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Significant Variation of Resected Meso-esophageal Tissue Volume in Two-Stage Subtotal Esophagectomy Specimens: A Retrospective Morphometric Study

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ABSTRACT

Background. Differences in the extent and quality of surgical resection for esophageal cancer may influence the pathological staging and patient outcome. There are no data in the literature qualitatively and/or quantitatively characterizing esophagectomy specimens.

Methods. Macroscopic images of 161 esophagectomy specimens were analyzed retrospectively. The extent of resection was qualitatively classified as "muscularis propria," "intra-meso-esophageal," or "meso-esophageal." The volume of meso-esophageal tissue was quantified morphometrically. The number of muscle defects per specimen was counted. Results were related to clinicopathological variables, including survival.

Results. Sixty-two (39 %) specimens were classified as "muscularis propria," 65 (40 %) as "intra-meso-esophageal," and 34 (21 %) as "meso-esophageal." The morphometrically measured meso-esophageal tissue volume was different between the three types ($P < 0.001$). The specimen type was related to the total number of lymph nodes ($P = 0.02$), number of metastatic lymph nodes ($P = 0.024$), and depth of tumor invasion ($P = 0.013$), but not related to extramural tumor volume, circumferential resection margin status, or the surgeon performing the resection. The number of muscle defects per specimen was similar in all resection types. The resection specimen classification was related to survival in patients treated by surgery alone ($P = 0.027$).

Conclusions. This is the first study to quantify and classify the volume of tissue resected during esophagectomy. Our study shows significant variation of the resected tissue volume impacting pathological tumor staging. This variation was not associated with individual surgeon performance. A prospective, multicenter study is needed to validate our results and to investigate the potential biological mechanisms influencing the resectable volume of meso-esophageal tissue in cancer patients.

Esophageal cancer (ECa) is the eighth most common cancer worldwide.[1] Despite the introduction of multimodality treatment in recent years, the prognosis for patients with this cancer type remains poor with an overall 5-year survival rate of 10–15 %.[2]

Only 20–30 % of all ECa patients in the United Kingdom are suitable for curative treatment, which usually includes radical surgical resection.[3] Since the results of the OE02 trial were published, neoadjuvant chemotherapy followed by surgery is the standard of care for locally advanced resectable ECa in the United Kingdom.[4] However, there is currently no nationally or internationally agreed standard for the surgical resection procedure for these patients.[5–7]

Several different types of operations have been described, including right transthoracic esophagectomy, transhiatal esophagectomy, left thoracoabdominal esophagectomy, and minimally invasive procedures.[8–11] The most commonly used surgical procedure for ECa resection throughout the world is the resection of the esophagus with two-field lymphadenectomy by a combined right-sided thoracic and abdominal approach, often referred to as "Ivor Lewis esophagectomy."

To establish whether there is a particular type of surgical resection that results in the best possible patient outcome, it is necessary to identify criteria that could be used to

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compare different ECa resection procedures and to establish the degree of variability of ECa resection specimens when applying these criteria. The term "meso-esophageal tissue" as described by Matsubara et al. was used in the current study for the resected tissue attached to the esophagus.[12]

The purpose of the current study was (1) to develop a reproducible, semiquantitative classification system to describe ECa resection specimens based on the volume of the resected meso-esophageal tissue, (2) to confirm this subjective classification by objective quantitative morphometry of the same resection specimen, and (3) to investigate the relationship of resected meso-esophageal tissue volume and clinicopathological variables, including survival.

METHODS

Patients

The study was approved by the Leeds (West) Research Ethics Committee, UK. Between 2001 and 2009, 307 patients were treated by Ivor Lewis esophagectomy at Leeds Teaching Hospitals NHS Trust, UK. Digital photographs from the macroscopic resection specimen taken after fixation at the time of specimen cut up in the pathology laboratory were retrieved from the image archive IBASE of the Department of Histopathology, Leeds. Cases where stored images were inadequate, e.g., out of focus, not including an overview image, taken without scale and pictures from specimens that had been opened longitudinally, were excluded from the current study leaving matched overview and cross-sectional images from 161 resection specimens for final analysis.

