RESEARCH ARTICLE

Re-considering the role of tumour length in oesophageal cancer staging: A prospective study from a tertiary care setting in South Asia

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Abstract

Objective: To specifically evaluate the association between pre-neoadjuvant computed tomography-defined tumour length and clinical tumour-node-metastasis staging in oesophageal cancer patients.

Method: The prospective study was conducted from August 2021 to August 2022 at the Dr Ruth K.M. Pfau Civil Hospital in Karachi, and comprised biopsy-confirmed oesophageal cancer inpatients. The tumour length was measured using pre-neoadjuvant computed tomography scans, and these were evaluated against clinical tumour-node-metastasis staging and other patient characteristics. Data was analysed using SPSS 26.

Results: Of the 171 patients, 90(52.6%) were females and 81(47.4%) were males. The overall mean age was 47.46±14.12 years (range: 17-80 years). The tumour length determined by pre-neoadjuvant computed tomography scans as <5 cm, 5-10cm and >10cm showed significant correlations with tumour stage (p=0.006) and metastasis (*p*=0.011). Univariate analysis indicated that tumour stage 3 (*p*=0.020) and metastasis (*p*=0.005) were significantly associated with tumour length >10cm. Multivariate analysis confirmed that tumour stage 3 was significantly linked to tumour length >10cm (*p*=0.039).

Conclusion: The tumour length determined by pre-neoadjuvant computed tomography scans in oesophageal cancer staging significantly correlated with clinical tumour-node-metastasis.

Keywords: Oesophageal cancer, Neoplasm size, Cancer staging, Computed tomography, South Asia.

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Introduction

Oesophageal cancer (OC) incidence has increased worldwide over the last few decades, leading to significant morbidity and mortality, ranking as the 6th leading cause of cancer-related deaths globally. Moreover, Asia has the highest incidence and mortality rates for OC among all continents. In Pakistan, it is the 4th most prevalent cancer and is rising exponentially.[1,2]

The introduction of neoadjuvant therapy marks a notable advancement in the overall prognosis for OC patients. However, the current practice of selecting candidates for neoadjuvant treatment relies solely on tumour-node-metastasis (TNM) staging, overlooking the crucial factor of tumour length.[3]

While the tumour length was also once considered a significant parameter as per the American Joint Committee on Cancer (AJCC) staging investigation guidelines, this practice was abandoned decades ago. However, some studies have reignited interest in re-evaluating the role of tumour length in cancer staging.[4-7] This contributes to the growing discussion regarding whether tumour dimensions hold some value in correlating with clinical TNM (cTNM) staging, and, more importantly, its implications in overall patient management.

Additionally, studies from South Asia, particularly Pakistan, investigating the importance of tumour length and its correlation with cTNM are limited. Therefore, to address this gap, the current study was planned to evaluate the potential of pre-neoadjuvant computed tomography (CT)-defined the tumour length, specifically assessing its correlation with cTNM staging, derived as per the AJCC/Union for International Cancer Control (UICC) guidelines[8] to determine if the tumour length provides comparable or greater value than TNM staging alone.

Patients and Methods

The prospective study was conducted from August 2021 to August 2022 at the Dr Ruth K.M. Pfau Civil Hospital, a prominent government-sector tertiary care facility. in Karachi, and comprised inpatients at Surgical Unit-I of the Department of Upper Gastrointestinal (GI) Surgery.

After approval from the institutional ethics review board, the sample size was determined using OpenEpi online calculator, considering the prevalence of pathological T4 (pT4) in large-sized tumours (LSTs) to be 73.6%[9] with margin of error 7% and confidence interval (CI) 95%. The sample was raised using non-probability consecutive sampling technique, and patients with biopsy-proven OC,

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including both squamous cell carcinoma (SCC) and adenocarcinoma, who had not received neoadjuvant treatment were included. Patients with incomplete data or those who left against medical advice were excluded. To ensure comprehensive data coverage, all the inpatients who met the inclusion criteria and furnished informed written consent, were enrolled.

