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Original Article

Treatment strategies in recurrent esophageal or junctional cancer

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SUMMARY. **Little evidence is available about survival rates in patients with recurrent disease after potentially curative surgery for esophageal or junctional cancer. Only in limited occasions, potentially curative salvage strategies are available. The aim of this study is to analyze survival rates and patterns of dissemination, and to identify independent prognostic factors in a consecutive series of patients who develop recurrent esophageal or junctional cancer. Between 1994 and 2015, patients who developed disease recurrence after neoadjuvant chemo(radio)therapy followed by radical esophagectomy for esophageal or junctional cancer were retrospectively analyzed. The Kaplan–Meier estimates were performed to calculate and compare overall survival between patients with different patterns of dissemination and to compare between different treatment strategies. Furthermore, univariate and multivariate Cox-regression analyses were performed to identify independent prognostic factors for post recurrence survival. In this study, we included 219 patients. The median overall survival of all included patients was 3.2 months (range: 0.0–101.1 months). The median overall survival in patients with exclusively locoregional recurrence ($n = 23$, 10.8%) was 4.9 months (range: 0.1– 55.6) and 2.9 months (range: 0.0–101.1) in patients who had distant metastases ($n = 189$, 89.2%), $P = 0.003$. Patients who received treatment aimed at complete tumor eradication ($n = 28$, 13.7%) had a median overall survival of 13.6 months (range: 1.1–101.1) and palliative treated patients ($n = 94$, 46.1%) of 4.7 months (range: 0.3–25.6), $P < 0.001$. In a selected group of patients survival of more than 20 months was achieved. Univariate and multivariate Cox-regression analysis showed that a higher age at the diagnosis of recurrent disease (hazard ratio: 1.087, $P \leq 0.001$), an irradical resection of the primary tumor (hazard ratio: 3.355, $P = < 0.001$), the number of positive lymph nodes after neoadjuvant therapy (hazard ratios: ypN2 = 1.724 ($P = 0.024$) and ypN3 = 2.082 ($P = 0.028$) and the presence of a single hematogenous distant metastases (hazard ratio: 2.281, $P = 0.003$) or more than one hematogenous distant metastasis (hazard ratio: 2.385, $P = 0.005$) were associated with a shorter postrecurrence survival. The prognosis of patients who develop recurrent esophageal or junctional cancer is poor. In a selected group of patients however relatively long survival can be achieved. This offers new perspectives to improve treatment strategies and survival rates.**

KEY WORDS: **esophageal neoplasms, local, neoplasm metastases, neoplasm recurrence, prognosis, regression analysis.**

INTRODUCTION

Esophageal cancer is an aggressive disease known for its rapid dissemination and poor survival. It is the eight most common cause of cancer worldwide and the sixth most common cause of death by cancer.[1]

The introduction of additional neoadjuvant chemo(radio)therapy to esophagectomy led to increased survival rates and reduced the incidence of recurrence.[2–4] Preoperative therapy followed by esophagectomy is now the primary potentially curative therapy in patients with resectable tumors. Reported 5-year survival rates are up to 50%.[5] Consequently, around 50% of these patients develop recurrent disease at some point during follow up.[4,6] Generally, patients with recurrent disease have a very poor survival.[7,8]

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Recurrent disease can be limited to locoregional sites, but more often overt distant metastases are present.[4,6] That the presence of distant metastases is altering the success of subsequent therapies is likely but unknown. Studies describe successful salvage therapies consisting of surgery, chemo- or chemoradiotherapy (CRT) or radiotherapy in patients who experience locoregional recurrence, after potentially curative surgery.[8–11] Evidence on the efficacy of salvage strategies in patients who underwent chemo(radio)therapy prior to surgery, however, is very scarce. Furthermore, even less is known about the correlation between widespread dissemination patterns and survival and the possibilities of salvage strategies. In the clinical setting, the results hopefully provide insight in different treatment options in specific groups of patients with recurrent esophageal cancer, and the corresponding prognosis.

Therefore the aim of the present study is to analyze a large cohort of patients, who developed recurrent disease after initially curative treatment with neoadjuvant therapy followed by esophagectomy for cancer of the esophagus or gastroesophageal junction (GEJ).

