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Research Article

Prognostic Impact of Lymph Node Localization in Node-Positive Esophageal Cancer

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ABSTRACT

Background: Recurrent disease remains a major problem for esophageal cancer. This study was designed to evaluate the impact of localization of lymph node metastasis for tumor recurrence following curative esophageal resection.

Methods: 273 patients undergoing esophagectomy for esophageal cancer between 2005 and 2014 at the Department of General, Visceral and Transplant Surgery, University Hospital of Münster were included. Tumor characteristics, treatment details, postoperative course and patients' outcome, including time point and localization of recurrent disease, were analyzed retrospectively. The median follow-up was 46.3 months.

Results: Median overall and disease-free survivals were 22.7 and 13 months, respectively. Tumor characteristics including presence and number of lymph node metastasis, and localization of lymph node metastases, paraesophageal, perigastric and intra-abdominal, had significant impact on both tumor recurrence (p<0.001, p=0.003, and p=0.001, respectively) and disease-free survival (p<0.001, p=0.001, and p<0.001, respectively). Univariate and multivariate analysis confirmed tumor stage, lymph node metastasis, G-, L- and V-category, and neoadjuvant treatment as independent predictors of tumor recurrence.

Conclusion: The tumor stage and response to neoadjuvant treatment remain the most important prognostic factors. In addition, localization and the number of resected lymph node metastasis can provide important additional information.

Background

Esophageal cancer is the sixth most common cause of cancer-related mortality worldwide with increasing prevalence [1]. Despite advances in multimodal treatment and perioperative care, the prognosis of patients after curative esophagectomy remains dismal with a 5-year survival of 15-41% [2-6]. The fact that up to 65% of all patients develop tumor recurrence within 5 years – a majority of these relapses occur even within the first 12 months after esophagectomy – highlights the importance of disease recurrence per se and time until recurrence for the management of patients with esophageal cancer [5-8].

Recent studies described histologic tumor type, tumor size, grading, the presence of lymph node metastasis, and the extent of lymph node dissection as prognostic factors for overall survival after curative esophagectomy [9-11]. The effect of additional factors such as postoperative complications (e.g., anastomotic leakage) on tumor relapse is currently under controversial discussion [12, 13]. Furthermore, Robb *et al*. demonstrated that the administration of neoadjuvant therapy resulted in the later occurrence of locoregional recurrence, whereas the period of occurrence of distant metastasis was not affected [14].

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The purpose of this study was to investigate the prognostic impact of localization of lymph node metastasis factors for recurrent disease and disease-free survival in esophageal cancer patients who underwent curative esophagectomy. In this context, we analyzed tumor characteristics in detail and patients' outcome, including time point and localization of recurrent disease with regards to local tumor recurrence, distant metastasis, and multifocal tumor recurrence.

Methods

I Data Collection

The study was performed in a tertiary referral medical center for esophageal cancer surgery. Between January 2005 and December 2014, a total of 360 patients underwent esophagectomy for esophageal cancer. Finally, 273 patients with curative esophagectomy and discharge from the hospital were included in this study. 87 patients were excluded due to the following reasons: missing data, insufficient attendance to follow-up, 30-day mortality, the appearance of another malignancy, death caused by other reasons (sovereign from the primary disease).

Preoperative investigations included clinical examination, assessment of physical condition, American Society of Anesthesiologists physical status classification system (ASA-Score), Karnofsky-Index, body mass index, concomitant diseases (cardiac comorbidities such as hypertension, coronary heart disease, myocardial infarction in the past and pulmonary comorbidities as well as diabetes mellitus), weight loss during the last six months before surgery, consumption of alcohol and nicotine, blood tests including tumor markers, lung and cardiac function tests. The staging consisted of endoscopy with biopsy and histological examination, endosonography, and computed tomography of the thorax and abdomen as described previously [15].

