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ORIGINAL ARTICLE

Minimally invasive esophagectomy for esophageal cancer in octogenarians. Clinical and oncological outcomes

Elias Sdralis[1], Spyridon Davakis[1,2], Athanasios Syllaios[1,2], Eustratia Mpaili[1,2], Bruno Lorenzi[1], Alexandros Charalabopoulos[1,2]

[1]Department of Upper Gastrointestinal Surgery, Regional Esophago-Gastric Cancer Centre, Broomfield Hospital, Mid Essex Hospital Services NHS Trust, Chelmsford, Essex, UK; [2]Upper Gastrointestinal Unit, 1st Department of Surgery, Laiko General Hospital, National and Kapodistrian University of Athens, Athens, Greece.

Summary

Purpose: *Studies on patients undergoing esophagectomy for esophageal cancer have shown that thoracic and abdominal surgery may be performed safely in patients without an uppermost age cut-off. The aim of this study was to evaluate the morbidity and mortality of radical minimally invasive esophagectomy for cancer in patients over 80 years old.*

Methods: *A retrospective analysis of prospectively collected data over a period of 4 years was conducted. During the study period 184 esophagectomies were performed. A total of 12 octogenarians that underwent Minimally Invasive Esophagectomy (MIE) for cancer were included in the study. Our results were compared to the UK national outcomes as presented in the National Esophago-Gastric Cancer Audit (NOGCA) 2017 report.*

Results: *Median overall survival (OS) was 16.5 months (range: 6-38) and progression-free survival (PFS) 14.5 months (tange:3-38). 30-and 90-day postoperative mortality was zero. Postoperative complications included chest infection (CI) in 4 (33.3%) patients, anastomotic leakage (AL) in 3 (25%) and atrial fibrillation in 2 (16.7%).*

Conclusions: *MIE should therefore be considered as an effective treatment strategy even in elderly patients over 80 years of age.*

Key words: *Esophageal cancer, minimally esophagectomy, octogenarians, clinical outcomes*

Introduction

Esophageal cancer (EC) is a highly lethal disease as indicated by the reported overall survival (OS) rate of 10-20%. Worldwide, approximately 400,000 patients are diagnosed with EC annually. It is the 8th most common cancer with morbidity rate ranking 6th among various cancer types. Due to an increase in life expectancy, EC is nowadays more frequent, representing 7% of all gastrointestinal malignancies [1]. Thus, an increased number of senior citizens become candidates for major operations, such as esophagectomy. Patients with unresectable disease are associated with overall poorer prognosis and surgery is a *sine qua non* when cure is intended. Esophagectomy with radical lymphadenectomy is challenging and associated with high morbidity and mortality that can reach up to 10% and 50% respectively [1-3]. Elderly patients are often considered a surrogate for increased medical comorbidity and diminished physiological reserve, leading to an increased perioperative risk, as reflected in higher than average American Society of Anesthesiologists (ASA) score. As a result, surgeons are generally more reluctant to perform major surgery on elderly patients, especially when

Corresponding author: Spyridon Davakis, MD. Laiko General Hospital, 17 Agiou Thoma Street, 11527, Athens, National and Kapodistrian University of Athens, Athens, Greece
Tel: +30 6973762451, Email: spdavakis@gmail.com
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thoraco-abdominal procedures are considered [4]. In the care of senior surgical patients, no age-related increase in operative morbidity and mortality has been observed, despite the expected age-related decline in human physiology.

Studies on surgical patients undergoing esophagectomy for malignancy have shown that thoracic and abdominal surgery may be performed safely in patients without an uppermost age cut-off. Comorbidities seem to have more impact on perioperative morbidity and mortality than age alone. The widespread recognition of this demographic and surgical trend has already been documented in the literature with no consensus regarding the best modality provided (operative or palliative therapy) [2,5-9].

Additionally, minimally invasive techniques (MITs) are associated with lower morbidity and recently a plethora of studies have reported superior clinical short-term outcomes compared to standard open techniques [10]. As centers of excellence maintain high standards of care, advanced surgical techniques can potentially reduce physiological stress with an outcome improvement and with time to progression; surgeons are becoming less conservative in patient selection.

