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Recurrence of esophageal cancer after R0 surgery. Risk factors and evolution

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ABSTRACT

Introduction: despite advances in surgical and adjuvant therapy, recurrence in esophageal cancer submitted to R0 surgery remains high. The aim is to define risk factors and recurrence patterns. Additionally, to show the management carried out and the outcome of patients showing recurrence.

Material and methods: observational and prospective study that included 61 patients. Neoadjuvancy therapy was indicated on T3, T4 and N+ tumors and every lymph node dissection was performed in two fields. Recurrence is defined at distance, regional or local, when, recurrence is detected after six months. According to clinical features and the recurrences, a palliative, chemotherapeutic or surgical management was indicated.

Results: there were 54 men and the mean age was 59.7 years. The most frequent stage was the IIA and 17 (27.9%) had positive lymph nodes. Thirty (49.2%) had showed recurrence with a median disease-free interval of 10.5 months. The pTNM, the absence of response to the neoadjuvancy and the presence of compromised lymph nodes were found to be risk factors for recurrence. Only the presence of compromised lymph nodes was significant in the multivariate analysis. After diagnosis of the recurrence, median survival was 7 months and 6 subjects survived beyond 1 year.

Conclusions: we confirmed the high incidence of recurrence in esophageal cancer, where the presence of compromised lymph nodes is probably the main risk factor. After the diagnosis of a relapse the prognosis would be bad, however there would be a small subsidiary group for treatment where outcomes would be better.

Key words: Esophageal cancer. Curative esophagectomy. Recurrence. Prognostic factors.

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INTRODUCTION

The esophageal carcinoma is a pathology that is traditionally catalogued as a bad prognosis and only a small number of patients will be candidates for surgery with curative intention (1-4), this being the cornerstone if the objective is to attain cure (1,2,5-8). Despite the surgical progress and mostly in the complementary therapy, the recurrence in esophageal cancer with R0 resection remains high, where the literature has reported rates between 34 and 79% (3-5,9,10). It is important to know the clinical, biological and pathological factors that may favor the appearance of recurrence and also the recurrence patterns and the later outcome, as they could condition the postoperatory follow-up and the attitude toward these patients. There are recent studies that describe encouraging results for the management of the recurrence on a selected group of patients (9,11-17). These observations support the need for a periodic follow-up after a curative surgery (3) and the need to develop action protocols when faced with a recurrence.

The objective of this study is to show the characteristics and outcomes of patients with esophageal cancer that underwent R0 surgery and define the risk factors for recurrence. Similarly, in those patients with recurrence, to show the recurrence patterns, the implemented management and their evolution.

MATERIAL AND METHODS

Patient selection

Observational study taken from a database with a prospective approach since 2002 in our Esophageal-Gastric Surgery Unit. Of 93 patients with esophageal cancer that had undergone surgery, we excluded 7 cases with R1 or R2 surgery, 8 cases of postoperative mortality, 14 cases with

follow-up below 1 year and 3 cases with recurrence before 6 months, because it was considered as a persistence of the neoplastic disease. Consequently, we include 61 patients who had undergone esophageal cancer surgery with curative intent and R0, regarded those whose surgical specimen had at least 1 mm of tumor free on the proximal, distal and circumferential margins (18). The patients are divided into two groups: those that showed recurrence after 6 months and those without recurrence that had at least 12 months of follow-up. The flow chart is shown in figure 1.

Diagnosis and patient management

The diagnosis was made by endoscopy and biopsies. The extension study was performed using computerized tomography (CT) of the thorax and the abdomen. Endoscopic ultrasound was utilized to differentiate patients with local disease (T1, T2, N0) and local-regional (T3, T4, N+) disease, with the purpose of defining those candidates for neoadjuvant therapy. The MRI and/or the PET is indicated in patients with suspected metastatic disease and/or distant lymph node involvement. In all cases of carinal or supracarinal tumors we performed fibrobronchoscopy.

For patients with a mural compromise greater than T2 and/or lymph node involvement, neoadyuvant therapy was indicated. We performed neoadyuvant radiochemotherapy (45 Gy + ECF) (19) in patients with squamous carcinoma and perioperative chemotherapy in patients with adenocarcinomas (mostly "XELOX" oxaliplatin 130 mg/m^2 [dose per cycle] + capecitabine 2,000 mg/m^2/day for 15 days, 3 cycles preoperative) (20). The clinical response was assessed using CT. Four weeks after the completion of the neoadjuvancy in the adenocarcinomas and 6 weeks in the squamous carcinomas, the patients underwent surgical intervention.

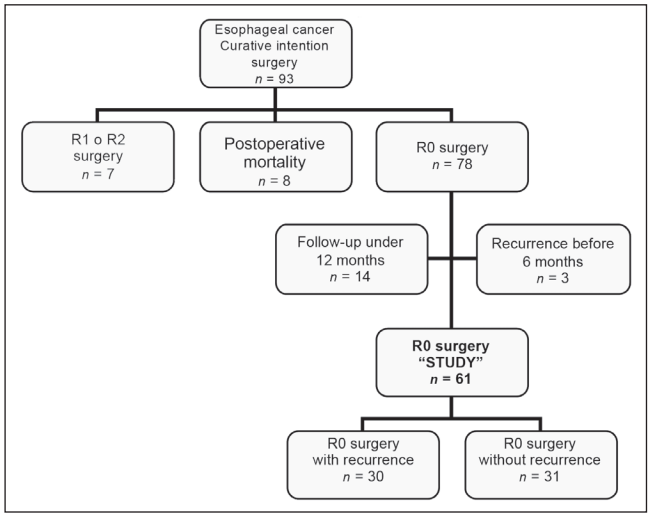

Fig. 1. Flow chart of patients diagnosed with esophageal cancer.

