss, hospital stay, and quality of life 6 weeks after surgery were all significantly improved in the MIO arm of the trial. No data have been published from this trial on long-term survival or oncological outcomes and concerns

The authors aimed to use the department's 8 years' experience to compare MIO and open oesophagectomy across a variety of tumour positions and stages to compare long-term survival and oncological outcome as primary and secondary outcomes.

Methods

A retrospective data analysis was undertaken on all patients who underwent oesophagectomy in a tertiary upper gastrointestinal surgery unit, from 2005 to 2012 inclusive. Data were collected from the departmental database which had been recorded till 2011 and the further case note review to up-date the records to end of November 2012, with follow-up and survival data to time of data collection. Survival was assessed by reviewing the patient records on the hospital's patient administration system. Patients were followed up from date of their operation until the time of data collection during November and December 2012 at which point they were censored if they were still alive.

Included were all patients undergoing oesophagectomy for high-grade dysplasia, adenocarcinoma or squamous cell carcinoma with or without neoadjuvant chemotherapy. This included patients deemed inoperable at the time of surgery or who had incomplete (R1/2) resections.

Patient selection for treatment

Patients were selected for surgery by the upper gastrointestinal cancer multidisciplinary team at University Hospitals Bristol NHS Foundation Trust. This central cancer team provides treatment decisions for all patients with upper gastrointestinal cancer in the Avon, Somerset and Wiltshire Cancer Network (population two million). Meetings occur weekly and information about disease type and stage, co-morbidity and patient choice are considered. Disease stage was defined by computed tomography of the chest and abdomen (CT), endoluminal ultrasonography (EUS) and selected patients underwent staging laparoscopy

and bronchoscopy. From August 2007 PET (Positron Emission Tomography), CT scans were performed in all patients selected for surgery. Primary surgery was offered to patients with high-grade dysplasia or early invasive cancer (T1/2N0M0), while those with more advanced tumours were all offered neoadjuvant chemotherapy in line with recommendations [16, 18].

Surgical techniques

Three approaches for oesophagectomy were undertaken in our institution during this study. Standard 'open' surgery involved a two-phase Ivor Lewis oesophagectomy [19]. In July 2005, two-phase laparoscopically assisted oesophagectomy (LAO) was introduced. Here, gastric mobilisation and abdominal lymphadenectomy were performed laparoscopically, followed by open right thoracotomy (for oesophageal mobilisation, mediastinal lymphadenectomy and anastomosis).

Minimally invasive oesophagectomy was introduced in April 2006. Our MIO technique is based on the Pittsburgh experience [19] with some modifications. First, thoracoscopic oesophageal mobilisation and mediastinal lymphadenectomy are performed in the left lateral position. The patient is then positioned supine to enable laparoscopic gastric mobilisation and abdominal lymphadenectomy, followed by a mini-laparotomy for conduit formation and placement of a feeding jejunostomy tube. A hand-sewn anastomosis is performed via a left cervical incision.

All procedures involved a two-field lymphadenectomy (chest and abdomen) and reconstruction was performed with a gastric conduit. The team comprised six consultant surgeons (CPB, JMB, AH, RK, CS, DT) as well as trainees under direct supervision.

Following the introduction of MIO, this technique was initially used in patients selected for primary oesophagectomy without neoadjuvant chemotherapy (although the indications were subsequently broadened). LAO was performed in patients with adenocarcinoma, and 'open-open' two-phase Ivor Lewis oesophagectomy was undertaken where patients had undergone previous gastric surgery or when only one oesophageal surgeon was available for the operating list.

Data collection and analysis

Clinical details were recorded including age, gender, preoperative chemotherapy regimen, cancer stage, site and type. Cancer site was defined as middle, lower or junctional as measured by EUS. Incomplete resection (R1) was defined as tumour cells present at the resection margin or within 1 mm of the circumferential resection margin (CRM). The primary outcome was defined long-term survival and this was compared between surgical techniques.

Statistical analysis was carried out using R (R Foundation for Statistical Computing, Vienna, Austria) with the R Commander interface and SPSS 20 (IBM). The survival data were analysed using univariate and multivariate Cox proportional hazard regression models to determine which variables affected survival. Categorical demographic data were compared across the defined groups using the Pearson Chi square test.

