ISSN : 2350-0743

www.ijramr.com

International Journal of Recent Advances in Multidisciplinary Research
Vol. 09, Issue 10, pp.8099-8103, October, 2022

RESEARCH ARTICLE

ANALYSES ON LYMPH NODES METASTASES PATTERN AND FACTORS RELATED TO SURVIVAL AFTER THORACIC ESOPHAGEAL CANCER SURGERY: A SYSTEMATIC LITERATURE REVIEW

Keita M[1, 2, *], Bah Malick[2], Kondano S.Y[3], Camara A.[2], Kouyaté Kaïra[3], Shen WB.[1], Traoré B[2] and Zhu SC.[1]

[1]Department of Radiotherapy, the Fourth Hospital, Hebei Medical University, Shijiazhuang, 050011, China
[2]Surgical Oncology Unit of Donka University Hospital, Conakry, 5575, Guinea
[3]Department of General Surgery - Ignace Deen National Hospital, Conakry, 1263, Guinea

ARTICLE INFO

Article History:
Received 28th July, 2022
Received in revised form
29th August, 2022
Accepted 17th September, 2022
Published online 30th October, 2022

Keywords:

Esophageal Carcinoma; Lymphnode Metastasis; Radiotherapy; Target Delineation.

ABSTRACT

Objective: To investigate the clinicopathological factors for thoracic esophageal cancer after radical esophagectomy, and provide the criteria to outline the target volume for adjuvant radiotherapy. ***Methods:*** Data from 803 patients with thoracic esophageal cancer who underwent radical esophagectomy between January 2014 and December 2018 were reviewed. The lymph nodes metastases and the clinicopathological factors for esophageal cancer were stratified by univariate and multivariate Cox regression analyses. ***Results:*** A total of 6,216 lymph nodes were dissected with an average of 9.5 lymph nodes. The lymph nodes metastases in the upper thoracic esophagus were mainly observed in the supraclavicular and paratracheal regions ($P<0.05$), metastatic lymph nodes in the middle thoracic esophagus were bidirectional, and those in the lower third of the esophagus mainly metastasized to the regions adjacent to the esophagus, the cardia and the left gastric artery ($P< 0.05$). For the whole group, the lymph node metastases rate was 32.2% for upper thoracic esophageal cancers, which was significantly lower than 44.0% for lower thoracic esophageal cancers ($P=0.049$) and 44.3%of middle thoracic esophageal cancers ($P = 0.030$). Multivariate analyses showed that patient performance status, T- stage, tumor length, and distant metastases were factors associated with overall survival, with $P< 0.05$ for all. ***Conclusion:*** Patient performance status, T- stage, tumor length, distant metastases, and operative procedures were the most important factors for overall survival. Therefore, in clinical practice, patients undergoing postoperative prophylactic radiotherapy may be selected according to these factors.

INTRODUCTION

Esophageal cancer (EC) is the eighth most common cancer in the world and is still dominated by squamous cell carcinoma (Marabotto, 2021). Compared to the United States of America and Europe, the incidence and mortality of EC in China are significantly high: 477,900 new cases are diagnosed each year, and about 375,000 people die from this disease each year, making it the fourth leading cause of death among all malignancies (Keita, 2018). Although surgical resection preceded by neoadjuvant treatments represents the standard of care for treatment in patients with locally advanced EC, definitive chemoradiotherapy is also known as a potentially curative non-surgical option for these patients, with reported 5-year survival rates in the range of 25–30% (Leng, 2021). For many years, several studies have shown that the tumor stage and lymph node metastases are the most important prognostic factors after radical esophagectomy. Moreover, adjuvant radiotherapy has the advantage of selecting patients based on pathological findings; in contrast, there are issues with patient tolerability after surgery and difficulties in target volume delineation because of the anatomy change. Nowadays, it is well known that lymph node metastases in thoracic EC are multidirectional, and the relationship between the distribution and pattern of lymph node metastases and the extent of the target volume for postoperative prophylactic radiotherapy is of major interest (Leng, 2021; Waters, 2022). In this setting, we retrospectively analyzed the pattern of lymph node metastases and prognostic factors associated with the overall survival of patients with thoracic EC. In addition, we discussed the indicative value of the lymph node metastases area for delineating the target volume for postoperative prophylactic radiotherapy.