MATERIALS AND METHODS

Patient population

All patients who underwent neoadjuvant chemotherapy or CRT followed by potentially curative esophagectomy in the Academic Medical Center of the University of Amsterdam in the Netherlands between March 1994 and August 2013 were selected from a prospectively maintained database. Patients had histologically confirmed squamous cell-, adeno-, or large-cell undifferentiated carcinoma of the mid-to-distal esophagus or GEJ and did not have metastatic disease at the time of esophagectomy. Patients who developed recurrent disease were included in this study after which further information was collected retrospectively.

On arrival at our outpatients clinic, patients were informed that data collected as part of standard care could be used for scientific purposes. Patients did have the opportunity to refuse permission to use their medical information for this goal. The local ethics committee of the Academic Medical Centre in Amsterdam approved this approach.

Treatment of the primary tumor

Neoadjuvant CRT or chemotherapy followed by esophagectomy was indicated in patients with histologically proven, locally advanced, resectable esophageal cancer without distant metastases (cT1N+M0 or cT2–3N0–3M0), and/or had tumors of borderline resectability (cT4a). In most patients, neoadjuvant therapy consisted of weekly administered chemotherapy, consisting of carboplatin (area under the curve of 2 mg/mL per minute) and paclitaxel (50 mg/m^2) and concurrent radiotherapy given in 23 fraction of 1.8 Grey (Gy), to a total dose 41.4 Gy. Another portion of patients received neoadjuvant chemotherapy without concurrent radiotherapy, which consisted of a schedule of epirubicin, oxaliplatin, and capecitabine (EOX) or cisplatin and etoposide. Some patients received additional panitumumab as part of an experimental trial.[12]

Between 1994 and 2000, patients underwent an open esophagectomy as part of a randomized, controlled trial comparing the transhiatal and transthoracic procedure. Based on the results of this trial, patients with a true esophageal tumor generally underwent, when deemed fit, a transthoracic resection in the period after 2000.[13] The minimally invasive procedure was performed as part of a randomized controlled trial between 2009 and 2011 and based on the results of this trial, patients generally underwent minimally invasive transthoracic resection in the period after 2011.[14] Surgery was performed within 6 to 10 weeks after completion of neoadjuvant therapy.

Follow-up

All patients were seen at the outpatient clinic at intervals of three to four months for the first two years after surgery. After three years, patients were seen every six months, until five years after esophagectomy. Only when recurrent disease was suspected on clinical grounds, additional imaging or other invasive diagnostic techniques were performed. The date on which the diagnosis was confirmed by additional examination was considered the date of recurrent disease.

Dissemination patterns

When recurrence was limited to locoregional lymph nodes or the anastomotic site (gastric tube or remaining esophagus) it was classified as locoregional. Lymph nodes were classified as locoregional depending on the location of the primary tumor: for proximal-, mid-, and distal tumors supraclavicular, mediastinal, and para-aortal nodes were classified as local. For junctional- and cardia tumors nodes para-aortal, mediastinal, and in the upper abdominal region were considered local. All other affected sites were classified as distant. Distant sites were divided in the subgroups, consisting of lymphatic affected sites, hematogenous metastases at a single site, and hematogenous metastases at more than one site. The overall survival (OS) in each group was analyzed to be able to provide specific prognostic data on specific groups.

Treatment strategies

Treatment strategies were classified as therapy aimed at total tumor eradication, palliative therapy, or best

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supportive care. The choice of a treatment strategy was based after consultation of a multidisciplinary team consisting of experienced oncologists, surgeons, pathologists, radiologists, and radiotherapists. We did not investigate the motivation for the choice of multidisciplinary team for a certain treatment strategy in each subject, which is of course also based on the age and status of the patient and individual patient preferences. Therapy aimed at total tumor eradication intended to achieve (tumor free) survival. Palliative therapy aimed at tumor control to achieve prolonged survival and/or reduction of symptoms. Best supportive care was classified as care aimed at the improvement of the quality of life without the use of antineoplastic methods. Patients were classified based on the treatment notes in the patient records.

