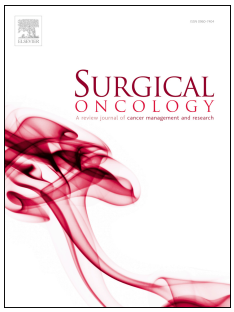

Pre- and postoperative prognostic factors for resectable esophageal adenocarcinoma

Pedro Serralheiro, Adeline Rankin, Allan Clark, Daniel Holyoake, Edward Cheong

PII: S0960-7404(20)30377-7

DOI: https://doi.org/10.1016/j.suronc.2020.08.026

Reference: SO 1436

To appear in: *Surgical Oncology*

Received Date: 27 October 2019

Revised Date: 22 May 2020

Accepted Date: 19 August 2020

Please cite this article as: Serralheiro P, Rankin A, Clark A, Holyoake D, Cheong E, Pre- and postoperative prognostic factors for resectable esophageal adenocarcinoma, *Surgical Oncology* (2020), doi: https://doi.org/10.1016/j.suronc.2020.08.026.

Pre- and postoperative prognostic factors for resectable esophageal adenocarcinoma

Authors

Pedro Serralheiro[1], Adeline Rankin[2], Allan Clark[3], Daniel Holyoake[4], Edward Cheong[2].

Affiliations

1. Faculty of Health Sciences, CICS-UBI-Health Sciences Research Centre, University of Beira Interior, 6201-506 Covilhã, Portugal. p.serralheiro@gmail.com

2. Department of Upper Gastrointestinal Surgery, Norfolk & Norwich University Hospital, Colney Lane Norwich NR4 7UY, UK. ADELINE.RANKIN@nnuh.nhs.uk, EDWARD.CHEONG@nnuh.nhs.uk

3. Norwich Medical School, University of East Anglia, NR4 7TJ Norwich, UK. ALLAN.CLARK@uea.ac.uk

4. Department of Oncology, Norfolk & Norwich University Hospital, Colney Lane Norwich NR4 7UY, UK. DANIEL.HOLYOAKE@nnuh.nhs.uk

Corresponding author

Pedro Azevedo Serralheiro, MD, PhD

Assistant Professor

Consultant Upper Gastrointestinal Surgeon

Faculty of Health Sciences, CICS-UBI-Health Sciences Research Centre, University of Beira Interior, 6201-506 Covilhã, Portugal

p.serralheiro@gmail.com

Tel: +351275329002

Running head

Prognosis of esophageal adenocarcinoma

Author's contributions

All authors provided scientific input, drafted the manuscript, and approved the final version.

Financial support

None

Highlights

- Single-centre study of 254 patients with esophageal adenocarcinoma.
- Pre and postoperatively variables models were studied for prognostication.
- Histopathological N-stage and tumor length were good prognostic factors.
- Age and preoperative radiological staging, were not associated with prognosis.
- Histopathological T-stage may be of less importance for prognostication.

Abstract

Background: Prognostication for esophageal cancer has traditionally relied on postoperative tissue specimens. This study aimed to use a histologically homogenous cohort to investigate the relationship between clinical, pathological or radiological variables and overall survival in patients undergoing esophagectomy for adenocarcinoma.

Methods: A single-centre study of patients who underwent esophagectomy for adenocarcinoma over 10 years in a tertiary centre was performed. By regression analysis, variables available preoperatively and postoperatively were studied for prognostication. The primary outcome was overall survival.

Results: 254 cases were analyzed. Over a median follow-up period of 31.8 months (IQR=42.5), overall survival was 51.5 months (95% confidence interval: 33.0-69.9). According to hazard ratios (HR) for all-cause death, adverse prognostic factors included: a higher postoperative N-stage (HR≥1.29; p≤0.024), histopathological tumor length ≥25mm (HR=2.04; p=0.03), poorer tumor differentiation (HR≥2.86; p≤0.042), and R1 status (HR=2.33; p=0.02). A lymph node yield ≥35 was a favorable prognostic factor (HR=0.022; p<0.001). Demographic and radiological variables, preoperative TNM stages, postoperative T-stage, and neoadjuvant/adjuvant treatment were not associated with overall survival.

Conclusions: This study identifies several postoperatively factors which are available for the prognostication and identifies factors that should not be used to exclude patients from curative surgery.

Keywords: esophagus, adenocarcinoma, prognosis, esophagectomy

1- Introduction

Esophageal cancer is the eighth most common malignancy worldwide, with an annual incidence of 450 000 cases, and is the sixth leading cause of cancer-related mortality with more than 400 000 deaths annually[1]. Surgery is central to curative treatment of esophageal cancer, although only up to 50% of patients are suitable for curative treatment[1]. The remainder are often offered either palliative or best supportive treatment, which may involve chemotherapy, radiotherapy, immunotherapy or esophageal stenting. The 5-year overall survival (OS) is currently estimated at 15%, but can range from 40% (in localized cancer treated with curative intent) to as low as 5% (in unresectable disease)[2]. Currently, the prognosis for patients with esophageal cancer largely relies on postoperative histopathology and has been criticized as being inadequate for prognostication at the pre-treatment stage[3].

