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Endoscopic tumour morphology impacts survival in adenocarcinoma of the oesophagus

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ABSTRACT

Background: Prognostication in oesophageal cancer on the basis of preoperative variables is challenging. Many of the accepted predictors of survival are only derived after surgical treatment and may be influenced by neoadjuvant therapy. This study aims to explore the relationship between pre-treatment endoscopic tumour morphology and postoperative survival.

Methods: Patients with endoscopic descriptions of tumours were identified from the prospectively managed databases including the OCCAMS database. Tumours were classified as exophytic, ulcerating or stenosing. Kaplan Meier survival analysis and multivariable Cox regression analyses were performed to determine hazard ratios (HR) with 95% confidence intervals.

Results: 262 patients with oesophageal adenocarcinoma undergoing potentially curative resection were pooled from St Thomas' Hospital (161) and the OCCAMS database (101). There were 70 ulcerating, 114 exophytic and 78 stenosing oesophageal adenocarcinomas. Initial tumour staging was similar across all groups (T3/4 tumours 71.4%, 70.2%, 74.4%). Median survival was 55 months, 51 months and 36 months respectively ($p < 0.001$). Rates of lymphovascular invasion ($P = 0.0176$), pathological nodal status ($P = 0.0195$) and pathological T stage ($P = 0.0007$) increased from ulcerating to exophytic to stenosing lesions. Resection margin positivity was 21.4% in ulcerating tumours compared to 54% in stenosing tumours ($p < 0.001$). When compared to stenosing lesions, exophytic and ulcerating lesions demonstrated a significant survival advantage on multivariable analysis (HR 0.56 95% CI 0.31–0.93, HR 0.42 95% CI 0.21–0.82).

Conclusion: This study demonstrates that endoscopic morphology may be an important pre-treatment prognostic factor in oesophageal cancer. Ulcerating, exophytic and stenosing tumours may represent different pathological processes and tumour biology.

Introduction

Oesophageal adenocarcinoma represents a significant oncological and surgical challenge. Understanding how variables influence survival and patterns of recurrence can help guide multimodality treatment. The problem is that many prognostic variables, such as pathological T-stage and nodal status, tumour regression grade and lympho-vascular invasion, are only available after resection and may themselves be influenced by neoadjuvant therapy. Multidisciplinary meetings (MDTs) rely on radiological and clinical staging to inform treatment choices yet these variables can be significantly less accurate than the pathological variables which they represent [1]. Therefore, any variable which gives early insight

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into how a tumour might behave and respond to treatment may prove useful in formulating patient tailored neo-adjuvant treatment strategies.

Endoscopic tumour morphology is a well explored phenomenon in gastric cancer. The Boorman classification describes 4 types of gastric tumour which correspond to differing survival [2]. The Japanese have expanded this system to oesophageal luminal tumours, but mainly squamous cell carcinoma. This study examined three endoscopic tumour morphologies of patients with oesophageal adenocarcinoma; stenosing (stricturing), exophytic (protruding) and ulcerating, to determine if these influence survival.

Methods

Study design

This cohort study was based on a prospectively collected database of consecutive resections performed at a high-volume tertiary oesophago-gastric cancer centre and from the OCCAMS database. Only patients with adenocarcinoma of the gastro-oesophageal junction (Siewert 1,2,3) who had undergone potentially curative oesophagectomy with a pre-treatment endoscopy report describing tumour morphology were included in the study.

Endoscopic morphology

Endoscopy reports were analysed in retrospect. Patients were categorised into three endoscopic tumour morphologies, ulcerating, exophytic and stenosing. A tumour growing into the lumen was classed as exophytic. This included any tumour described polypoidal. If a tumour was flat with mucosal loss it was deemed ulcerating. If a tumour was impassable it was recorded as stenosing (Table 4).

Clinical management

Patients underwent a standard protocol of investigation including oesophago-gastro-duodenoscopy, computed tomography, endoscopic ultrasound and fluorodeoxyglucose positron emission tomography (FDG-PET). Neo-adjuvant chemotherapy practice evolved during the study period and followed standard indications and regimens as supported by randomised controlled trial evidence [3]. The majority of patients were treated with epirubicn, cisplatin and either 5 FU or capecitabine. Surgical resection included transthoracic or transhiatal oesophagectomy determined by individual surgeon preference. Previous studies in our institution have demonstrated no survival difference between these approaches [4]. Histological staging was standardised to meet the 7th edition TNM criteria, which was the current TNM edition at that time. Adjuvant therapy was determined by the multidisciplinary team consensus based on the positivity of resection margins, presence of lympho-vascular invasion, pathological nodal status and the post-operative performance status of the patient.