The aim of this study was to evaluate the morbidity and mortality of radical minimally invasive esophagectomy (MIE) for cancer in patients over 80 years old. Our results were compared to the UK national outcomes as presented in the National Oesophago-Gastric Cancer Audit (NOGCA) 2017 report [11].

Methods

A retrospective analysis of prospectively collected data over a period of 4 years was conducted. The study took place at the Regional Esophago-Gastric Cancer Centre in Essex, UK. During the study period 184 esophagectomies were performed. A total of 12 octogenarians that underwent MIE for cancer were included in the study. Esophagectomies for benign disease, patients younger than 80 years old, as well as open procedures were excluded from the study. Patients enrolled in the study were diagnosed with adenocarcinoma of either mid-/lower- esophagus or esophago-gastric junction (EGJ) (Siewert I, II). Siewert type III EGJ cancers were excluded from the study as during the study period, these were treated with extended total gastrectomy.

All patients were staged with Positron Emission Tomography-Computed Tomography (PET-CT), Endoscopic Ultrasound (EUS), Computed Tomography (CT), staging laparoscopy and underwent Cardio-pulmonary Exercise Test (CPET) to assess surgical fitness.

Clinical data were collected through medical records and by personal interview of the patients during follow-up.

Statistics

Descriptive statistical analysis was conducted for all of the encountered parameters, measuring the accumulated values; all repeated measures are expressed as mean ± Standard Deviation, with reference to its corresponding range. Survival rates were analyzed by the Kaplan-Meier survival method. All results were analyzed using the SPSS v22.0 (Statistical Package for Social Sciences Inc., Chicago, IL).

Table 1. Patient demographics and surgical characteristics

Patient	*Sex*	*Age*	*ASA score*	*Cancer differentiation*	*Tumor location*	*Clinical stage*	*Neoadjuvant treatment*	*Pre-operative stenting*	*Feeding jejunostomy*	*Operation*	*Operative time (min)*	*Blood loss (mL)*
1	M	83	2	G1	DE	T1bN0	No	No	No	2-s MIE	300	80
2	F	83	3	G3	DE	T2N1	No	No	No	2-s MIE	380	150
3	M	81	3	G3	DE	T3N2	No	No	No	2-s Hybrid	320	200
4	F	80	3	G3	DE	T3N0	No	No	No	2-s Hybrid	280	240
5	M	81	2	HGD	GOJ-S1	T3N0	CT	No	Yes	2-s RAMIE	350	120
6	M	80	3	G2	ME	T3N0	No	Yes	No	3-s MIE	400	450
7	F	82	3	G3	DE	T3N1	No	No	No	2-s Hybrid	310	300
8	M	80	3	G2	DE	T3N1	CT	No	Yes	2-s Hybrid	280	280
9	M	82	2	G3	DE	T3N1	No	No	No	2-s Hybrid	300	320
10	M	83	3	G2	GOJ-S1	T1bN0	No	No	No	2-s Hybrid	290	350
11	M	85	3	G3	GOJ-S2	T3N0	No	No	No	2-s Hybrid	300	100
12	M	81	3	G3	GOJ-S2	T2N0	No	No	No	2-s Hybrid	260	350

M=Male, F=Female, HGD=high grade dysplasia, G1=well differentiated tumor, G2=moderately differentiated tumor, G3=poorly differentiated tumor, DE=distal esophagus, ME=mid-esophagus, GOJ= gastroesophageal junction,S1=Siewert type1, S2=Siewert type 2, 2s-two stage, 3s=three stage, MIE=totally minimally invasive esophagectomy, Totally=laparoscopic abdomen-laparoscopic chest, Hybrid=laparoscopic abdomen-open chest, RAMIE=robot-assisted MIE (laparoscopic abdomen-robotic chest), CT= epirubicin-oxaliplatin-capecitabine (EOX - 3-cycles)

Results

Twelve octogenarians with cancer were treated with MIE. Three were females (25%) and 9 males (75%), with a median age of 82 years (range: 80-85). Main presenting complaints was dysphagia, abdominal pain and reflux in 58.3%, 8.3% and 8.3%, respectively. Three cases were diagnosed on surveillance endoscopy for Barrett's esophagus. One patient (8.3%) had undergone pre-operative esophageal stenting for relief of dysphagia and two patients (16.6%) had a feeding jejunostomy tube placed during the staging laparoscopy. Patients' demographics are listed in Table 1. Three patients (25%) were classified as ASA 2 and the majority (n=9, 75%) were ASA 3. None of them was considered unfit for esophagectomy.