***Corresponding author:** Keita M.,*
Department of Radiotherapy, the Fourth Hospital, Hebei Medical University, Shijiazhuang, 050011, China.

METHODS

Patient and tumor characteristics: We reviewed the database of 1013 patients, 803 of whom were diagnosed with thoracic EC and underwent radical surgery at The Fourth Hospital Affiliated to Hebei Medical University between January 2014 and December 2018.

They all had CT scans of the neck, chest and abdomen before surgery and had complete clinicopathological data. Of the 803 patients, 560 were males and 243 were females, with a male to female ratio of 2.3: 1; ages ranged from 27 to 89 years, with a median age of 68 years Table 1. The lesions were located in the upper thoracic esophagus in 118 cases, in the middle thoracic esophagus in 514 cases, and in the lower thoracic esophagus in 171 cases. The barium esophagogram showed that the length of the lesion was ≤ 5.0 cm in 528 cases, and 275 cases >5.0 cm. The postoperative pathological tumors stages were Tis stage 16, T1 -3 stage 669, and T4 stage 118, N0 stage 501, N1 stage 302, M0 stage 767, M1 stage 36. There were 56 cases in stage 0 - I, 372 cases in stage IIA, 71 cases in stage IIB, 212 cases in stage III, 56 cases in stage IVA and 36 cases in stage IVB. There were 738 cases of squamous carcinoma, 36 cases of small cell carcinoma, 12 cases of adenocarcinoma cases, and 17 cases of other types. The degree of differentiation was high 36 cases and 657 cases were moderately differentiated, 87 cases were poorly differentiated and 23 cases were undifferentiated Table 1. In the whole group, there were 302 (37.6%) cases of positives lymph nodes metastases, of which 152 cases had one lymph node metastases, 83 cases had 2, 19 cases had 3 and 48 cases of >4. Radical esophagectomy was performed in 621 cases using a single left incision (thoracotomy), 95 cases using a combined double incision (cervicothoracotomy)and 87 cases using a combined triple incision (cervicothoraco- laparotomy).

Evaluation criteria: The TNM staging was based on the 2017 UICC criteria (Bertero, 2018), and the grouping of regional lymph nodes in thoracic EC was based on the American Thoracic Society grouping criteria (Hu, 1988).

Follow-up: All patients were followed up to 31 September 2020, with a follow-up time range of 1 - 84.6 months and a median follow-up time of 36.7months. The follow-up rate was 97.3% and 22 patients were lost to follow-up. The survival time was calculated from the date of surgery to death or the date of last follow-up.

Statistical analysis: The SPSS 23.0 software package was used for statistical analysis of the data, multivariate logistic regression analysis was used to test for correlation between lymph node metastases and clinicopathological factors, and the Kaplan-Meier method was used for survival analysis. P≤ 0.05 was considered as statistically significant.