Cross-sectional imaging is routinely used for diagnosis, staging and prognosis of esophageal cancer. Positron emission tomography with computed tomography (PET-CT) is increasingly used for preoperative staging to assess for distant metastatic disease and it adds information on tumor metabolic activity[4].

In a previous work on a histologically heterogeneous cohort of 229 cases, our group concluded that both tumor length and SUV_{max} on pre-treatment PET-CT were associated with OS[5]. However, esophageal adenocarcinoma (OAC) and esophageal squamous cell carcinoma (SCC), which are the most common types of

esophageal cancer, are separate diseases in terms of epidemiology, anatomical location and natural history, with implications on treatment[6]. In the current study, we sought to re-examine the above association, along with other clinicopathological variables, in a histologically homogeneous cohort.

2 - Methods

A retrospective observational study was performed. Patients who underwent esophagectomy at a single tertiary unit (the Norfolk & Norwich University Hospital, Norwich, United Kingdom) over a 10-year period (March 2007 - March 2017) were identified from local records. This was facilitated by the general electronic hospital database and the data collection was performed by the authors. Patients were included if they had undergone elective esophagectomy (either open, minimally invasive, or hybrid) for cancer with curative intent.

The exclusion criteria were patients without a pre-treatment PET-CT, without a reported tumor length on PET-CT, with a tumor type other than OAC and submitted to palliative surgery. Patients who died within 30 days postoperatively were also excluded, in order to minimize the influence of early postoperative death due to non-oncological causes.

The variables of interest were categorized into those which are available to the multidisciplinary teams (MDT) preoperatively, and those which become available

postoperatively. Preoperative variables included age, sex, neoadjuvant treatment status, tumor length (TL) and maximal standardized radioisotope uptake value (SUV_{max}) on PET-CT, and tumor-node-metastasis (TNM) stage. Postoperative variables included histopathological tumor length, number of lymph nodes retrieved, tumor differentiation (poor versus moderate/well differentiated), pTNM stage, resection radicality (R status), and adjuvant therapy status. The primary outcome was OS. All pathological specimens were pinned down on a plaque prior histological fixation which allowed a comparison of tumour length measurements.

2.1 - Staging

Standard staging practice for OAC at the Norfolk & Norwich University Hospital (NNUH) involves endoscopy with biopsy, thoraco-abdomino-pelvic CT scan, and PET-CT scan for all patients. All images are reviewed by an upper gastro intestinal expert radiographer in MDT. In cases of liver lesions which are not PET-avid, magnetic resonance imaging (MRI) of the liver is performed. Endoscopic ultrasonography (EUS) is employed for patients where a distinction between T4a and T4b tumors is required. Patients with T4b do not undergo curative resection at the NNUH. Patients with Siewert type-2 and type-3 tumors also undergo laparoscopic staging. During the study period, the NNUH Esophageal Cancer MDT followed the 6^{th} and 7^{th} editions of the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumours[7, 8]. The TNM staging data used

for analysis were collected from the local MDT consensus electronic database and were reclassified to meet the 7th edition TNM criteria.

2.2 - Analysis

Statistical analysis was performed using IBM SPSS v.25 and STATA. Normally distributed variables are expressed as means with standard deviation. Non-normally distributed variables are expressed as medians with interquartile range (IQR). Cox regression analysis was performed to investigate for relationships between variables of interest and OS (calculated from the date of surgery to the date of death). Three separate Cox regression analyses were performed: 1) using an unadjusted model which included all variables of interest, 2) using only preoperative variables (preoperative model), and 3) using variables which are only available postoperatively (postoperative model). Strongly inter-related variables were excluded from regression modeling.

This retrospective study was based on data collected and available as part of routine clinical practice and did not involve any deviations from the standard of care. For the purposes of this study, data were anonymized. Formal ethical approval was therefore not requested, nevertheless data collection was registered and reviewed by the local institutional review board.

3 - Results

345 patients who underwent esophagectomy for cancer at the NNUH between March 2007 and March 2017 (inclusive) were screened for eligibility. Forty patients were excluded as they either did not have an available pre-treatment PET-CT (28), or the tumor length on pre-treatment PET-CT was not reported (12). Five patients were excluded as they had died within 30 postoperative days. Forty-six patients were excluded as their tumor type was preoperatively diagnosed as other than adenocarcinoma. The analysis was performed on a cohort of 254 patients, and follow-up was censored on the 30th of August 2018. Figure 1 presents the study flowchart.

3.1 - Preoperative variables

The median age at time of diagnosis was 67.0 years (interquartile range [IQR]= 12.0 years). Most patients (n=211; 83.1%) were male. 81.5% (n=207) of patients received neoadjuvant treatment. The mean tumor length on pre-treatment PET-CT was 40.8mm (standard deviation [SD]=26.1mm), and the mean SUV_{max} was 10.1 (SD=8.8). A detailed report of preoperative variables, including staging parameters, is presented in Table 1.

3.2 - Postoperative variables

Following esophagectomy, the mean histopathological tumor length was 31.5mm (SD=20.0mm), and in 21 cases (8.3%) there was complete pathological

response to treatment. The mean number of lymph nodes retrieved was 25.8 (SD=12.5). The mean number of lymph nodes positive for malignancy was 2.2 (SD=3.9), and the mean positive-to-total lymph node ratio (LNR) was 0.086 (SD=0.139). These variables, along with tumor differentiation, stage, resection radicality and adjuvant therapy status are presented in Table 2.