Results

Three-hundred and thirty-four patients were included in the database from 5/1/2005 to 22/10/2012. 31 (9.1 %) patients had absent or incomplete data. Only patients that proceeded to operation were included in the database. There was a M:F 3.75:1, and mean age of 69 and median follow-up of 27 months (range 5 days to 8 years 4 months). The majority, 294 (88 %), had adenocarcinoma on histology, which is in keeping with previous studies in Western populations. 257 (77 %) had neoadjuvant chemotherapy; the majority (82 %) of those who did not were in the low T stage group (T1/2). Fifty-six percent of tumours resected were at the gastro-oesophageal junction (these were not differentiated by Siewert classification in this study), while 36.5 % were in the distal third with the remaining 7.5 % in the proximal or middle thirds of the oesophagus.

The data were separated into three groups based on operative technique used. Of the 334 oesophagectomies included there were 67 MIOs, 184 laparoscopic-assisted Ivor Lewis resections and 83 open procedures. There was no significant difference between the groups on age, gender and histological type (see Table 1). However, there was a significant difference between the proportions of the tumour positions operated on ($p = 0.032$). There were also significantly less patients that received neoadjuvant chemotherapy and significantly less advanced tumours and node positive disease amongst the MIO group ($p < 0.001$) (see Table 1).

There was an incomplete (R1) resection rate of 13.2 % over the 8 years across all the groups. The MIO had a lower R1 rate when compared to the LAO and open groups; 6.1 % ($n = 4$) compared to 20.3 % ($n = 37$) and 15.6 % ($n = 12$), respectively.

Table 2 shows the results of Cox proportional hazard regression analysis of each variable in the univariate analysis column (column 1). These are used to establish any significant effect upon survival and as such show significantly improved survival in the MIO group compared to the open and group (Hazard Ratio 0.293, 95 %

Table 1 Clinical details for patients undergoing open surgery, laparoscopically assisted (LAO) or minimally invasive oesophagectomy (MIO)

	LAO $n = 184$	MIO $n = 67$	Open $n = 83$	p value
Median age/years	64.8	65.4	63.9	0.854†
(Range)	(38.0–79.3)	(35.7–79.3)	(43.0–77.4)	
Sex (%)				0.185*
Male	151 (82.1)	48 (71.6)	67 (80.7)	
Female	33 (17.9)	19 (28.4)	16 (19.3)	
Tumour site (%)				0.284*
Middle	12 (6.5)	5 (7.5)	5 (6.0)	
Lower	71 (38.6)	28 (41.7)	23 (27.7)	
Junctional	100 (54.3)	32 (47.8)	55 (66.3)	
Not recorded	1 (0.5)	2 (3.0)	0 (0)	
Histological type (%)				<0.001*
High-grade dysplasia	0 (0)	7 (10.4)	0 (0)	
Adenocarcinoma	167 (90.8)	53 (78.7)	74 (89.1)	
Squamous cell	14 (7.6)	7 (10.4)	8 (9.6)	
Other	3 (1.6)	0	1 (1.2)	
Neoadjuvant				<0.001*
Chemotherapy (%)				
Yes	158 (85.9)26	23 (34.3)	76 (91.6)	
No	(14.1)	44 (65.7)	7 (8.4)	
T Stage (%)				<0.001*
0	6 (3.2)	3 (4.5)	1 (1.2)	
1	32 (17.4)	37 (55.2)	12 (14.4)	
2	25 (13.6)	9 (13.4)	10 (12.0)	
3	119 (64.7)	18 (26.9)	60 (72.3)	
4	2 (1.1)	0 (0)	0 (0)	
N stage				<0.001*
0	87 (47.3)	53 (79.1)	39 (47.0)	
1	97 (52.7)	14 (20.9)	44 (53.0)	