RESULTS

Patients with thoracic EC who underwent radical esophagectomy were recruited from 2014 and 2018; a total of 6,216 lymph nodes were dissected in 803 patients, with an average of 9.7 lymph nodes cleared (range: 0 - 36 nodes per patient). The histopathological analyses confirmed 824 positive lymph nodes, with a metastases rate of 13.3%. Of the 803 EC patients, positives lymph nodes metastases were observed in 302 patients, with a metastases rate of 37.6% Table 2. The postoperative lymph nodes metastases rate and metastases ratio in the thoracic and abdominal cavities for the whole group are shown in Table 2. Metastases were mainly located in the pulmonary artery, supraclavicular, paratracheal, pulmonary hilum para-esophageal, cardia and left gastric artery area. As shown in Tables 3, there was no significant difference in lymph nodes metastases ratio regarding the primary tumor site. The lymph nodes metastases ratio in upper, mid and lower thoracic esophagus were 11.4%, 13.6% and 12.8%, respectively ($\chi2$= 0.535, P=0.813). By contrast, the lymph nodes metastases rates were 32.2%, 44.0% and 44.3%, respectively, and the differences were statistically significant when comparing mid and lower esophageal carcinomas to the upper thoracic esophageal carcinoma ($\chi2$=5.173, P=0.035; $\chi2$=5.632, P=0.020) Tables 3. The metastases in the upper thoracic EC are most prevalent in the supraclavicular and paratracheal lymph nodes; metastases in mid-thoracic EC are bilateral; upstream metastases occur mainly in the supra-clavicular, paratracheal and para-esophageal lymph nodes; downstream metastases occur mainly in the cardia and lymph nodes adjacent to the left gastric artery; metastases in the lower thoracic EC mainly occur to the para-oesophageal, cardia and left gastric artery lymph nodes. However, the metastases rates and metastases ratio in lower thoracic EC were higher than those of upper and mid-thoracic EC($\chi2$=9.918, P<0.009; $\chi2$ =14.218, P<0.002). Of the 621 patients with a single left thoracotomy, 72 had cancer located to the upper thoracic oesophagus, 408 to the mid-thoracic oesophagus,141to the lower thoracic oesophagus. As shown in the Table 4, no significant difference was observed between the upper, mid and lower thoracic EC in terms of metastases ratio, with a metastases ratio of 16.4%, 17.7% and 19.3%, respectively ($\chi2$ =3.119, P=0.165). Similarly, the metastases rates were 27.4%, 34.9% and 41.8% respectively, with no statistically significant differences ($\chi2$=0.581, P =0.515) Table 4.

Survival analysis: The survival time for the whole group ranged from 1 – 84.6 months, with a median survival time of 36.7 months. The survival rates at 1-, 3- and 5-years after surgery for the whole group were 83.4%, 56.3% and 47.2% respectively. In the current study, Karnofsky performance status (KPS), tumor length, T- stage and distant metastases were prognosis factors associated to survival, with higher survival rates at 1-, 3- and 5- year for patients with KPS >70 ($\chi2$=8.412, P = 0.049) tumor length less than 5 cm ($\chi2$= 8.523, P = 0.041), early T - stage ($\chi2$=83.942, P = 0.000) and no distant metastases ($\chi2$=87.526, P = 0.000) Table 5. These statistically significant differences persisted after multivariate logistic regression analysis. The results showed that KPS, T-stage, tumour length and distant metastases were independent factors associated with poor overall survival in patients with thoracic EC Table 6.

DISCUSSION

The current study has several limitations. Firstly, due to the socioeconomic concerns in mainland China, PET/CT was not routinely used in this study. Therefore, the clinical stage and clinical response evaluation were mainly done by CT scans. The results were not as accurate as that obtained by PET/CT. Secondly, most of our patients had squamous cell carcinoma. As squamous cell carcinoma and adenocarcinoma of the esophagus have relative difference in terms of epidemiology, location, and pathways of progression, it is difficult to extrapolate our results for patients with adenocarcinoma. Moreover, our patients were recruited retrospectively, and some unmeasurable factors might have effects on the final results, although there was strict accordance with the treatment protocol.

Table 1. Clinicopathological characteristics of 803 patients with thoracic esophageal carcinomas

Patients characteristics		Number	%
KPS			
	≤70	138	17.2
	>70	665	82.8
Smoking status			
	Yes	113	14.1
	No	690	85.9
Age			
	27 - 60	421	52.4
	> 60	382	47.6
Gender			
	Male	560	69.7
	Female	243	30.3
Tumor length (cm)			
	≤5	528	65.8
	>5	275	34.2
Location in thorax			
	Upper	118	14.7
	Middle	514	64.0
	Lower	171	21.3
pT- stage			
	Tis	16	2.0
	T1 - 3	669	83.3
	T4	118	14.7
LN status			
	N0	501	62.4
	N+	302	37.6
Stage			
	0 - I	56	7.0
	IIA - IIB	443	55.2
	III - IVA	268	33.4
	IVB	36	4.4
Pathology			
	SqCC	738	91.9
	ADK	12	1.5
	SCC	36	4.5
	Other types	17	2.1
Degree of differentiation			
	High	36	4.5
	Moderately	657	81.8
	Poorly	87	10.8
	Undifferentiated	23	2.9
Sugery			
	Left thoracotomy	621	77.3
	Cervico-thoracotomy	95	11.8
	Cervico-thoraco-laparotomy	87	10.8

