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ORIGINAL ARTICLE

Results of upfront surgery in a mixed stage population of patients with esophageal carcinoma: early outcome and long term survival

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Summary

Purpose: *To evaluate early outcome and long term survival in a mixed stage population of patients undergoing upfront esophagectomy for esophageal cancer.*

Methods: *Retrospective analysis of the data of 92 patients who underwent esophagectomy (thoracoabdominal: 76, Ivor-lewis: 16) between 1998 and 2017. Tumors were located in gastro-esophageal junction (52), lower third (31) and middle third (9) of the esophagus. Histology was: 73 adenocarcinomas and 19 squamous cell carcinomas. The stomach was used for reconstruction in 90 patients. A neck anastomosis was performed in 7 patients. End points of the study included: mortality, morbidity and long term survival. Kaplan-Meier and Cox regression analyses were used to identify prognostic factors for survival.*

Results: *The mortality was 10.9% and 29 patients presented 49 complications. Anastomotic dehiscence occurred in 17.4% of the patients and represented the most common cause of death with mortality of 37.5%. Reoperation was necessary in 14 patients. Median survival reached 25 months with 3 and 5 year survival of 30.5% and 21% respectively. Early stage tumors, absence of nodal disease, well differentiated carcinomas and lymph node ratio ≤ 0.2 were associated with 5 year survival of 82.6%, 81.6%, 83.3% and 40.4% respectively. In multivariate analysis early stage disease (OR: 15.746, 95%CI: 4.332-58.579, p < 0.001) and lymph node ratio (OR: 1.700 95%CI: 1.051-2.752, p = 0.031) were statistically associated with long term survival.*

Conclusions: *Our results support the role of upfront surgery as the treatment of choice in early stage esophageal carcinomas without or with low nodal involvement.*

Key words: *dehiscence, esophagectomy, early stage, esophageal carcinoma, lymph node ratio, survival*

Introduction

Esophageal carcinoma represents the 8th more frequent cancer and the 6th cause of mortality from cancer globally. Although it is considered highly lethal, an improved 5-year relative survival of approximately 20% has been recently reported in the SEER database [1]. Esophagectomy remains the standard of care among patients with early-stage disease and it additionally can be used for better local disease control in locally advanced tumors in the setting of multidisciplinary treatment protocols; an expected 5-year survival of up to 40-60% can be achieved among patients under-

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going curative esophagectomy without or with low nodal involvement [2]. This study was conducted to evaluate the outcome of patients undergoing esophagectomy for esophageal cancer at a tertiary hospital and to define prognosticators for long term survival.

Methods

The study was approved by the Hospital's Human Clinical Research and Ethics Committee at University Hospital of Patras (194/19.05.2020). All patients gave informed consent prior to surgery and every procedure was performed according to the rules of good clinical practice.

Patients' data

Data of 92 patients who underwent esophagectomy for esophageal carcinoma over a 20 year period (1998 to 2017) were retrospectively evaluated (Table 1). The diagnosis of esophageal carcinoma was carried out via esophagoscopy and biopsy of the lesions. Indications for surgery included localized or regional disease without evidence of metastatic involvement. The preoperative work up consisted of chest and abdominal computed tomography, echocardiography and lung function testing. During the last 2 years of the study all patients planned for surgery also underwent positron emission/computed tomography (PET/CT). Fifteen patients received preoperative nutritional support by either enteral or parenteral feeding. Six patients were operated after chemotherapy or chemoradiotherapy. Two patients had induction chemotherapy within a multidisciplinary treatment protocol. Four patients underwent salvage esophagectomy; two patients failed to respond to definitive chemoradiotherapy and the other two presented with persistent hematemesis. Sixty one patients received adjuvant therapy as shown in Table 1.

Surgical technique and postoperative management

The data regarding the surgical approaches are shown in Table 2. In some patients the proximal extent of the tumor required a more aggressive approach. In the Ivor-Lewis esophagectomy group there were 2 patients with the anastomosis performed at the neck. In the group of patients treated with left thoracoabdominal incision 8 patients needed full mobilization of the upper thoracic esophagus behind the aortic arch and posterior to the subclavian artery via an additional access at the 5th intercostal space; the anastomosis was carried out either above the arch (3 patients) or at the neck (5 patients). All patients requiring neck anastomosis had a left cervical incision added to the procedure. For upper gastrointestinal reconstruction a gastric conduit was used in the vast majority of the cases. A 26 to 28 mm circular stapler was used in all anastomoses fashioned inside the chest; a hand sew technique was preferred in all neck reconstructions. Two-field lymphadenectomy was performed in all patients.

