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A single center experience

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The prognostic value of Tumor Volume Index in patients with esophageal cancer who had curative resection. A single center experience

AIM: *We aim to evaluate the prognostic significance of tumor volume in esophageal cancer.*
METHODS: *Patients who underwent curative resection due to esophageal cancer between the years 2015 and 2019 were included in the study. The Tumor Depth Parameter (TDP) was defined as mucosa and submucosa =1, muscularis propria =2, adventitia =3, and invasion into adjacent organs=4. The Tumor Volume Index (TVI) was defined as the major axis X the minor axis X TDP. Two groups were formed based on TVI: Group 1 (low TVI) and Group 2 (high TVI). In the groups; patients were compared in terms of demographic and clinical features, intraoperative and postoperative outcomes, characteristics of the tumor and average survival.*
RESULTS: *The patients were divided into two groups based on the cut-off value of 4,000. Group 1 (low TVI) consisted of 16 patients and Group 2 (high TVI) consisted of 28 patients. Male sex ratio was higher in Group 2 (50% vs 85%, p:0.011) Tumor diameter was observed to be larger in Group 2 (3.06 vs 5.54, p:0.000). Adenocarcinoma histologic type was more common in Group 2 (25% vs 64.3%, p:0.012). Incidence of respiratory complications was higher in Group 2 (0% vs 35.7%, p:0.024),Survival time (months) was shorter in Group 2 (36 vs 11, p:0.005). TVI's being over 4000 (HR)(95%-Confidence Interval ((Cl) 0.057 (0.011-0.311),p:0.001) was an independent risk factor to determine the rate of survival.*
CONCLUSION: *TVI can be used as a prognostic factor in patients with esophageal cancer who underwent surgical therapy. TVI is closely associated with tumor histology and postoperative outcomes.*

KEY WORDS: Esophageal cancer, Prognosis, Postoperative complication, Surgical manangment, Survey, Tumor volume,

Introduction

According to the statistics from 2018; esophageal cancer is the 7th most common malign tumor with 572,000 new cases worldwide, and the sixth most common cause of cancer-related mortality with 509,000 deaths [1]. In spite of the advancements in surgical and neoadjuvant therapies, prognosis is still poor. Most of the patients with esophageal cancer die within 1 year following the diagnosis. Only 8% to 20% of patients survive for 5 years after the first diagnosis. A 5-year survival of approximately 17%, and an average survival time of 18 months are reported [2,3].

Prognostic factors play a significant role in predicting survival and determining optimal therapeutic strategies in patients with esophageal cancer. Tumor-Nodes-Metastases (TNM) stage is the most significant prognostic factor. However, many studies have found that

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the prognosis is different even for patients that are in the same TNM stage. Therefore, defining the other prognostic factors is significant in terms of determining suitable treatment strategies [4,5]. In many studies in the literature; pathological state of the lymph nodes, tumor invasion depth, and a lot of molecular markers, and the combination thereof in patients with esophageal cancer have been identified as prognostic factors [6,7].

According to the TNM classification of the Union for the International Cancer Control (UICC); tumor diameter is included in the staging systems for lung cancer, breast cancer, and many other cancers. This is because tumor diameter has prognostic value in these diseases. However, tumor diameter is not included in esophageal cancer staging system; however, some studies suggest that tumor diameter and length might have a prognostic value in this malignancy [4,6,8,9]. In their study, Miyamoto [4] introduced the pathological tumor volume index for esophageal cancer. The pathological Tumor Volume Index (TVI) was defined as the major axis x the minor axis x The Tumor Depth Parameter (TDP). In their study, they found TVI as a prognostic factor for survival.

Our clinical experience suggests that the diameter and volume of malign esophageal tumors might affect the results of the patients independently of the TNM stage. Starting from this, in our study, we aim to determine the relationship between Tumor Volume Index (TVI) and the postoperative complications and prognosis in patients who underwent curative esophagectomy due to esophageal cancer.

Methods

Forty-four patients who underwent curative esophagectomy due to esophageal cancer between the years 2015 and 2019 were included in this study. This retrospective study was approved by the Erciyes University Institutional Review Board (IRB No. 2020/264, dated 10.06.2020.) A prospective common data base was created by investigating patients' files and the hospital information system records. Patients were analyzed retrospectively using this data base. Patients whose records could not be accessed and whose pathological diagnosis were not malign were excluded from the study.

