World J Surg (2016) 40:913–920
DOI 10.1007/s00268-015-3334-8

ORIGINAL SCIENTIFIC REPORT

Late Recurrence After Radical Resection of Esophageal Cancer

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Published online: 9 November 2015

Abstract

Background Approximately 10–20 % of esophageal cancer patients in whom recurrence is diagnosed experience late recurrence beyond 2 years after esophagectomy. However, the risk of late recurrence is still unclear. The aim of this study was to identify the risk factors of late recurrence for appropriate postoperative surveillance.

Methods A total of 447 patients underwent radical esophagectomy and reconstruction for esophageal cancer from 2005 to 2014. Patients who had recurrence beyond 2 years after esophagectomy were defined as the late recurrence group and the remaining patients with recurrence as the early recurrence group. A comparison of the clinicopathological factors and prognosis was performed between patients with early recurrence, late recurrence, and no recurrence.

Results Recurrences were recognized in 117(26.2 %) of the 447 patients. Recurrence was diagnosed within 2 years after surgery in 103 patients (88.0 %) and after 2 years in 14 patients (12.0 %). Patients with late recurrence showed a favorable prognosis compared with those with early recurrence ($P = 0.0131$), and late recurrence was an independent factor associated with a favorable prognosis after recurrence (HR 0.199, $P = 0.025$). In the comparison between patients with late recurrence and those with no recurrence who had a minimal recurrence-free survival of 2 years, pathological lymph node metastasis at esophagectomy was found to be an independent predictor of late recurrence (HR 7.296, $P = 0.043$).

Conclusions Pathological lymph node metastasis at esophagectomy is a risk factor of late recurrence for esophageal cancer, and a close, lifelong follow-up is recommended for such patients.

Introduction

Esophageal cancer is a highly lethal disease and also one of the most common neoplasms. Recent advances in multimodal treatment, including endoscopic treatment, chemotherapy, chemoradiotherapy (CRT), and surgery, have improved the prognosis of patients with esophageal cancer. Although the overall 5-year survival rate currently exceeds 50 %, recurrence still develops within 1–3 years after resection in more than half of these patients [1–8]. It

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is therefore important to understand the characteristics and patterns of recurrence after curative resection in order to select appropriate surveillance and therapeutic strategies.

Previous reports have shown that recurrence develops within 2 years in more than 80 % of patients in whom recurrence is diagnosed, even after curative esophagectomy with radical lymph node dissection [4, 5, 8]. Therefore, we highly recommend meticulous follow-up of such patients during the 2-year period following esophagectomy. A number of factors are known to be associated with a poor prognosis in esophageal cancer [9, 10], and Davies et al. have demonstrated that esophageal cancer patients with poorly differentiated tumors and three or more involved lymph nodes have a particularly high risk of early recurrence after surgery [11]. On the other hand, approximately 10–20 % of patients in whom recurrence is diagnosed experience recurrence beyond 2 years after esophagectomy [4, 5, 8]. Abate et al. have demonstrated recurrence time and pattern after esophagectomy for esophageal adenocarcinoma and suggested optimal follow-up intervals and testing after esophagectomy [12]. However, the clinicopathological characteristics and predictive factors for late recurrence have not been definitely determined, and the risk of late recurrence is still unclear. As a result, limited evidence exists on the optimal follow-up regimen, and guidelines differ on the method and interval of follow-up for postoperative surveillance [6, 13].

In the present retrospective study, we evaluated the clinicopathological factors of patients who experienced late recurrence of esophageal cancer beyond 2 years after radical esophagectomy comparing with those of patients who experienced early recurrence within 2 years after surgery and no recurrence, respectively. The aim of this study is to elucidate the clinicopathological features associated with late recurrence and to identify the risk factor of late recurrence for appropriate postoperative surveillance.