Clinical data, including age at diagnosis, gender, treatment information, and follow-up data, including mortality, were retrieved from electronic patient records. Histopathological data, including length of the esophagus and lesser curve of the stomach, depth of invasion (pT), lymph node status (pN), total number of lymph nodes, number of lymph nodes containing tumor ("metastatic lymph nodes"), circumferential resection margin (CRM) status according to the Royal College of Pathologists guidelines, tumor morphology according to the WHO classification, and Mandard tumor regression grade were extracted from the histopathology reports.[13–15] Pathological staging was performed using the 7th edition International Union Against Cancer (UICC) tumor, node, metastasis (TNM) system.[16] Cases were reclassified if originally staged using a different TNM edition.

Ivor Lewis Esophagectomy

The resections included in the current study were performed by four different consultant surgeons, who all specialized in upper gastrointestinal tract surgery. Two of the surgeons had more than 10 years of esophageal cancer resection experience; the other two had less than 10 years of resection experience. In all patients, surgical resection was performed as a two-stage procedure to resect the middle and lower third of the esophagus together with a sufficient length of the proximal stomach to achieve tumor-free longitudinal resection margins and with all meso-esophageal tissue anterior to the aorta and laterally, including lymph node groups 107–112 and lesser curvatures nodes (lymph node groups 1, 2, 3, 7, and 20). The spleen was preserved wherever possible and pericardium was not removed routinely.

Histopathology

The esophagectomy specimen was delivered fresh to the histopathology department where it was opened along the distal gastric resection margin leaving the esophageal tube intact. All meso-esophageal and perigastric tissue was left attached to the specimen. The specimen was pinned onto a corkboard and fixed for at least 48 h in 10 % buffered formalin. After fixation, the specimen was photographed from anteriorly and posteriorly. The outer surfaces devoid of serosa lining (=circumferential resection margin, CRM) were inked before serial cross-sectional slicing at 4 mm intervals of the esophageal tube and the gastroesophageal junction. Cross-sections were photographed. All digital specimen photographs were stored in the IBASE database.

Extent of Resection—Visual Classification of Resection Specimens

Two independent observers (HG and AI) classified the extent of resection visually by assessing the volume and continuity of the attached meso-esophageal tissue from the proximal resection margin to the gastroesophageal junction using the anterior and posterior specimen overview images. No distinction was made between tumor, fibrosis/scar tissue, lymph nodes, or fatty tissue when visually assessing the volume and continuity of the attached meso-esophageal tissue.

Resection specimens with very little or no attached meso-esophageal tissue and large areas of visible muscularis propria were categorized as "muscularis propria" (type A), those with a moderate amount of meso-esophageal tissue and intermittent small areas of visible muscularis propria as "intra-meso-esophageal" (type B), and those with a large amount of meso-esophageal tissue covering nearly the whole length of the muscular tube in an almost continuous fashion as "meso-esophageal" (type C). A representative image of each classification group is

FIG. 1 Resection specimen classification. Type A "Muscularis propria" specimen with minimal meso-esophageal tissue and large areas of visible muscularis propria. Type B "Intra-meso-esophageal" specimen with a moderate amount of meso-esophageal tissue and intermittent small areas of visible muscularis propria. Type C "Meso-esophageal" specimen with large amounts of meso-esophageal tissue covering the majority of the muscular tube. Scale: one unit represents 1 cm

shown in Fig. 1. Interobserver agreement of this classification was assessed.

Extent of Resection—Morphometric Measurement of Resected Meso-esophageal Tissue Volume

Morphometric analysis of cross-sectional images was performed using Cell-D V 2·6 image analysis software (Olympus, UK). All cross-sections from the proximal resection margin to the gastroesophageal junction defined by the presence of gastric folds were reviewed by two observers (PJ and HG) and cross-sections with macroscopically visible tumor were identified. All cross-sections were subjected to morphometric measurements irrespective of whether they contained macroscopically visible tumor or not. Incomplete cross-sections consisting of only part of the circumference of the esophageal tube due to suboptimal slicing by the histopathologist at time of cut up were excluded from the measurements.

After calibration of the image analysis system using the scale included in the specimen image, the following parameters were measured as illustrated in Fig. 2:

1. Total cross-sectional area (mm^2)
2. Area of the esophagus: lumen and wall including muscularis propria excluding any meso-esophageal tissue (mm^2)
3. Area of macroscopically identifiable tumor outside the muscularis propria (extramural tumor, mm^2)
4. Maximum and minimum distance between muscularis propria and CRM (mm)
5. Maximum and minimum distance between the edge of the tumor and CRM (mm)

Intraobserver agreement of measurements was assessed on a random subset of 26 specimens.