Other than demographic details, findings from endoscopic examinations were noted, and pertinent information from medical reports, such as biopsy, CT scan, and positron emission tomography (PET) scan, were extracted. The tumour length was determined based on contrast-enhanced CT imaging, assessed by a board-certified radiologist. All scans were performed using a standardised imaging protocol, and the tumour length was measured in the craniocaudal dimension from the proximal to the distal extent of visible tumour. These raw length values were recorded for all patients before any grouping was applied for analysis. The clinical staging of the cancer was determined using the UICC/AJCC criteria,[9] which are identical for cTNM. All the patients underwent laboratory assessments at the same facility, ensuring standardised evaluation.

The data was analysed using SPSS 26. Descriptive statistics for continuous variables were reported as mean ± standard deviation when normally distributed, while frequencies and percentages were reported for all categorical characteristics. The continuous variables were compared using one-way analysis of the variance (ANOVA), whereas Pearson chi-square or Fisher's exact tests were used to assess the correlation between the categorical variables with tumour length which was categorised into <5cm, 5-10cm and >10cm groups. All independent variables were included in the univariate multinomial logistic regression model, with the lowest category of tumour length being the baseline. Covariates with $p<0.10$ in univariate analysis were considered for multivariate analysis. Multivariate multinomial logistic regression model was used to explore the associated risk factors of tumour length, and took the first category as the reference. Relative risk ratios (RRR) and their corresponding 95% CIs were calculated for each covariate included in the model. Two-tailed $p<0.05$ was regarded as statistically significant.

Results

Of the 171 patients, 90(52.6%) were females and 81(47.4%) were males. The overall mean age was 47.46±14.12 years (range: 17-80 years). The majority of the patients had squamous cell carcinoma 128(74.9%) compared to adenocarcinoma 43(25.1%). The most common location of the tumour was in the lower thoracic oesophagus 89(52%), followed by the middle thoracic 70(41%) and upper thoracic oesophagus 12(7%). Most of the cases 108(63.2%) were moderately differentiated, followed by 44(25.7%) poorly differentiated, and 19(11.1%) well differentiated. Based on the cT stage, 19(11.1%), 74(43.3%) and 78(45.6%) cases had T1-T2, T3, and T4 stages, respectively. The distribution of lymph node showed 13(7.6%) patients having N0, followed by 54(31.6%) N1, 58(33.9%) N2, and 46(26.9%) N3. Metastasis was present in 57(33.3%) cases. The overall mean tumour length was 6.9±3.11 cm. When stratified by tumour stage, the mean tumour length was 5.5 ±2.50cm in patients with T1-T2, 6.38±2.86cm in T3, and 7.88±3.23cm in T4a and T4b. Based on nodal involvement, the mean tumour length was 6.46±2.84cm in N0, 6.93±2.94cm in N1, 6.76±3.21cm in N2, and 7.43±3.29cm in N3. The mean tumour length was 7.88±3.42cm in patients with metastasis, compared to 2.85±0.26cm in those without. There were 51(29.8%) patients with tumour length <5cm, 89(52.1%) with 5-10cm, and 31(18.1%) with >10cm (Table 1).

Table-1: Patient characteristics (n=171).

	n (%)
Mean Age, Range (years)	47.46±14.12 (17-80)
Gender	
Male	81 (47.4)
Female	90 (52.6)
Histopathology	
Adenocarcinoma	43 (25.1)
Squamous cell carcinoma	128 (74.9)
Tumour site	
Upper thoracic (20 to 25 cm)	12 (7.0)
Middle thoracic (25 to 30 cm)	70 (41.0)
Lower thoracic (30 to 38 cm)	89 (52.0)
Tumour grade	
Well differentiated	19 (11.1)
Moderately differentiated	108 (63.2)
Poorly differentiated	44 (25.7)
Tumour length	
< 5 cm	51 (29.8)
5 to 10 cm	89 (52.1)
> 10 cm	31 (18.1)
T stage	
T1 & T2	19 (11.1)
T3	74 (43.3)
T4 a & b	78 (45.6)
N stage	
N0	13 (7.6)
N1	54 (31.6)
N2	58 (33.9)
N3	46 (26.9)
M: Metastasis	
No	114 (66.7)
Yes	57 (33.3)

T: Tumour, N: Node, M: Metastasis, SD: Standard deviation.