The cut-off value was determined using the receiver operating characteristic curves (ROC curves). The patients were divided into two groups according to the cut-off value: Group 1 (low TVI) and Group 2 (high TVI). These two groups were compared in terms of their demographic and clinical features, body mass index (BMI), American Society of Anesthesiologists (ASA) scores, localization of the tumor (Upper 1/3 and cervical esophagus, Middle 1/3, Lower 1/3, gastro oesophageal junction (GOJ) and cardia), pathological types, differentiation levels, TNM stages, numbers of total and metastatic lymph nodes excised, lymph node positivity, tumor diameters, anastomosis types, duration of operation, average blood loss, intraoperative complications, status of postoperative complications according to the Clavien-Dindo classification[10], respiratory complications, wound site infection, anastomosis leakages, postoperative hospitalization durations and 90-day unplanned rearrival at the hospital and reoperation and average survival time.

Anastomotic leakage was defined as disruption of anastomotic integrity authenticated with a combination of clinical, radiological and operative tools. Tumor-nodes-metastases (TNM) 2010 or 2016 systems were used in tumor staging [11,12]. Unplanned hospitalization within the first 90 days following discharge was accepted as unplanned rearrival at the hospital. In line with the definition of American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), we acknowledged unplanned reoperation as a surgical procedure with general, spinal or epidural anaesthesia within 30 days following the index operative procedure for reasons other than follow-up procedures that are based on pathology results [13].

Operative Technique

Transthoracic esophagectomy open resection of the esophagus employing thoracotomy, including all single-, 2- and 3-stage procedures utilizing either a right or left thoracotomy or thoracoabdominal incision

Tumor Volume Evaluation

Tumor volume was measured as part of the routine pathological assessment by visual estimation. The area of the tumor was outlined and measured in the x- and y-axes, where x was the diameter of the major axis (MM) and y was the diameter of the minor axis (MM) of the largest area. The Tumor Depth Parameter (TDP) was defined as mucosa and submucosa = 1, muscularis propria = 2, adventitia = 3, and invasion into adjacent organs = 4. The Tumor Volume Index (TVI) was defined as X x Y x TDP.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 23.0 was used in the statistical analysis of data. Categorical measurements were summarized in numbers and percentages, whereas continuous measurements were summarized as averages and standard deviation (median and minimum-maximum, where necessary). Pearson's Chi-squared test statistic was employed in the comparison of categorical variables. Shapiro-Wilk test was employed in determining whether the parameters in the study dis-

played a normal distribution or not. Distributions were examined during the comparison of continuous measurements between the groups, and independent Student's t-test was used for parameters displaying a normal distribution and the Mann Whitney U tests were used for parameters not displaying a normal distribution. In the study, the cut-off value was determined by estimating the sensitivity and specifity values for the TVI value taking survival as a basis and by investigating the area under the ROC curve. Kaplan-Meier analysis and Log Rank test were used in survival analyses. 0.05 was acccepted as the statistical significance level in all tests.

Results

A total of 44 patients were included in our study. To confirm TVI cutoff value, we used the receiver operating characteristic (ROC) curve (Fig. 1). The patients were divided into two groups based on the cut-off value of 4000: Group 1 (low TVI) and Group 2 (high TVI). Group 1 consisted of 16 patients and Group 2 consisted of 28 patients.

Age average was similar in the groups. Male sex was predominant in both groups and the male sex ratio was higher in Group 2 (p:0.011). ASA score distribution and BMI were similar. Preoperative hemoglobin (HGB) levels were similar (p: 0.883). Albumin level was lower in Group 2 (p:0.044). Preoperative CEA level was higher in Group 2 (p:0.008). The tumor was most frequently located in Lower 1/3 in both groups (Table I).

The anastomosis technique, duration of the operation , intraoperative blood loss , and presence of intraoperative complications were similar in the groups(Table II).

Tumor diameter was observed to be larger in Group 2 (p:0.000). Adenocarcinoma histologic type was more common in Group 2 (p:0.012). Tumor differentiation was similar in both groups ; T3 and T4 were higher in Group 2 (p:0.00), and the N stage was similar . Number of lymph nodes dissected and number of metastatic lymph nodes were similar in the groups (Table III).

Incidence of respiratory complications was higher in Group 2 (p:0.025). Anastomosis leakage , wound complication (and distribution of complications according to the Clavien-Dindo classification were similar in the groups. None of the patients needed reoperation. Postoperative duration of hospital stay was longer in Group 2 (p:0.00). Incidence of rearrival at the hospital within 90 days was similar (Table IV).