Radiotherapy with concurrent chemotherapy was considered treatment aimed at total tumor eradication, as were fractionated dosing schedules mentioned as such in the obtained data. Palliative radiotherapy (i.e. aimed at prolonged survival) was classified as such if the dose ranged from 25 to 39 Gy, independent of the fractionated schedules. If the dose ranged from 8 to 30 Gy or when a dose was administered as a single session, radiotherapy was considered supportive (i.e. symptom reduction), also independent of the fractionated schedules. If radiotherapy consisted of a dose ranged between 25 and 30 Gy, it depended on the clinical status of a patient whether radiotherapy was classified as palliative or supportive.

Data analysis

The primary endpoints were post recurrence survival, and identifying independent prognostic factors for survival. The Kaplan–Meier estimates were performed to calculate OS, log-rank tests were indicative for the level of significance. Data were considered statistically significant when $P < 0.05$. When an event had not yet occurred, the date of the last follow-up was used. Univariate and multivariate Cox-regression analyses were carried out to identify independent prognostic factors. Variables were included in the multivariate analysis when the *P*-value of a variable in the univariate analysis was lower than 0.5. If the variable was divided in subgroups, and at least one subgroup would show a *P*-value below 0.5, the variable would also be included in the multivariate analysis. IBM SPSS Statistics 22 was used to perform statistical calculations.

Table 1 Patients' characteristics

	N	(%)
Included patients	219	100
Gender		
Male	163	74.4
Female	56	25.6
Median age at diagnosis recurrence (years)	63.5 (33.4–83.5)	
Median interval surgery—recurrence (months)	10.4 (0.0–92.5)	
Location primary tumor		
Middle esophagus	47	21.5
Distal esophagus	132	60.3
Gastroseophageal junction	40	18.3
Histology		
Adenocarcinoma	145	66.2
Squamous cell carcinoma	71	32.4
Large cell (undifferentiated) carcinoma	2	0.9
Missing	1	0.5
T stage before neoadjuvant therapy		
T1	3	1.4
T2	26	11.9
T3	171	78.1
T4	5	2.3
T stage not available	14	6.4
N stage before neoadjuvant therapy		
N0	46	21.0
N1	85	38.8
N2	69	31.5
N3	7	3.2
N stage missing	12	5.5
Neoadjuvant chemotherapy	47	21.5
EOX	8	3.7
Cisplatin and etoposide	36	16.4
Cisplatin, etoposode, and hyperthermia	3	1.4
Neoadjuvant chemoradiotherapy	172	78.5
CROSS	137	62.6
CROSS + hyperthermia	16	7.3
CROSS + panitumumab	15	6.8
CROSS adjusted	4	1.8
T stage after neoadjuvant therapy		
T0	29	13.2
T1	27	12.3
T2	40	18.3
T3	121	55.3
T4	2	0.9
N stage after neoadjuvant therapy		
N0	91	41.6
N1	69	31.5
N2	40	18.3
N3	19	8.7
Surgery		
Transthoracic	156	71.2
Laparatomic	94	42.9
Transhiatal	63	28.8
Laparaotomic	60	27.4

RESULTS

Study characteristics

Between March 1994 and January 2015, 503 patients underwent potentially curative therapy for cancer of the esophagus or GEJ, consisting of neoadjuvant therapy followed by esophagectomy. Eventually, 219 (43.5%) of the treated patients developed recurrent disease, and were included in the present study (Table 1).

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Table 2 Overview of locations of recurrence and treatment strategies

	Total tumor eradication ($n = 28$)			Palliative therapy ($n = 94$)			
	Surgery[†]	CRT	RT	Surg.+RT	CT+RT[‡]	CT	RT
n (%)	7 (25)	18 (64.3)	3 (10.7)	4 (4.3)	21 (22.3)	25 (26.6)	44 (46.8)
Locoregional ($n = 17$)	1	9	1	0	1	1	4
Distant sites ($n = 105$)	6	9	2	4	20	24	40
Median OS (months)	10.3	13.6	18.7	5.4	6.5	6.4	2.8
CI 95%	7.3–13.4	5.8–21.4	8.9–28.6	0.0–17.0	4.3–8.6	4.0–8.8	1.3–4.4

[†]Three patients received respectively chemotherapy (CT), radiotherapy (RT) or chemoradiotherapy (CRT) concurrent to surgery. [‡]CT and RT were not concurrent administered.

Recurrence patterns

Data on recurrence patterns were available in 212 patients (96.8%), and were subsequently analyzed. Data on seven patients were missing, either because the diagnosis and treatment occurred in another hospital which could not provide the records, or the hard-copy records of the older inclusions were not fully present in the archives.

