Clinical impact of tumour involvement of the anastomotic doughnut in oesophagogastric cancer surgery

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ABSTRACT

INTRODUCTION Published colorectal cancer surgery data suggest no role for the analysis of the anastomotic doughnuts following anterior resection. The usefulness of routine histological analysis of the upper gastrointestinal doughnut is not clear. Our study assessed the impact of cancer involvement of the doughnut on clinical practice. Factors associated with doughnut involvement and the effect on patients' survival were also analysed.

PATIENTS AND METHODS The clinicopathological details of 462 patients who underwent potentially curative oesophagogastric resection for cancer with a stapled anastomosis between 1994 and 2006 in two specialist centres were retrospectively analysed. Univariate, multivariate and survival analyses were carried out.

RESULTS Approximately 5% of doughnuts (22 of 462) were histologically involved with cancer. Microscopic involvement of the proximal resection margin, local lymph node metastasis and lymphatic invasion within the main resected specimen were independently associated with doughnut involvement (all $P < 0.05$). However, these three factors taken together failed to predict doughnut involvement. Doughnut involvement was an independent adverse prognostic factor for overall survival ($P = 0.0013$).

CONCLUSIONS In contrast to findings in colorectal surgery, doughnut involvement with cancer appears to have useful prognostic information following oesophagogastric resection. Routine histological analysis of upper gastrointestinal doughnuts is justified. Doughnut involvement could potentially strengthen the indications for adjuvant therapy in the future.

KEYWORDS

Oesophageal cancer – Anastomotic doughnut – Histology

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The upper gastrointestinal doughnut is a ring of tissue that is removed from the staple gun following gastro-oesophageal anastomosis. Inspection of the doughnut serves two purposes. First, in the intra-operative setting as a complete circumferential full-thickness ring, it is indicative of a satisfactory anastomosis. Second, in the postoperative period, information is gained from the histology report. This is particularly important in cancer surgery.

This study aims to answer three questions. First, does it make sense to routinely analyse the doughnut histologically? In a case series of 100 stapled anterior resections and colectomies, Morgan *et al.*¹ did not find a single anastomotic doughnut involvement by cancer. Other, similar studies maintain that routine histological examination of colorectal

cancer surgery doughnuts is not clinically justified.^{2,3} The Royal College of Pathologists states that it is only necessary to examine the resection margins of the main resected colorectal specimen if the tumour extends macroscopically to within 30 mm of one of these.⁴ No published study has investigated whether the situation is different in upper gastrointestinal cancer. Second, is doughnut involvement with cancer associated with adverse characteristics identified within the main resected specimen? Third, is there a survival difference between patients with doughnut cancer involvement and those without?

The Royal College of Pathologists guidelines state that the distal and proximal resection margins of oesophagectomies, gastrectomies, and oesophagogastric resections,

removed for neoplasia, should always be examined histologically.^{5,6} However, the guidelines are not clear on doughnut examination. This study may clarify whether the doughnut should be included in the minimum dataset.

Patients and Methods

A retrospective study was carried out of 539 consecutive patients who underwent oesophagogastrectomy with stapled anastomosis between 1994 and 2006 in two specialist centres in North West England, (University Hospital of South Manchester and Liverpool Cardiothoracic Centre). Inclusion criteria were surgery with curative intent and histological examination of the anastomotic doughnut. It has been the policy of both hospitals for anastomotic doughnuts

Table 1 Patients and tumour characteristics

Factor	n (462)
Median age (years)	65 (50–85)
Median survival (years)	3.4
Neoadjuvant chemotherapy	
Yes	179
No	283
Hospital	
South Manchester	262
Liverpool	200
Barrett's oesophagus	
Yes	160
No	302
Histology	
Adenocarcinoma	355
Squamous	100
Adenosquamous	5
Leiomyosarcoma	1
Malignant melanoma	1
Differentiation	
Well	33
Moderate	262
Poor	167
T stage	
1	57
2	95
3	310
N stage	
N ₀	177
N ₁	295
N ₂	285
M stage	
M ₀	452
M _{1a}	10
M ₁	0
Overall stage	
1	44
2	184
3	224
4A	10