Patients with an initial tumor stage < uT2, N0 were assigned to primary surgery (n=84, 30.8%), whereas patients with an advanced tumor stage were referred to neoadjuvant therapy followed by surgery (n=189, 69.2%). Neoadjuvant chemotherapy comprised of cisplatin and 5-fluorouracil (n=73, 38.6%) - in case of neoadjuvant radiochemotherapy (n=115, 60.8%) accompanied with radiotherapy. Esophagectomy was performed by an open technique using median laparotomy and right-sided thoracotomy with D2 lymphadenectomy and total mediastinal lymphadenectomy (n=251, 91.9%). A transhiatal approach (n=10, 3.7%) was indicated in patients with very distal tumor localization. In patients with transhiatal esophagectomy, mediastinal lymphadenectomy was performed up to tracheal bifurcation.

The surgical specimens were classified according to the 7th edition of UICC classification [16]. Additionally, in case of lymph node-positive disease, lymph node metastasis were characterized based on their localization into seven subgroups: superior mediastinal lymph nodes (lymph node stations 105-112), inferior mediastinal lymph nodes (lymph node stations 100, 102, 104), paraoesophageal lymph nodes (lymph node stations 101, 103, 108, 110, 111), abdominal lymph nodes (lymph node stations 10-13), paraaortic lymph nodes (lymph node stations 14-16), peri gastric lymph nodes (lymph node stations 1-6) and lymph nodes in region of coeliac trunk (lymph node stations 7-9) [17]. Response to

neoadjuvant therapy was assessed clinically and histopathologically, as described previously [18].

Postoperative complications were classified pursuant to the Clavien-Dindo classification and additionally following the recommendation of the Esophagectomy Complications Consensus Group (ECCG) [19, 20]. The postoperative oncological follow-up included follow-up examinations every 3 months for the first two years and six-monthly afterward. During the first two years after surgery, computed tomography of the thorax and abdomen were performed in half-year intervals. The average duration of follow-up for all patients was 46.3 months. Tumor recurrence was documented based on the time of occurrence after esophageal resection and localization of their current disease. Local recurrence was defined as a recurrent disease in local tumor area, including the regional lymph nodes and near the anastomosis. Distant metastasis was defined as tumor recurrence appearing in any other location. Multifocal recurrence included both aspects.

II Statistical Analysis

The data were presented as mean values ± standard deviations. Statistical analysis was performed by using the Chi Square test to compare categorical variables and by using the t-test to compare numeric variables. Multivariate analysis was performed using the Cox proportional hazards regression reporting hazard ratios (HR) and 95% confidence intervals (CI). Survival was evaluated according to the Kaplan-Meier method, and prognostic factors and survival rates were compared using the log-rank test. A p-value ≤ 0.05 was considered statistically significant.

Results

Recurrent disease was documented in 107 patients (39.2%): "local recurrence" occurred in 33 patients (30.8%), "distant recurrence" in 30 patients (28.0%) and "multifocal recurrence" in 44 patients (41.2%).

I Demographics, Physical Condition or Comorbidities

Comparing the entire population of patients with and without recurrent disease, the number of male patients with disease recurrence was higher (p=0.007). However, patients' age, tumor entity, and tumor localization were comparable between groups. While a significant higher preoperative weight loss was associated with disease recurrence (p=0.024), neither the Karnofsky Index nor ASA-Score differed between groups (data not shown). Patients with recurrent disease presented significantly more often increased levels of CA 19-9 (p=0.037) (data not shown).

II Treatment Details, Postoperative Complications, Tumor Staging

Neoadjuvant treatment was performed more frequently in patients with disease recurrence (p<0.001). There were no significant differences in the use of epidural analgesia, surgical access, the extent of lymphadenectomy, intraoperative blood loss, duration of surgery,

anastomotic technique or esophageal reconstruction between the two groups (data not shown).

47.6% of all patients developed postoperative complications, including anastomotic insufficiency type III in 19 patients (7%). Neither occurrence of complications in general (p=0.142) nor the level of severity according to Clavien-Dindo classification (p=0.173), the incidence of pulmonary complications (p=0.197), or anastomotic leakage (p=0.169) had an influence on tumor recurrence.

Patients with tumor recurrence had significantly higher T-, N-, G-, L- and V-stages. Concerning neoadjuvant therapy, patients with recurrent disease had significantly higher rates of non-response as assessed via clinical response evaluation (p=0.005) and histopathologic response, according to Baldus (p=0.043) (Table 2).