Materials and methods

Patients

Between April 2005 and December 2014, 447 Japanese patients consecutively underwent radical (R0) esophagectomy and reconstruction for esophageal cancer in the Department of Gastroenterological Surgery at Kumamoto University. The clinicopathological characteristics are summarized in Table 1. The histological type was squamous cell carcinoma (SCC) in 395 patients (88.4 %). Positive lymph node metastasis was pathologically confirmed in 202 patients (45.2 %). Among the patients with lymph node metastasis, the number of metastasized nodes was 1–36. The metastasized nodes were located in 1 field ($n = 121$), 2 fields ($n = 60$), or 3 fields ($n = 21$). The postoperative pathologies were classified as stage 0 in 23 patients (5.1 %), stage I in 182 patients (40.7 %), stage II in 108 patients (24.2 %), stage III in 102 patients (22.8 %), and stage IV in 32 patients (7.2 %) by the tumor-node-metastasis (TNM) classification defined by the Union for International Cancer Control (UICC International Union Against Cancer, TNM Classification of Malignant Tumors, 7th edition). Preoperative or postoperative therapy (chemoradiotherapy or chemotherapy or radiotherapy) was performed in 236 patients (52.8 %). The study protocol and patients' informed consent statements were approved by the Institutional Review Board of Kumamoto University Hospital.

Surgical procedure

We principally performed preoperative CRT for tumors that were suspected to be T4. For patients with non-T4 and node-positive tumors, either adjuvant chemotherapy (April 2005 to July 2008) or neoadjuvant chemotherapy (August 2008 to 2014) was administered in addition to esophagectomy. As a general rule, adjuvant chemotherapy was started within 2 months after surgery. As shown in Table 1, for 260 patients, we performed radical lymphadenectomy with dissection not only of the regional lymph nodes consisting of the middle or lower mediastinal nodes and the perigastric nodes, but also of the superior mediastinum, including the nodes along the right and left recurrent laryngeal nerves and cervical nodes, in particular the supraclavicular nodes (three-field lymphadenectomy). The other 187 patients underwent one- or two-field lymphadenectomy. Postoperative complications were classified using the Clavien-Dindo classification [14] and grades II or more were regarded as being complication positive.

Follow-up evaluation

The patients were followed up at 3-month intervals until the fifth year. Recurrence was confirmed by clinical examinations including computed tomography (CT), endoscopy, and [18F]-fluorodeoxyglucose–positron emission tomography CT (FDG-PET CT). The patients visited the outpatient clinic, and their tumor marker levels were measured every 3 months until 5 years after surgery. CT scanning from the neck to the upper abdomen was performed at least twice a year for 3 years after surgery and then once each year from 4 years until 5 years after surgery. FDG-PET CT was added to these exams for patients considered to be at high risk for recurrence and if recurrence was strongly suggested by another diagnostic method, such as CT or elevated tumor marker levels. Endoscopy was annually performed to detect anastomotic

Table 1 Clinicopathological characteristics of patients enrolled in the present study

Characteristic	Radical esophagectomy for esophageal cancer ($n = 447$)
Age	
Median (range)	66 (41–89)
Gender	
M/F	392/55
Location of tumor	
Upper/middle/lower	70/223/154
Lymph node dissection	
0–2 field/3 field	187/260
Postoperative complication	
−/+	259/188
Histological type	
SCC	395
Adenocarcinoma	30
Adenosquamous	5
Basaloid carcinoma	16
Small cell	1
Pathological T	
0/is/1/2/3/4	18/13/226/58/128/4
Pathological N	
0/1/2/3	245/107/62/33
Pathological stage	
0/I/II/III/IV	23/182/108/102/32
Neoadjuvant or adjuvant therapy	
−/+	211/236

recurrence as well as second primary cancers, particularly in the head and neck.

The patients who had recurrence beyond 2 years after esophagectomy were defined as the late recurrence group and the remaining patients with recurrence as the early recurrence group. Some previous studies, which demonstrated patterns and the time of recurrence of esophageal cancer after resection, indicated that 12–19 % of patients in whom recurrence was diagnosed experienced late recurrence beyond 2 years after esophagectomy [4, 5, 8]. The reason why we used a 2-year cutoff in the present study was to elucidate the clinicopathological features of such late recurrence.