Tumour length groups were significantly related to cT stage

Table-2: Patient characteristics in relation to tumour length.

	Tumour length			*p*-value
	< 5 cm (n=51)	5 to 10 cm (n=89)	> 10 cm (n=31)	
	n (%)	n (%)	n (%)	
Mean Age (years)	47.55±13.67	46.30±14.67	50.65±13.15	0.339
Gender				
Male	29 (56.9)	40 (44.9)	12 (38.7)	0.228
Female	22 (43.1)	49 (55.1)	19 (61.3)	
Histopathology				
Adeno	14 (27.5)	23 (25.8)	6 (19.4)	0.707
Squamous cell	37 (72.5)	66 (74.2)	25 (80.6)	
Tumour site				
Upper thoracic	2 (3.9)	9 (10.1)	1 (3.2)	0.260
Mid thoracic	24 (47.1)	30 (33.7)	16 (51.6)	
Lower thoracic	25 (49.0)	50 (56.2)	14 (45.2)	
Tumour grade				
Well	7 (15.7)	9 (10.1)	2 (6.5)	0.601
Moderate	33 (64.7)	55 (61.8)	20 (64.5)	
Poor	10 (19.6)	25 (28.1)	9 (29.0)	
T stage				
T1 & T2	9 (17.6)	9 (10.1)	1 (3.2)	0.006*
T3	27 (52.9)	39 (43.8)	8 (25.8)	
T4 a & b	15 (29.5)	41 (46.1)	22 (71.0)	
N stage				
N0	5 (9.8)	7 (7.9)	1 (3.2)	0.816
N1	17 (33.3)	29 (32.6)	8 (25.8)	
N2	18 (35.3)	29 (32.5)	11 (35.5)	
N3	11 (21.6)	24 (27.0)	11 (35.5)	
M: Metastasis				
No	39 (76.5)	61 (68.5)	14 (45.2)	0.011*
Yes	12 (23.5)	28 (31.5)	17 (54.8)	

T: Tumour, N: Node, M: Metastasis, SD: Standard deviation.

(*p*=0.006) and metastasis (*p*=0.011). However, age, gender, histopathology, tumour site, tumour grade, and node stage were not significantly associated with tumour length groups (*p*>0.05) (Table 2).

Univariate analysis revealed that T3 individuals were more likely to be in the highest tumour length group of >10cm as compared to the <5cm group (RRR=13.20; 95%CI: 1.51-115.34; *p*=0.020). Individuals with metastasis were more likely to be in the highest tumour length group compared to the <5cm group (RRR=3.94; 95%CI: 1.51-10.29; *p*=0.005). No significant association was detected between age, gender, histopathology, tumour site, tumour grade, and cN stage with tumour length >10cm.

In multivariate analysis, T3 patients were still significantly associated with tumour length group >10cm compared to the <5cm group (RRR: 10.86; 95%CI: 1.13-104.14; *p*=0.039), while age, gender and metastasis did not show any significant association (p>0.05). No significant association was observed for any clinical variable with tumour length 5-10cm in both univariate and multivariate analyses when compared with the <5cm group, and, hence, no graded dose-response relationship was observed (Table 3).

Discussion

The current study underscores the significant role of tumour length in the staging and management of OC, showing a prominent association with established cTNM.

Recent studies have shown that larger tumour sizes are linked with poorer prognosis, but most of these studies have focussed on the significance of tumour length in correlation with pathological TNM (pTNM) staging rather than cTNM, which forms the basis for major treatment decisions.[10-12] Bollschweiler et al. found significant correlations between tumour length and the tumour stages, while Zhang et al. demonstrated significant outcomes when comparing tumour lengths with tumour and node stages.[9] The current study observed a somewhat similar and pronounced trend in the cohort.

However, the link between tumour size and metastasis is not unprecedented, and studies have hinted at a similar connection, suggesting LSTs might facilitate a more favourable environment for cancer cell dissemination.[14] These findings align with the notion that greater tumour length/mass could potentially provide a greater source of circulating tumour cells, which could contribute to the heightened likelihood of metastatic progression. However, it is essential to recognise that the underlying mechanisms driving this association are likely to be multifaceted, including local tissue invasion, immune response, angiogenesis and other cellular interactions.

