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Tumour length as an independent prognostic factor in resectable oesophageal carcinoma

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ABSTRACT

INTRODUCTION Oesophageal longitudinal tumour length has been investigated as a prognostic indicator for disease recurrence and overall survival in resectable oesophageal carcinoma. However, there is conflicting evidence regarding its use in clinical practice. This study aims to assess the prognostic significance of histological tumour length in potentially curative oesophageal resections for cancer.

MATERIALS AND METHODS Patients with locally advanced oesophageal carcinoma (squamous or adenocarcinoma) were identified in a single centre between July 2000 and December 2016. Patient demographics, tumour characteristics and survival outcomes were assimilated. Unifactorial and multifactorial analysis was performed to assess tumour length correlation with oncological outcomes.

RESULTS A total of 281 patients were included; 226 (80.4%) male and 55 (19.6%) female, with a median age of 66 years; 39 patients (13.9%) developed local recurrence and 104 (37%) distant metastases. Disease progression rate was 44.8% with a median progression-free survival of 21 months and median overall survival of 30 months. Median tumour length was 3 cm (interquartile range 2–4.5 cm). Multivariate analysis demonstrated longer tumours to be significantly associated with a higher rate of local recurrence (p=0.028), metastases (p=0.016), disease progression (p=0.001) and shorter progression-free survival (p=0.001).

DISCUSSION This study demonstrates histological tumour length as an independent prognostic factor for local recurrence, metastases, disease progression and progression-free survival. Further larger multicentre studies are required to define the role of longitudinal tumour length as a marker to identify patients who are at higher risk of poor oncological outcomes following surgery.

KEYWORDS
Oesophageal cancer – Prognosis – Tumour length

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Introduction

Oesophageal cancer is the fifth most common cancer in England and Wales, with 13,000 new cases diagnosed annually.[1] It carries a poor prognosis, with only 15% surviving the disease beyond five years.[2] The role of maximal tumour diameter has been established but the significance of the longitudinal tumour length continues to be widely debated as an independent risk factor predicting long-term survival in those with early stage disease.[3–9] It is becoming increasingly important to stage the disease accurately to guide pre- and postoperative treatment. Several published studies have suggested tumour lengths of 2–5 cm as predictors of survival in patients with locally advanced oesophageal cancer.[3,5–7] Bolton *et al* presented a new risk stratification system with pT1 tumours showing a 90% five-year survival in tumours less than 3 cm and no submucosal involvement, reducing to 22% with a length greater than 3 cm and submucosal involvement.[10] However, there is conflicting evidence on the importance of longitudinal tumour length and whether it should be incorporated into a more comprehensive risk stratification system to predict survival outcomes.[3,10–11] The current American Joint Committee on Cancer (AJCC) considers tumour depth as a significant component in TNM staging for prognostic purposes.[8] The primary objective of this study was to assess the prognostic significance of the longitudinal tumour length in the postoperative histology specimen, in relation to postoperative progression of the disease and survival, in patients undergoing oesophageal resection for cancer with curative intent. This may influence whether tumour length could be used as a marker to identify patients who are at higher risk of poor oncological outcomes following surgery.

Materials and methods

Patient data

Consecutive patients who underwent surgery for resectable oesophageal or gastro-oesophageal junction carcinoma in a single centre between July 2000 and December 2016 were selected retrospectively. Patients with intraoperative metastases or insufficient data recorded regarding tumour length and outcomes were excluded from the study. Parameters studied included demographic information, tumour location and type, grade of differentiation, pathological TNM staging, lymphovascular invasion, length of tumour, involved to harvested lymph node ratio in the histology specimen, administration of neoadjuvant and adjuvant chemoradiotherapy, performance status and American Society of Anesthesiologists (ASA) score. The main outcomes studied were local recurrence, development of distant metastases, progression, mortality, overall and progression-free survival. Local recurrence was defined as tumour recurrence at or near the resection site or involving nearby lymph nodes. Tumour location was defined as upper, middle, lower third of the oesophagus or gastro-oesophageal junction tumours.[13] Follow-up was calculated as the interval between surgery and either death or the end of data collection (April 2017). These encounters included clinical appointments, radiological or endoscopic assessments. Progression was defined as the date of encounter when a new diagnosis of recurrence or metastatic disease was made. Progression-free survival was defined as the interval between surgery and progression date or April 2017, provided that it was within one year of the previous encounter. Progression-free survival was omitted in the analysis for patients whose last encounter exceeded one year. Overall survival was determined as the interval between surgery and death or April 2017. The hospitals online medical notes system, pathology results and picture archiving and communicating system were used to assimilate the data on to a spreadsheet.