Statistical analysis

The association between the recurrence time and the clinicopathological factors was assessed using the Chi-square two-tailed test or Fisher's exact test. Survival curves were plotted according to the Kaplan–Meier method, with the differences between two curves analyzed using the log-rank test. The independent factor associated with late recurrence and the prognosis after recurrence was evaluated using a logistic regression analysis and cox regression analysis, respectively. All statistical analyses were performed using the SPSS version 11 software program (IBM, Chicago, IL, USA). A P value less than 0.05 was considered to be significant.

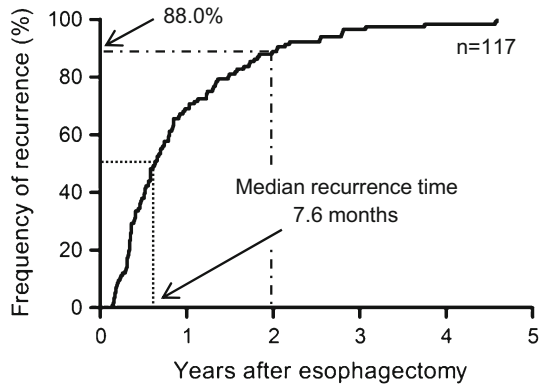

Fig. 1 Times of recurrence after radical resection in 117 patients with esophageal cancer. Recurrences were diagnosed within 2 years after surgery in 103 patients (88.0 %) and after 2 years in 14 patients (12.0 %)

Results

Recurrences were recognized in 117 (26.2 %) of the 447 patients. Figure 1 shows the time of recurrence after radical esophagectomy for all 117 patients. The median recurrence time was 7.6 months. Recurrence was diagnosed within 2 years after surgery in 103 patients (early recurrence, 88.0 %) and beyond 2 years after surgery in 14 patients (late recurrence, 12.0 %). Of 330 patients without recurrence after esophagectomy, 174 patients (52.7 %) had a minimal recurrence-free survival of 24 months.

Figure 2 shows the results of the Kaplan–Meier analysis for the cancer-specific survival after the initial recurrence. All patients with recurrence ($n = 117$) were stratified into 3 groups according to the time of recurrence. The patients with early recurrence ($n = 103$) showed a poor prognosis compared with those with late recurrence ($n = 14$) ($P = 0.0131$). In particular, patients who recurred within 6 months after surgery ($n = 44$) showed the worst prognosis.

Table 2 shows the factors associated with the prognosis after recurrence of esophageal cancer. The type of recurrence was classified into three patterns: loco-regional, hematogenous, and mixed type (loco-regional recurrence concomitant with hematogenous recurrence, as previously reported [6]). In addition, the three patterns were classified into two groups according to the presence of distant

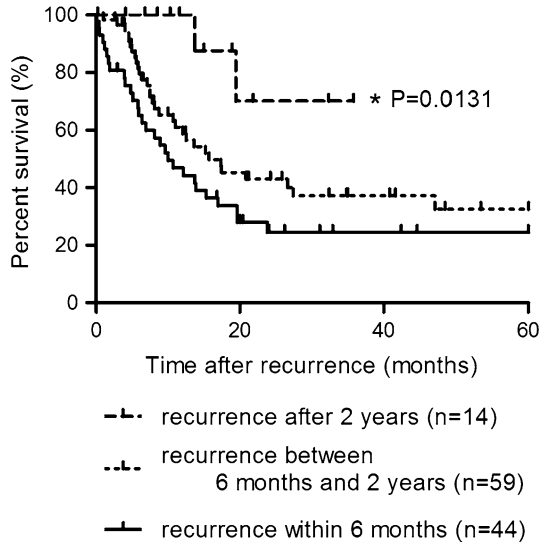

Fig. 2 Cancer-specific survival after the recurrence of esophageal cancer. Patients with recurrence ($n = 117$) were stratified into 3 groups according to the time of recurrence. Patients with late recurrence (recurrence after 2 years) showed a more favorable prognosis compared with patients with early recurrence (within 2 years)