Survival time was shorter in Group 2 (36 months vs 11 months, p:0,005). Survival times are shown in Fig. 2 and Table V.

In the univariate and multivariate analysis carried out to determine survival rates; TVI's being over 4000 (HR (95%-CI) 0.057 (0.011-0.311), p: 0.001), the patient's being over 65 (p:0.004), increased differentiation (p:0.024), T3 (p: 0.038), T4 (p:0.023), Stage 3 (p: 0.016), tumor's being located in Lower 1/3 (p: 0.024) and lower 1/3 + cardia (p: 0.018) were independent risk factors. Factors associated with overall survival are shown in Table VI.

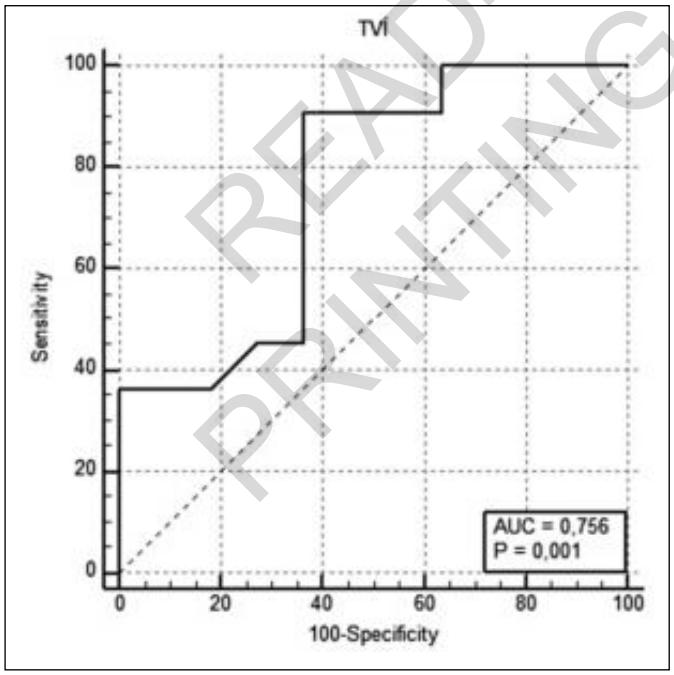

Fig. 1: Receiver operating characteristic (ROC) curve of the Tumor Volume Index (TVI). ROC curve analysis for prognostic factor in patients with esophageal carcinoma. As a result, the prognostic TVI cutoff value was set at 4000.

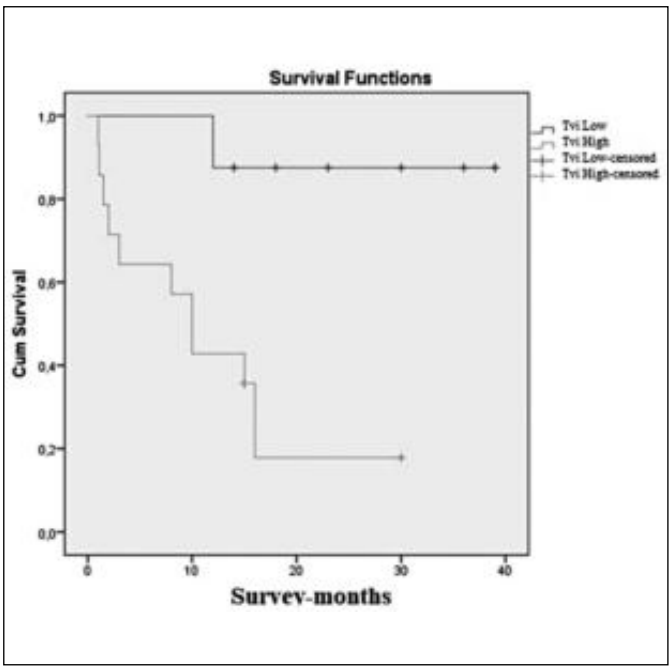

Fig. 2: Average survival graphic of TVI groups.