Table 2 Statistical analysis of independent associations of doughnut involvement with cancer

Variables	Doughnut		P-value
	Negative	Positive	
R category			
R ₀	409	8	< 0.0005
R ₁	31	14	
Lymphatic channel invasion			
No	365	9	< 0.0005
Yes	75	13	
Lymph node metastasis			
No	190	4	0.012
Yes	278	20	

R₀, both macroscopic and microscopic clearance of the longitudinal resection margins; R₁, microscopic evidence of tumour at the longitudinal resection margins.

to be routinely analysed histologically after resection. Patients who had resections for benign conditions, incomplete histopathological minimum datasets and peri-operative deaths were excluded from the study. A total of 462 patients met the inclusion criteria of whom 262 underwent resection by four surgeons in Manchester and 200 underwent resection by a single surgeon in Liverpool. The pathology variables collected were those of the Royal College of Pathologists minimum dataset for the histopathological reporting of oesophageal or gastric carcinoma.^{5,6} This allowed uniformity and consistency in data analysis.

Resected specimens were all fixed in formalin prior to analysis. There was no information in the histology reports or completed minimum datasets regarding prefixation handling and whether the specimens were pinned out prior to formalin fixation. However, pinning of specimens was common practice in one hospital (University Hospital of South Manchester) during the later phase of the study. Macroscopic examination data collected included tumour length and distance from the proximal and distal resection margins. Microscopic data collected included tumour type, differentiation, proximal, distal and circumferential resection margin status, TNM stage and evidence of lymphovascular invasion. Doughnuts were fixed in formalin and sampled in their entirety. Microscopic data collected included evidence of dysplasia, neoplasia or lymphovascular invasion.

Overall survival data were gained from the medical records, NHS tracking database, North West Cancer Registry and, when required, correspondence with general practitioners.

Statistical analysis

Statistical analysis was performed using SPSS® v.11.5 (SPSS, Chicago, IL, USA). Survival time was defined as the time from the date of surgery until death or until most recent follow-up appointment. Univariate survival analyses were performed using the Kaplan–Meier method with cancer-specific survival as the end-point. Factors were compared using the log-rank test. Multivariate survival analysis was performed on factors which achieved statistical significance ($P \leq 0.05$) on univariate analysis using the Cox proportional hazards method to identify independent predictors of survival.

Results

Table 1 summarises the characteristics of the 462 patients who had potentially curative oesophagogastrectomy with complete histopathological dataset, doughnut analysis and survival data.

Approximately 5% (22 of 462) had doughnut involvement with cancer. In one case, cancer was only present within lymphovascular channels (lymphovascular invasion); the remaining 21 cases showed tissue infiltration by cancer cells. On univariate analysis, microscopic involvement of the proximal resection margin (R_1 resection), lymphovascular invasion, circumferential resection margin (CRM) infiltration and lymph node metastasis observed within the main specimen were found to be associated with doughnut involvement (all $P < 0.05$). Neoadjuvant chemotherapy, tumour type (squamous vs adenocarcinoma) and Barrett's oesophagus were not found to be associated with doughnut invasion by tumour cells. Multivariate analysis revealed R_1 category, lymphatic channel invasion and lymph node metastasis but not CRM infiltration to be independently associated with doughnut invasion with cancer. Table 2 summarises the distribution of patients according to