The above measurements allowed the calculation of the meso-esophageal tissue volume per cross-section by subtracting the area of the esophagus (item 2 above) from the total cross-sectional area (item 1 above) and multiplication with the slice thickness (4 mm).

Extramural tumor was identifiable on the cross-sectional images in 52 specimens. To assess whether the extramural tumor volume is related to the meso-esophageal tissue volume, the total volume of extramural tumor per specimen was calculated by multiplying the extramural tumor area (item 3 above) with the slice thickness. With the exception of the extramural tumor, no other tissue type, such as fibrosis/scar of lymph nodes, was measured separately.

The total meso-esophageal tissue volume per specimen, total extramural tumor volume per specimen, and the single longest and shortest distance from the tumor edge or the muscularis propria to the CRM per specimen were used for statistical analysis. In addition, a subgroup analysis was performed to establish the relationship between CRM status and volume of the meso-esophageal tissue attached to extramural tumor containing slices.

Quality of Resection—Number of Muscle Defects

While reviewing the macroscopic cross-sectional images, we noted that small areas of the outer layer of the muscularis

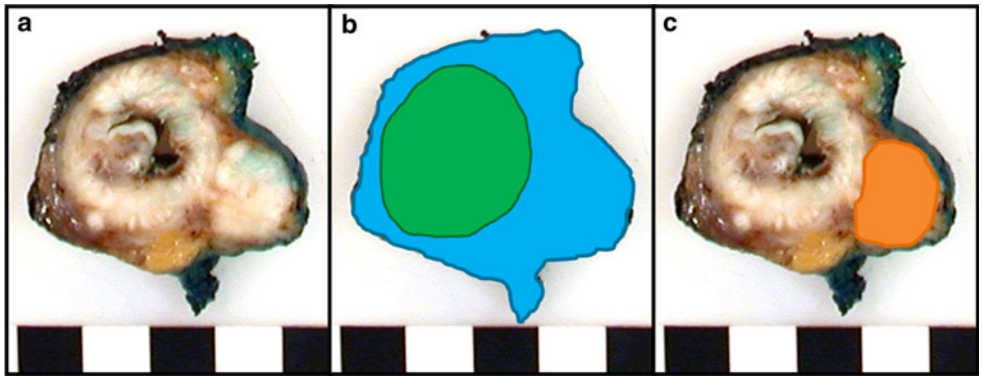

FIG. 2 Illustration of the morphometric measurements in specimen cross-sections. **a** Cross-section of esophagus with tumor. **b** Morphometric annotation of total cross-sectional area (*blue*) and area of the esophagus (*green*). **c** Morphometric annotation of the tumor area outside muscularis propria (*orange*). *Scale* one unit represents 1 cm

propria appear to be missing in some specimens. We therefore decided to quantify this item and to use the total number of macroscopically visible "defects" in the muscularis propria ("muscle defects") per specimen as a surrogate of the quality of resection. We assumed that the surgeon would always aim to resect the specimen without cutting into the muscle wall. An example of such a muscle defect is shown in Fig. 3.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows 16.0 (Chicago, IL). The relationship between visual resection specimen classification, morphometric measurement values, and clinicopathological variables was analyzed using Mann–Whitney *U* test (for variables with two groups) or Kruskal–Wallis test (for variables with more than two groups). Analysis of the relationship between the specimen classification and cancer-specific survival was performed using the Kaplan–Meier method, and differences between groups were tested using the log-rank test. Survival analysis was performed separately for patients treated by surgery alone and those treated by neoadjuvant chemotherapy. Follow-up time from the date of diagnosis to death or last seen was used for both group. Data from patients who died within 30 days after surgery were excluded from survival analysis. Prognostic relevance was also investigated by multivariate Cox regression analysis adjusting the multivariate model for pT (depth of tumor invasion) and pN (lymph node status). Bland–Altman plots and Kappa statistics were used to assess intra- and interobserver agreement, respectively. $P < 0.05$ was considered significant.