Statistical analysis

The following tumour and treatment variables were collected: pre-operative clinical T- and N-stage, Siewert type, neoadjuvant chemotherapy, pathological T- and N-stage, tumour differentiation, Mandard tumour-regression grade (TRG), lympho-vascular invasion (LVI) and circumferential resection margin (CRM). These were compared across morphology groups using chi-squared or Fisher's exact test as appropriate. The primary outcome measure was overall survival.

Overall survival was compared across groups using a Kaplan-Meier plot. Single variable Cox survival regression analysis was performed using pre-treatment variables: cT stage, cN stage, Siewert type, tumour differentiation, and tumour morphology. Multiple variable regression was conducted with block entry of cT stage, cN stage, and tumour differentiation, with subsequent entry of tumour morphology to determine the incremental improvement in model fit with this additional information. Single and multiple variable regression was similarly performed for post treatment variables: neaoadjuvant chemotherapy, pT stage, pN stage, LVI, Mandard score, CRM status, as well as tumour differentiation given the known association of this variable with outcome. All analysis was performed using SPSS Statistics version 24 (IBM, Armonk, NY, US).

Results

Cohort characteristics

262 patients were included in the study. 161 patients from a high volume oesophagogastric unit and 101 patients from the OCCAMS database. Patient characteristics are shown in Table 1. There were 70 ulcerating, 114 exophytic and 78 stenosing tumours. Initial clinical T stage of T3/T4 tumours was 71.4% with ulcerating tumours, 70.2% with exophytic and 74.4% with stenosing. In the entire cohort there were 7 cT4 tumours, 2 of which were stenosing on initial endoscopy. Although these tumours were T4 on initial staging, they were later deemed resectable following neo-adjuvant treatment.

67.1% of ulcerating tumours and 64.0% of exophytic tumours had positive nodal disease at clinical staging compared to 76.9% of patients with stenosing tumours. More patients with stenosing tumours underwent neo-adjuvant chemotherapy (89.7%) compared to ulcerating (82.3%) and exophytic (76%) tumours. A higher proportion of stenosing tumours had poor or no response to chemotherapy (64.1%) compared to ulcerating (54.3%) and exophytic tumours (52.6%) although this did not reach significance ($P = 0.4679$). 79.5% of stenosing tumours had a pT3/4 stage following resection compared to 50% with ulcerating tumours and 62.3% of exophytic.

Stenosing tumours were associated with significantly higher rates of lympho-vascular invasion (71.8% $p = 0.0176$) and circumferential resection margin positivity (56.4% $p < 0.0001$) when compared to ulcerating (LVI 51.4%, CRM 21.4%) and exophytic tumours (LVI 55.5%, CRM 29.8%).

Survival analysis

Median survival for the cohort overall was 50.3 months. Median survival for stenosing tumours was 36.3 months, 55.8 months for ulcerating tumours and 51.8 months for exophytic tumours ($p = 0.0001$). On Kaplan Meier analysis there were a significant survival difference seen between the three groups ($p = 0.001$) (Fig. 1). The association between pre-treatment variables and outcome was examined on single and multiple variable analysis (Table 2). The addition of tumour morphology significantly improved model fit (chi square change 13.024, df = 2, $p = 0.001$).

There was a significantly lower risk of death with ulcerating tumours (HR 0.328 95% CI 0.172–0.624 p0.001) and exophytic tumours (HR 0.569 95% I 0.328–0.932 p0.025) compared to stenosing tumours after adjusting for clinical nodal status, clinical T stage and differentiation. Regression analysis was also performed using pathological variables available after surgery. Again, model fit was improved by inclusion of tumour morphology (chi square change 6.116, df = 2, $p = 0.047$). The risk of death was significantly lower with ulcerating (HR 0.509 0.270–0.960 0.037) and exophytic

Table 1
Patient characteristics by tumour morphology.