In the immediate postoperative period all patients remained nil per mouth and were treated with antibiot-

Table 1. Patient data

Parameters	*No of patients n (%)*
Gender	
Male	75 (81.5)
Female	17 (18.5)
Age (years)	
Mean	65.5 ± 11.6
Median	66
Range	38-86
Clinical presentation	
Dysphagia-odynophagia	92 (100)
Difficulty in swallowing	45 (48.9)
Weight loss (> 10 g)	22 (23.9)
Anemia (Hb < 10 g/dl)	6 (6.5)
Retrosternal pain	3 (3.3)
Hematemesis	2 (2.2)
Localization	
Gastroesophageal junction	52 (56.5)
Lower third	31 (33.7)
Middle third	9 (9.8)
Histology	
Adenocarcinoma	73 (79.3)
Squamous cell carcinoma	19 (20.7)
Differentiation (grade)	
High	7 (7.6)
Medium	58 (63.0)
Low	27 (29.4)
Stages (AJCC 8th edition)	
0	3 (3.3)
IB	7 (7.6)
IC	3 (3.3)
IIA	1 (1.1)
IIB	7 (7.6)
IIIA	2 (2.2)
IIIB	28 (30.4)
IV / IV (M1 positive)	41 / 7 (44.6/7.6)
Early (stages 0-II)	21 (22.8)
Advanced (stages III-IV)	71 (77.2)
Lymph nodes	
N0	20 (21.7)
N1	16 (17.4)
N2	23 (25)
N3	33 (35.9)
No.of resected lymph nodes	
Mean	17.2 ± 4.5
Median	18
Range	7-38
Lymph node ratio	
0-0.2	45 (48.9)
0.21-0.5	24 (26.1)
>0.5	23 (25)
Preoperative therapy vs Adjuvant therapy*	
Preoperative therapy	6/92 (6.5)
Adjuvant chemotherapy	47/82 (57.3)
Adjuvant chemoradiotherapy	14/82 (17.1)
Long term outcome (82 patients)	
Survived	10 (12.2)
Deceased	72 (87.8)

* 8 patients, (two stageIIB-N1 and 6 advanced stage tumors) refused adjuvant therapy

Table 2. Surgical approaches

Tumor location	*Surgical approach*		*Reconstruction*	
	Left thoracoabdominal	*Ivor-Lewis*	*Gastric tube*	*Colon*
Gastroesophageal junction	49	3	52	
Lower third	27	4	31	2 (Ivor-Lewis)
Middle third		9	9	

ics, bronchodilators, prokinetic agents, analgesics and prophylactic low molecular weight heparin. Oxygen supplementation with a Venturi mask at a fraction of inspired oxygen of 40% was administered in all patients. A nasogastric tube was used for decompression until recovery of gastrointestinal function was achieved. Postoperative immunonutrition was provided by either a nasojejunal feeding tube or a surgically fashioned jejunostomy at the time of surgery. Chest x-rays took place in the 1st, 3rd and 5th postoperative days. An upper gastrointestinal contrast swallow study was performed in the 6th or 7th postoperative day. If normal, oral feeding was started and the chest tubes were removed thereafter.

End points of the study and follow up

The end points of the study were 30 day mortality, morbidity and long-term survival. All patients were followed up with chest and abdominal computed tomography and esophagogastroscopy every 6 months for the first 3 years and annually thereafter. Imaging and endoscopic studies were performed earlier than scheduled if needed. Additional information regarding the postoperative treatment of the patients and their final outcome were also obtained by the databases of the departments of medical oncology and radiotherapy. The follow up was concluded in December 2019.