Twenty-three (10.8%) patients were diagnosed with exclusively locoregional recurrence: Local lymphatic recurrence occurred in 16 patients, anastomotic recurrence in six patients and one patient had recurrence in both.

Metastases at distant sites were found in 189 patients (89.2%). Dissemination to distant sites occurred exclusively lymphatic in 23 patients (10.8%), hematogenous to at most one site in 113 patients (53.3%), and 53 patients (25.0%) had more than one hematogenous distant site affected. Twenty-eight patients with distant metastases were also diagnosed with locoregional recurrence.

Treatment strategies

Two-hundred and four (93.2%) of 219 patients who developed recurrence were evaluable for description of treatment strategies. Treatment aimed at total tumor eradication was applied in 28 patients (13.7%), palliative treatment was applied in 94 patients (46.1%) and in 82 patients (40.2%) best supportive care was the only treatment option.

Treatment aimed at total eradication

CRT was the primary choice if therapy was aimed at total tumor eradication (Table 2). Eighteen of the 28 patients received CRT, of whom 17 received the combination of carboplatin and paclitaxel. Most of these patients received concurrent radiotherapy to a dose of 50.4 Gy, in 28 fractions of 1.8 Gy. Seven patients who received CRT lived beyond 20 months. Five of those patients were diagnosed with locoregional recurrence, and two patients had a single supraclavicular metastasis.

Seven patients underwent surgery: A patient who had a resection of a brain metastasis has been tumor free up to the last follow-up 19 months after the diagnosis of the metastasis. A second patient had a resection of a lung metastasis but developed progressive disease and was again successfully treated with radiotherapy. This patient has been tumor free up to the last follow-up 22 months after the diagnosis of recurrence. All five other patients who had surgery developed progressive disease and died within three to 10 months.

Palliative treatment

Chemotherapy and radiotherapy were most frequently applied as palliative therapy (Table 2). Capecitabine as monotherapy in nine patients and capecitabine and oxaliplatin combined (CAPOX) in seven patients were applied most frequently in patients who received palliative chemotherapy. One patient who received capecitabine with palliative intent had a survival of 26 months, metastases were present in a local lymph node and in the lung. Interestingly, no significant improvement in survival in patients palliative treated with chemotherapy was found in the course of time.

In patients who received chemotherapy with concurrent palliative radiotherapy, schedules with capecitabine in seven patients or CAPOX in three patients were most frequently applied. Concurrent supportive radiotherapy and supportive radiotherapy as monotherapy were mainly performed to treat bone and brain metastases. Palliative radiotherapy as monotherapy was applied in six patients (median OS 4.8 months, CI 95% 0.0–10.2), supportive radiotherapy as monotherapy was applied in 26 patients (median OS 2.0 months, CI 95% 1.1–2.9).

Surgery was performed if no tumor response was achieved with initial radiotherapy. Two patients had vertebral surgery because of existing spinal cord injury and spinal cord compression, in both patients survival was about five months. Surgery of a brain metastasis was performed in one patient (survival 16.6 months), and another patient underwent surgery of the femur as prevention of a pathological fracture (survival 21.4 months); this patient also had brain metastases for which palliative radiotherapy was given (next to

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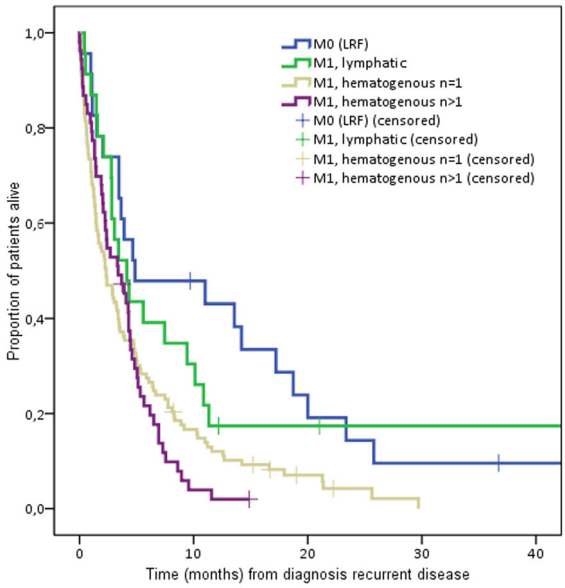