Pathological examination of tumour length

Surgical resection was performed either as an open or laparoscopic procedure by a specialist upper gastrointestinal surgeon. The type of surgery included an Ivor–Lewis oesophagectomy, McKewon oesophagectomy and total or extended total gastrectomy. All resected oesophageal specimens were fixed in formalin and analysed by a specialist gastro-oesophageal pathologist. Tumour length was defined as the longitudinal length of the tumour in the oesophageal specimen, measured closest to 1 mm. TNM staging was recorded according to the American Joint Committee on Cancer (sixth edition prior to 2010 and seventh edition thereafter).[13] The key difference relates to the location of locoregional lymph node metastasis.

Statistical analysis

Tumour length was examined as: a) in increments of 1 cm (0–1 cm, 1–2 cm, 2–3 cm and > 3 cm); b) using a cut-off value of 3 cm (< 3 cm compared with ≥ 3 cm); and c) a continuous variable. Bivariate correlations were assessed using Fisher's exact test for dichotomous categorical variables, chi square for categorical variables with more than two categories, Spearman's correlation for scale variables and log rank for time-lines (progression-free and overall survival). Medians were compared across groups using the Mann Whitney U test for dichotomous categorical variables and the independent samples median test for categorical variables with more than two categories. Multivariate analysis was performed using logistic regression for all examined dependent variables including patient age, sex, ASA, T, N and M stages and use of neoadjuvant therapy; with the exception of progression-free and overall survival, which were assessed using Cox regression analysis. A p-value of less than 0.1 in bivariate correlations was considered as a cut-off for inclusion in multivariate analysis. A p-value of less than 0.05 was considered statistically significant. Two-tailed comparisons were consistently used where applicable. Statistical analysis was conducted using SPSS version 23.

Results

Patient characteristics

A total of 322 patients were initially considered for the study. Two hundred and eighty-one patients with oesophageal or gastro-oesophageal junction cancer who underwent surgical resection with curative intent were included in the study according to set criteria (Fig 1). The cohort included 226 (80.4%) males and an overall median age of 66 years (interquartile range, IQR, 59–73 years). Median duration of follow-up was 30 months (IQR 12–65 years). Patients who received neoadjuvant treatment have been included in the study and this parameter has been considered for multivariate regression to ensure it was not a confounding factor influencing the effect of tumour length on progression-free and overall survival.

Tumour characteristics and outcomes

Some 39 patients (13.9%) developed local recurrence and 104 (37%) developed distant metastases. The overall disease progression rate was 44.8% (n=126) with a median progression-free survival of 21 months (IQR 8–56 months). One hundred and twenty-four patients (44.1%) were alive on most recent follow-up with a median overall survival of 30 months (IQR 12–65 months). Median tumour length was 3 cm, ranging from 0.2 cm to 12 cm (IQR 2–4.5 cm). Tumour characteristics are displayed in Table 1.

Bivariate analysis

Bivariate analysis for tumour length in increasing increments of 1 cm demonstrated significant correlations with local recurrence, distant metastases, progression-free and overall survival; p<0.001. Similarly, comparison between tumour lengths less than or above 3 cm showed a significant correlation with progression-free and overall survival (p<0.001; Table 2).

Multivariate analysis

Multivariate analysis of increasing increments and cut-off for tumour length showed no significant difference in progression-free and overall survival. However, when multivariate analysis was performed assessing tumour length as a continuous variable, longer tumours were found to be significantly associated with a higher rate of local recurrence (p=0.028), metastases (p=0.016), disease progression (p=0.001) and shorter progression-free survival (p=0.001; Tables 3 and 4).