TABLE I - *Demographic characteristics and preoperative findings of the patients*

		Group 1 Low TVI (n: 16)	Group 2 High TVI (n: 28)	p
Age		60,13±7,49(50-73)	63,86±15,22(27-86)	0,365
Sex	Male	8 (50,0)	24 (85,7)	0,011
	Female	8 (50,0)	4 (14,3)	
ASA score	1	3 (18,8)	9 (32,1)	0,625
	2	10 (62,5)	15 (53,6)	
	3	3 (18,8)	4 (14,3)	
BMI		23,91±4,94(16-34)	22,35±2,91(18-30)	0,221
Preoperative Hgb (gr/dl)		13,10±1,16(11,3-14,7)	12,79±3,14(7,3-18,6)	0,883
Preoperative albumin (gr/dl)		4,16±0,43(3,60-4,70)	3,82±0,58(2,50-4,50)	0,044
Preoperative CEA (ng/ml)		3,93±4,69(0,79-13,9)	9,15±10,53(0,5-41,3)	0,008
Tumor localization	Lower 1/3	12 (75,0)	20 (71,4)	0,064
	Lower 1/3+Cardia	0 (0,0)	6 (21,4)	
	Middle 1/3	2 (12,5)	2 (7,1)	
	Cervical oesophageal	2 (12,5)	0 (0,0)	

Values are presented as mean ± standard deviation (minimum-maximum) or number (%),ASA -American Society of Anesthesiologist ,BMI-Body Mass Index

TABLE II - *Intraoperative characteristics*

		Group 1 Low TVI (n: 16)	Group 2 High TVI (n: 28)	p
Anastomosis Technique	Handsewn	4 (25,0)	6 (21,4)	0,533
	Stapler	12 (75,0)	22 (78,6)	
Duration of operation		272,50±74,40(180-420)	271,07±90,88(140-450)	0,932
Intraoperative blood loss		263,13±185,67(50-600)	213,93±151,15(10-600)	0,563
Intraoperative complications	Yes	2 (12,5)	0 (0,0)	0,127
	No	14 (87,5)	28 (100,0)	

Values are presented as mean ± standard deviation (minimum-maximum) or number (%)

TABLE III - *Tumor characteristics*

		Group 1 Low TVI (n: 16)	Group 2 High TVI (n: 28)	p
Tumor diameter (min-max)	3,06±0,97(2-5)	5,54±1,36(4-9)	0,000	
Pathology	Adenocarcinoma	4 (25,0)	18 (64,3)	0,012
	Squamous Cell Carcinoma (SCC)	12 (75,0)	10 (35,7)	
Differentiation	High grade	4 (25,0)	14 (50,0)	0,134
	Low grade	4 (25,0)	2 (7,1)	
	Middle grade	8 (50,0)	10 (35,7)	
	Signet-ring	0 (0,0)	2 (7,1)	
Pathologic T	T1	2 (12,5)	2 (7,1)	0,000
	T2	10 (62,5)	0 (0,0)	
	T3	2 (12,5)	20 (71,4)	
	T4	2 (12,5)	6 (21,4)	
Pathologic N	N0	4 (25,0)	2 (7,1)	0,097
	N1	12 (75,0)	26 (92,9)	
Pathologic TNM staging	Stage1B	6 (37,5)	2 (7,1)	0,000
	Stage 2B	6 (37,5)	2 (7,1)	
	Stage 3A	2 (12,5)	2 (7,1)	
	Stage 3B	2 (12,5)	22 (78,6)	
Total number of lymph nodes dissected		29,63±8,57(21-44)	26,29±11,11(12-52)	0,304
Number of metastatic lymph nodes		6,00±7,60(0-24)	8,14±5,73(0-18)	0,077

Values are presented as mean ± standard deviation (minimum-maximum) or number (%)

TABLE IV - *Perioperative and Postoperative Clinical Outcomes, Oncologic outcomes*

		Group 1 Low TVI	Group 2 High TVI	p
Respiratory complications	None	16 (100,0)	18 (64,3)	0,025
	Pneumonia	0 (0,0)	2 (7,1)	
	Unplanned reintubation	0 (0,0)	8 (28,6)	
Anastomotic Leakage	Yes	1 (6,3)	3 (10,7)	0,537
	No	15 (93,8)	28 (89,3)	
Wound complication	Yes	2 (12,5)	6 (21,4)	0,380
	No	14 (87,0)	22 (78,6)	
Complications according to Clavien-Dindo classification	Grade 2	10 (62,5)	12 (42,9)	0,132
	Grade 3a	6 (37,5)	8 (28,6)	
	Grade 3b	0 (0,0)	4 (14,3)	
	Grade 5	0 (0,0)	4 (14,3)	
Postoperative hospital stay (min-max)		11,31±2,75(7-16)	25,75±15,87(9-60)	0,000
Rearrival at the hospital within 90 days	Yes	4 (25,0)	3 (10,7)	0,205
	No	12 (75,0)	25 (89,3)	
Actual Situation	Dead	2 (12,5)	20 (71,4)	0,000
	Alive	14 (87,5)	8 (28,6)	
Postoperative 90-day mortality	Yes	0 (0,0)	10 (35,7)	0,005
	No	16 (100,0)	18 (64,3)	