* Pearson Chi square test

† ANOVA

CI 0.158–0.541), but no significant difference between LAO and open groups (HR 0.762, 0.530–1.095). However, the following factors were also found to be correlated to survival: use of neoadjuvant chemotherapy (Hazard Ratio 2.889, 95 % CI 1.737–4.806), T stage 3 or 4 (3.749, 2.475–5.72), Node positive (5.225, 3.561–7.665) and R1 resection (2.182, 1.425–3.341) (see Table 2). Columns 2 and 3 show the results of sequential multivariate analysis; used to account for the influence of other variables that also have a significant effect on survival and as such establish any independent effect on outcome. The only factors present in the final model to predict survival were T stage, N stage and type of operation (Table 2). Figures 1 and 2 show the Kaplan–Meier survival curve for each of the operative groups after adjustment for T stage and N stage.

Discussion

Numerous studies have shown comparable efficacy of MIOs when compared to other modalities of oesophagectomy when looking at operative or short-term end-points [8, 20–22]. Though the majority of these were case studies or case match series, they have recently culminated in a randomised control trial (TIME-trial) which has shown significant reduction in, specifically, pulmonary complications following oesophagectomy [2, 7, 20]. Very few studies have looked at long-term outcomes and oncological effect. Dantoc et al.'s recent systematic review identified 17 case-controlled studies that showed no significant difference in 30-day and 5-year survival [23]. These studies were hindered by heterogeneity of data and low numbers. The reported over-all 5-year survival for oesophagectomy

Table 2 Sequential univariate and multivariate cox proportional hazard regression models; showing independence of effect upon survival

	Univariate			Multivariate (initial model)			Multivariate (final model)		
	Hazard ratio	95 % CI	*p*	Hazard ratio	95 % CI	*p*	Hazard ratio	95 % CI	*p*
Age									
Age	1.009	0.9883, 1.029	0.4053						
Neoadjuvant									
No neoadj	1 (ref)			1 (ref)					
Neoadjuvant	2.889	1.737, 4.806	0.0000	0.7769	0.4145, 1.4560	0.4311			
T stage									
T 0,1 or 2	1 (ref)			1 (ref)			1 (ref)		
T 3 or 4	3.749	2.457, 5.72	0.0000	2.1510	1.2930, 3.5790	0.00318	1.9690	1.2480, 3.1050	0.00358
N stage									
N0	1 (ref)			1 (ref)			1 (ref)		
N1	5.225	3.561, 7.665	0.0000	3.8850	2.530, 5.9640	0.00000	3.8330	2.5480, 5.7660	0.00000
Complete resection									
R0	1 (ref)			1 (ref)					
R1	2.182	1.425, 3.341	0.0003	1.3750	0.8876, 2.1550	0.1644			
Position of tumour									
Distal oesophagus	1 (ref)								
Proximal/mid oesophagus	1.142	0.576, 2.266	0.7038						
OGJ	1.214	0.8443, 1.744	0.2957						
Histology									
Adenocarcinoma	1 (ref)								
HGD	3.8×10^{-8}	0.000, inf	0.9946						
Squamous CC	1.072	0.6050, 1.90	0.8111						
Other	3.80	0.9275, 15.57	0.06354						
Type of op									
Open	1 (ref)			1 (ref)			1 (ref)		
Lap assisted	0.7619	0.5302, 1.095	0.1416	0.7244	0.4946, 1.0610	0.0978	0.7992	0.5541, 1.1530	0.2303
MIO	0.2926	0.1584, 0.5407	0.00008	0.4291	0.2182, 0.8438	0.0142	0.5186	0.2766, 0.9723	0.0406

The table shows sequential analysis of confounders that carry a significant effect upon survival, as demonstrated by the hazard ratios in column one. The continued multivariate analysis in columns 2 and 3 take into account the other factors that still carry a significant effect, in order to establish any independent effect upon survival of each variable

is still low, estimated at 17.3 % by the National Cancer Institute at the end of 2013, thus an important area for consideration [24, 25].