Tumors were located at the distal esophagus in 7 (58.33%), at the EGJ in 4 (33.33%) and mid esophagus in 1 (8.33%).

High grade dysplasia was noted in 1 (8.33%) patients, whereas invasive tumors were well differentiated in 1(8.33%), moderately differentiated in 3 (25%) and poorly differentiated in 7 (58.33%) patients.

Only 2 (16.6%) patients received neo-adjuvant chemotherapy, with 3-cycles of EOX (epirubicin- oxaliplatin- capecitabine).

Three surgeons performed all the procedures. Eight patients underwent hybrid two-stage esophagectomy (laparoscopic abdomen-open chest). Two had totally minimally invasive two-stage esophagectomy (laparoscopic abdomen-laparoscopic chest); one had totally minimally invasive three-stage esophagectomy (lap abdomen-lap chest- neck) and one robot-assisted two-stage minimally invasive esophagectomy (laparoscopic abdomen-robotic chest). Mean operative time (±SD) was 314 min (±42) and mean blood loss (±SD) was 250 mL (±50).

Six patients (50%) had an uneventful recovery with no postoperative complications. Chest infection (CI) was noted in 4 (33.3%) patients, anastomotic leakage (AL) in 3 (25%) and atrial fibrillation (AF) in 2 (16.7%). Mean length of hospital stay (LHOS) was 14±5.25 days.

Oncological and clinical parameters are shown in Table 2. R0 resection according to the Royal College of Pathologists (1mm clear circumferential resection margin) was achieved in 9 (75%) patients and R1 resection in 3 (25%). All patients had a standard 2-field lymph node dissection. The mean number of lymph nodes harvested was 25 (range: 14-51). Only one, underwent adjuvant treatment post-operatively. Histopathological staging and clinical outcomes are given in Table 2.

Follow-up period ranged from 6 to 38 months, whilst median follow-up was 18 months. Thirty-day and 90-day postoperative mortality was 0%. During follow-up, one patient suffered a myocardial infarction at the 10th postoperative month and passed away. Four patients (33.33%) developed systematic disease recurrence and passed away 3-16 months post-operatively. Seven patients (58.33%) are alive and disease-free. One patient was readmitted for food bolus obstruction at the anastomotic level and was treated endoscopically. No anastomotic strictures were seen. One patient was read-

Table 2. Patient oncological parameters and clinical outcomes

Patient	*Pathological stage*	*Lymph-node harvest*	*R-status*	*Adjuvant treatment*	*LOS (days)*	*Complications*	*Overall survival (months)*	*Disease free survival (months) - current status*
1	T1aN0	31	R0	No	9	None	11	11 alive-cancer free
2	T2N2	20	R0	No	13	CI	9	9 alive-cancer free
3	T3N3	51	R0	No	16	CI	24	24 alive-cancer free
4	T3N2	14	R0	No	10	None	18	18 alive-cancer free
5	HGD	22	R0	No	15	AL, AF	20	20 alive-cancer free
6	T3N0	18	R1	No	23	AL, AF	17	13 (RIP at 17 months)
7	T3N1	41	R0	No	11	None	32	32
8	T3N1	37	R1	Yes	10	None	13	13 months (RIP 13 months)
9	T3N2	23	R1	No	9	None	15	12 (RIP 15 months)
10	T1bN0	11	R0	No	15	CI	38	38
11	T3N1	23	R0	No	25	AL, CI	6	6 (RIP 6 months)
12	T3N2	16	R0	No	12	None	16	16 (RIP 16 months)

TNM stage according to TNM 7th edition, R-status according to the Royal College of Pathologists (R1 equals to CRM positive <1mm), LHOS= length of stay, CI= chest infection, AL= anastomotic leak, AF= atrial fibrilation, MI= myocardial infraction, RIP=death

mitted and underwent esophageal stenting due to chronic anastomotic leakage and one underwent laparoscopic repair of hiatus hernia 6 months post primary procedure.