3.3 - Survival analysis

The median follow-up period was 31.8 months (IQR=42.5 months), during which 134 patients (52.8%) died. The median estimated OS by Kaplan-Meier analysis was 51.5 months (95% confidence interval [CI]: 33.0-69.9 months; Figure 2).

In the unadjusted Cox regression model, the hazard ratio (HR) for all-cause death was significantly increased (i.e. OS was significantly reduced) in cases with a histopathological tumor length of ≥25mm, poorer tumor differentiation, increasing postoperative T and N stages, and in patients who underwent adjuvant radiotherapy or with resection margins which were microscopically positive for malignancy (i.e. R1). Demographics, neoadjuvant therapy, PET-CT variables (TL and SUV_{max}), pre-treatment T and N stage, number of lymph nodes retrieved, and adjuvant chemotherapy were not associated with a significantly reduced or increased HR. Detailed results of the unadjusted analysis are presented in Table 3.

In the adjusted preoperative model, the only factor significantly associated with OS was a tumor SUV_{max} of 15 or more (HR=0.55; 95%CI=0.33-0.91; p=0.02).

In the adjusted postoperative model, OS was significantly associated with the number of lymph nodes retrieved ≥35 (i.e. lymph node yield [LNY]; HR=0.22; 95%CI=0.11-0.44; p<0.001), a histopathological tumor length of ≥25mm (HR=2.04; 95%CI=1.07-3.89; p=0.03), histopathological lymph node positivity (HR_{N1}=1.9; HR_{N2}=3.09; HR_{N3}=4.7; p<0.025 in all cases), and with R1 status (HR=2.33; 95%CI=1.38-3.94; p=0.002). In this model, there was no significant association between OS and sex, age, chemotherapy, radiotherapy, PET-CT variables, and postoperative T-stage. Table 4 presents the results of both adjusted models.

4 - Discussion

This study evaluated several clinicopathological variables in relation to OS for patients with resectable OAC. As mentioned in a recent review on staging, prognosis has been largely based on postoperative pathological findings, and has been criticized as being inadequate for patients at the pre-treatment stage or for those undergoing multimodal treatment[3]. The current study aimed to identify both preoperatively and postoperatively prognostic factors which are relevant to the decision-making process. It was noted that, taking into account the factors that were studied, it is still very difficult to accurately prognosticate this disease on a preoperative setting. This is due, most likely, to a great disparity of cancer biological behaviors and responses to neoadjuvant therapies.

The two main histological subtypes of esophageal cancer, SCC and OAC, have been identified as socioeconomically, anatomically, and biologically different diseases, with implications on treatment strategies and prognosis[6]. Therefore, and further to previous work from our group[5], patients with histological subtypes other than OAC were excluded from this study, in order to reduce heterogeneity.

The median estimated OS (51.5 months) was achieved most certainly due to all patients included in the study having had a full oncological resection intention, where none of them had a palliative surgical procedure. In addition, the mean number of lymph nodes retrieved was 25.8 and only 15.7% of patients had R1 resections.

4.1 - Demographic variables

The demographic variables of age and sex were not associated with OS in any of the three regression models. This is in keeping with the results published by *Bus et al.[9]*, *who* performed a population-based study and analyzed a heterogeneous cohort (OAC: 62%; SCC: 37%) of 703 patients. Their multivariable regression analysis determined that age was not independently associated with 1-year, 3-year or 5-year survival. Although sex was not associated with 1-year or 3-year survival, it was associated with 5-year survival. Specifically, female patients were more likely to be alive at 5 years after diagnosis, with an odds ratio for death of 0.56 vs. men[9]. The median follow-up period in our study was less than 3 years (31.8 months), which may account for the fact that sex was not identified as a predictor

of OS. On this basis, it could be concluded that, within the range observed in this study, age per se should not be a contraindication to curative surgery, or multimodal treatment for resectable OAC.

4.2 - Radiological variables

The potential role of PET-CT in identifying patients for curative vs. palliative treatment was reported in a small cohort (n=82), including the following variables: tumor length, SUV_{max}, and the length-SUV index (tumor length x SUV_{max})[10]. Although the authors conclude that tumor length on PET-CT is associated with OS[10], the proportion of patients with OAC in this cohort is not specified. In our previous heterogeneous cohort, PET-CT tumor length was associated with OS[5], which is in keeping with the conclusions mentioned by *Roedl et al[10].* Our current analysis on a homogeneous OAC cohort however, did not demonstrate an association PET-CT tumor length and OS. This may be due to a more aggressive behavior of longer esophageal SCC when compared to OAC or the fact that SCC tumors present less response variability with neoadjuvant treatment.