Location of recurrence	Number of patients at risk (%)					
	0	5 months	10 months	20 months	30 months	40 months
M0 (LRF)	23 (100)	10 (43)	9 (39)	4 (17)	2 (9)	1 (4)
M1, lymphatic	23 (100)	9 (39)	6 (26)	1 (4)	1 (4)	1 (4)
M1, hematogenous n=1	113 (100)	34 (30)	17 (15)	4 (4)	0 (0)	0 (0)
M1, hematogenous n>1	53 (100)	14 (26)	1 (2)	0 (0)	0 (0)	0 (0)

Fig. 1 Kaplan-Meier survival curve from diagnosis recurrent disease until death, comparing dissemination patterns. Note: Locoregional recurrence may also be included in all subgroups M1. Subgroup M1, hematogenous (both $n = 1$ and $n > 1$) may include distant lymphatic metastases.

the radiotherapy preoperative applied for the metastasis in the femur).

Survival analyses

Patients who were diagnosed exclusively with locoregional recurrence had a median post recurrence survival of 4.9 months (range: 0.1–55.6) and patients who were diagnosed with metastases at distant sites had a median post recurrence survival of 2.9 months (range: 0.0–101.1, $P = 0.03$). The patients who were diagnosed with metastases at distant sites were divided in three subgroups (Fig. 1): At first those who had exclusively lymphatic distant sites affected (M1, lymphatic) had a median post recurrence survival of 4.1 months (range: 0.4–101.1), at second patients with at most one hematogenous metastasis (M1, hematogenous $n = 1$) 2.3 months (range: 0.1–29.7), and at third patients with more than one hematogenous metastasis (M1, hematogenous $n > 1$) had a median post recurrence survival of 3.4 months (range: 0.0–14.9). The difference between the first (M1, lymphatic) and the third (M1, hematogenous $n > 1$) subgroup ($P = 0.019$) were statistically significant ($P = 0.019$).

Survival analysis between subgroups divided by treatment strategy is as follows (Fig. 2): Patients who received treatment aimed at total tumor eradication had a median post recurrence survival of 13.6 months (range: 1.1–101.1), palliative treated patients of 4.7 months (range: 0.3–25.6), and patients who received best supportive a median post recurrence survival of 1.1 month (range: 0.0–7.6). All comparisons between subgroups were statistically significant (all $P = 0.01$).

Prognostic factors

Univariate Cox-regression analysis shows that age at the time of diagnosis of recurrent disease, the histologic subtype of the tumor, the number of positive lymph nodes before (cN stage) and after (ypN stage) neoadjuvant therapy, an irradical resection of the primary tumor and the presence and number of distant sites affected with metastases met the criteria to be included in the multivariate analysis (Table 3). Multivariate Cox-regression analysis demonstrated that the

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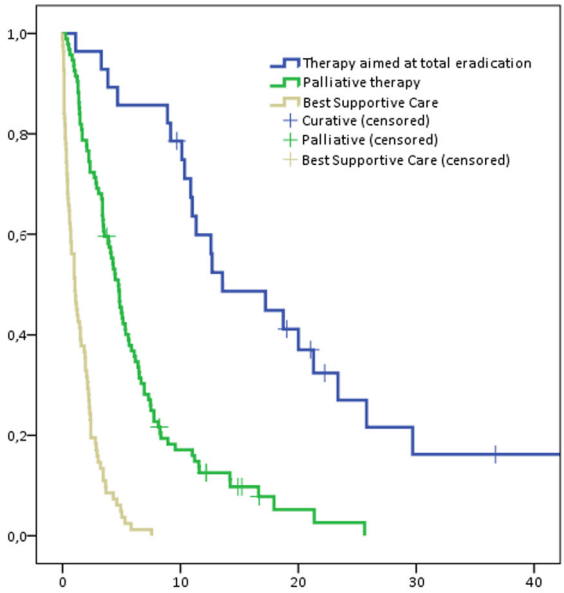

Treatment modality	Number of patients at risk (%)					
	0 months	5 months	10 months	20 months	30 months	40 months
Total tumor eradication	28 (100)	23 (82)	20 (71)	9 (39)	2 (7)	1 (4)
Palliative	94 (100)	40 (43)	14 (15)	1 (1)	0 (0)	0 (0)
Best supportive care	82 (100)	3 (4)	0 (0)	0 (0)	0 (0)	0 (0)

Fig. 2 Kaplan-Meier survival curve from diagnosis recurrent disease until death, comparing treatment strategies.

age at the diagnosis of recurrent disease, the number of positive lymph nodes before and after neoadjuvant therapy, the location of the primary tumor, an initial irradical resection and the presence and number of distant sites affected with metastases were significantly and independently associated with post recurrence survival (Table 4).