Predictors for survival

The evaluated prognostic factors for long term survival included gender, location and histology of the tumor, grade of differentiation, early versus advanced stage disease and nodal status. Early-stage tumors comprise those without (N0) or with minimal (N1) nodal involvement (stages 0-II) while advanced-stage disease refers to stages III and IV. The nodal status was evaluated both as nodal positivity (N0 versus N+ tumors) and lymph node ratio (0-2 versus 0.21-0.5 versus > 0.5).

Statistics

Statistical analyses were performed using the IMB SPSS software (version 25.0; IBM SPSS Statistics for Windows, Armonk, NY). Values for continuous data are presented as mean ± standard deviation, median and range. Kaplan-Meier life table analysis was performed and the long rank test was used to evaluate the effect of the variables examined on the long-term survival. The Cox proportional hazard model was applied to identify the concurrent effects of the prognosticators on the long-term outcome of the patients. P values <0.05 were considered statistically significant.

Table 3. Complications and mortality

Complications	*No of events*
Anastomotic dehiscence /leak	16
Gastric conduit necrosis	1
ARDS	1
Pulmonary embolism/ cardiac arrest	1
Aspiration-pneumonia- respiratory insufficiency	8
Sputum retention/atelectasis	3
Atrial fibrillation	8
Wound infection	2
Chylothorax	2
Delayed gastric emptying	4
Gastroparesis	3
Total	49
Cause of death	*No of patients*
Anastomotic dehiscence	6
Gastric conduit necrosis/perforation	1
ARDS	1
Pulmonary embolism/ cardiac arrest (early postoperative death)	1
Aspiration-pneumonia- sepsis- respiratory insufficiency	1
Total	10

Results

Early postoperative outcome

A total of 49 complications (Table 3) were recorded in 29 out of the 92 patients (31.5%); 15 patients presented more than one complications. The perioperative mortality was 10.9%; the causes of death are shown in Table 3. Anastomotic dehiscence/leak occurred in 16 patients (17.4%) and it was the most frequent among postoperative complication (32.7%); an uncontained anastomotic dehiscence also was the most frequent cause of death (6 out of the 10 deaths, 60%). Reoperation was necessary in 14 patients. Eleven patients with uncontained anastomotic rupture and one patient with gastric conduit necrosis and perforation underwent upper GI bipolar exclusion and cervical

esophagostomy (8 patients), primary repair of the perforation (3 patients) and resection and reconstruction of the anastomosis (1 patient). Two patients required ligation of the thoracic duct for chylothorax. Additionally one patient had an intrathoracic leak and right side empyema treated by chest tube thoracostomy converted to an open empyema tube after 4 weeks of antibiotic treatment. Finally 4 patients presented with small/contained leaks at the esophagogram performed after surgery and were treated conservatively; the leaks sealed spontaneously within 7 to 14 days. Intensive Care Unit recovery was necessary in 15 patients. Nine of them are included among those succumbed with the final cause of death being sepsis and multi-organ failure. The mean postoperative stay was 17±16 days (range 2 to 104 days).

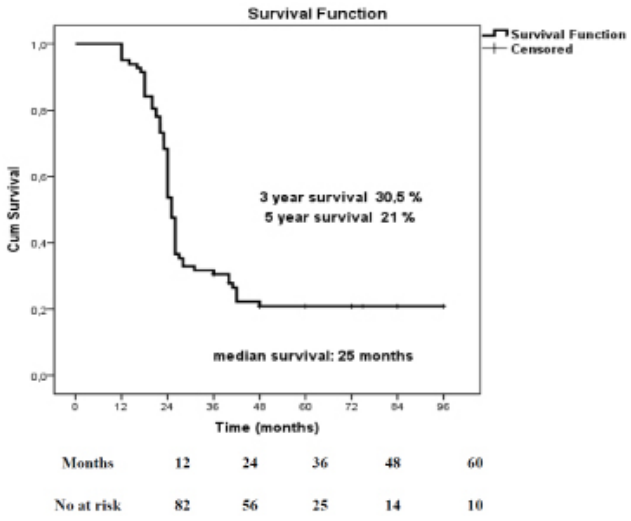

Figure 1. Cumulative overall survival (82 patients).