Variable	Cohort		Ulcerating		Exophytic		Stenosing		P
	N	%	N	%	N	%	N	%	
Number	262		70		114		78		
cT									
T1-2	65	24.8%	17	24.3%	31	27.2%	17	21.8%	P = 0.7212
T3/4	188	71.8%	50	71.4%	80	70.2%	58	74.4%	
cN									
cN0	78	29.8%	23	32.9%	38	33.0%	17	21.8%	P = 0.1739
cN1,2,3	180	68.7%	47	67.1%	73	64.0%	60	76.9%	
Tumour location									
Siewert type 1	113	43.1%	32	45.7%	49	43.0%	32	41.0%	P = 0.2916
Siewert type 2	113	43.1%	24	34.3%	51	44.7%	38	48.7%	
Siewert type 3	24	9.2%	10	14.3%	9	7.9%	5	6.4%	
Neo-adjuvant treatment									
NAC	215	82.1%	58	82.3%	87	76%	70	89.7%	P = 0.057
Surgery alone	47	17.9%	12	17.1%	27	24%	8	13.2%	
pT									
CPR	17	6.5%	7	10.0%	4	3.5%	4	5.1%	**P=0.0007**
pT1/2	77	29.4%	28	40.0%	38	33.3%	11	14.1%	
pT3/4	168	64.1%	35	50.0%	71	62.3%	62	79.5%	
pN									
pN0	106	40.1%	35	50.0%	49	43.0%	22	28%	**P=0.0195**
pN1	45	17.2%	10	14.2%	22	19.3%	13	16.7%	
pN2/3	108	41.2%	24	34.3%	42	36.8%	42	53.8%	
Pathological grade									
Poorly differentiated	138	52.7%	35	50.0%	53	46.5%	50	64.1%	P = 0.0797
Mod differentiated	109	41.6%	28	40.0%	55	48.2%	26	33.3%	
Mandard score									
1 Complete response	17	6.5%	7	10.0%	4	3.5%	4	5.1%	P = 0.4679
2–3 Partial or Good	44	16.8%	10	14.2%	18	15.8%	16	20.5%	
4–5 Poor or No response	148	56.5%	38	54.3%	60	52.6%	50	64.1%	
LVI									
Yes	153	58.4%	36	51.4%	61	53.5%	56	71.8%	**P=0.0176**
No	104	39.7%	33	47.1%	50	43.9%	21	26.9%	
CRM									
R0	163	62.2%	53	75.7%	76	66.7%	34	43.6%	**P<0.0001**
R1	93	35.5%	15	21.4%	34	29.8%	44	56.4%	
Median survival									
Months		50.3		55.8		51.8		36.3	**P=0.0001**

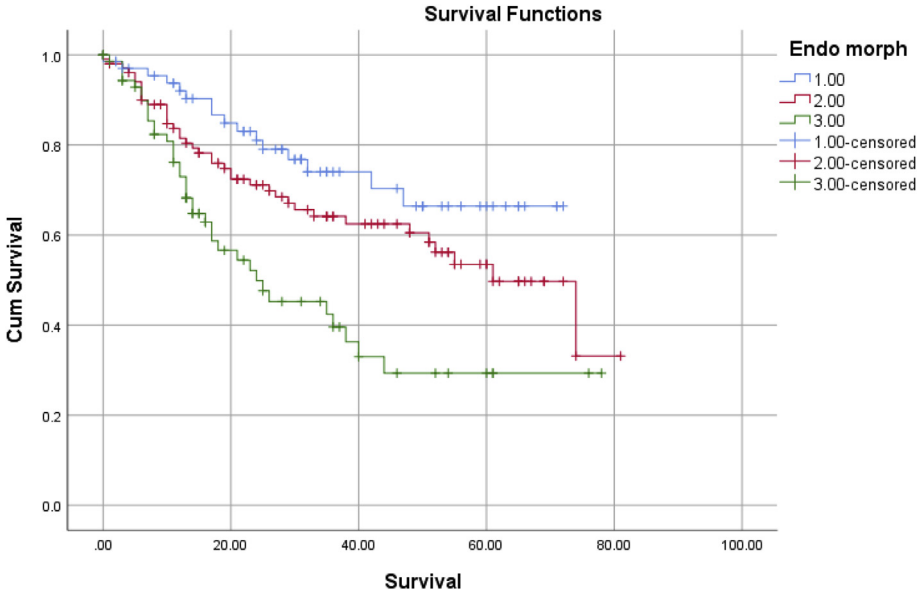

Fig. 1. Kaplan Meier survival curves 1 = Ulcerating, 2 Exophytic and 3 Stenosing.

Table 2
Univariable and multivariable analysis with pre-treatment variables.