RESULTS

Visual Classification Identifies Three Types of Resection Specimens

In total, images from 161 Ivor Lewis esophagectomy specimens were analyzed. 62 (39 %) resection specimens were classified visually as "muscularis propria" (type A), 65

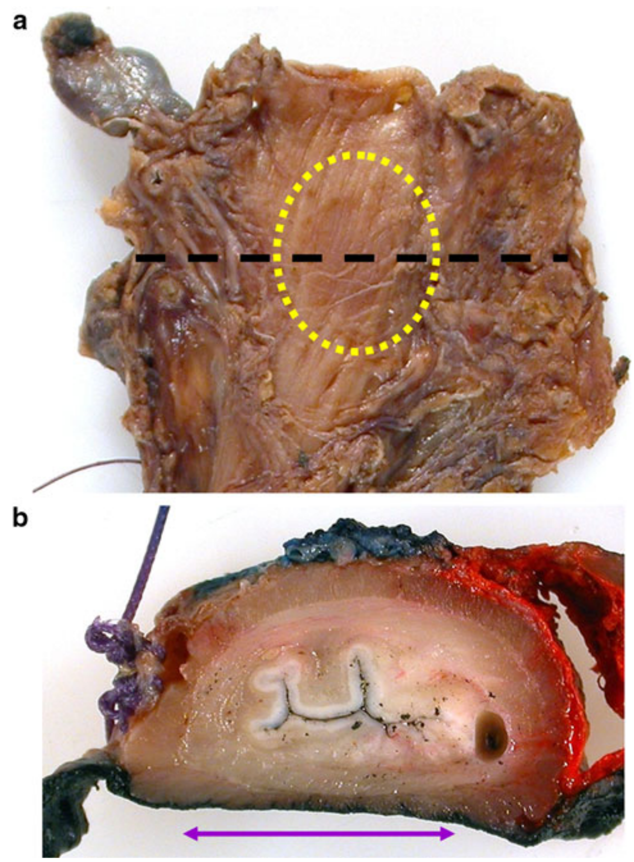

FIG. 3 Muscle defect analysis. **a** Overview image of the proximal end of a resection specimen showing a defect in the muscularis propria (*within dashed circle*). **b** Cross-section of the specimen from the dashed line showing a defect in the outer layer of the muscularis propria (*arrow*)

(40 %) as "intra-meso-esophageal" (type B), and 34 (21 %) as "meso-esophageal" (type C). Interobserver agreement for the visual classification was excellent ($\kappa = 0.801$).

Relationship Between Visual Resection Specimen Classification and Clinicopathological Variables

The visual resection specimen classification was significantly related to depth of tumor invasion (pT), lymph

TABLE 1 Relationship of visual resection specimen classification and clinicopathological variables

	Total (n = 161) n (%)	Type A ("muscularis propria") (n = 62) n (%)	Type B ("intra-meso-esophageal") (n = 65) n (%)	Type C ("meso-esophageal") (n = 34) n (%)	P value[c]	P value[d]
Gender						
Male	119 (74)	40 (34)	48 (40)	31 (26)	0.018	0.005
Female	42 (26)	22 (52)	17 (41)	3 (7)		
Morphology						
Adenocarcinoma	118 (73)	40 (34)	49 (42)	29 (25)	0.101	0.039
Squamous	39 (24)	21 (54)	14 (36)	4 (10)		
Other[a]	4 (3)	1 (25)	2 (50)	1 (25)		
Neoadjuvant therapy						
Yes	114 (71)	39 (34)	50 (44)	25 (22)	0.207	0.293
No	47 (29)	23 (49)	15 (32)	9 (19)		
Depth of invasion (T)						
pT0	7 (4)	3 (43)	4 (57)	0 (0)	0.013	0.015
pT1a/b[b]	39 (24)	24 (62)	9 (23)	6 (15)		
pT2	16 (10)	5 (31)	7 (44)	4 (25)		
pT3/4a/4b[b]	99 (62)	30 (30)	45 (46)	24 (24)		
Lymph node status (N)						
pN0	77 (48)	35 (46)	34 (44)	8 (10)	0.019	0.005
pN1	33 (21)	12 (36)	10 (30)	11 (33)		
pN2	25 (16)	7 (28)	10 (40)	8 (32)		
pN3	26 (16)	8 (31)	11(42)	7 (27)		
Circumferential resection margin (CRM) status						
Positive	75 (47)	25 (33)	32 (43)	18 (24)	0.427	0.237
Negative	86 (53)	37 (43)	33 (38)	16 (19)		

Because of rounding, the sum of the percentages is not always 100 %

[a] Other morphology: adenosquamous ($n = 2$), small cell carcinoma ($n = 1$), and in situ carcinoma ($n = 1$)

[b] pT1a/b: pT1a ($n = 17$) was combined with pT1b ($n = 22$), pT3/4a/b: pT3 ($n = 92$) was combined with pT4a/b ($n = 7$)