Estimated median OS was 16.25 months (range:6-38 months), while PFS was 14.5 months (range:6-38). Survival rates are shown in Figures 1 and 2. Of the 2 patients receiving neoadjuvant chemotherapy, one received adjuvant chemotherapy, thus completing the whole peri-operative treatment scheme. Of the study group, none received adjuvant therapy only.

Table 3. Outcomes of minimally invasive esophagectomy in octogenarians compared to UK national standards (all esophagectomies) (NOGCA 2017 report).

	Study group n(%)	*UK standards n(%)*
Gender (Male/Female)	9 (75)/ 3 (25)	2989 (80/20)
Age, years, mean±SD	81.5 (±1.54)	71 (±NI)
ASA score		
II	3 (25)	82
III	9 (75)	17
Tumor location		
Mid-esophagus	1 (8.33)	13.2
Distal esophagus	7 (58.33)	38.4
Esophago-gastric junction (Siewert I,II)	4 (33.33)	12.4
Peri-operative therapy	1 (8.33)	2390 (80)
Operation		
Minimally invasive procedures	12 (100)	40.8
Lymph node harvest (>15)	(91.66)	82.3
R-status (pathology reports)		
R0	9(75)	67.5
R1 (CRM<1mm)	3(25)	27.9
Complications	50	36.4
Chest infection	4 (33.33)	16.9
Cardiac	2 (16.7)	5.3
Anastomotic leak	3 (25)	6.3
Mean length of hospital stay (±SD) (days)	14±5.25	12±5.25
30-day mortality rate	0	1.9
90-day mortality rate (%)	0	3.3

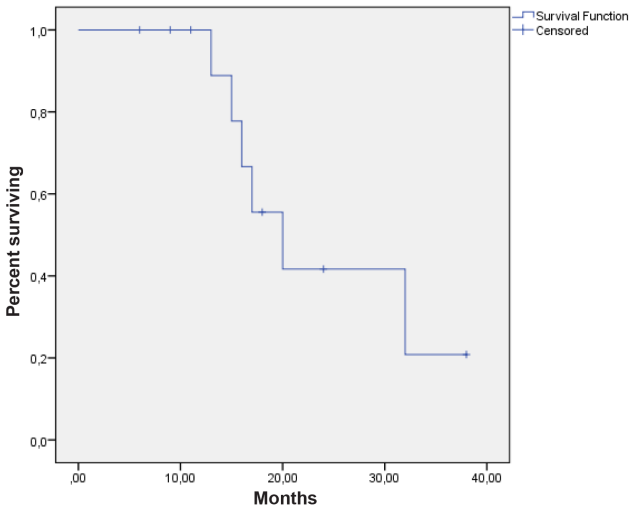

Figure 1. Kaplan-Meier curve of the estimated overall survival.

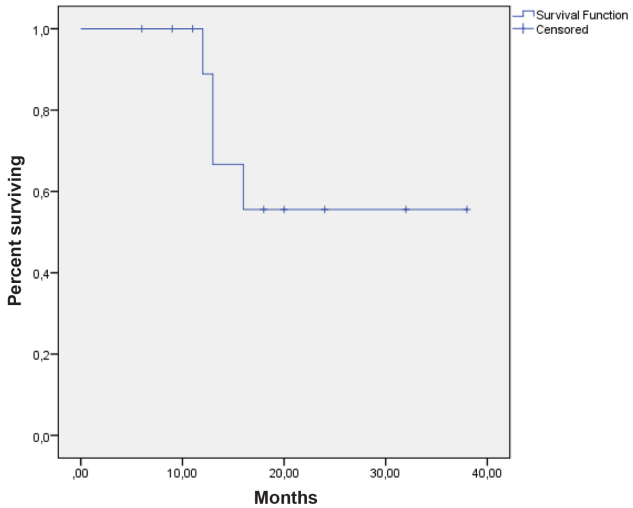

Figure 2. Kaplan-Meier curve of the estimated progression-free survival.