metastasis in the present study: the Loco-regional group and Distant or Mixed group. Ninety of 103 patients in the early recurrence group and 13 of 14 patients in the late recurrence group were treated with one of the multimodal therapies such as chemotherapy, radiotherapy, and surgical resection after the detection of recurrence. According to a univariate analysis, age, gender, postoperative complication, histological type, pathological T factor, pathological N factor, pathological TNM stage, and the rate of perioperative therapy did not show any significant associations with the prognosis after recurrence. On the other hand, 3-field lymph node dissection (HR 0.586, $P = 0.046$), late recurrence (HR 0.201, $P = 0.026$) and therapy for recurrence (HR 0.178, $P = 0.0001$) were associated with a favorable prognosis, and the presence of distant metastasis was associated with a poor prognosis (HR 1.709, $P = 0.037$). The fact that the therapy for recurrence was associated with a favorable prognosis might indicate that the therapy had a favorable effect on the prognosis. However, it is also possible that the patients who received therapy for recurrence had a better general status because their age tended to be higher ($P = 0.094$) and the incidence

Table 2 Factors associated with the prognosis after recurrence of esophageal cancer

Factor	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Age				
−64/65–	1.366 (0.826–2.258)	NS		−64/65–
Gender				
M/F	1.204 (0.548–2.648)	NS		
Lymph node dissection				
0–2 field/3 field	0.586 (0.346–0.992)	0.046	0.866 (0.451–1.661)	NS
Postoperative complication				
−/+	0.609 (0.357–1.038)	NS		
Histological type				
SCC/other	1.233 (0.529–2.871)	NS		
Pathological T				
012/34	1.265 (0.763–2.096)	NS		
Pathological N				
−/+	0.946 (0.503–1.777)	NS		
Pathological stage				
0–II/III, IV	1.158 (0.675–1.989)	NS		
Late recurrence				
−/+	0.201 (0.049–0.823)	0.026	0.199 (0.049–0.819)	0.025
Type of recurrence				
Loco-regional/distant or mixed	1.709 (1.033–2.828)	0.037	1.362 (0.786–2.362)	NS
Neoadjuvant or adjuvant therapy				
−/+	0.676 (0.378–1.211)	NS		
Therapy for recurrence				
−/+	0.178 (0.087–0.364)	0.0001	0.220 (0.092–0.526)	0.001

of distant metastasis among such patients was significantly lower ($P = 0.017$) in comparison to the patients who did not receive the therapy. In the multivariate cox regression analysis, late recurrence (HR 0.199, $P = 0.025$) and therapy for recurrence (HR 0.220, $P = 0.001$) were independent prognostic factors after recurrence of esophageal cancer.

The comparison of the clinicopathological findings between the early recurrence group and late recurrence group are summarized in Table 3. Compared with early recurrence, late recurrence was associated with early pT stage (pT0-2 vs. pT3-4) in resected primary tumors ($P = 0.001$). On the other hand, there were no significant differences between the two groups with regard to age, gender, lymph node dissection, postoperative complication, histological type of primary tumor, pathological *N* factor, pathological TNM stage, type of recurrence, or the rate of perioperative therapy and therapy for recurrence. The number of metastasized nodes was similar between two groups (data not shown).

Table 4 shows a comparison of the clinicopathological factors between patients with late recurrence and those without recurrence who had a minimal recurrence-free survival of 2 years. The median follow-up time of the late recurrence group and no recurrence group was 49.2 months and 48.8 months, respectively. There was no significant association in age, gender, lymph node dissection, postoperative complication, histological type, and pathological T factor between the two groups. On the other hand, late recurrence was significantly associated with a higher rate of lymph node metastasis ($P < 0.001$), more advanced TNM stage ($P = 0.001$), and higher rate of neoadjuvant or adjuvant therapy ($P = 0.023$). The number of metastasized nodes (median) was significantly higher in the patients with late recurrence than in the patients without recurrence [3 (range 0–8) vs. 0 (range 0–15); $P < 0.0001$]. In the multivariate logistic regression analysis, the presence of pathological node metastasis was an independent predictive factor of late recurrence (HR 7.296, $P = 0.043$) when compared to the no recurrence group.