[c] Kruskal–Wallis test comparing type A with type B with type C

[d] Mann–Whitney U test comparing type A with type C

node status (pN), total number of lymph nodes, number of metastatic lymph nodes, tumor morphology, and patient gender (Tables 1, 2). Resection specimens with lower pT cancers were more frequently classified as "muscularis propria." The total number of lymph nodes and the number of metastatic lymph nodes were highest in the "meso-esophageal" group. Resection specimens from females and from patients with squamous cancers were more frequently classified as "muscularis propria." Whereas the length of the specimen was significantly different between the three groups, the length of the lesser curve of the stomach was similar (Table 2). No relationship was found between the visual resection specimen classification and CRM status or any other variables. In particular, there was no relationship between the visual resection specimen classification and the surgeon who performed the resections ($P = 0.486$), patients who died within 30 days after surgery ($n = 8$ patients, $P = 0.068$), or patients who required a postoperative intervention ($n = 28$, $P = 0.185$). The subgroup analysis of the neoadjuvantly treated patients with available tumor regression data ($n = 62$) showed no relationship between visual resection specimen classification and Mandard tumor regression grade ($P = 0.124$).

Relationship Between Visual Resection Specimen Classification and Cancer-Specific Survival

Follow-up information was available for 45 patients treated with surgery alone and 107 patients treated with neoadjuvant chemotherapy. Univariate survival analysis showed a significantly poorer outcome for patients with "meso-esophageal" resection specimens (type C: $n = 9$, mean survival time 3.4 years, 3 cancer deaths) compared with patients with "muscularis propria" (type A: $n = 22$, mean

TABLE 2 Relationship of visual resection specimen classification, histopathological variables, and morphometric measurements

	Total (n = 161)	Type A ("muscularis propria") (n = 62)	Type B ("intra-meso-esophageal") (n = 65)	Type C ("meso-esophageal") (n = 34)	P value[d]	P value[e]
Total no. of lymph nodes						
Median	32	28	32	34	0.02	0.013
Range	(4–104)	(5–76)	(9–104)	(4–77)		
No. of metastatic lymph nodes						
Median	1	0	0	2	0.024	0.005
Range	(0–28)	(0–28)	(0–18)	(0–15)		
Length of lesser curve of stomach (mm)[a]						
Median	110	120	110	110	0.387	0.223
Range	(10–300)	(13–250)	(35–300)	(10–150)		
Length of esophagus (mm)[b]						
Median	105	120	100	95	<0.001	<0.001
Range	(33–210)	(33–200)	(40–210)	(60–140)		
"Meso-esophageal" tissue volume including tumor (mm^3)						
Median	24,889	19,562	24,577	33,459	<0.001	<0.001
Range	(1,874–76,824)	(4,604–56,652)	(1,874–76,824)	(3,275–72,624)		
Maximum clearance from muscle (mm)						
Median	25	22	24	29	0.006	0.005
Range	(8–68)	(8–68)	(8–56)	(13–64)		
Minimum clearance from tumor (mm)						
Median	0.11	0.16	0	0.33	0.649	0.628
Range	(0–25)	(0–4)	(0–6)	(0–25)		
Extramural tumor volume (mm^3)[c]						
Median	984	743	1,081	1,177	0.889	0.71
Range	(24–8,081)	(24–6,294)	(27–6,161)	(205–8,081)		

Because of rounding, the sum of the percentages is not always 100 %

[a] 38 missing values

[b] 1 missing value

[c] Subgroup analysis of cases with extramural tumor (n = 52; type A: n = 16, type B: n = 24, type C: n = 12)

[d] Kruskal–Wallis test comparing type A with type B with type C

[e] Mann–Whitney U test comparing type A with type C

survival time 7.2 years, 2 cancer deaths) or "intra-meso-esophageal" (type B: n = 14, mean survival time 7.1 years, 1 cancer death) resection specimens, P = 0.027 (Fig. 4). The prognostic value of the resection specimen classification was lost in multivariate analysis when pT and pN were included in the model. No relationship was found between resection specimen classification and survival in patients treated with neoadjuvant chemotherapy (P = 0.132).

Morphometric Measurement of Resected Meso-esophageal Tissue Volume Confirms Validity of Visual Resection Specimen Classification

The median number of cross-sections measured per resection specimen was 13 (range, 3–28 cross-sections) reflecting the substantial difference in the length of the resected esophagus. Analysis of the intraobserver agreement of the morphometric cross-sectional measurements showed that only 2 % of measurements fell outside of two standard deviations of the mean, indicating an excellent intraobserver agreement (Fig. 5).