Lymph node involvement

The median number of lymph nodes resected was 20 (IQR 15 to 29); 153 patients (54.6%) had at least one positive lymph node. There was on average one neoplastic lymph node confirmed histologically (IQR 0–3). Pathological N staging (p=0.005), as well as the proportion of positive nodes in the sample (p<0.001) were correlated with tumour length as a continuous scale variable.

Discussion

The prognostic use of longitudinal tumour length in oesophageal cancer has been widely debated for decades. This study demonstrates a positive correlation between increasing tumour length and local recurrence, metastases, disease progression and shorter progression-free survival. An independent association between tumour length and progression-free rather than overall survival is suggested based on the principle that tumour length affects progression via local recurrence and involved lymph nodes affect progression by metastases. Therefore, overall survival is directly affected by positive lymph nodes and the risk of metastatic disease, rather than local recurrence.

A retrospective review of over 100 patients supports this study reporting shorter tumours are correlated with improved progression-free survival rates.[14] However, larger studies are required to further support the findings for the relationship between increasing tumour length and progression-free survival. This study did not demonstrate a significant association between tumour length and overall survival; however, several studies have established that tumour length in non-metastatic oesophageal carcinoma is associated with more frequent concurrent lymph node involvement, risk of locoregional recurrence and poorer survival.[3,4,9] Bolton *et al* reported tumours greater than 3 cm in longitudinal length without lymph node involvement had a median survival of 30 months compared with less than 3 cm with a median survival of 204 months.[10] Conflicting studies have failed to describe a significant relationship between tumour length and survival and therefore its clinical use remains undetermined.[7,15–17]

The initial AJCC TNM staging considered oesophageal longitudinal tumour length less than 5 cm equivalent to T1

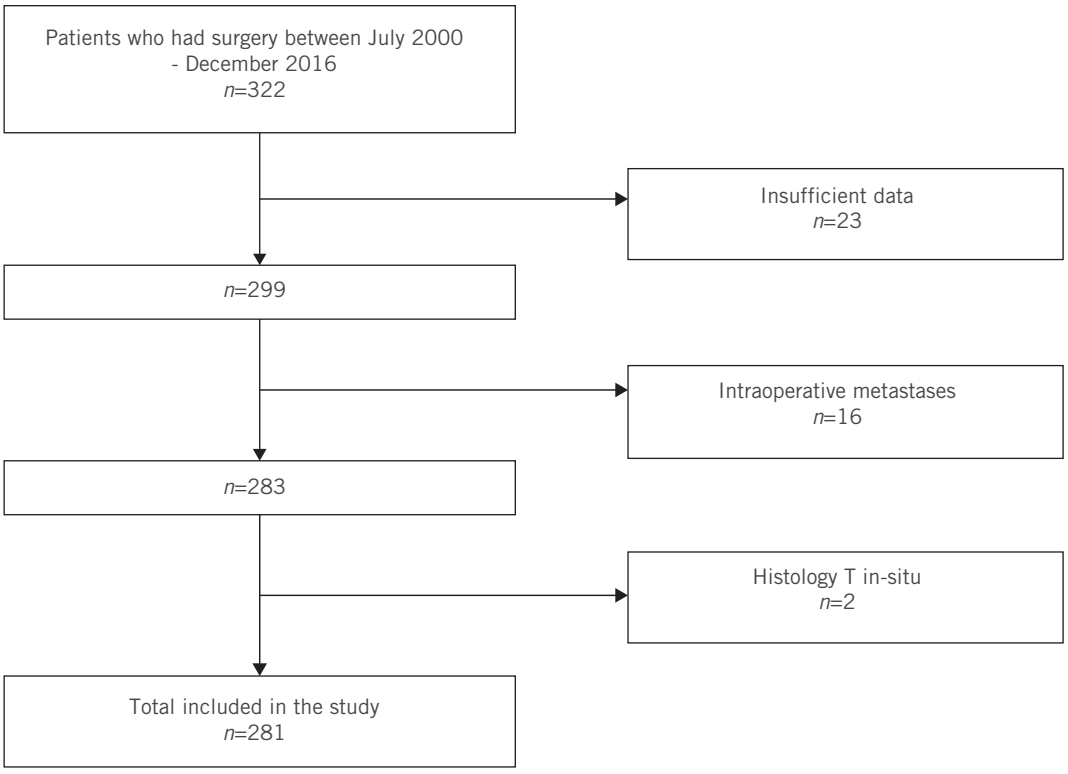

Figure 1 Patient inclusion in the study.