Table 3 Statistical analysis of predictors of survival on univariate analysis

Variable		<i>n</i>	Hazard ratio (95% CI)	<i>P</i> -value
Doughnut involvement	No	440	1.00	0.001
	Yes	22	2.25 (1.39–3.64)	
Lymphatic invasion	No	374	1.00	< 0.0005
	Yes	88	1.91 (1.45–2.51)	
Vascular invasion	No	388	1.00	< 0.0005
	Yes	74	1.96 (1.47–2.62)	
Neural invasion	No	398	1.00	< 0.0005
	Yes	64	2.07 (1.53–2.81)	
LN metastasis (N_0 vs N_1)	No	177	1.00	< 0.0005
	Yes	285	3.142 (2.60–4.47)	
Tumour length (cm)	< 3.5	194	1.00	< 0.0005
	≥ 3.5	268	1.86 (1.45–2.38)	
Tumour differentiation	Well	33	1.00	< 0.0005
	Moderate	262	1.81 (1.06–3.07)	
	Poorly	167	2.88 (1.68–4.93)	
T-stage	1	61	1.00	< 0.0005
	2	104	2.28 (1.23–4.22)	
	3	327	3.78 (2.03–7.04)	
Overall stage (TNM)	1	44	1.00	< 0.0005
	2	184	1.76 (1.05–2.94)	
	3	224	4.27 (2.59–7.04)	
	4A	10		
Neoadjuvant chemotherapy	No	283	1.00	0.009
	Yes	179	0.70 (0.54–0.91)	
CRM involvement	No	329	1.00	0.001
	Yes	133	1.51 (1.18–1.95)	
Patient age (years)	< 60	131	1.00	0.034
	60–70	203	1.38 (0.88–2.17)	
	> 70	128	1.60 (1.01–2.53)

doughnut involvement and tumour characteristics. Approximately 10% (45 of 462) of the patients had R_1 resection. Of the 45 patients who underwent R_1 resection, about one-third (14 of 45) had doughnut involvement with cancer cells. Logistic regression analysis revealed a statistically significant association between doughnut involvement with cancer and R category (R_0 vs R_1 , $P < 0.0005$), lymphatic channel invasion ($P < 0.0005$) and lymph node metastasis ($P = 0.012$). However, further logistic regression analysis showed the three factors taken together did not predict doughnut involvement. It is also evident from Table 2 that 1.7% (8 of 462) of patients with microscopically clear longitudinal resection margins had doughnut infiltration with cancer cells.

Table 3 shows the univariate Cox regression analysis of predictors of overall survival. Results from our data are consistent with previously published adverse prognostic factors following oesophagogastrectomy on univariate analysis. These include R_1 resection, increasing tumour length, poor differentiation, lymph node metastasis, worse TNM stage, circumferential resection margin (CRM) involvement, lymphovascular invasion, advanced patient age and no neoadjuvant chemotherapy. In addition, we also discerned that doughnut involvement was associated with worse outcome ($P = 0.001$).

Multivariate analysis revealed doughnut involvement as an independent predictor of survival ($P = 0.0013$). The

median survival for the group with doughnut involvement was 10 months compared with 22 months for those without doughnut involvement. Figure 1 illustrates the Kaplan-Meier survival curve for doughnut as an independent predictor of survival. R_1 resection was not found to be significant when doughnut involvement was included in the analysis. Other independent predictors of survival were patient age, tumour overall stage, tumour length, lymphatic channel invasion and lymph node metastasis.

Discussion

We are not aware of any previous work that has assessed the clinical significance of tumour involvement of the anastomotic doughnut in oesophagogastric cancer. We found that 5% of the patients (22 of 462) have doughnut involvement with cancer and that doughnut status was not predicted by adverse histological features within the main resected tumour specimen. The median survival for cancer patients with doughnut involvement was 10 months versus 22 months in patients with tumour-free anastomotic

Table 4 Multivariate analysis: independent predictors of survival including doughnuts

Variable	n	Hazard ratio/ 95% CI	P-value
Doughnut involvement			
No	440	1.00	
Yes	22	2 (1.24–3.24)	0.0013
Lymph node metastasis			
No	177	1.00	
Yes	285	1.95 (1.28–2.97)	0.002
Tumour length			
< 3.5 cm	193	1.00	
≥ 3.5 cm	268	1.62 (1.26–2.09)	<0.0005
Lymphatic invasion			
No	374	1.00	
Yes	88	1.82 (1.33–2.49)	< 0.0005
Overall stage (TNM)			
Stage 1	44	1.00	
Stage 2	184	2.14 (1.17–3.91)	< 0.0005
Stage 3	224	6.15 (3.41–11.08)	
Stage 4A	10	6.08 (2.55–14.49)	
Tumour differentiation			
Well	33	1.00	
Moderate	262	1.44 (0.93–2.24)	0.007
Poor	167	1.82 (1.15–2.82)	

CI= Confidence interval

doughnuts. We also found that doughnut involvement by cancer cells was an independent predictor of overall survival ($P = 0.0013$).