DISCUSSION

This study demonstrates that the post recurrence survival in patients who were diagnosed with recurrent disease after potentially curative treatment for cancer of the esophagus or GEJ is very poor.

Patients who were diagnosed with exclusively locoregional recurrence have the most favorable prognosis with 4.9 months. Prolonged survival rates of 13 and 17 months were found in similar studies which investigated survival rates in patients diagnosed with locoregional recurrence after potentially curative esophagectomy.[7,10] A study which investigated patients with locoregional recurrence of squamous cell carcinoma of the esophagus and received CRT achieved a median OS of 26 months.[15] The disappointing survival rates in this study may be attributed to the absence of routine imaging or other diagnostic techniques during follow-up in the Netherlands. Only when recurrent disease is suspected on the basis of symptoms such as dysphagia, imaging is performed. Prolonged survival might be achieved by routine imaging, although it is still unclear whether earlier detection of recurrent disease improves post recurrence survival rates.[16,17] The prolonged survival in studies which perform routine imaging during follow-up may, in fact, be attributable to lead time bias; routine imaging may lead to an early detection and a longer perceived OS, while the actual course of the disease remains unaffected. Randomized studies are needed to assess whether the use of extensive diagnostic techniques during follow-up not only leads to early recurrence detection, but also to prolonged survival rates. Another factor that may attribute to the longer survival rates in the other studies is the long time span in which patients were included in this current study, with possibly worse post recurrence survival rates in the older inclusions. This can be debated however, since in a study by Blom *et al.* shows that post recurrence survival did not change in the past 18 years.[18] Furthermore, correction of survival rates for performance status could not be performed in this

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Table 3 Univariate Cox-regression analysis

	Hazard ratio	95% CI	*P*-value
Age at recurrence (1 year increment)	1.024	1.009–1.039	0.001
Male gender	1.099	0.799–1.512	0.563
Histologic subtype primary tumor			
Squamous cell carcinoma	Reference		
Adenocarcinoma	1.169	0.871–1.571	0.298
Location primary tumor			
Mid to distal esophagus	Reference		
GEJ	0.826	0.578–1.180	0.293
cT stage			
cT1–2	Reference		
cT3–4	0.999	0.668–1.492	0.995
cN stage			
cN0	Reference		
cN1	0.697	0.483–1.007	0.054
cN2	0.752	0.512–1.102	0.144
cN3	0.905	0.408–2.009	0.807
yT0 (pathological complete response)	0.789	0.526–1.185	0.254
ypN stage			
yN0	Reference		
yN1	1.025	0.739–1.420	0.884
yN2	1.313	0.891–1.936	0.169
yN3	1.574	0.946–2.619	0.081
Irradical (R1) resection	2.853	1.666–4.884	<0.001
Interval surgery—recurrence (1 month increment)	0.997	0.987–1.007	0.579
Location of recurrence[†]			
M0 (locoregional only)	Reference		
M1 (lymphatic)	1.303	0.692–2.452	0.413
M1 (hematogenous, $= 1$)[‡]	2.088	1.284–3.397	0.003
M1 (hematogenous, $n > 1$)[‡]	2.367	1.382–4.054	0.002
Treatment strategy			
Best supportive care	Reference		
Palliative	0.219	0.154–0.310	<0.001
Total tumor eradication	0.057	0.032–0.103	<0.001

[†]M1 can also include locoregional recurrence. [‡]Can also include lymphatic distant metastases

study, in contrast to the other studies, because in very few patients we were able to obtain data. This biased our results, because a patients' performance status has direct influence on survival.[19]