The visual resection specimen classification was significantly related to the morphometrically measured meso-esophageal tissue volume confirming the validity of the subjective visual classification by demonstrating that the attached meso-esophageal tissue volume was indeed largest in the "meso-esophageal" group and smallest in the "muscularis propria" group (Table 2). No relationship was found between the visual resection classification groups and the morphometrically measured extramural tumor volume. The maximum clearance from the muscularis propria was significantly different between the three

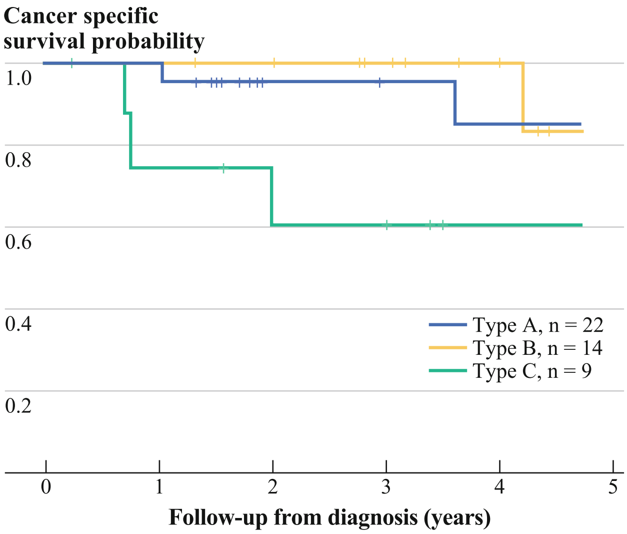

FIG. 4 Visual specimen classification and cancer-specific survival. Kaplan–Meier plot showing a significantly poorer survival probability in surgery alone treated patients ($n = 45$) with a large volume of meso-esophageal tissue (type C specimen; $P = 0.027$)

groups, whereas the minimum clearance from the muscularis propria was 0 cm in all groups (Table 2).

Relationship Between the Meso-esophageal Tissue Volume and CRM Status in Extramural Tumor Containing Cross-sections

No relationship was seen between the CRM status (positive vs. negative) and the visual resection specimen classification (Table 1) or the total volume of meso-esophageal tissue ($P = 0.424$). A subgroup analysis of the meso-esophageal tissue attached to the tumor containing cross-sections of the 52 resection specimens with extramural tumor showed that 37 specimens were classified as CRM-positive and 15 as CRM-negative. There was no significant difference in the total volume of tissue attached to the tumor containing cross-sections between CRM-positive and CRM-negative cases (median (range) meso-esophageal tissue volume CRM-positive cases: 2,417 mm^3 (581–6,478 mm^3), CRM-negative cases: 2,604 mm^3 (918–6,654 mm^3), $P = 0.402$).

Quality of Resection

In 129 (80 %) resection specimens, the muscularis propria was always intact. Twenty-two (14 %) specimens had a single muscle defect in the whole specimen and ten (6 %) specimens had more than one muscle defect. The total number of muscle defects per specimen was not related to the visual resection specimen classification ($P = 0.503$).

DISCUSSION

The resection of the esophagus together with its surrounding structures, the latter called meso-esophageal tissue in the current study in line with Matsubara T et al.,[12] is a central part of the multimodal treatment strategy for patients with locally advanced resectable esophageal cancer. Controversy still exists over the type and extent of surgery to be performed.[17] Work in colorectal cancer resection specimens has shown that extent of surgical resection varies between surgeons as well as between different types of procedures and can predict patient outcome.[18–20] Completeness of resection defined as tumor-free resection margins and number of examined lymph nodes have been suggested as indicators of surgical quality for esophagectomy procedures in the past.[21] The prognostic value of tumor within 1 mm of the circumferential resection margin has been demonstrated in univariate analysis in esophageal cancer patients treated with surgery alone and