Table 1: Patients' characteristics.

Patients' characteristics		Overall (n=273) n (%)	No tumor Recurrence (n=166) n (%)	Tumor Recurrence(n=107) n (%)	p-value
Gender	Male	225 (82.4)	129 (77.7)	96 (89.7)	**0.007**
Median age (range)		63 (37-88)	64 (37-88)	62 (39-77)	0.066
Weight loss (%)	< 10	246 (90.1)	156 (94.0)	90 (84.1)	**0.024**
	10-20	23 (8.4)	8 (4.8)	15 (14.0)	
	> 20	4 (1.5)	2 (1.2)	2 (1.9)	
Tumor entity	Adenocarcinoma	183 (67.0)	113 (68.1)	70 (65.4)	0.372
	Squamous cell carcinoma	90 (33.0)	53 (31.9)	37 (34.6)	
Tumor localization	Proximal	5 (1.8)	1 (0.6)	4 (3.7)	0.1
	Middle	61 (22.3)	41 (24.7)	20 (18.7)	
	Distal	207 (75.8)	124 (74.7)	83 (77.6)	

Significant values were printed in bold.

Table 2: Clinicopathological characteristics.

Patients' characteristics		Overall (n=273) n (%)	No tumor Recurrence (n=166) n (%)	Tumor Recurrence (n=107) n (%)	p-value
Tumor stage	(y)pT0	45 (16.5)	31 (18.7)	14 (13.1)	**< 0.001**
	(y)pT1	72 (26.4)	56 (33.7)	16 (15.0)	
	(y)pT2	61 (22.3)	39 (23.5)	22 (20.6)	
	(y)pT3	94 (34.4)	39 (23.5)	55 (51.4)	
	(y)pT4	1 (0.4)	1 (0.6)	0 (0)	
Nodal stage	(y)pN0	165 (60.4)	123 (74.1)	42 (39.3)	**< 0.001**
	(y)pN1	81 (29.7)	35 (21.1)	46 (43.0)	
	(y)pN2	13 (4.8)	3 (1.8)	10 (9.3)	
	(y)pN3	14 (5.1)	5 (3.0)	9 (8.4)	
Distant metastasis	(y)pM0	263 (96.3)	165 (99.4)	98 (91.6)	**0.001**
	(y)pM1	10 (3.7)	1 (0.6)	9 (8.4)	
G-category	Gx	16 (5.9)	16 (9.6)	0 (0)	**< 0.001**
	G1	12 (4.4)	11 (6.6)	1 (0.9)	
	G2	120 (44.0)	76 (45.8)	44 (41.2)	
	G3	102 (37.4)	50 (30.1)	52 (48.6)	
	Not specified	23 (8.3)	13 (7.8)	10 (9.3)	
L-category	L0	225 (82.4)	149 (89.8)	76 (71.0)	**< 0.001**
	L1	47 (17.2)	16 (9.6)	31 (29.0)	
	Not specified	1 (0.4)	1 (0.6)	0 (0)	
V-category	V0	260 (95.2)	163 (98.2)	97 (90.7)	**0.006**
	V1	13 (4.8)	3 (1.8)	10 (9.3)	
Resection margin	R0	250 (91.6)	156 (94.0)	94 (88.7)	0.265
	R1	19 (7.0)	9 (5.4)	10 (9.4)	
	R2	3 (1.1)	1 (0.6)	2 (1.9)	
Location of lymph node metastasis	Superior mediastinal	4 (1.5)	1 (0.6)	3 (2.8)	0.139
	Para- oesophageal	85 (31.1)	34 (20.5)	51 (47.7)	**< 0.001**
	Inferior mediastinal	5 (1.8)	1 (0.6)	4 (3.7)	0.059

	Perigastric	20 (7.3)	6 (3.6)	14 (13.1)	**0.003**
	Truncus coeliacus	1 (0.4)	0 (0)	1 (0.9)	0.212
	Intra-abdominal	20 (7.3)	5 (3.0)	15 (14.0)	**0.001**
Clinical response*	Non-responder	50 (26.5)	19 (18.6)	31 (36.6)	**0.005**
	Partial responder	99 (52.4)	54 (52.9)	45 (51.7)	
	Complete responder	40 (21.2)	29 (28.4)	11 (12.6)	
Histopathological response**	Grade I	29 (15.3)	14 (13.7)	15 (17.2)	**0.043**
	Grade II	14 (7.4)	7 (6.9)	7 (8.0)	
	Grade III	16 (8.5)	7 (6.9)	9 (10.3)	
	Grade IV	51 (27.0)	37 (36.3)	14 (16.1)	

Significant values were printed in bold.