Long term outcome

By the end of follow up 72 out of the 82 patients surviving surgery had died. The study group for long term survival included 19 patients (23.2%) with early stage tumors and 63 patients (76.8%) with advanced stage disease. The cause of death was cancer related in 67 patients. The median survival for the 82 patients was 25 months while the overall 3 and 5 year cumulative survival reached 30.5% and 21% respectively (Figure 1). Patients with early stage disease and those without any nodal involvement exhibited median survival of 60 months. A median survival of 66 months was recorded among patients with well differentiated tumors. The 3 and 5 year survival was significantly better in patients with early stage carcinomas (3 year: 100% vs 9.5%, 5 year: 82.6% vs 1.9% at 48 months, p<0.001) (Figure 2A). Similarly the probability for long term survival was much better in patients with well differentiated tumors (3 year: 83.3% vs 25% vs 29.2%; 5 year: 83.3% vs 13.6% vs 20.8%, p=0.016) and in those tumors that didn't show any nodal involvement in the final pathological report (3 year: 100% vs 9.5%, 5 year: 81.6% vs 3.2% at 48 months, p<0.001) (Figures 2B and 3A). The 3 and 5 year survival for lymph node ratio of 0-0.2 was 57.5% and 40.4% respectively and it was better than the cumulative survival for lymph node ratios of 0.21-0.5 (3 year: 9.5% and 4.8% at 48 months) and > 0.5 (2 year: 9.5% and 0% at 26 months); the difference was statistically significant

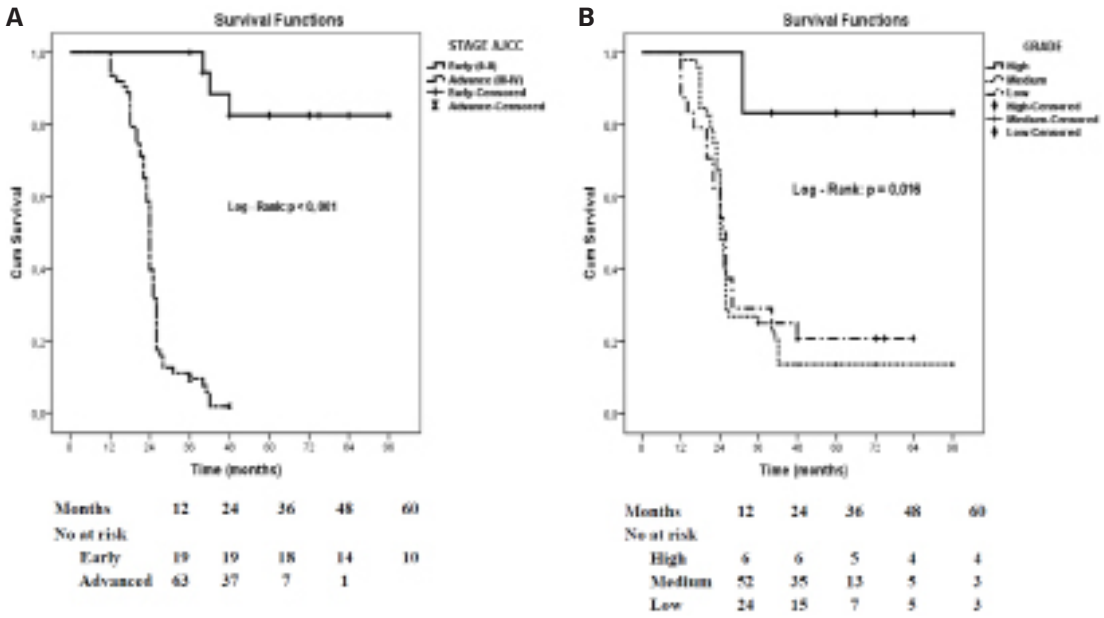

Figure 2. Effect of tumor's stage **(A)** and grade of differentiation **(B)** on long-term survival.