SUV_{max} is a standard measure of radioisotope (18F-fluorodeoxyglucose; 18F-FDG) uptake by esophageal tumor and represents metabolic activity[4]. It is defined as the activity concentration in tissue divided by the activity injected per unit body weight[4]. With regards to SUV_{max} and survival, the evidence[4, 5, 11, 12] appears to be conflicting. For example, in their study of 103 esophageal cancer patients (including 76 patients with OAC, and 25 patients with SCC) *Foley et al.[13]*

found SUV_{max} to be a significant factor in univariate, but not in multivariate analysis. They recognized that tumors such as adenocarcinoma yield lower SUV_{max} values, which may be responsible for the negative result[13]. Furthermore, the cohort examined by *Foley et al.* included 68 patients treated with curative intent and 35 treated with palliative intent. Our analysis identified SUV_{max} as predictor of OS only in the adjusted preoperative model. The reasons for this inconsistency are unclear but may involve less confounding factors on the preoperative model data when compared with the unadjusted model. Nonetheless SUV_{max} measurements are known to involve several pitfalls, such as a lack of standardization in their calculation, and variation in the timing of FDG administration[4]. Furthermore, PET-CT image reconstruction techniques can render lesions larger and less bright, thus leading to SUV_{max} underestimations[4].

4.3 - TNM staging

The Union for International Cancer Control (UICC) regularly publishes updates on the TNM (tumor-node-metastasis) Classification of Malignant Tumors, a widely implemented cancer staging tool. During the period of this study, the 6th, followed by the 7th edition of the UICC TNM Classification were used. The current (8th) edition was published in December 2016[14], approximately three months prior to the end of the study period.

The transitions from the 6th to the 7th, and subsequently to the 8th edition have resulted in changes of definitions and of criteria for using either the esophageal

cancer or gastric cancer schema depending on the epicenter and extent of the tumor[14]. By design, the T, N, and M stages should be reproducible and should allow stratification of patients into prognostic groups, whereby survival diminishes as the stage increases. In a validation study of the 7th edition, Talsma et al.[15] analyzed a cohort of 358 patients who underwent transhiatal esophagectomy for OAC. On univariate analysis, the authors concluded that pT, pN, and pM stages significantly predicted OS, and that the 7th edition provides superior prognostic stratification than the 6th edition[16]. The 7th edition[7] introduces subclassifications of T1 (i.e. T1a: Tumor invasion of the lamina propria or muscularis mucosae; T1b: Tumor invasion of submucosa), and a new N-stage (i.e. N3: metastasis in ≥7 regional lymph nodes).

The first significant observation in our cohort is that all patients had M0 stage, as patients with metastatic OAC do not undergo surgery with curative intent in NNUH. Also, although histologically homogeneous, our cohort was heterogeneous with respect to surgical approach, as patients may have either undergone a two-stage (Ivor Lewis) resection, a transhiatal resection, or a three-stage (McKeown) resection by either minimally invasive, hybrid, or open approaches (Table 2).

Within this context, the unadjusted regression model did not identify preoperative T-stage or N-stage as predictors of OS. This model however identified increasing postoperative T and N stages as negative predictors of OS. Specifically, patients with tumors of stage ≥T2, as well as those with stage ≥N1 had a greater

hazard ratio for all-cause death. In the adjusted preoperative model, staging was not associated with OS. In the adjusted postoperative model, pT stage was not associated with OS, yet pN stage was.

The safest conclusion that can be drawn from our TNM data is that pN stage is a predictor of OS in resectable OAC. This was statistically evident despite confounding which may have arisen from the introduction of N3 in the 7th edition of the TNM Classification. The fact that pT stage was seen as a predictor of OS in the unadjusted analysis but not in the more reliable adjusted analysis, may be due to confounding factors in the unadjusted analysis. It is also possible that pT may not be as good predictor of OS in OAC as in SCC. Although the 7th edition was based on a strong international evidence base, which included more than 7 800 patients with esophageal cancer, it has been noted that these databases were limited in granularity and by their retrospective nature[16]

4.4 - Neoadjuvant & adjuvant therapy

In the current cohort, most patients (78.7%) received neoadjuvant chemotherapy, a well-established treatment modality which confers a survival benefit to patients with resectable esophageal cancer[1, 17]. A small minority received chemoradiotherapy (2.8%). No patients received neoadjuvant radiotherapy alone. Neoadjuvant treatment was not associated with OS in any regression model, and neither was adjuvant chemotherapy. Conversely, adjuvant radiotherapy was a negative predictor of OS, but only in the unadjusted model. It is

worth noting here that only 15 patients received adjuvant radiotherapy and that all of these patients presented microscopically incomplete (R1) resections, therefore this (arguably) cannot be regarded as a reliable predictor based on this study. Neoadjuvant chemotherapy would be expected to increase OS. The absence of an observed association between neoadjuvant chemotherapy and OS may be due to the fact that most resections (85.3%) in this cohort were R0, with a relatively high mean LNY of 25.8, which may have decreased the positive effect valuation for this treatment. In addition, other implicated factor may have been that patients not submitted to neoadjuvant treatment generally presented earlier TNM stages (Table 1), being less likely that this cohort would benefit from neoadjuvant chemotherapy due to overall good prognosis.

In summary, this study has not identified neoadjuvant or adjuvant therapy as reliable predictors of OS in resectable OAC. Cohort size, staging differencesand good surgical outcomes may be responsible for the absence of associations. Frailty may also be a confounder, especially amongst patients who did not receive neoadjuvant therapy but proceeded directly to esophagectomy. Additionally, there may be variation in tumor biology which remains undetected, owing to the retrospective nature of this study. Finally, resection status may confound the relationship between adjuvant radiotherapy and OS, as this was administered to patients with microscopically incomplete (R1) resections.