* Response evaluation included all patients who underwent neoadjuvant therapy (n =189) and differed in clinical response and histopathological response according to Baldus (Non-Responder: grade I and II, responder grade III and IV).

** Patients not specified according to the histopathological response (n=79) were excluded from the statistical analysis.

III Localization of Lymph Node Metastasis

In the overall collective, 39.5% of all patients were node positive. Tumor recurrence was significantly associated with the presence of lymph node metastasis: 25.9% versus 60.7%, p<0.001. According to the classification mentioned above, localization of lymph node metastasis was predominant paraoesophageal (62.9%) followed by perigastric and intraabdominal (each 14.8%). Consequently, patients with recurrent disease presented significantly more often lymph node metastasis localized paraoesophageal (p<0.001), perigastric (p=0.003) and intra-abdominal (p=0.001), whereas there was no difference between groups with regards to the presence of lymph node metastasis located in the superior or inferior mediastinum or in proximity to the coeliac trunk (Table 2). With regard to the potential influence of distantly located lymph node in patients suffering from adenocarcinoma located in the distal third of the esophagus (n=161), superior-mediastinal (n=6) lymph node metastasis were found to correlate with tumor recurrence (5/6 (83.3%) versus 1/6 (16.7%), p=0.034). However, there was no significance proven to patients suffering from SCC localized in the proximal or middle third of the esophagus (n=44) with abdominal localization of lymph node metastasis (n=1 without tumor recurrence).

Table 3: Multivariate analysis of risk factors for recurrence of esophageal carcinoma.

	HR	95% CI	p-value
Weight loss	1.486	1.002-2.202	**0.049**
CA 19-9	0.656	0.372-1.159	0.146
NAT	0.401	0.244-0.658	**< 0.001**
T-category	1.309	1.051-1.629	**0.016**
N-category	1.584	1.253-2.002	**< 0.001**
L-category	2.512	1.501-4.204	**< 0.001**
V-category	2.354	1.149-4.821	**0.019**
R-category	1.125	0.629-2.011	0.691
G-category	1.945	1.359-2.783	**< 0.001**
LOCATION OF LYMPH NODE METASTASIS			
Paraoesophageal	1.094	0.565-2.117	0.790
Perigastric	1.199	0.572-2.510	0.631
Intra-abdominal	1.534	0.834-2.823	0.169

Cl: confidence interval; HR: hazard ratio; NAT: neoadjuvant therapy.

Significant values were printed in bold.

IV Multivariate Analysis

Multivariate analysis was performed for factors indicating significance between patients with and without recurrent disease in univariate analysis. Based on multivariate analysis, predictive value of weight loss (p=0.049), implementation of neoadjuvant therapy (p<0.001) and postoperative tumor stage depicted by T-category (p=0.016), N-category (p=0.001), L-category (p<0.001), V-category (p=0.019) and G-category (p<0.001) correlated with disease recurrence. Localization of lymph node metastasis was without significant influence in the multivariate analysis (Table 3).

V Factors Influencing Disease-Free Survival in Esophageal Cancer

Median overall survival and disease-free survival (DFS) were 22.7 months (range 1-125) and 13 months (range 1-125), respectively. There was no significant difference in DFS between patients with adenocarcinoma and squamous cell carcinoma (p=0.891). Patients with local tumor recurrence, distant metastasis, and multifocal disease recurrence had a median DFS of 9.2 months (range 1.4-82.1), 9.4 months (range 0.5–65.9), and 8.1 months (range 2.3-37.1), respectively. In the case of neoadjuvant therapy, patients without clinical response had a median DFS of 6.6 months versus 30.5 months in complete responders

(p<0.001). Interestingly, localization of lymph node metastasis had a significant impact on DFS. Patients with lymph node metastasis paraoesophageal, perigastric and intra-abdominal had an even worse median DFS compared to pN1 staged patients in general: 9.3 months, 8.9 months, and 6.8 months, respectively versus 11.5 months. Table 3 summarized the patient´s DFS referring to relevant factors demonstrated in our study, including tumor entity and therapy regime.