Characteristic	Single variable analysis				Multiple variable without morphology				Multiple variable with morphology			
	HR	95% CI Lower	Upper	*p*	HR	95% CI Lower	Upper	*p*	HR	95% CI Lower	Upper	*p*
cT1/2	Ref				Ref				Ref			
cT3/4	1.815	1.082	3.046	.024	1.704	0.920	3.157	.090	1.735	0.953	3.157	.071
cN0	Ref				Ref				Ref			
cN1/2/3	1.220	0.774	1.924	.392	0.820	0.473	1.422	.480	0.825	0.484	1.406	.480
Siewert 1	Ref				Ref				Ref			
Siewert 2	0.928	0.599	1.437	.737	0.817	0.514	1.299	.392	0.707	0.443	1.130	.147
Siewert 3	0.697	0.314	1.551	.377	0.516	0.228	1.168	.112	0.593	0.262	1.344	.211
Well/mod diff	Ref				Ref				Ref			
Poor diff	1.977	1.249	3.128	.004	2.129	1.317	3.441	.002	1.994	1.219	3.262	.006
Stenosing	Ref				–				Ref			
Exophytic	0.532	0.338	0.838	.007					0.569	0.347	0.932	.025
Ulcerated	0.332	0.184	0.598	<.001					0.328	0.172	0.624	.001

Table 3
Univariable and multivariable analysis with post treatment variables.

Characteristic	Single variable analysis				Multiple variable without morphology				Multiple variable with morphology			
	HR	95% CI Lower	Upper	*p*	HR	95% CI Lower	Upper	*p*	HR	95% CI Lower	Upper	*p*
NAC	Ref				Ref				Ref			
No chemo	0.597	0.325	1.096	.096	0.000	0.000	2E227	.970	0.000	0.000	5E219	.969
pCR	Ref				Ref				Ref			
pT1/2	1.515	0.339	6.773	.587	1.086	0.121	9.703	.941	1.143	0.128	10.236	.095
pT3/4	6.381	1.564	26.036	.010	1.451	0.171	12.319	.733	1.525	0.180	12.929	.699
pN0	Ref				Ref				Ref			
pN1	3.085	1.584	6.010	.001	2.051	.891	4.720	.091	2.162	0.939	4.979	.070
pN2/3	5.747	3.287	10.049	<.001	2.358	1.051	5.290	.037	2.394	1.059	5.410	.036
Well/mod diff	Ref				Ref				Ref			
Poor diff	1.977	1.249	3.128	.004	0.990	0.576	1.700	.971	0.910	.526	1.573	.734
LVI negative	Ref				Ref				Ref			
LVI positive	4.639	2.759	7.800	<.001	2.533	1.210	5.303	.014	2.519	1.188	5.340	.016
TRG 1	Ref				*				*			
TRG 2/3	2.504	0.548	11.441	.236	Ref				Ref			
TRG 3/4	5.557	1.355	22.782	.017	1.345	0.661	2.735	.413	1.313	0.638	2.835	.460
CRM -ve	Ref				Ref				Ref			
CRM + ve	3.545	2.336	5.381	<.001	1.926	1.138	3.260	.015	1.637	0.946	2.835	.078
Stenosing	Ref				–				Ref			
Exophytic	0.532	0.338	0.838	.007					0.541	0.305	0.962	.036
Ulcerated	0.332	0.184	0.598	<.001					0.509	0.270	0.960	.037

Table 4
Tumour endoscopic morphology classification.

Tumour type	Description
Ulcerating	Any tumour where there is marked ulceration and mucosal loss. May have intraluminal components especially at the edge of the tumour but overall tumour extends towards the adventitia
Exophytic	Where the majority of the tumour extends intraluminally as seen endoscopically There may be a polypoidal component
Stenosing	Where the lumen is narrowed and the scope is impassable

tumours (0.541 0.305–0.962 p = 0.036) when compared to stenosing tumour when adjusting for pathological variables (Table 3).

Discussion

This study demonstrates that endoscopic tumour morphology is a useful pre-treatment variable which may offer an early insight into tumour biology. Three distinct tumour morphologies have been described here. When adjusted for both pathological and clinical variables, ulcerating and exophytic tumours correspond to an independent survival advantage when compared to stenosing tumours. The sample size was too small to determine if there are genetic determinants to these tumour morphologies.