This is in contrast with published work in colorectal cancer. In a series of patients undergoing stapled anterior resection and colonic resections, Morgan *et al.*¹ and Pullybank *et al.*² found no evidence of malignant involvement of the doughnuts. Two doughnuts demonstrated benign abnormalities: inflammatory changes and metaplastic polyps.¹ In another series of 308 anterior resections, only one patient with Dukes' C disease had distal anastomotic doughnut involvement with positive longitudinal resection margins; and the surgeon commented on the 'high likelihood of local residual tumour at the end of the procedure'.³ The national Surgical Adjuvant Breast and Bowel Project published in 1986 found no difference in disease-free survival of colorectal cancer patients with 2-cm longitudinal margin clearance and those with more than 3-cm clearance.⁷

These differences may be explained by the differing tumour biology of upper and lower gastrointestinal cancers. Oesophageal cancers have a propensity for longitudinal sub-mucosal spread.⁸ This is exemplified by our finding that 1.7% of the patients (8 of 462) with doughnut involvement had negative proximal resection margins. Consequently, a minimum of 5-cm distal clearance and up to 10-cm proximal clearance are recommended for resections with curative intent.^{9,10}

Three histologically adverse features within the main tumour specimen were independently associated with doughnut involvement: R₁ resection ($P < 0.0005$), lymphatic invasion ($P < 0.0005$) and lymph node metastasis ($P = 0.012$). Logistic regression was used to assess whether these three independent factors taken together could predict doughnut involvement with cancer. The model only correctly predicted 5 doughnut involved cases out of the observed total of 22 and incorrectly predicted two patients to be doughnut involved when they were actually tumour-free. It can be inferred that factors within the main tumour specimen do not substitute for the prognostic value of histological examination of the anastomotic doughnut and hence its routine analysis is justified.

Our study concurs with published data on the prognostic significance of tumour length,¹¹ histological grade,¹² longitudinal resection margin and CRM involvement,^{13,14} and neoadjuvant chemotherapy.¹⁵ Zafirellis *et al.*¹⁴ showed that R₁ resection is an independent predictor of survival. Our study echoes these findings in univariate analysis. However, R-category lost its prognostic significance when proximal doughnut involvement was factored into the multivariate analysis. This suggests that doughnut status is prognostically more important than microscopic involvement of the proximal resection margin (Table 4).

Given the relatively poor outcome of patients with doughnut involvement, there is a potential value for its intra-operative frozen section. The small size of the doughnut allows easy handling and transportation to the histopathology laboratory. A positive frozen section report would justify the need for more proximal resection of the oesophagus. Whether further longitudinal resections in such situation would afford improved patient outcome is unknown. In the future, doughnut involvement with cancer, and its prognostic implications, could also potentially strengthen the indication for adjuvant therapy in an appropriately selected cohort of patients.

The strengths of this study lie in its originality, its agreement with poor prognostic features already published in the literature and the large cohort of patients operated on by experienced surgeons in two specialist centres. Potential weaknesses are its retrospective nature, and the unknown degree of pre-fixation handling of the resected specimens between the two centres. The essence of pinning the specimen to a cork board prior to formalin fixation is to help minimise shrinkage of the longitudinal resection margins and reduce the discrepancy in the margin of resection lengths reported by surgeons and pathologists.¹⁶ However, it was interesting to find in this work that macroscopic tumour distance from the longitudinal margins was not found to be associated with doughnut involvement with cancer.

Conclusions

Doughnut involvement with cancer appears to have useful prognostic information following oesophagogastrectomy for cancer. Routine histological analysis of upper gastrointestinal doughnut is justified. Doughnut invasion could potentially strengthen the indications for adjuvant therapy in the future.

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