KPS: Karnofsky performance status; **LN**: Lymph nodes; **ADK**: Adenocarcinoma; pT- stage: Pathological tumor stage; **SCC**: Small cell carcinoma; **SqCC**: Squamous cell carcinoma

Table 2. Distribution of thoracic esophageal cancer lymph nodes metastases

Lymph nodes sites	Dissected LN	All LN+	Metastases ratio	All Patients	All LN+	Metastases rate
	n	n	%	n	n	%
Supra clavicular	116	34	29.3	46	29	63.0
Paratracheal	315	87	27.6	169	63	37.3
Pulmonary artery	178	11	61.8	77	13	16.9
Pulmonary hilum	418	106	25.4	142	18	12.8
Carina	1735	136	7.8	587	74	12.6
Paraesophageal	1527	171	11.2	546	153	28.0
Cardia	528	82	15.5	351	67	19.1
Left gastric artery	1232	176	14.3	566	142	25.1
Coeliac trunk	167	13	7.8	62	21	33.9
Total	6216	824	13.3	803	302	37.6

LN: Lymph nodes

Table 3 Distribution of lymph nodes metastases by primary tumor site (n= 803)

Primary tumor site	Dissected LN	LN+	LN ratio	Dissected LN	LN+	LN rates
Upper thoracic	817	93	11.4	202	65	32.2
Middle thoracic	3756	512	13.6	436	192	44.0
Lower thoracic	1482	189	12.8	185	82	44.3

LN: Lymph nodes

Table 4 Distribution of lymph nodes metastases by primary tumor site (n= 621)

Primary tumor site	Dissected LN	LN+	LN ratio	Dissected LN	LN+	LN rates
Upper thoracic	627	103	16.4	197	54	27.4
Middle thoracic	1756	310	17.7	536	187	34.9
Lower thoracic	1315	254	19.3	347	145	41.8

LN: Lymph nodes

Table 5. Univariate analysis of the effect of potential prognostic factors on OS in patients with esophageal cancer (n= 803)

Prognostics factor	Patients	Univariate analysis			χ^2	P
		1-y OS	3-y OS	5- y OS		
KPS						
≤70	138	92.1	72.7	32.9	8.412	0.049
>70	665	98.3	82.4	56.4		
Smoking status					3.254	0.272
Yes	113	81.6	72.4	42.1		
No	690	77.4	58.6	37.3		
Age					5.543	0.066
40 - 60	421	89.7	76.2	49.6		
> 60	382	91.8	53.4	43.7		
Gender					2.041	0.209
Male	560	92.7	71.6	55.8		
Female	243	88.7	52.1	47.8		
Tumor length					8.523	0.041
≤5	528	97.2	69.6	46.4		
>5	275	87.2	61.7	32.1		
Location in thorax					3.427	0.214
Upper- thoracic	118	89.4	72.6	36.7		
Mid- thoracic	514	82.9	76.8	41.7		
Lower- thoracic	171	88.3	78.1	57.4		
TNM - stage					83.942	0.000
0 - IIA	428	93.8	69.5	48.3		
IIB - III	283	75.2	42.7	23.0		
IV	92	85.4	32.1	0.0		
Distant metastases					87.526	0.000
Yes	302	78.2	33.9	16.7		
No	501	93.4	63.1	48.8		

KPS: Karnofsky performance status; LN: Lymph nodes; OS: Overall survival

Table 6. Multivariate analysis of the effect of potentials prognostic factors on OS