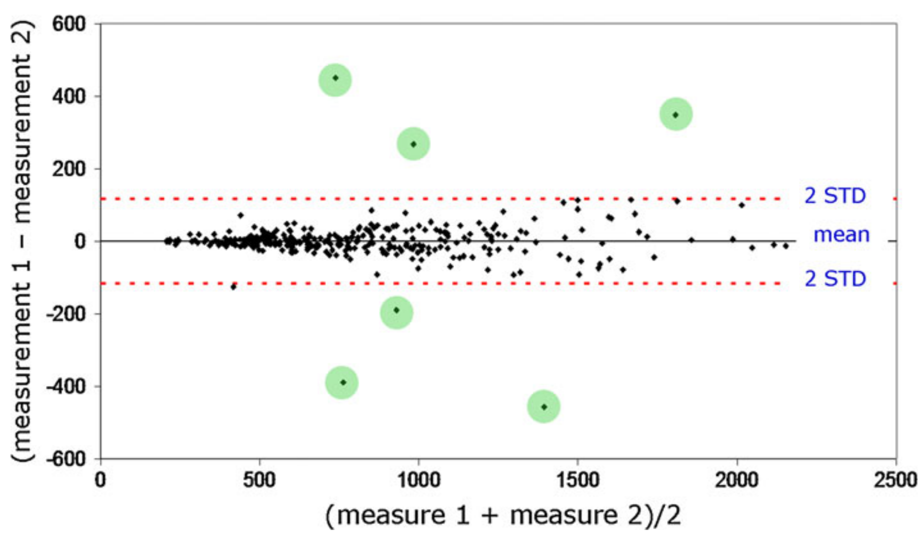

FIG. 5 Bland-Altman plot to assess intraobserver agreement; 328 independent measurements were performed. Measurements outside 2 standard deviations (STD) of the mean (outliers) shown in *green*

in patients treated with chemotherapy/chemoradiotherapy followed by surgery (see Ref. [22] and references therein). However, it is still controversial whether the CRM status is an independent prognostic factor in esophageal cancer patients.

To date, no attempt has been made to quantify the volume of the resected meso-esophageal tissue and to establish a reproducible semiquantitative classification system to be used in the routine pathology laboratory for the assessment of esophagectomy specimen. Such classification system is urgently needed to assess the variation in the resected tissue volume and enable the comparison of esophageal resection specimens produced by the same surgeon as well as by different surgeons performing the same procedure and to compare different surgical procedures, such as open surgery versus minimally invasive surgery.

Our study focused on Ivor Lewis type esophagectomy specimens, because this type of surgery is currently the most commonly used surgical procedures for esophageal cancer patients in our department and in the United Kingdom.[11]

This is the first study to show that esophagectomy resection specimens can be classified visually with excellent interobserver agreement into three major types. We were able to demonstrate the validity of the visual resection specimen classification by quantitative morphometric measurements of the cross-sectional specimen images.

Using this classification and the morphometric measurements, we show for the first time that the resected meso-esophageal tissue volume (here used as surrogate of the extent of resection) varies significantly between specimens despite the fact that all patients were operated on using the same surgical procedure.

Studies in colorectal cancer demonstrated that the extent of resection was surgeon as well as procedure-dependent, related to the presence of tumor at the circumferential resection margin (R1 resection) as well as lymph node yield and related to patient survival.[20,23–27] In contrast, our study in esophagectomy specimen does not confirm a relationship between surgeon and extent of resection, and all four surgeons produced all three types of resection specimens at similar frequency. There was no direct relationship between circumferential resection margin involvement and volume of tissue attached to the extramural tumor containing esophageal cross-sections. However, there was a relationship between extent of resection and gender, histological subtype, and depth of invasion.

In contrast to rectal cancer surgery where the surgeon has much more freedom with respect to the amount of resectable lateral tissue up to the pelvic wall, the esophageal cancer surgeon faces unresectable vital structures, such as aorta, trachea, bronchi, heart within few millimeters of the esophageal tube, providing a "natural" limit of the possible lateral extent of the resection. Our surgeons operated always with the intention to remove all accessible meso-esophageal tissue irrespective of any tumor-related factors, such as disease stage, histological type, and CRM status, or patient-related factors, such as gender or pretreatment by chemotherapy. This intention appears to be achieved successfully by the fact that there was no difference in the resected tissue volume between patients treated with surgery alone or neoadjuvant chemotherapy. Similarly, the total volume of the meso-esophageal tissue attached to the extramural tumor containing cross-section was not different between CRM-positive and CRM-negative cases, because the surgeon would always "maximize" the resected tissue volume.

However, we were very surprised to find that the same surgeon operating with the same intention produces resection specimens with very different tissue volumes attached to the esophagus. Together with the identified gender-related difference in the resected tissue volume, this might point toward preexisting anatomical variation in the meso-esophageal tissue volume in different patients. No reports in the literature describe the natural variation of the mediastinal anatomy between different people. On the other hand, one can speculate that the increasing meso-esophageal tissue volume with increasing depth of tumor penetration through the wall and the increased tissue volume in adenocarcinoma compared with squamous cell carcinoma might represent a "tumor-induced" phenomenon related to yet unknown biological factors of the cancer.