Values are presented as mean ± standard deviation (minimum-maximum) or number (%)

TABLE V - *Survival times of TVI groups*

		Average	95% Confidence Interval		
TVI	**Estimated Average Survival Time**	**Standard Error**	**Lower Limit**	**Upper Limit**	**p**
Low	35.62	2.32	31.25	40	0,000
High	11.90	2.13	7.72	16.07	

TABLE VI - *Analysis of factors associated with overall survival in Esophageal Cancer*

Measurements		**Univariate**	**Multivariate**	
		p	**HR (95% - CI)**	**p**
Age	65	0,002	1,000	0,004
	<65		0,127 (0,032-0,509)	
Sex	Female	0,005	1,000	0,013
	Male		8,333 (1,556-44,642)	
Asa score	1-2	0,680	1,000	0,681
	3		1,407 (0,276-7,182)	
Tumor Diameter	<5	0,178	1,000	0,184
	> 5		0,400 (0,104-1,544)	
Differentiation	High	0,134	1,000	0,024
	Low		1,600 (0,273-2,950)	0,999
	Middle		1,292 (0,573-2,103)	0,942
T	T1	0,000	1,000	0,119
	T2		0,975 (0,752-1,354)	0,547
	T3		1,124 (0,942-1,852)	0,039
	T4		1,253 (0,652-1,958)	0,023
N	N0	0,097	1,000	0,235
	N1		0,543 (0,212-1,975)	
Pathologic TNM staging	Stage 1-2	0,011	1,000	0,016
	Stage 3		0,185 (0,047-0,729)	
Tumor Localization	Lower 1/3	0,010	1,000	0,024
	Lower 1/3+Cardia		0,886 (0,458-1,345)	0,018
	Middle 1/3		1,025 (0,658-1,738)	0,314
	Cervical oesophageal		0,957 (0,235-1,671)	0,285
Anastomotic Leakage	Yes	0,284	1,000	0,317
	No		3,316 (0,317-34,654)	
TVI score	< 4000	0,000	1,000	0,001
	> 4000		0,057 (0,011-0,311)	

Discussion

Surgical therapy or radiation therapy are primary treatment modalities for esophageal cancer. Pre-treatment precise staging is critical for development of a personalized treatment program, and increases the efficiency of the treatment and prognostic accuracy [14].

Many scientific studies have recently shown that such clinical parameters as the anterior-posterior extension of the primary tumor, and tumor volume, which is still known as tumor burden, are associated with general final outcomes [15]. In the literature, tumor volume is predicted to be associated with general survival in laryngeal, lung, kidney and prostate cancers [16-19].

Studies relating to the prognostic significance of tumor volume in esophageal cancer have concentrated on Squamous Cell Carcinoma (SCC), which is treated with radiotherapy, in particular. In these studies, tumor volume is measured through imaging methods. Créhange et al reported for the first time in 2006 that tumor volume affects the results of esophageal cancer. They analyzed 148 patients with esophageal cancer who were treated with radiotherapy retrospectively and demonstrated that patients with a tumor volume of ≥100 cm^3 had significantly poorer average survival rates than patients with a tumor volume of <100 cm3 (p:0.041) [20]. In a similar study, Chen et al [15] demonstrated that tumor volume is a prognostic factor for esophageal SCC patients treated with definitive radiotherapy. Patients with a gross tumor volume (GTV) of >9.41 cm^3 had significantly poorer progression-free survival and overall survival rates than patients with a GTV of <39.41 cm^3 (P=0.000 and P=0.000, respectively) .

Studies on esophageal cancer that is treated with surgery concentrate more on tumor diameter and tumor length [6,22]. In fact, tumor length combined with tumor diameter might reflect the gross tumor volume to some extent but, still, volume is completely different from that. While the first two parameters represent the initial characteristics of the tumor, volume is based on a secondary calculation [21]. Vadhwana, B[22]. evaluated patients with esophageal adenocarcinoma and SCC that underwent surgical therapy. In her study, in which she found the average tumor length to be 3 cm; tumors that were longer than 3 cm had a higher incidence of local recurrence (p=0.028), metastasis (p=0.016), disease progression (p=0.001), and shorter progression-free survival (p=0.001). In the study carried out by Ma, M et al, a tumor length of over 4.0 cm was again observed to be associated with poorer general survival rates than shorter tumors (P<0.001). Tumor length of over 4.0 cm was associated with advancing T stage (P=0.001), N stage (P=0.046) and increasing tumor differentiation (P=0.033) [6]. It can be concluded from these studies that increasing tumor diameter and length are associated with an advanced T stage.