Prognostics factor	B	SE	Wald	OR	P
KPS	0.684	0.476	6.102	1.523	0.035
T- stage	2.536	0.719	11.213	6.232	0.000
Tumor length	2.345	0.442	9.628	3.912	0.003
Distant metastases	3.251	0.814	12.332	15.126	0.021

KPS: Karnofsky performance status; T: Tumor

Nowadays, among the prognostic factors studied in the literature, lymph nodes metastases appear to be the most important factor associated with the prognosis of EC patients, and the inclusion of the number of metastatic lymph nodes in the TNM staging system for EC further demonstrates the importance of lymph node metastases on the prognosis of these patients (Keita, 2018; Pan, 2019; Minsky, 2012). The anatomical evidence basis for lymph nodes metastases in EC is based on the high density of lymphatic vessels along the oesophageal submucosa. Several studies have shown that lymph node metastases from EC are multidirectional, with some skip nodes. From this point onwards, some authors defined the target volume for prophylactic radiotherapy after radical esophagectomy. This volume includes the tumor bed, supraclavicular, mediastinum, left gastric artery, and cardia regions (Keita, 2018; Wang, 2017). Some authors have shown that such extensive postoperative prophylaxis significantly reduces the locoregional recurrence rate however, the effect on long-term survival was not significant, which may be due to the uneven dose distribution of radiotherapy, the normal tissues receiving more than the tolerated dose, resulting in increased toxic effects (Shuchai, 2019; Jiang, 2015).

To date, the use of intensity-modulated radiotherapy allows precise localization of the location and area of the lymph node metastases from EC. The present study was conducted to identify the distribution pattern of lymph node metastases in thoracic EC at different segments of the esophagus, as well as the factors associated with overall survival, which will allow accurate mapping of the exact target volume after radical surgery for thoracic EC, with a view to improve local control and reduce damage to normal tissues, thereby improving long-term survival. Our results showed that supraclavicular lymph node metastases were predominant in the upper thoracic EC, while both upper and lower lymph nodes metastases were more obvious prevalent in the mid-thoracic EC, which is consistent with the results of previous studies (Keita *et al*., 2018; Liu, 2019). The rate of metastases and the ratio of the lymph nodes metastases of the lower thoracic EC in the supraclavicular and paratracheal regions were also higher in this study. However, the number of lymph nodes removed from the lower thoracic region is relatively small. In fact, radical esophagectomy in our institution is mainly performed through a single approach on the left side of the chest, which makes it very difficult to remove supraclavicular and upper

mediastinal lymph nodes. The surgeon can only remove one suspicious lymph node in these areas during the surgery, resulting in a high rate of metastases and lymph node metastases ratio. We further analyzed of 621 patients who underwent a single left thoracotomy, the results showed that the lower thoracic EC only had higher lymph node metastases in the para-esophageal, cardia, and left gastric artery regions, and the differences in the rate of metastases and the lymph node metastases ratio between the upper thoracic, mid and lower thoracic EC were not statistically significant, which was consistent with the previously reported results (Shuchai, 2019; Yang, 2018). For patients who had a single left thoracotomy approach, the lesion was located in the upper thoracic segment, the target volume for adjuvant radiotherapy after radical EC surgery includes the supraclavicular, para-esophageal, paratracheal, and the carina regions. For those lesions located in the lower thoracic segment, the target volume includes the para-esophageal, cardia, and left gastric artery regions. In contrast, if the lesion is located in the mid-thorax, the target volume should be set according to the specific distribution of postoperative lymph node metastases. Exception for the single left thoracotomy, cervicothoracolaparotom allows complete clearance of the superior mediastinum and supraclavicular lymph nodes. However, the development of lymph node metastases in EC is influenced by several factors, but there is anevidence that the depth of local infiltration is the most important indicator of the TNM stage of EC, while the effect of lesion length on lymph node metastases has been reported differently. (Yang, 2018) suggest that lesion length does not influence lymph node metastases when the T- stage of EC is the same. Our prognostic factors analysis showed that patient performance status, lesion length, T- stage, and distant metastases were the main prognosis factors associated with poor overall survival in thoracic EC patients. These clinicopathological factors are the most important reference criteria for patients' selection for prophylactic lymph nodes area irradiation after radical EC surgery. Therefore, to determine the target volume for prophylactic radiotherapy after radical EC surgery, we must be considered the distribution of lymph node metastases by the different primary tumor sites, the extent of lymph node dissection by different surgical procedures, and the impact primary tumor stage.