No study has examined survival of patients with adenocarcinoma according to their initial endoscopic morphology. The Boorman classification system in gastric cancer is well established and the type1 and 2 show a survival advantage when compared to type 3 and 4[2]. The Japanese classification of the macroscopic appearance of non-superficial oesophageal tumours is similar to the Bormann classification. Type 1 is protruding, type 2 is ulcerating, type 3 is ulcerating and infiltrative and type 4 is diffusely infiltrative [5]. The Japanese system, however, encompasses both adenocarcinoma and squamous cell carcinoma. Adenocarcinoma of the oesophagus remains a heterogenous disease with complex genetic underpinning and is now considered a separate disease [6,7]. Early histological classification systems of oesophageal adenocarcinoma described medullary (ulcerating), fungating (protruding/exophytic) and scirrhous (scarring/stenosing) [8]. Stenosing tumours have long been

known to be associated with a poor prognosis [9–13]. This paper describes a simplified morphological classification system specific to adenocarcinoma of the oesophagus.

The study had several limitations. This was a retrospective study relying on the quality of endoscopy reports where the endoscopists were not classifying tumours according to a prospectively defined classification system. Only patients with clear morphological descriptions of the tumour were included in the study. However, this lack of prospective standardisation may be a source of bias. Image capture was not was not available for all patients and was not used routinely in this study. Furthermore, although multivariable adjustments were made using both clinical and pathological variables in this retrospective study, confounders will never be eliminated sufficiently to allow separation between causation and correlation of the involved variables. Although the majority of patients were treated at one institution, the 101 patients from the OCCAMS database came from different institutions making it difficult to fully control for variations in treatments pathways. However, the fact that endoscopic morphology emerged as an independent predictor of survival despite variation across institutions, strengthens the findings of this study. Prospective studies will be needed to validate these findings.

It was thought by the authors on initial analysis that tumour morphologies described here may simply be a reflection of how advanced the tumour was at diagnosis. However, clinical T stage at diagnosis was equivalent in the three groups. 21.8% of stenosing tumours were clinically staged at T1-2. Even if the stenosing tumours are a result of a more advanced disease, this was not discernible on imaging, confirming the importance of the morphology characteristics.

In this analysis, stenosing tumours are associated with higher rates of adverse prognostic factors; lympho-vascular invasion, poor differentiation, pathological nodal status, poor response to chemotherapy and higher resection margin positivity. These patients are also likely to suffer from poor nutrition and weight loss, which is associated with worse outcomes [14].

Studies looking at gastric cancer have shown Bormann type 1 (exophytic) and 2 (ulcerating) share similar survival curves, with types 3 and 4 showing progressively worse outcomes [2]. In this cohort there appeared to be a survival advantage with ulcerating tumours when compared to exophytic tumours, although this did not reach significance on multivariable analysis. This was not an expected finding. It was theorised that exophytic tumours, growing luminally, would localise the tumour whilst ulcerating tumours, growing towards the adventitia, would show higher rates of LVI and therefore a worse prognosis. Studies have shown that superficial ulcerating (type 0-iii) lesions in the stomach and oesophagus differ [15]. In the stomach these ulcerating lesions contain viable tumour at the more superficial periphery of the ulcer and do not permeate into the submucosa. Barrett's associated Type 0-iii lesions in the oesophagus show viable tumour at the base of the ulcer. It would follow that if the precursor ulcerating lesions of the oesophagus have tumour invading the submucosa then this would translate to a survival disadvantage. This does not appear to be the case. Siewert has postulated that the overall survival advantage seen with AC compared to squamous cell carcinoma may be due to inflammation associated with the Barrett's pathophysiology [16]. This inflammation is said to have a disrupting effect on the lymphovasculature which has an initially protective effect on tumour dissemination. It is possible that disruption of the lymphovasculature may also explain the relative survival advantage seen with ulcerating tumours. However, further studies will be needed to determine this.

In conclusion this study has examined the survival outcomes of three distinct endoscopic morphologies, ulcerating, exophytic and stenosing tumours. Ulcerating and exophytic tumours are associated with independent survival advantage compared to stenosing tumours. Further prospective studies will be needed to validate these findings.

CRediT authorship contribution statement

William R.C. Knight: Conceptualization, Data curation, Formal analysis, Writing - original draft. **Ricardo McEwen:** Data curation, Writing - original draft. **Ben E. Byrne:** Formal analysis, Writing - review & editing. **Wais Habib:** Data curation. **Rebecca Bott:** Data curation, Writing - review & editing. **Janine Zylstra:** Project administration, Writing - review & editing. **Ula Mahadeva:** Conceptualization, Data curation. **James A. Gossage:** Conceptualization, Writing - review & editing, Supervision.

Declaration of competing interest

We have no conflicts of interest to disclose.

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