Furthermore, in the positive metastasis group in the current study, there was a notable increase in RRR value for tumour length >10cm. This higher RRR indicates a stronger risk of metastasis with larger tumour lengths, suggesting that tumours >10cm could potentially serve as predictive markers for a higher risk of metastasis in OC. These findings support previous evidence suggesting a similar pattern, where Mehta et al. proposed that tumour size >3cm was a significant risk factor for metastasis.[15]

Moreover, in the current cohort, larger tumour lengths (5-10cm and >10cm) in T3 stage tumours showed a substantial increase in RRR, reflecting the potential interplay between tumour size, local invasiveness, and disease progression. The absence of significant association of tumour length with T1-T2 and T4a-b stages further suggests that tumour size's impact on these stages either may be less pronounced, or influenced by other factors that were not explored by the current study.

The current study has several limitations as the sample size was relatively small, which may have affected the

Table-3: Univariate and multivariate multinomial logistic regression analyses.

	Univariate Tumour length ratio				Multivariate Tumour length ratio			
	5 cm to 10 cm Relative risk ratio (95% CI)	*p*-value	>10 cm Relative risk ratio (95% CI)	*p*-value	5 cm to 10 cm Relative risk ratio (95% CI)	*p*-value	>10 cm Relative risk ratio (95% CI)	*p*-value
Age (years)	0.99 (0.97-1.02)	0.613	1.01 (0.98-1.05)	0.336				
Gender								
Male	1		1					
Female	1.61 (0.81-3.23)	0.176	2.08 (0.84-5.18)	0.113				
Histopathology								
Adeno	1							
Squamous cell	1.08 (0.49-2.36)	0.836	1.57 (0.53-4.65)	0.41				
Tumour site								
upper thoracic	1		1					
mid thoracic	0.44 (0.08-2.21)	0.322	1.12 (0.09-13.48)	0.929				
lower thoracic	0.27 (0.05-1.40)	0.122	1.33 (0.11-15.96)	0.82				
Tumour grade								
well	1		1					
moderate	2.22 (0.66-7.39)	0.193	3.60 (0.60-21.60)	0.161				
poor	1.48 (0.52-4.22)	0.461	2.42 (0.46-12.57)	0.292				
T stage								
T1 & T2	1		1		1		1	
T3	2.73 (0.91-8.18)	0.072*	13.20 (1.51-115.34)	0.020*	2.65 (0.82-8.55)	0.101	10.86 (1.13-104.14)	0.039*
T4 a & b	1.44 (0.51-4.11)	0.491	2.66 (0.29-24.34)	0.385	1.45 (0.50-4.20)	0.494	3.04 (0.31-29.47)	0.336
N stage								
N0	1		1					
N1	1.55 (0.40-6.02)	0.52	5.00 (0.49-50.06)	0.171				
N2	1.15 (0.32-4.17)	0.831	3.05 (0.31-29.70)	0.336				
N3	1.22 (0.33-4.44)	0.765	2.35 (0.23-23.60)	0.467				
M: Metastasis								
No	1		1		1		1	
Yes	1.49 (0.67-3.27)	0.319	3.94 (1.51-10.29)	0.005*	1.54 (0.43-5.51)	0.503	1.58 (0.35-7.13)	0.549

Univariate multinomial logistic regression presented relative risk ratio of all independent covariates while multivariate multinomial logistic regression presented relative ratio of covariates after mutual adjustments; T: Tumour, N: Node, M: Metastasis, SD: Standard deviation.

generalisability of the findings. Additionally, the study was conducted at a single centre, potentially limiting diversity of the patient population to some extent. Future studies with larger, multi-centre cohorts are necessary to validate the findings.

Conclusion

Tumour length determined by pre-neoadjuvant CT scans in OC staging significantly correlated with cTNM staging. This association can significantly enhance the ability to make informed treatment decisions for OC patients in South Asia.

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Author Contribution:

SQ: Concept, literature review and critical appraisal.
WAA: Literature review, data interpretation and writing.
HAJ: Literature review and data collection.
HFW: Data analysis and interpretation.
MSQ: Supervision, critical appraisal and final approval.