Discussion

Clinical outcomes following esophagectomy in elderly patients over 80 years old have not yet been overtly standardized. This group of patients frequently presents with increased cardiopulmonary risk coarsely reflected by a higher ASA score compared to the general population. This high-risk cohort of patients poses surgeons to great reluctancy to proceed with a highly invasive procedure such as radical esophagectomy, vastly in view of the existing comorbidities that are predisposing to increased postoperative complications and mortality; it is thus not infrequent for surgeons to choose a more conservative, non-operative treatment [4].

The purpose of this study was to investigate if age over 80 relates to outcome of minimally invasive radical esophagectomy for cancer. Since, according to long-term survival, surgical treatment has proven to be more effective in treating EC compared to non-operative one, surgeons have to consider the risks and benefits of confronting elderly patients when a surgical approach is encountered [12]. Reports on advancement in peri-operative care suggest that advanced age alone should not be regarded as an absolute contraindication for a major operation like esophagectomy [13]. Our study investigated the outcomes following esophagectomy for carcinoma of the esophagus and EGJ in patients older than 80 years of age and identified the potential risk factors for higher postoperative morbidity and mortality rates in this particular age group.

In recent decades, the improved peri-operative patient care has contributed to the reduction of procedure-related morbidity (especially pulmonary complications) and mortality and all patients, irrespective of age, have benefited from those advancements [13]. It is well established that presence, number and severity of comorbidities directly influence postoperative morbidity and mortality. Our results indicate that octogenarians have a good recovery and low possibility of cancer recurrence, with an OS rate of 58.3% at 20 months, while the UK national figures show a survival rate up to 69% within the first 12 and 60% survival rate within the first 20 months (Figure 1) [3,11,14]. It could be postulated that the significant number of R0 resections combined with the high lymph node yield were the main factors affecting oncological outcomes in our study cohort of octogenarians.

The present study, in line with NOGCA outcomes, shows a similar gender distribution of esophageal/EGJ cancer; 75% males and 25% females diagnosed. Preoperative comorbidity seems to be higher for octogenarians, with 75% of them being ASA grade 3 and 25% ASA grade 2, whereas 82% of the overall UK cohort has an ASA grade 2 and 17% an ASA grade 3 [3,11].

Other characteristics of patients' condition were also noted. All of the patients in this study were diagnosed with adenocarcinoma, when in general UK population adenocarcinoma accounted for 74% of the cases of esophageal cancer, squamous cell carcinoma for 17% and 9% of the cases were undifferentiated. As it comes to the location of the tumor, 58.3% of our patients had tumors located at the distal esophagus, 33.33% at the GOJ and 8.3% at the mid-esophagus, whereas in UK the esophageal and GOJ cancer prevalence rates were 42.1% and 10.9%, respectively [3,11].

Neoadjuvant treatment is used to downstage or locally control the disease in patients with advanced stage (stage II or III) [15]; it is also considered one of the factors that can improve esophagectomy outcomes, as tumor complete response, with a direct implication in overall survival, can be seen in a percentage of patients that can reach up to 30% [15]. In many countries, perioperative chemotherapy for lower-third esophageal tumors, staged T2 or greater, has been the standard of care since 2006 [16]. Although a trend towards tri-modality therapy with neoadjuvant chemoradiation and surgery is seen worldwide and may become the standard of care in the future, in elderly patients such as in our cohort, it is less utilized due to increased risk of toxicity and limited life expectancy [17]. Two (16.7%) of our patients received neoadjuvant chemotherapy (3 cycles), whereas in the UK national report, 78-87% received a complete perioperative care scheme [3,11].