In their study carried out based on growing evidence; Miyamoto et al [4] included the depth of the tumor in the layers of the esophagus as well as tumor length and diameter. In their study, high volume tumors were significantly deeper and larger, and involved more lymph node metastasis. TVI had a significant adverse effect on general survival. Five-year general survival rates of 63.5% and 27.9% were identified in low and high volume tumors, respectively. In groups classified under the N stage, TVI was an independent prognostic factor in patients with a pN0/N1 tumor. However, tumor volume did not have an effect on prognosis in patients with advanced lymph node metastasis (pN2/N3).

The main difference between our study and the study of Miyamoto, H et al [4] is that we included patients with adenocarcinoma pathology in our study, as well, and adenocarcinoma histologic type was more dominant in the group with high TVI. Unsurprisingly, TVI was associated with increased tumor diameter and depth of invasion. Patients with a high TVI were concordantly at a more advanced stage. High tumor volume was associated with increased tumor marker levels and decreased albumin levels. We can associate decreased albumin levels with malnutrition, tumor-related increased consumption and increased systemic inflammatory response. We found respiratory complications to be associated with increased tumor volume. Duration of hospitalization due to increasing complication rates was prolonged in this group. High tumor volume was also associated with 90-day mortality. Average survival was distinctively shorter in patients with a high TVI than those with a low TVI. In the multivariate analysis we carried out to determine survival rate, TVI was an independent risk factor at a cut-off value of 4000. Other risk factors were, unsurprisingly, advanced age, male sex, degree of differentiation, T stage, pathological stage and tumor localization. The most significant limitation of our study was its retrospective design and inclusion of a limited number of patients. Furthermore, the correlation between TVI and the actual tumor volume is unclear because it is very difficult to measure the actual tumor volume.

Conclusion

In our study, we determined that pathologic TVI is a significant independent prognostic factor in patients with esophageal carcinoma. Furthermore, TVI was closely associated with tumor histologic type, depth of invasion and postoperative outcomes. We believe that TVI can be included in esophageal cancer staging system.

Riassunto

Si è voluto valutare il significato prognostico del volume del tumore nel cancro esofageo. Per questo sono stati inclusi nello studio i pazienti sottoposti a resezione cura-

tiva di cancro esofageo nell'intervallo tra il 2015 e il 2019. Il Tumor Depth Parameter (TDP) è stato definito come mucosa e sottomucosa = 1, muscolare propria = 2, avventizia = 3 e invasione negli organi adiacenti = 4. Il Tumor Volume Index (TVI) è stato definito come l'asse maggiore X l'asse minore X TDP. Sono stati formati due gruppi sulla base del TVI: Gruppo 1 (TVI basso) e Gruppo 2 (TVI alto). Nei gruppi; i pazienti sono stati confrontati in termini di caratteristiche demografiche e cliniche, esiti intraoperatori e postoperatori, caratteristiche del tumore e sopravvivenza media.

Risultati: I pazienti sono stati divisi in due gruppi in base al valore di cut-off di 4.000. Il gruppo 1 (TVI basso) era composto da 16 pazienti e il gruppo 2 (TVI alto) era composto da 28 pazienti. Il rapporto tra i sessi maschili era più alto nel gruppo 2 (50% vs 85%, p: 0,011) Il diametro del tumore è stato osservato essere maggiore nel gruppo 2 (3,06 vs 5,54, p: 0,000). Il tipo istologico di adenocarcinoma era più comune nel gruppo 2 (25% vs 64,3%, p: 0,012). L'incidenza delle complicanze respiratorie è stata maggiore nel Gruppo 2 (0% vs 35,7%, p: 0,024), il tempo di sopravvivenza (mesi) è stato più breve nel Gruppo 2 (36 vs 11, p: 0,005) .TVI è superiore a 4000 (HR) (95 L'intervallo di confidenza% ((CI) 0,057 (0,011-0,311), p: 0,001) è stato un fattore di rischio indipendente per determinare il tasso di sopravvivenza.

Conclusione: TVI può essere utilizzato come fattore prognostico nei pazienti con cancro esofageo sottoposti a terapia chirurgica. La TVI è strettamente associata all'istologia del tumore e agli esiti postoperatori.

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