Discussion

In the present retrospective study, we evaluated the clinicopathological factors of patients who had late recurrence of esophageal cancer beyond 2 years after radical esophagectomy.

Table 3 Comparison of the clinicopathological findings between patients with early recurrence and those with late recurrence after esophagectomy

Factor	Recurrence time		*P* value
	Early recurrence (n = 103)	Late recurrence (n = 14)	
Age			
−64/65−	53/50	6/8	NS
Gender			
M/F	90/13	13/1	NS
Lymph node dissection			
0–2 field/3 field	35/68	5/9	NS
Postoperative complication			
−/+	58/45	11/3	NS
Histological type			
SCC/other	92/11	14/0	NS
Pathological T			
is, 1, 2/3, 4	41/62	12/2	0.001
Pathological N			
0/1–3	23/80	2/12	NS
Pathological stage			
0–2/3, 4	34/69	6/8	NS
Type of recurrence			
Loco-regional/distant or mixed	61/42	9/5	NS
Neoadjuvant or adjuvant therapy			
−/+	21/82	3 / 11	NS
Therapy for recurrence			
−/+	13/90	1/13	NS

Table 4 Comparison of the clinicopathological factors between patients without recurrence and those with late recurrence after esophagectomy

Factor	No recurrence ($n = 174$)	Late recurrence ($n = 14$)	P value	Multivariate analysis	
				HR (95 % CI)	P value
Age					
−64/65–	78/96	6/8	NS		
Gender					
M/F	153/21	13/1	NS		
Lymph node dissection					
0–2 field/3 field	76/98	5/9	NS		
Postoperative complication					
−/+	104/70	11/3	NS		
Histological type					
SCC/other	156/18	14/0	NS		
Pathological T					
is, 1, 2/3, 4	141/33	12/2	NS		
Pathological N					
0/1–3	117/57	2/12	<0.001	7.296 (1.064–50.049)	0.043
Pathological stage					
0–II/III, IV	148/26	6/8	0.001	2.363 (0.627–8.902)	NS
Neoadjuvant or adjuvant therapy					
−/+	96/78	3/11	0.023	1.069 (0.213–5.368)	NS

Recurrences were recognized in 26.2 % of total patients, and it was diagnosed within 2 years after surgery in 103 patients (88.0 %) and after 2 years or more in 14 patients (12.0 %). The patients with late recurrence showed a favorable prognosis compared with those with early recurrence. Late recurrence and treatment after recurrence were independent factors associated with a favorable prognosis after recurrence. Compared with early recurrence, late recurrence was associated with an early pT stage. In comparison between the patients with late recurrence and those with no recurrence who had a minimal recurrence-free survival of 2 years, pathological lymph node metastasis at esophagectomy was an independent predictor of late recurrence. To the best of our knowledge, this is the first report to analyze the clinicopathological characteristics and prognosis of patients with late recurrence of esophageal cancer.

The time and patterns of recurrence after complete resection of esophageal cancer have been reported in several studies. In particular, 11.5 % [5], 16.0 % [8], and 18.8 % [4] of esophageal cancer patients in whom recurrence was diagnosed experienced late recurrence beyond 2 years after esophagectomy. In the current study, 12.0 % of patients who had been cancer-free for more than 2 years after esophagectomy had late recurrence, and this proportion of late recurrence was similar to that of the previous studies. Although the proportion is low, it is important to elucidate the risk factors for late recurrence in order to establish a rational follow-up surveillance program.