4.5 - Histopathological variables

All four histopathological variables were associated with OS in at least one regression model.

LNY was not associated with OS in the unadjusted model, however a LNY of ≥35 was associated with OS in the postoperative model, with a HR of 0.22 when compared to a LNY <16. In a recent meta-analysis by Visser et al. a high LNY was identified as a positive prognostic factor for patients with esophageal cancer[18]. The authors recognized variation in the threshold between low and high LNY between studies and managed this heterogeneity by comparing the lowest to the highest LNY groups from each study[18]. They also recognize that although a high LNY enhances pathological staging, the therapeutic value of this practice is debatable[18]. Our findings would suggest that extended lymphadenectomy during esophagectomy is beneficial in terms of OS. In a recent international survey of experts by van Rijswijk et al.[19], Asian surgeons reportedly performed more extended cervical lymphadenectomies than their European colleagues. The authors highlighted the paucity of comparable data with regards to worldwide lymphadenectomy practice, in the context of various coexisting classification systems[19].

Histopathological tumor length was associated with OS both in the unadjusted, and in the adjusted postoperative models. Specifically, a tumor length of ≥25mm (vs. ≤15mm) carried a HR for all-cause death of 2.55 in the unadjusted model, and

2.04 in the postoperative model. These findings are in keeping with multiple previous studies[20-24], although most studies included patients with SCC. Longitudinal tumor growth along the esophageal submucosa has been implicated as a predisposing factor towards lymph node metastasis and the development of micrometastases[20], thereby reducing survival. Interestingly, *Rollins et al.[25]* identified that tumor length on PET-CT and histopathology were significantly correlated, with a Pearson r = 0.5977[25]. Given this correlation, we would expect to observe an association between PET-CT tumor length and OS in our study. The lack of any association may be related to the SUV_{max} calculation pitfalls mentioned above, which would suggest that tumor length on PET-CT is an unreliable predictor of OS in resectable OAC.

Tumor differentiation was associated with OS, albeit only in the unadjusted model. In this case, patients with well-to-moderately differentiated tumors and patients with poorly differentiated tumors had a HR for all-cause death of 2.86 and 4.28 respectively vs. patients with complete response to neoadjuvant therapy. Tumor differentiation was not included in the adjusted postoperative model due to a very strong association with postoperative T stage. In a univariate and multivariate analysis of a predominantly OAC cohort, *Griffiths et al.[21]* also found that a lesser degree of differentiation was associated with poorer survival.

A microscopically incomplete resection (R1) was associated with an all-cause death HR of 3.25 and 2.33 in the unadjusted and in the adjusted postoperative

models respectively. The impact of tumor differentiation and resection radicality on OS is expected and has been identified in previous studies[1, 21].

4.6 - Strengths and limitations

The main strength of this study is the relative homogeneity of its cohort, with regards to histological cancer subtype, consistent use of PET-CT, and a common treatment pathway. Furthermore, regression analysis was performed according to three different models, thus arguably reducing the probability of a type-1 error, since any associations which appear only in one model are interpreted cautiously.

The main limitation arises from the retrospective observational nature of this study and the relatively long study period of 10 years, during which surgical techniques and perioperative therapies are liable to evolve. Additionally, TNM staging has evolved and with the current study design it was not possible to ascertain which UICC TNM version was applied to each specific case. Ideally, with this knowledge, all cases could be retrospectively re-staged according to the latest version. In 2014, our centre implemented an ERAS (Enhanced Recovery After Surgery) protocol for all patients undergoing esophagectomy. Since ERAS involves standardization in patient preparation, and in the management of postoperative complications which may influence the timely progression to adjuvant treatment, this could have conceivably affected OS in a positive way for all patients. Finally, our dataset lacked the granularity required to accurately report cancer-related death or disease-free survival. The analysis therefore was focused on OS.

5 - Conclusions

This study analyzed 16 variables against OS in patients with resectable OAC. There was no clear association between demographic or radiological variables and OS, although a higher PET-CT tumor SUV_{max} predicted worse outcomes in an adjusted model. There was also no obvious association between neoadjuvant or adjuvant treatments and OS. Postoperative N-stage, and the histopathological variables of LNY, tumor length, differentiation and resection radicality were all associated with OS. In conclusion, we would recommend that the esophageal cancer MDT does not exclude patients from curative treatment on the basis of age, sex, or PET-CT parameters, and that the discussion surrounding prognosis focuses on postoperative histopathological variables.

Acknowledgments

This study was not preregistered in an independent institutional registry and did not receive any funding. The authors have no conflict of interest to declare.

We would like to thank Mr. Christopher Hadjittofi for his most valuable help in this project.

References

1. van Rossum PSN, Mohammad NH, Vleggaar FP, van Hillegersberg R: **Treatment for unresectable or metastatic oesophageal cancer: current evidence and trends**. *Nat Rev Gastroenterol Hepatol* 2018, **15**(4):235-249.

2. **Survival | Oesophageal cancer | Cancer Research UK. [online]** [https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/survival]

3. Rice TW, Gress DM, Patil DT, Hofstetter WL, Kelsen DP, Blackstone EH: **Cancer of the esophagus and esophagogastric junction-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual**. *CA Cancer J Clin* 2017, **67**(4):304-317.