In some patients in this study relatively long survival was achieved. Five patients with locoregional recurrence and two patients who had a recurrence in a positive supraclavicular lymph node achieved a survival of at least 20 months after receiving CRT. In two patients who both had a distant metastasis in the lung, survival of more than 20 months was observed. These patients were allocated in different subgroups: Both patients with locoregional failure and with distant sites affected were able to achieve relatively long survival. Even the purpose with which therapy was started (total tumor eradication or palliative therapy) differed. The similarity between the patients is the sufficient clinical condition they had to achieve chemotherapy or surgery, and the limited sites which were affected by the recurrent disease. Thus, for these patients relatively long survival can be achieved. But despite the relatively long survival in some patients with distant metastases, the overall survival in this group is evidently very poor (2.9 months). A Dutch study by Parry *et al*. who investigated patients with recurrent esophageal cancer after esophagectomy with curative intent found a median OS in patients with metastases at distant sites of two months.[8] Follow-up in Parry *et al*. was similar to our study, so imaging was only performed when recurrence was suspected. The treatment of the primary tumor however differed from our population; 42% underwent esophagectomy without any neoadjuvant treatment compared to 100% in our study. Nonetheless, relatively long survival is possible in some patients diagnosed with distant metastases, so it should be investigated whether early detection of recurrent disease due to routine imaging during follow-up leads to an increased numbers of patients with only one site affected at the moment of diagnosis of recurrent disease.

Predictive factors for survival found in a multivariate survival analysis using a Cox-regression model were age at the diagnosis of recurrent disease, the N-stage before and after surgery, an irradical (R1) resection of the primary tumor and the location of

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Table 4 Multivariate Cox-regression analysis

	Hazard ratio	95% CI	*P*-value
Age at recurrence (1 year increment)	1.027	1.011–1.045	0.001
Histologic subtype primary tumor			
Squamous cell carcinoma	Reference		
Adenocarcinoma	1.210	0.857–1.708	1.708
Location primary tumor			
Mid to distal esophagus	Reference		
GEJ	0.667	0.429–1.037	0.072
cN stage			
cN0	Reference		
cN1	0.599	0.395–0.910	0.016
cN2	0.581	0.380–0.887	0.012
cN3	0.662	0.276–1.586	0.355
yT0 (pathological complete response)	1.042	0.650–1.670	0.863
ypN stage			
ypN0	Reference		
ypN1	1.296	0.891–1.885	0.175
ypN2	1.724	1.074–2.768	0.024
ypN3	2.082	1.081–4.009	0.028
Irradical (R1) resection	3.355	1.783–6.314	<0.001
Location of recurrence[†]			
M0 (locoregional recurrence)	Reference		
M1 (lymphatic)	1.120	0.558–2.246	0.750
M1 (hematogenous, n = 1)[‡]	2.281	1.320–3.942	0.003
M1 (hematogenous, *n* > 1)[‡]	2.385	1.306–4.354	0.005

[†]M1 can also include locoregional recurrence. [‡]Can also include lymphatic distant metastases.

recurrence. Parry *et al*. also found that the type of recurrence (e.g. local, distant, or combined) and the number of locations were significant prognostic factors.[8] It may not be a surprise that patients with metastases at distant sites have an increased risk for a shorter survival, but interestingly the presence of lymphatic distant metastases had no significant influence on survival after recurrent disease. Furthermore, it is interesting to note that an irradical resection of the primary tumor has the highest hazard ratio for shorter post recurrence survival, even more than the presence and number of distant metastases.

The histological subtype of the primary tumor was in both this study and in Perry *et al*. not considered a significant prognostic factor for survival, while the histological subtype is indeed a prognostic factor for the development of recurrent disease after surgical resection.[4]

Including assessment of quality of life in future studies would certainly be of added value of the decision making concerning (palliative) therapy. A review by Al-Batran and Ajani showed that chemotherapy can maintain quality of life in patients with metastatic esophageal cancer and seemed to correspond with the efficacy of chemotherapeutical therapy.[20] More aggressive therapy, however, is also related to increased toxicities and worsened quality of life.[21]

Future studies should evaluate the efficacy of different therapies in recurrent disease of the esophagus or GEJ and prognostic factors that influence the success of therapies and survival. Finally, it should be studied whether elaborate screening during follow-up is able to detect disease recurrence earlier, and the possible benefit that early detection of recurrent disease could have on the quality of therapies, survival rates, and quality of life.

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