Similar to studies in colon cancer, the extent of resection was directly related to the total number of lymph nodes and the number of positive lymph nodes in the current study. The lymph node yield is a well-recognized, independent prognostic factor for ECa patients.[2,23,28] This suggests that less radical resection of the meso-esophageal tissue might affect the accuracy of the pathological lymph node staging and hence make patient prognosis prediction less reliable. Studies in the past have indicated that lymph node yield may vary by surgical procedure and by extent of lymphadenectomy.[28–30] To the best of our knowledge, this is the first study to highlight a significant variation in lymph node yield within the same surgical procedure.

The detailed analysis of the macroscopic specimen images also showed that 20 % of the resection specimens had at least one surgically induced superficial defect of the muscularis propria. In contrast to rectal cancer studies where intraoperative perforation rate of up to 36 % have been reported, all muscle defects seen in the esophagectomy specimens were superficial in nature and no transmural defect was seen.[19] The presence of muscle defects in esophagectomy specimens has not been quantified before, and hence there were no data in the literature for comparison. Interestingly, the presence of muscle defects was not related to visual specimen classifier. This could suggest that muscle defects are related to the anatomical challenges of the esophagectomy procedure and might be reduced in the future by identification of technically difficult areas and raising awareness for these areas amongst surgeons.

Limitations

The current study has some limitations, which are mainly related to the fact that this was a retrospective, single-center study. We had to assume that all pathologists involved in the specimen processing used a similar force to stretch the esophageal tube when pinning it onto the cork board and cut cross-sections at thickness of 4 mm. In our hospital, the total number of nodes was not reported by location (lymph node station) and therefore represents the sum of the thoracic and abdominal nodes. Because the length of the lesser curve of the stomach with attached fat was not significantly different between specimen types, we assumed that there was no significant variation in the number of abdominal nodes. Unfortunately, we did not have body weight or body mass index (BMI) data for the current study cohort to assess whether there is a relationship between BMI and meso-esophageal tissue volume. To the best of our knowledge, there is no published evidence that the meso-esophageal tissue volume might increase with increasing body mass index. However, several recent studies in esophageal cancer patients all demonstrate that the total lymph node yield is not related to BMI.[31–33] These findings could potentially provide some indirect evidence that the meso-esophageal tissue volume also might not be related to the BMI.

The median follow-up time of patients was relatively short: 2.9 (range, 0.2–8) years for patients treated with surgery alone ($n = 45$), and 1.9 (range, 0.3–8.1) years for patients treated with neoadjuvant chemotherapy ($n = 107$). In addition, the number of patients in each subgroup was small. Hence, the statistical relationship found between a larger meso-esophageal tissue volume and poorer survival in the surgery alone-treated cohort needs to be interpreted with caution, in particular, because no such relationship was found in the larger cohort of neoadjuvantly treated patients. Similarly, our information regarding postoperative morbidity was very limited in this retrospective study and was restricted to 30-day mortality and the requirement of an invasive postoperative intervention. Based on this limited information, we have no reason to believe that there is a relationship between resection of a larger meso-esophageal tissue volume and increased postoperative morbidity.

Conclusions and Further Study

In summary, we have developed a new classification of the macroscopic esophageal cancer resection specimen to be used at the time of pathology specimen cut up. We consider this current work as the first step toward the assessment of quality and quantity of esophageal cancer surgery in the near future. Ideally, the assessment of the resection specimen should be combined with an assessment of the in situ resection bed to establish both the volume of the tissue that has been resected and the volume of the tissue that has not been resected.

This subjective specimen classification is reproducible between independent observers and was objectively confirmed by morphometric measurement. Using this new classifier, we have shown that there is a significant variation in the resected meso-esophageal tissue volume, which effects pathological lymph node staging but does not appear to be related to the surgeon performing the procedure, indicating that the patient anatomy and biology of the underlying disease might play a role.

This new classification needs to be validated prospectively as part of a large, multicenter, clinical trial where the surgical procedure, specimen processing, and other potentially confounding variables are strictly controlled. Further work will need to be done to understand fully the potential causes underlying the variation in the meso-esophageal tissue volume and its potential impact on patient outcome before we will be able to start comparing different surgical procedures and identify the optimal surgical procedure for individual patients with esophageal cancer.

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