Table 1 Patient and tumour characteristics.

Variable	Patients
Age (years)[a]	66 (59–73)
Sex:[b]	
Male	226 (80.4)
Female	55 (19.6)
Type:[b]	
Adenocarcinoma	244 (87.8)
Squamous cell carcinoma	31 (11.2)
Other	3 (1.1)
Grade:[b]	
Well differentiated	32 (12)
Moderately differentiated	125 (46.8)
Poorly differentiated	110 (41.2)
Location:[b]	
Middle	7 (2.5)
Lower	65 (23.2)
Gastro-oesophageal junction	208 (74.3)
Surgery:[b]	
Ivor Lewis oesophagectomy	255 (90.8)
McKeown	2 (0.7)
Extended total gastrectomy	18 (6.4)
+ Total gastrectomy	6 (2.1)
Lymphovascular invasion:[b]	
No	154 (61.1)
Yes	98 (38.9)
Lymph node ratio[a]	0.04 (0–0.17)
Pathological TNM staging:[b]	
T stage	
T0	11 (3.9)
T1	58 (20.7)
T2	56 (20)
T3	145 (51.8)
T4	10 (3.6)
N stage	
N0	127 (45.4)
N1	108 (38.6)
N2	27 (9.6)
N3	18 (6.4)
Performance status:[b]	
0	151 (61.1)
1	75 (30.4)
2	20 (8.1)
3	1 (0.4)
ASA:[b]	
1	79 (33.1)
2	109 (45.6)
3	49 (20.5)
4	2 (0.8)
Neoadjuvant chemotherapy:[b]	
No	84 (30)
Yes	196 (70)
Neoadjuvant radiotherapy:[b]	
No	264 (94.3)
Yes	16 (5.7)
Adjuvant chemotherapy:[b]	
No	167 (59.6)
Yes	113 (40.4)
Adjuvant radiotherapy:[b]	
No	251 (89.6)
Yes	29 (10.4)

[a] Median (interquartile range).
[b] Count (%).

staging, however, in 1987 tumour depth superseded length as it was considered a more reliable predictor of 10-year survival in patients with oesophageal carcinoma.[8] Recent attempts at conceiving a survival prediction model using tumour length have not been successful, demonstrating only a marginal improvement in predicting outcomes.[11] The National Cancer Institute Surveillance Epidemiology End Results (SEER) database is the largest review, analysing 10,441 patients with oesophageal adenocarcinoma reporting the association between longitudinal tumour length over 3 cm and reduced overall survival.[4] Two-year survival in patients with 1-cm tumours was 78% compared with 18% with 9–10 cm tumours. Where some studies have shown an association between tumour lengths of 3–4 cm and survival,[3–5,7,9,10,14] others have failed to show this association and therefore suggested that tumour length cannot be considered as an independent prognostic indicator.[16,17]

Tumour size is an established prognostic indicator for other diseases such as breast, lung, and endometrial cancers.[5] This study demonstrates an association between oesophageal longitudinal tumour length and outcomes such as local recurrence, disease progression and progression-free survival, regardless of other previously mentioned parameters such as neoadjuvant chemoradiotherapy and lymph node involvement.

The use of oesophageal longitudinal tumour length in the staging process and in predicting long-term outcomes is still undefined but may need to be reconsidered. Moreover, tumour length may be of value preoperatively to estimate local advancement, lymph node involvement and long-term outcomes as suggested by other studies. The

feasibility of endoscopic assessment or radiological assessment should be considered as it may be a valuable prognostic predictor.[6,18] Tumour length may also be assessed after resection of the pathological specimen, prior to fixation in formalin. This additional information may be considered for inclusion in the TNM staging system or be used to establish an additional classification system to help predict patient outcomes. Arigami *et al* have proposed a primary tumour score classification incorporating tumour length and tumour depth, demonstrating it is a strong independent predictor of depth of tumour invasion, lymphovascular invasion and metastases, and overall cancer stage.[19]

Limitations of the study

Limitations to be considered include how the interpretation of longitudinal tumour length may be influenced by neoadjuvant therapy and by specimen

Table 2 Increasing tumour length and association with survival using bivariate analysis.