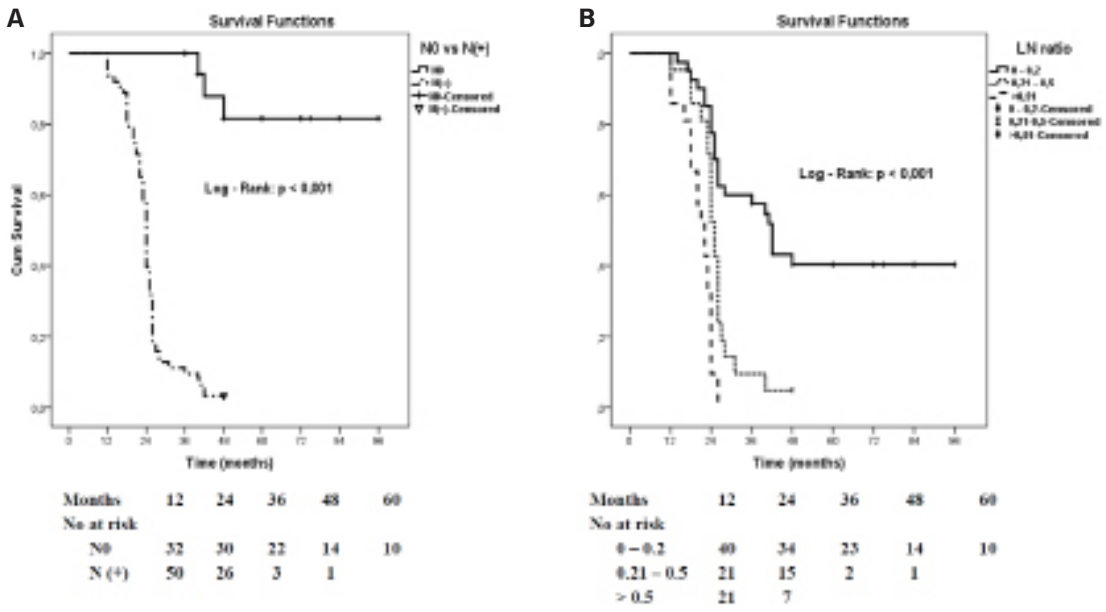

Figure 3. Effect of nodal status (N negative vs N positive tumors - panel **A** and lymph node ratio- panel **B**) on long term survival.

Table 4. Univariate (Kaplan-Meier) and Multivariate (Cox Regression) analysis of predictors of long term survival

Variables	*Kaplan-Meier*	*Cox regression*	
	p value	*OR (95% CI)*	*p value*
Tumor stage (Early vs Advanced)	<0.001	15.746 (4.332-58.579)	<0.001
Grade	0.016	1.100 (0.680-1.779)	0.699
N0 vs N (+)	<0.001	0.986 (0.417-2.328)	0.974
LN Ratio	<0.001	1.700 (1.051-2.752)	0.031

(p<0.001) (Figure 3B). The Cox proportional hazard model identified tumor stage (odds ratio 15.746, 95% CI: 4.332-58.579, p<0.001) and lymph node ratio (odds ratio 1.700, 95% CI: 1.051-2.752, p=0.031) as the only independent predictors for long-term survival (Table 4).

Discussion

In the current scientific report we present the results of surgery, mainly as primary treatment, for esophageal carcinoma in a mixed stage group of patients. The most common surgical approach was left thoracoabdominal esophagectomy (82.6%) which is excellent for the resection of tumors of the gastroesophageal junction and lower part of the thoracic esophagus. Additionally it's a procedure that allows, with an additional entry at the 5th intercostals space, the full mobilization of the esophagus behind and above the aortic arch in order to achieve safe resection margins even for tumors with proximal/cranial extension [3]. All Ivor-Lewis esophagectomies were performed for middle esophageal tumors for better and safer control of the carina during tumor mobilization. Both types of surgery can be supplemented with an additional neck incision in case a neck anastomosis should be fashioned.

At least one morbidity event occurred in 31.5% of the patients while the mortality reached 10.9%; the former is similar while the latter is higher than the respective values reported by The Society of Thoracic Surgeons General Thoracic Surgery Database [4]. However, in a previous study from the same Database the mortality was strongly related to the severity of postoperative complication reaching up to 11% among patients suffering of major morbidity [5]. The most common complication was anastomotic dehiscence/leak (17.4%) which is within the range reported in the literature including series of minimally invasive approaches [6,7]. Three out of four of these events were considered to be major morbidity. Though the anastomotic leak was the most common cause of death (60%)