4. Brown C, Howes B, Jamieson GG, Bartholomeusz D, Zingg U, Sullivan TR, Thompson SK: **Accuracy of PET-CT in predicting survival in patients with esophageal cancer**. *World J Surg* 2012, **36**(5):1089-1095.

5. Rankin A, Clarke A, Serralheiro P, Cheong E, Kumar B: **Longitudinal tumour length and maximum standardised uptake value (SUV) on PET scan are important predictors of survival in oesophageal carcinoma**. *British Journal of Surgery* 2017, **104**(S7 - Abstracts of the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, 20th Annual Scientific Meeting, 21–22 September 2017):5-68.

6. Siewert JR, Ott K: **Are squamous and adenocarcinomas of the esophagus the same disease?** *Semin Radiat Oncol* 2007, **17**(1):38-44.

7. Sobon LH, Gospodarowicz MK, Wittekind C: **TNM Classification of Malignant Tumours - International Union Against Cancer**, 7th edn. New York, USA: John Wiley & Sons; 2011.

8. Sobon LH, Wittekind C: **TNM Classification of Malignant Tumours - International Union Against Cancer**, 6th edn. New York, USA: John Wiley & Sons; 2002.

9. Bus P, Lemmens VE, van Oijen MG, Creemers GJ, Nieuwenhuijzen GA, van Baal JW, Siersema PD: **Prognostic factors for medium- and long-term survival of esophageal cancer patients in the Netherlands**. *J Surg Oncol* 2014, **109**(5):465-471.

10. Roedl JB, Sahani DV, Colen RR, Fischman AJ, Mueller PR, Blake MA: **Tumour length measured on PET-CT predicts the most appropriate**

stage-dependent therapeutic approach in oesophageal cancer. *Eur Radiol* 2008, **18**(12):2833-2840.

11. Fathinul Fikri AS, Dharmendran R, Vikneswaran P, Nordin AJ: **18F-FDG PET/CT as a potential predictor of survival in patient with oesophageal cancer: a preliminary result**. *Abdom Imaging* 2015, **40**(6):1457-1464.

12. Hatt M, Visvikis D, Albarghach NM, Tixier F, Pradier O, Cheze-le Rest C: **Prognostic value of 18F-FDG PET image-based parameters in oesophageal cancer and impact of tumour delineation methodology**. *Eur J Nucl Med Mol Imaging* 2011, **38**(7):1191-1202.

13. Foley KG, Fielding P, Lewis WG, Karran A, Chan D, Blake P, Roberts SA: **Prognostic significance of novel (1)(8)F-FDG PET/CT defined tumour variables in patients with oesophageal cancer**. *Eur J Radiol* 2014, **83**(7):1069-1073.

14. Brierley JD, Gospodarowicz MK, Wittekind C: **TNM Classification of Malignant Tumours - International Union Against Cancer**, 8th edn. UK: Wiley-Blackwell; 2017.

15. Talsma K, van Hagen P, Grotenhuis BA, Steyerberg EW, Tilanus HW, van Lanschot JJ, Wijnhoven BP: **Comparison of the 6th and 7th Editions of the UICC-AJCC TNM Classification for Esophageal Cancer**. *Ann Surg Oncol* 2012, **19**(7):2142-2148.

16. Rusch VW, Rice TW, Crowley J, Blackstone EH, Rami-Porta R, Goldstraw P: **The seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Staging Manuals: the new era of data-driven revisions**. *J Thorac Cardiovasc Surg* 2010, **139**(4):819-821.

17. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, Gebski V, Australasian Gastro-Intestinal Trials G: **Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis**. *Lancet Oncol* 2011, **12**(7):681-692.

18. Visser E, Markar SR, Ruurda JP, Hanna GB, van Hillegersberg R: **Prognostic Value of Lymph Node Yield on Overall Survival in Esophageal Cancer Patients: A Systematic Review and Meta-analysis**. *Ann Surg* 2019, **269**(2):261-268.

19. van Rijswijk AS, Hagens ERC, van der Peet DL, van Berge Henegouwen MI, Gisbertz SS: **Differences in Esophageal Cancer Surgery in Terms of**

Surgical Approach and Extent of Lymphadenectomy: Findings of an International Survey. *Ann Surg Oncol* 2019, **26**(7):2063-2072.

20. Eloubeidi MA, Desmond R, Arguedas MR, Reed CE, Wilcox CM: **Prognostic factors for the survival of patients with esophageal carcinoma in the U.S.: the importance of tumor length and lymph node status**. *Cancer* 2002, **95**(7):1434-1443.

21. Griffiths EA, Brummell Z, Gorthi G, Pritchard SA, Welch IM: **Tumor length as a prognostic factor in esophageal malignancy: univariate and multivariate survival analyses**. *J Surg Oncol* 2006, **93**(4):258-267.

22. Hollis AC, Quinn LM, Hodson J, Evans E, Plowright J, Begum R, Mitchell H, Hallissey MT, Whiting JL, Griffiths EA: **Prognostic significance of tumor length in patients receiving esophagectomy for esophageal cancer**. *J Surg Oncol* 2017, **116**(8):1114-1122.

23. Yendamuri S, Swisher SG, Correa AM, Hofstetter W, Ajani JA, Francis A, Maru D, Mehran RJ, Rice DC, Roth JA *et al*: **Esophageal tumor length is independently associated with long-term survival**. *Cancer* 2009, **115**(3):508-516.