In our study, MITs were used in all patients. To our knowledge this is the first study to investigate the clinical and oncological outcomes of MIE in octogenarians. MITs may be associated with lower mortality rates than the conventional open technique [18]. Two-stage operation is considered to be less invasive and thus found to be appropriate for patients with severe surgical risk [13]. The type of esophagectomy used in the majority of UK patients is the Ivor Lewis Esophago-Gastrectomy [3]. In the UK, the proportion of esophageal operations carried out with MIEs accounted from 0.6% in 1997 to 16% in 2007 and to 40.8% in 2017 [11,18]. The transhiatal esophagectomy is rarely used for patients of high pre-operative comorbidity such as the elder patients (ASA score 3) [18]. On the other hand, Alexiou et al suggested that the type of surgical approach used in octogenarians is not an important factor affecting immediate postoperative outcome, and instead they emphasized the need for effective

analgesia, the provision of vigorous physiotherapy and the prompt treatment of pulmonary infection, arrhythmias, and other complications as soon as they occur [13]. It should be noted, however, that in the past MIEs were not as extensively used as nowadays.

Postoperative morbidity and procedure-related complications are main factors making surgeons skeptical about operating on elderly patients. Half of our patients (50%) had no postoperative complications. Anastomotic leakage was one of the main complications we had to confront in 25% of the patients, and chest infection in 33.4% of them. Another main complication was arrhythmias affecting 16.7% of our patients. Postoperative complications mentioned in the national UK outcomes included anastomotic leakage in 6.3% of the patients, chest sepsis in 16.9% and cardiac complications in 5.3% [3,11,14]. Overall UK complication rate was 36.4% [3,11,14]. Other rare complications recorded were bleeding, chylothorax and small bowel obstruction. Our reported postoperative complication rate is similar to that described in the current literature for elders. Other authors report a postoperative complication rate in elders between 24.7% and over 50% [13,19,20,21]. Especially in patients over 80 years of age, we believe perioperative and cardiopulmonary complications to be critical and thus they should be promptly treated. Moskovitz et al observed that the postoperative rate of pneumonia, infection, and anastomotic leak in octogenarians was similar to that of younger patients [2]. Although postoperative comorbidity seems to be high for octogenarians, in our study 30-day mortality was 0%.

Median LOHS for our patients was 14 days, similar to the 12 days in the UK national outcomes [3,11,14]. Those findings could be partially explained to the use of MIE in the octogenarians along with the prompt recognition and management of postoperative complications. Two of our patients (16.7%) were readmitted in less than 42 days after esophagectomy, whereas 14% of the general UK cases were readmitted in a period of 28 days after surgery [3,11,14].

A major index of potential successful outcome is the R-status of the dissected tumor [22]. In our study in 75% of the cases, the dissected tumor was R0 and there were 3 R1 cases (25%) with positive circumferential restriction margin (CRM) according to the Royal College of Pathologists. Similar were the national UK outcomes, with 67.5% of the cases found to be R0, while 32.1% of them were R1 [3,11,14].

In order to come to our final conclusion, regarding the risk of esophagectomy in octogenarians, we note that we have not experienced any perioperative death, with 30-day and 90-day mortality being 0%. The 6-month mortality was 8.3 %. According to UK national outcomes 30-day mortality rate was 1.9% and 1-year mortality rate was 31% [3,11,14]. Postoperative mortality in octogenarians is 5.6-19.4% in other reports arguing whether those rates are similar or higher to that of younger patients [2,13]. One-year mortality rate in our series is 16.7% so far. All the aforementioned parameters from our study as well as the UK National outcomes are summarized in Table 3.

Limitations of the study are the fact that it is a retrospective study with a small size number and a short follow-up. Thus, it is difficult to extrapolate conclusive results. To overcome the limitation of the small number of octogenarians undergoing MIE and so reaching accurate conclusions about this cohort of patients regarding their short- and long-term outcomes, high-power multicenter studies are needed.

Conclusion

Compared to UK national outcomes, there is no significant difference in comorbidity and especially in mortality, after MIE in octogenarians. The strict indications for surgery and the less invasive procedures enabled surgeons to decrease the morbidity rate even in patients over 80 years of age. MIE should therefore be considered as an effective treatment strategy even in elderly patients over 80 years of age, for whom age should not be a denominator of inclusion and/or exclusion, offering good quality of life and life expectancy, especially when a curative resection can be expected preoperatively.

Ethics

All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinky declaration of 1964 and later version.

Conflict of interests

The authors declare no conflict of interests.

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