Discussion

Despite the improvement in multimodal treatment during the past several years, the prognosis of esophageal cancer remains poor [2-5, 21-24]. One of the main reasons is the high frequency of tumor recurrence following curative-intended surgery [5, 25]. The presented study was performed to evaluate potential relationships between occurrence and localization of lymph node metastasis after surgical resection and postoperative tumor recurrence. In the study population of 273 patients with a median follow-up of 46.3 months, the recurrent disease was found in 39.2% with a DSF of 8.9 months, including occurrence of local recurrence after 9.2 months, distant metastasis after 9.4 months and multifocal recurrence after 8.1 months. Other studies reported very similar data for recurrence of esophageal carcinoma with tumor recurrence rates ranging from 39% up to 60% [6, 8, 14].

In line with the current literature, risk factors for tumor recurrence such as an increased ASA-score, elevated levels of CA 19-9, or an advanced tumor stage have been described [11, 25-29]. Whether postoperative complications like anastomotic leakage affect the incidence of tumor relapse is discussed controversially [12, 13]. In our study, neither postoperative complications in general, nor pulmonary complications or anastomotic leakage were associated with recurrent disease. This supports the results of prior studies showing that long-term survival of patients suffering from esophageal carcinoma is not influenced by postoperative complications [13, 30-32].

In this study, following neoadjuvant therapy, tumor relapse occurred more often, resulting in a shorter DFS compared to patients undergoing primary surgery (46% versus 24%, p<0.001; median DFS 23.3 months versus 11.7 months, p<0.001). However, this applies sovereign from the therapy regime of the neoadjuvant treatment. Interestingly, referring to disease-free survival, there were distinct differences between the various types of therapy regimes. Lee *et al.* announced that the use of induction therapy, consisting of platinum-based chemotherapy in some cases in combination with radiotherapy, is an independent predictor of disease-free survival [2]. Blackham *et al.* revealed a significantly decreased risk of postoperative locoregional tumor recurrence in patients with complete response to neoadjuvant chemoradiotherapy (local tumor recurrence in complete responders 11% versus 20% in partial or no responders to nCRT, p<0.001) [33].

Parry *et al.* indicated that neoadjuvant treatment has no demonstrable impact on location of disease recurrence (locoregional recurrence, distant metastasis or multifocal recurrence; p=0.601), median DFS (11 months NAT plus surgery vs. 8 months primary surgery; p=0.110) or long-term survival (overall 5-year survival 35% in both groups; p=0.351), the only exception being complete responder with a significantly better outcome referring to both, overall survival (p=0.003)

and relapse-free survival (p=0.048), in comparison to non-responders [34]. This thesis asserts perfectly to our finding, as for the total of our patients, partial or non-responders had an evident higher risk of experiencing recurrent disease compared to complete responders (45.5% versus 62% versus 27.5%, p=0.005). Besides, referring to DFS, complete responders had an obvious benefit. Complete responders had a median time to disease recurrence of 30.5 months, patients with a partial response had a median to tumor recurrence of 15.2 months, and non-responders had the shortest median time to recurrent disease with 6.6 months. In conclusion, while neoadjuvant therapy has limited influence on the occurrence of tumor relapse, it can extend the relapse-free survival in case of complete tumor response.

Ninomiya *et al.* demonstrated that among others, lymph node metastasis is a significant predictive parameter for reduced recurrence-free survival [35]. A recent study of Gulben *et al.* defined a cut-off value and demonstrated the prognostic value of ≥3 lymph node metastasis as an independent risk factor for overall survival in pathological T3 (pT3) esophageal carcinoma [36]. According to the current literature, an evaluation of the prognostic value of localization of lymph node metastasis is missing. Our examination detected a strong correlation between the anatomical localization of resected lymph node metastasis and tumor recurrence. For superior- and inferior-mediastinal lymph node metastasis, there was no statistical significance in univariate analysis. In contrast, referring to intra-abdominal, paraoesphageal and perigastric located lymph node metastasis, analysis illustrated that both, the presence of lymph nodes metastasis in these areas as well as the amount of lymph node metastasis were significantly associated with postoperative tumor recurrence.