24. Zhang X, Wang Y, Qu P, Liu-Helmersson J, Zhao L, Zhang L, Sang S: **Prognostic Value of Tumor Length for Cause-Specific Death in Resectable Esophageal Cancer**. *Ann Thorac Surg* 2018, **106**(4):1038-1046.

25. Rollins KE, Lucas E, Tewari N, James E, Hughes S, Catton JA: **PET-CT offers accurate assessment of tumour length in oesophageal malignancy**. *Eur J Radiol* 2015, **84**(2):195-200.

Figure legends

Figure 1: Study Flowchart

Figure 2: Kaplan-Meier overall survival curve (n=254)

Tables & figures

Table 1: Preoperative variables

Variable	***Value***	
	Neoadjuvant therapy + Surgery (n=207)	***Surgery alone (n=47)***
Median age at diagnosis in years (IQR)	66.0 (11.0)	73.0 (16.0)
Sex (female / male)	33 / 174 (15.9% / 84.1%)	10/37 (21.3% / 78.7%)
Neoadjuvant treatment		
Chemotherapy only	200 (96.6%)	
Radiotherapy only	0	
Chemoradiotherapy	7 (3.4%)	
Mean tumor length on PET-CT in mm	45.5 (SD=24.9)	20.0 (SD=20.5)
Tumor SUV_{max} on PET-CT	12.0 (SD=8.9)	5.1 (SD=5.8)

Preoperative TNM Stage			
	IA	12 (5.8%)	13 (27.7%)
	IB	12 (5.8%)	6 (12.8%)
	IIA	62 (29.9%)	3 (6.4%)
	IIB	17 (8.2%)	8 (17.0%)
	IIIA	43 (20.8%)	5 (10.6%)
	IIIB	24 (11.6%)	4 (8.5%)
	IIIC	26(12.6%)	4 (8.5%)
	IV	0	0
	N/A	11 (5.3%)	4 (8.5%)

Preoperative T-stage			
	T0	0	2 (4.3%)
	T1	16 (7.7%)	19 (40.4%)
	T2	27 (13.1%)	9 (19.2%)
	T3	141 (68.1%)	14 (29.8%)
	T4	12 (5.8%)	1 (2.1%)
	N/A	11 (5.3%)	2 (4.2%)
Preoperative N-stage			
	N0	95 (45.9%)	26 (55.3%)
	N1	66 (31.9%)	12 (25.5%)
	N2	30 (14.5%)	6 (12.8%)
	N3	16 (7.7%)	3 (6.4%)
Preoperative M-stage			
	M0	207 (100%)	47 (100%)
	M1	0	0

IQR: Interquartile range; N/A: Not available / not reported; PET-CT: Positron emission tomography with computed tomography; SD: Standard deviation; SUV_{max}: Standardized maximal radioisotope uptake value.

Table 2: Postoperative variables

Variable	***Value***
Type of esophagectomy	
Ivor Lewis	221 (87.0%)
McKeown	19 (7.5%)
Thoracoabdominal	13 (5.1%)
Transhiatal	1 (0.4%)
Surgical access	
Minimally invasive	98 (38.6%)
Open	86 (33.9%)
Hybrid	70 (27.6%)
Anastomosis	
Stapled	155 (61.0%)
Handsewn	99 (39.0%)

Mean histopathological tumor length (mm)	31.5 (SD=19.7)
Mean number of lymph nodes retrieved	25.8 (SD=12.5)
Mean number of lymph nodes positive for malignancy	2.2 (SD=3.9)
Mean positive-to-total lymph node ratio	0.086 (SD=0.139)
Postoperative diagnosis	
Residual adenocarcinoma	233 (91.7%)
Complete response	21 (8.3%)
Tumor differentiation*	
Well	6 (2.4%)
Moderate	99 (39.0%)
Poor	117 (46.1%)
Not applicable (complete response)	21 (8.3%)
Not reported	11 (4.3%)

Postoperative TNM stage		
	IA	65 (26.5%)
	IB	26 (10.2%)
	IIA	41 (16.1%)
	IIB	19 (7.5%)
	IIIA	47 (18.5%)
	IIIB	20 (7.9%)
	IIIC	28 (11.0%)
	IV	8 (3.1%)
Postoperative T-stage		
	T0	22 (8.7%)
	T1	56 (22.0%)
	T2	43 (16.9%)
	T3	124 (48.8%)
	T4	8 (3.1%)
	Not reported	1 (0.4%)

Postoperative N-stage		
	N0	132 (52.0%)
	N1	70 (27.6%)
	N2	26 (10.2%)
	N3	26 (10.2%)
Resection radicality		
	R0	214 (84.3%)
	R1	40 (15.7%)
	R2	0
Adjuvant treatment		111 (43.7%)
	Chemotherapy only	78 (30.1%)
	Radiotherapy only	15 (5.9%)
	Chemoradiotherapy	18 (7.1%)

*SD: Standard deviation; *In this analysis, the highest tumor grade (i.e. the lowest differentiation component) was quoted (e.g. "moderately-to-poorly" differentiated tumors were categorized as "poorly-differentiated").*