Acknowledgments

We would like to thank our colleagues in China and in Guinea for providing their continuous support as well as patients for their cooperation.

Conflict of Interest: The authors indicated no potential conflicts of interest for this study.

Financial support: The authors are grateful to the Natural Science Foundation of Hebei Province (No., H2021206429).

Compliance with ethical standards: The research involved human participants only and institutional ethical clearance was obtained. Informed consent was obtained from every participant of the study in the presence of a neutral witnesses.

REFERENCES

Marabotto E, Pellegatta G, Sheijani AD *et al*. Prevention Strategies for Esophageal Cancer-An Expert Review. Cancers (Basel). 2021 May 1 ;13(9):2183.

Keita M, Zhang Xueyuan, Deng Wenzhao, *et al*. Comparison and Prognostic Analysis of Elective Nodal IrradiationUsing Definitive Radiotherapy versus Chemoradiotherapy forTreatment of Esophageal Cancer**.** Res Rev Med & Clin Oncol | Volume 2 | Issue 1 | June, 2018.

Leng X, He W, Yang H *et al*. Prognostic Impact of Postoperative Lymph Node Metastases After Neoadjuvant Chemoradiotherapy for Locally Advanced Squamous Cell Carcinoma of Esophagus: From the Results of NEOCRTEC5010, a Randomized Multicenter Study. Ann Surg. 2021 Dec 1;274(6): e1022-e1029.

Waters JK, Reznik SI. Update on Management of Squamous Cell Esophageal Cancer. Curr Oncol Rep. 2022 Mar ;24(3) :375-385.

Hamai Y, Hihara J, Emi M, *et al*. Evaluation of Prognostic Factors for Esophageal Squamous Cell Carcinoma Treated with Neoadjuvant Chemoradiotherapy Followed by Surgery. World J Surg. 2018 May;42(5):1496-150.

Bertero L, Massa F, Metovic J, *et al*. Eighth Edition of the UICC Classification of Malignant Tumours: an overview of the changes in the pathological TNM classification criteria-What has changed and why? Virchows Arch. 2018 Apr;472(4):519-531.

Hu F, Wu W, Hua Y. (Grouping of thoracic lymph nodes on CT scan according to American Thoracic Society classification). Zhonghua Zhong Liu Za Zhi. 1998 Jan;20(1):51-3.

Pan G, Pan H, Zhang Y, Shuai H. Effects of lymph node metastasis of thoracic esophageal squamous cell carcinoma on design of radiotherapy target volume. Pak J Med Sci. 2019;35(1):177-182.

Minsky BD, Pajak TF, Ginsberg RJ *et al*. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. J Clin Oncol. 2002 ;20(5) :1167-1174.

Wang X, Miao C, Chen Z, Li W, Yuan S, Yu J, Hu X. Can involved-field irradiation replace elective nodal irradiation in chemo radiotherapy for esophageal cancer? A systematic review and meta-analysis. Onco Targets Ther. 2017 Apr 11; 10:2087-2095.

Z Shuchai and M. Keita. The long-term survival of definitive radiotherapy by elective nodal irradiation with or without chemotherapy for esophageal squamous cell cancer International Journal of Radiation Oncology Biology Physics Volume 105, Issue 1, Supplement, 1 September 2019, Pages E197-E198.

Jiang L, Zhao X, Meng X, Yu J. Involved field irradiation for the treatment of esophageal cancer: is it better than elective nodal irradiation? Cancer Lett. 2015 Feb 1;357(1):69-74.

Liu T, Ding S, Dang J, Wang H, Chen J, Li G. Elective nodal irradiation

****