The prognosis of patients with recurrence of esophageal cancer was generally very poor. Regarding the prognostic factor of recurrent esophageal cancer, Morita et al. have demonstrated that the prognosis of patients with loco-regional recurrence tended to be better than that of those with distant metastasis. In addition, patients with recurrence treated by chemotherapy alone or multimodal therapy, such as radiation or surgery combined with systemic chemotherapy, survived significantly longer than those with untreatable recurrence [8]. Furthermore, some previous reports have demonstrated surgical resection to be an acceptable treatment that could improve the survival of patients with recurrence of esophageal cancer [15], especially in lymph node recurrence [16–18], lung recurrence [19–21], and local recurrence [22]. Consistent with the previous reports, we demonstrated that multimodal therapy for recurrence was associated with a favorable prognosis, and the presence of distant metastasis was associated with a poor prognosis of patients with recurrent esophageal cancer according to the univariate survival analysis. In addition, we elucidated that late recurrence was associated with a favorable prognosis and may be an independent prognostic factor. Naturally the patients with late recurrence showed a longer disease-free survival after esophagectomy compared to those with early recurrence. These findings imply that esophageal cancer resulting in late recurrence may have less aggressive features compared to that causing early recurrence. Matsuura et al. [23] investigated the relationship between the DNA distribution pattern and survival

time. They demonstrated that a low ploidy pattern was associated with late recurrence of esophageal cancer and long-term survival. This may indicate that DNA ploidy can be used as a biological marker of late recurrence.

To reveal the biological difference of recurrent esophageal cancer between patients with early recurrence and late recurrence, we compared the clinicopathological findings between patients with early recurrence and late recurrence of esophageal cancer. Our results showed that late recurrence was significantly associated with an early pT stage in resected primary tumors compared to early recurrence while there were no significant differences between the two groups regarding other factors. This finding demonstrates that the tumor causing late recurrence appears to be a locally slow-growing tumor, which may be associated with a favorable disease-free survival and survival after recurrence.

In order to identify the patients with long-term recurrence-free survival and high risk of late recurrence of esophageal cancer, it is important to define the risk factor of late recurrence of esophageal cancer by comparing the clinicopathological findings between patients with late recurrence and those with long-term recurrence-free survival. Although factors associated with early recurrence and death after esophagectomy for esophageal cancer have been previously reported [11], the predictors of late recurrence have not been definitely determined. In the present study, we demonstrate that the presence of lymph node metastasis at initial esophagectomy was an independent predictor of late recurrence when compared to patients with no recurrence. Late recurrence was also significantly associated with pathological TNM staging and neoadjuvant or adjuvant therapy in the univariate analysis; however, they are not independent predictors of late recurrence. According to these results, the effects of lymph node metastasis appeared to be the main reason for the association between tumor stage (stage III–IV vs stage 0–II) and late recurrence. Similarly, neoadjuvant or adjuvant therapy was mostly applied to patients with node metastasis; thus, these therapies cannot be an independent predictor of late recurrence. Our results suggests that the patients with lymph node metastasis at initial esophagectomy and more than 2 years recurrence-free survival have a risk of late recurrence and should be followed up carefully in postoperative surveillance even though they show long-term recurrence-free survival. The median DFS (range) of patients with late recurrence was 2.80 years (range: 2.04-6.26). These data suggest that patients with high risk of late recurrence should be followed up for 7 years after surgery, hopefully. In the surveillance, the advances in imaging modalities such as endoscopy, ultrasonography, and CT have enabled the detection of recurrent esophageal cancer at an early stage. In addition, FDG-PET can be used to detect recurrent disease in the whole body with high sensitivity [24] and may be a useful tool for the detection of late unexpected recurrence.

There are several limitations associated with the present study. The data on recurrence were retrospectively obtained and are therefore are subject to significant bias. As this is a single-institution experience, our results may have limited generalizability to other practices. The statistical power for the survival and risk factor analyses may be weak as the number of subgroups was relatively small. Prospective, large-number, multicenter studies are needed to establish appropriate surveillance regimens and effective treatment strategies for late recurrence of esophageal cancer. Another limitation is that we could not analyze the cost-effectiveness of postoperative surveillance; this should be investigated in a future prospective study.

In conclusion, this study highlighted the significance of late recurrence after esophagectomy for esophageal cancer. Pathological lymph node metastasis, at the time that esophagectomy is performed, is a risk factor for late recurrence of esophageal cancer, and a close, lifelong follow-up is recommended for such patients. The patients who had late recurrence had a favorable prognosis as expected. A rational surveillance considering late recurrence and appropriate treatment for recurrence may improve the prognosis of patients with esophageal cancer.

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