the mortality related to its occurrence was 37.5% which is also within the range reported by previous studies [6]. Its management is challenging and should be carried out after thorough evaluation case by case. Small leaks clinically silent or with minor clinical signs can be treated conservatively or with the placement of an esophageal stent and may seal spontaneously, while larger ones, conduit necrosis and severe sepsis, irrespective of the size of disruption of the anastomosis, require reoperation for surgical debridement, primary repair, anastomotic revision or esophageal bipolar exclusion and cervical esophagosotomy as in most cases of anastomotic leak in the current series [8]. Endoluminal stenting has been shown to be effective in the management of anastomotic leaks after esophagectomy with success rate of 72-75%; the reported mean mortality is 15% while the rate of death for surgical repair, although reported to be between 3.3% and 11.6%, may be as high as 50% [9,10]. Its main advantage is the early resumption of oral feeding and maybe a lower length of stay. Alternatives to endoluminal stenting in the field of conservative treatment include endoscopic vacuum therapy, endoscopic clips and sealants and more recently endoscopic overstitch devices and sponge over a stent.

In the current series 77.2% of the patients were classified as having advanced stage disease. During the study period there have been modifications in the AJCC staging system for esophageal cancer leading to the 8th edition and the upstaging of many of the tumors. Moreover, the lack of novel staging techniques currently incorporated in the staging of these tumors has limited our preoperative knowledge on the exact extent of the disease. Similar comments were made by Saddoughi et al [11] in their report on the surgical management of stage IV esophageal carcinomas. The current evidence does not support the role of surgery in metastatic stage IV neoplasms and there is clear shift in treatment paradigm with evaluation of the patients with locally advanced non metastatic stage disease within multidisciplinary treatment protocols [12]. The 5 year cumulative survival for the group of 82 patients was 21% which is comparable with the 5 year survival rate reported in a recent SEER database analysis regarding the trends in survival of patients with esophageal cancer [1]. Nevertheless, the cumulative 5 year survival reached 82.6% among patients with early stage disease consisting in tumors without or with low nodal involvement. Most of them presented N0 tumors with 5 year survival of 81.6%. The long term outcome in this specific subgroup of patients is better than the one reported by Semenkovich et al in two different reports on the management of stages T1,N0 and T2,N0 tumors undergoing upfront surgery for esophageal carcinomas [13,14]. Moreover, in a multicenter randomized trial comparing long term outcome after hybrid minimally invasive and open esophagectomy, where 96% of the patients presented with N0/N1 disease and the rate of induction treatment was 74%, the 5 year overall survival and the disease free survival were 60% and 40%, and 53 % and 43% respectively [2]. Apart the nodal status itself we found that the pathological lymph node ratio was a prognosticator for survival; patients with ratio up to 0.2 showed 5 year survival of 40.4% which was better that the survival for patients with ratios of 0.21-0.5 and > 0.5. The lymph node ratio was an independent factor associated with the long term outcome (Odds ratio 1.700, CI 95%: 1.051-2.752, p=0.031). Although a specific cutoff point for pathological lymph node ratio has not been clearly defined, in a literature base pooled analysis of the data from 18 different studies Zhao et al [15] reported that, irrespective of the cutoff point used, higher lymph node ratios are significantly associated with poorer long term survival in esophageal carcinomas. Finally, in the current series of patients, tumor grade was statistically associated with long term survival in univariate analysis; patients with well differentiated esophageal cancers had 5 year survival of 83.6% (Figure 2B). However, tumor's differentiation as a predictive factor was lost in multivariate analysis indicating a more prominent role of the stage and nodal status on the long-term outcome of these patients.

The present study suffers of the high percentage of patients operated for esophageal cancer having an advanced stage of disease and the relatively high mortality and morbidity. Despite the fact that tumors in stage 0-II represented 22.8% of all patients operated and 22.3% of those available for the evaluation of long-term outcome, and on the basis of a long follow up period, there is clear evidence to support the role of upfront esophagectomy as the treatment of choice for early stage esophageal carcinomas without or with low nodal involvement [16, 17]. This makes clear the need for screening protocols among high risk patients for the early diagnosis of esophageal cancer and highlights the need for appropriate patient selection for primary surgery based on thorough preoperative staging and work up [18].

Conflict of interests

The authors declare no conflict of interests.

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