In keeping with other studies, there is selection bias in our series; during our learning curve in minimally invasive surgery, less advanced tumours were resected utilising this technique. This may be due to the relative reluctance of surgeons to use the newer procedure in advanced tumours and the lack of conclusive evidence of it efficacy in such cases [7, 15], and [21]. However, at the conclusion of this review, 20 T3/T4 and 14 node positive tumours had been resected by MIO. There was a significantly lower R1 resection rate in the MIO group; this would be expected from the significantly higher proportion of low grade (T 0–2) tumours in that group. In this study, we adjusted for differences in case mix using multivariate regression, and found improved survival in the MIO group compared to the open group (Table 2; Fig. 2). The only factor we found to be correlated with survival other than T stage and N stage was the type of operation.

Conclusion

In conclusion, this non-randomised study was unable to adjust for all the risk of statistical type 1 error, a risk for any study of survival data, and lack of adjustment for confounder variables and therefore, cannot conclude that MIOs produce better oncological effect or long-term survival outcomes than open surgery These results, however, should begin to question the accepted reluctance to use this procedure on more advanced tumours and emphasise the need for a large scale, multicentre pragmatic-randomised control trial in this area [26].

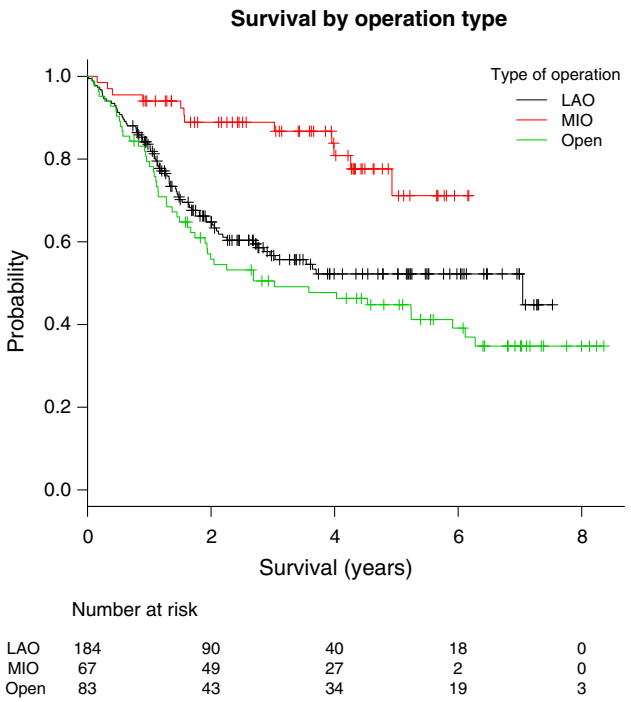

Fig. 1 Kaplan–Meier curve of the probability of survival against years for each of the three operative groups, with no adjustment for T or N stage which also carried a significant effect upon survival (Color figure online)

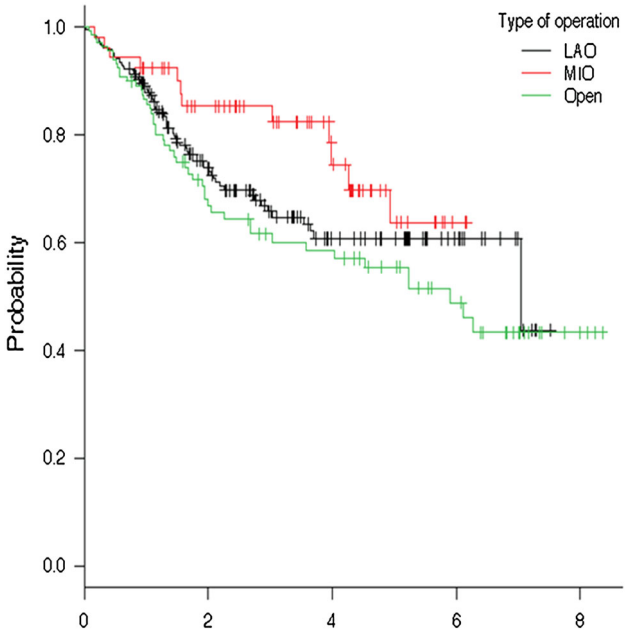

Fig. 2 Kaplan–Meier curve of the probability of survival against years for each of the three operative groups, with correction for differences in T and N stage of the tumour (Color figure online)

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