According to Tachimori *et al.*, tumor cells of the upper esophagus normally spread upwards to mediastinal and cervical lymph nodes, middle thoracic esophageal cancer spread both up and down into cervical, mediastinal, paraoesophageal and perigastric lymphatic nodes, whereas distal esophagus carcinoma drains first and foremost in lymphatics in the perigastric area [37]. Concluding, lymphogenic metastasis in general as well as localization of lymph node metastasis are significant risk factors for tumor recurrence following curative intended surgery.

Comparing the different types of esophageal carcinoma (EAC versus SCC), our study revealed no significant difference regarding DFS between both tumor entities. Moreover, there was no significant difference in patients with local disease recurrence or multifocal tumor recurrence. Nevertheless, with regard to patients with distant metastasis suffering from SCC, our data showed prolonged DFS in contrast to patients with distant metastasis suffering from EAC (median DFS 13.23 months versus 7.56 months). A recent study of Saigi *et al.* declared that patterns of disease recurrence differentiate regarding histological tumor subtype. According to this study, distant metastasis was more abundant in adenocarcinoma, whereas local disease recurrence was related to SCC (62% versus 50%, p=0.027) [38].

In subgroup analysis, we correlated tumor subtype and intraoperative resected lymph nodes. On the one hand, we evaluated patients suffering from EAC and mediastinal located resected lymph node metastasis, and on the other hand, patients with SCC and intra-abdominal located lymph

node metastasis. The superior-mediastinal location of intraoperative resected lymph node metastasis of patients suffering from distal located EAC significantly correlated with early tumor recurrence, whereas patients with SCC and intraoperative resected abdominal lymph node metastasis had no increased risk of tumor relapse. Superior-mediastinal lymph node involvement in patients with distal EAC might hint at a more aggressive variant of esophageal cancer that consecutively might recur more frequently.

Our study has several limitations: First of all, it was implemented based on a retrospective and single-center design. Moreover, our study embraces a small sample size and a heterogeneous group of patients. Subgroup analysis was performed to avoid the negative impact of heterogeneity and to prove the significance of our results. The particularized follow-up and standardized postoperative care have to be highlighted, though. Moreover, our data is based on precise documentation of tumor recurrence.

Conclusion

In univariate analysis, tumor response to neoadjuvant therapy, tumor stage, and lymphatic spread are relevant prognostic factors for esophageal carcinoma. Besides, the multivariate analysis confirmed the value of preoperative weight loss, implementation of neoadjuvant therapy, and postoperative tumor stage predicted by T-, N-, L-, V-, and G-category as independent predictors of disease-free survival. Although the presence of lymph node metastasis is an established prognostic factor, the localization and amount of resected lymph node metastasis should also be considered as potential predictive factors for recurrent disease.

Ethical Approval

Ethikkommission der Ärztekammer Westfalen-Lippe der Westfälischen Wilhelms Universität (Münster), reference number: 2018-589-f-S.

Consent

Written consent was obtained from the participants.

Competing Interests

None.

Author Contributions

FK, AKE, DP, RH, NS, KL: acquired data.
FK, AKE, DP, KL: data analysis.
FK, KL: wrote paper.
FK, AKE, DP, RH, NS, KL: read and approved the final manuscript.

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Abbreviations

ASA: American Society of Anesthesiologists
SCC: squamous cell carcinoma
ECCG: Esophagectomy Complications Consensus Group
EAC: esophageal adenocarcinoma
DFS: disease-free survival
nCRT: neoadjuvant chemoradiotherapy
nCRTS: neoadjuvant chemoradiotherapy followed by surgery
NAT: neoadjuvant therapy
CTX: chemotherapy
RTX: radiotherapy
RCTX: radio-chemotherapy

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