Tumour length stratification (cm)	Patients *n* (%)	Progression-free survival (months)	*p*-value	Overall survival (months)	*p*-value
1:			< 0.001		< 0.001
≤ 1	17 (6.7)	53 (38–107)		75 (43–119)	
> 1 to ≤ 2	38 (15)	34 (9–75)		44 (13–79)	
> 2 to ≤ 3	64 (25.2)	17 (10–61)		29 (14–78)	
> 3	135 (53.1)	17 (6–40)		22 (9–55)	
2:			< 0.001		< 0.001
≤ 3	119 (46.9)	33 (12–75)		41 (15–83)	
> 3	135 (53.1)	17 (6–40)		22 (9–55)	

Table 3 Multivariate significances correlating variables with patient outcomes.

Variable	Local recurrence	Metastases	Progression	Death	Progression free survival	Overall survival
Age						*p*<0.001 RR: 1.040 (1.021–1.059)
Length	*p*=0.028 RR 1.021 (1.002–1.039)	*p*=0.016 RR 1.022 (1.004–1.040)	*p*=0.001 RR 1.063 (1.025–1.102)		*p*=0.001 RR 0.984 (0.976–0.994)	
Lymph node ratio		*p*<0.001 RR: 185.247 (13.735–2498.466)	*p*=0.013 RR: 159.280 (2.905–8734.122)		*p*=0.014 RR: 5.346 (1.397–20.451)	
Progression-free survival				*p*=0.037 RR 0.969 (0.941–0.998)		*p*<0.001 RR 0.916 (0.901–0.930)
Circumferential resection margin					*p*=0.019 RR: 0.586 (0.374–0.917)	
Adjuvant radiotherapy	*p*=0.001 RR: 0.215 (0.087–0.534)					
Disease progression				*p*=0.04 RR: 0.074 (0.013–0.439)		
Nodal staging					*p*=0.034 RR 0.569 (0.338–0.959)	

Table 4 Increasing tumour length as a continuous variable and outcomes using multivariate analysis.

Variable	Multivariate risk ratio (95% CI)	*p*-value
Local recurrence	1.02 (1–1.04)	*p*=0.028
Distant metastasis	1.02 (1–1.04)	*p*=0.016
Disease progression	1.06 (1.03–1.10)	*p*=0.001
Progression-free survival	0.98 (0.98–0.99)	*p*=0.001
Overall survival	–	*p*>0.05
Mortality	–	*p*>0.05

fixation in formalin, as several reports have suggested shrinkage by up to 50%.[20,21] In addition, this cohort comprised patients spanning a change in TNM classification. Studies have reported a similar approach in retrospective oesophageal cancer prognostic studies, most commonly the SEER database analysing 10,441 retrospective cases.[3,22] There are two different systems for data collection on progression-free (encounter-based) and overall (electronic surveillance record) survival; overall survival is considered accurate. However, most patients who were not followed-up for more than one year until death or the end of the study may have had a recurrence that was not recorded. Owing to the retrospective nature of this study, it was not possible to acquire this missing data, thus progression-free survival is underestimated. This study reports on a relatively smaller sample size compared with other studies; however, it adds to the current evidence base for the potential clinical application of longitudinal tumour length as the prognostic role remains undetermined. The association with progression-free survival is important as it indicates the risk of recurrence which may affect adjuvant treatment.

Conclusion

Longitudinal tumour length is an independent prognostic factor for progression-free survival determined by local recurrence and disease progression, regardless of other parameters such as neoadjuvant chemoradiotherapy, histological type and lymph node involvement. These findings require validation in multicentre studies but provide a basis for considering inclusion of longitudinal tumour length in future outcomes prediction models to guide adjuvant treatment. The ambiguous evidence for the role of longitudinal tumour length merits further assessment and will be addressed in a meta-analysis currently being performed.[23]

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