Table 3: Unadjusted Cox regression model (n=254)

Factor		HR (95%CI)	p-value
Male (vs. Female)		1.17 (0.73-1.86)	0.521
Age (1-year increments)		1.00 (0.98-1.02)	0.687
Neoadjuvant chemotherapy		0.96 (0.62-1.48)	0.838
Neoadjuvant radiotherapy		0.61 (0.19-1.93)	0.403
Tumor SUV_{max} on PET-CT (≥15)		0.98 (0.96-1.00)	0.13
Tumor length on PET-CT		1.00 (1.00-1.01)	0.254
Preoperative T-stage			
	T0 or T1	1	
	T2	0.69 (0.34-1.41)	0.311
	T3 or T4	1.42(0.87-2.33)	0.166

Preoperative N-stage			
	N0	1	
	N1	0.99 (0.65-1.52)	0.978
	N2	0.95 (0.58-1.55)	0.837
	N3	0.61 (0.36-1.03)	0.063
Number of lymph nodes retrieved			
	≤16	1	
	17-25	0.99 (0.65-1.52)	0.978
	26-34	0.95 (0.58-1.55)	0.837
	≥35	0.61 (0.36-1.03)	0.063
Histopathological tumor length (mm)			
	0-15	1	
	16-24	1.59 (0.86-2.97)	0.142
	≥25	2.55 (1.51-4.30)	**<0.001**

Tumor differentiation			
	N/A	1	
	Moderate or Well	2.86 (1.04-7.90)	**0.042**
	Poor	4.28 (1.56-11.73)	**0.005**
Postoperative T-stage			
	T0	1	
	T1	1.99 (0.69-5.75)	0.205
	T2	2.93 (1.01-8.52)	**0.048**
	T3 or T4	5.06 (1.85-13.82)	**0.002**
Postoperative N-stage			
	N0	1	
	N1	2.71 (1.79-4.1)	**<0.001**
	N2	4.54 (2.68-7.7)	**<0.001**
	N3	5.37 (3.18-9.07)	**<0.001**

Adjuvant chemotherapy	0.89 (0.62-1.27)	0.525
Adjuvant radiotherapy	2.83 (1.86-4.30)	**<0.001**
R1 status	3.25 (2.18-4.86)	**<0.001**

HR: Hazard ratio for all-cause death; CI: Confidence interval; SUV_{max}: Maximal standardized radioisotope uptake value; PET-CT: Positron emission tomography with computed tomography; N/A: Not available / not reported.

Table 4: Adjusted Cox regression models

Factor		Preoperative model (n=228)		Postoperative model (n=233)	
		HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Male (vs. Female)		0.95 (0.58-1.58)	0.857	1.03 (0.61-1.75)	0.9
Age (1-year increments)		1 (0.98-1.03)	0.668	1 (0.98-1.02)	0.988
Neoadjuvant chemotherapy		0.89 (0.5-1.58)	0.682	0.65 (0.36-1.19)	0.166
Neoadjuvant radiotherapy		0.52 (0.13-2.17)	0.372	0.52 (0.11-2.48)	0.413
Tumor SUV_{max} PET-CT (≥15)		0.55 (0.33-0.91)	**0.02**	0.79 (0.47-1.33)	0.377
Tumor length PET-CT		1 (0.99-1.01)	0.486	1 (0.99-1.01)	0.787
Preoperative T-stage					
	T0 or T1	1		-	-
	T2	0.78 (0.36-1.7)	0.532		
	T3 or T4	1.47 (0.76-2.84)	0.256		

Preoperative N-stage				
N0	1			
N1	1.15 (0.73-1.78)	0.55	-	-
N2	1.31 (0.74-2.32)	0.356		
N3	1.6 (0.81-3.17)	0.179		
Number of lymph nodes retrieved				
≤16			1	
17-25	-	-	0.71 (0.42-1.17)	0.179
26-34			0.56 (0.3-1.04)	0.066
≥35			0.22 (0.11-0.44)	**<0.001**
Histopathological tumor length (mm)				
0-15			1	
	-	-		
16-24			1.94 (0.97-3.86)	0.061
≥25			2.04 (1.07-3.89)	**0.03**

Postoperative T-stage				
	T0		1	
	T1	-	-	0.92 (0.3-2.84)	0.888
	T2			1.63 (0.51-5.21)	0.409
	T3 or T4			1.78 (0.58-5.49)	0.318
Postoperative N-stage				
	N0		1	
	N1	-	-	1.9 (1.09-3.33)	**0.024**
	N2			3.09 (1.57-6.08)	**0.001**
	N3			4.7 (2.41-9.16)	**<0.001**
Adjuvant chemotherapy		-	-	0.77 (0.49-1.19)	0.231
Adjuvant radiotherapy		-	-	1.49 (0.86-2.56)	0.151
R1 status		-	-	2.33 (1.38-3.94)	**0.002**

HR: Hazard ratio for all-cause death; CI: Confidence interval; SUVmax: Maximal standardized radioisotope uptake value; PET-CT: Positron emission tomography with computed tomography.

Patients screened for eligibility
n=345

Excluded: n=91
- No pre-treatment PET-CT or TL reported: n=40
- Death within 30 postoperative days: n=5
- Tumor other than adenocarcinoma: n=46

Cases analyzed
n=254