Classical or minimally invasive surgery was utilized on patients. The classical surgical techniques used were the Ivor Lewis or McKeown (21-23). Those operated with minimally invasive surgery were performed with a three fields approach, according to McKeown's technique, in which the thoracic part is always performed by videothoracoscopy. Lymphadenectomy was done on two fields on all patients and the reconstruction is preferentially carried out using Akiyama's gastric plasty and its ascent through the posterior mediastine. The immediate postoperative period was done in the Recovery Unit and according to their evolution, patients were transferred to clinical rooms until their discharge.

Follow-up and definition of recurrence

Follow-up was carried out through periodic visits, with clinical evaluation and a thorax and abdomen CT once every 6 months, for 2 years and then annually for up to 5 years. Endoscopy, ultrasonography, bone scintigraphy, brain CT or PET were requested only when there was a clinical suspicion of recurrence. Recurrence is defined as the detection of relapse of neoplastic disease during follow-up, after 6 months. There may be recurrence at distance, regional or local, which is evidenced through a clinical examination, endoscopic or imaging study (CT, PET, ultrasonography or bone scintigraphy) and confirmed by PET, histopathology and/or cytology (4).

Management and follow-up of patients with recurrence

The patients with recurrence are analyzed within a multi-disciplinary committee, where their management is defined mainly according to their general state, location, focalization, and the number of lesions suggesting recurrence. All of them undergo a complementary study of other secondary location using CT. PET is only used on those where there is a predicted management with curative intention. Patients with a good general state and a good Karnofsky index were included in a chemotherapy protocol. Resection was considered in the cases with localized metastasis that were subsidiary of R0 surgery. Those patients in poor general condition and/or contraindicated for chemotherapy were entered into a palliative management protocol.

Variables analyzed

We collected the following clinical variables: age, gender, ASA classification, transfusion (first 24 hours of surgery), minimally invasive surgery, type of surgery performed –Ivor Lewis (intrathoracic anastomosis) or

McKeown (cervical anastomosis)–, operatory complications (Clavien and cols classification) (24) and histological type. The tumor location was defined endoscopically in supracarinals, infracarinals and esophageal-cardials (Siewert I) (25,26). Staging was done according to TNM's 6th edition, 2002. The response to neoadyuvant therapy was shown, based on the histopathological findings as compared to clinical staging, and was defined as a complete response (no evidence of the tumor), partial response (tumor shrinkage) and no response (stable disease or progression of the tumor) (27,28). The technique used for the diagnosis of the recurrence was mentioned and if there was pathological confirmation. We show the follow-up and the curves for overall survival and disease free interval (DFI) by stages, for the series. We defined the patterns of recurrence as local recurrence (location of the primary tumor and/or anastomosis), regional (compromised regional lymph nodes), and distant (metastatic) (1). Those with concomitant regional and distant recurrence, that is mixed relapses, are included in the group of distant recurrences, and it indicated the organ involved as the site of recurrence. The disease free interval is mentioned and is defined as the time elapsed between the surgery and the diagnosis of the recurrence. We also mention factors associated with the recurrence pattern, the management carried out on patients with recurrence and the overall post-recurrence survival.

Statistical analysis

For the overall survival and the DFI study we used the Kaplan Meier curves and the test log Rank when comparing fact*ors.* To determine predictors of relapse, we used the binary logic regression model, where the entry point for the model was defined as 0.1. In order to determine the association of qualitative variables, we performed the χ^2 test. A confidence value of 95% ($p<0.05$) was considered significant for all the tests run. For the statistical analysis, we used the SPSS program for Windows.

RESULTS

Characteristics and series survival

Of the 61 patients, 54 (88.5%) were male and 7 (11.5%) female, the median age was 59.7 (SD ± 10.4). The location of the tumors was: 17 (27.9%) supracarinals, 23 (37.7%) infracarinals and 21 (34.4%) in the esopahagel-cardial area. Of the tumors, 31 (50.8%) were adenocarcinomas and 30 (49.2%) were squamous. According to ASA's classification, there were 6 (9.8%), 23 (37.7%) and 32 (52.5%) for ASA I, II and III, respectively. Forty nine (80.3%) of the patients received neoadjuvancy; of those, 23 (46.9%) underwent chemoradiotherapy and 26 (53.0%) chemotherapy. The response to the neoadjuvancy was 11 (20.4%), 21 (46.9%) and 17 (32.7%) for a complete, partial and without response, respectively. The approach through classical surgery was done on 48 (78.7%) of the cases and minimally invasive surgery was used on 13 (21.3%) of the cases. In 42 (68.8%) of the cases the anastomosis was intrathoracic and cervical in 19 (31.1%) and 31 (50.8%) patients were transfused. Thirty five (57.4%) patients showed no complications and of the 26 (42.6%) with complications, 1 (1.6%), 9 (14.8%), 2 (3.3%), 4 (6.6%), 9 (14.8%) and 1 (1.6%) presented postoperatory complications of type I, II, IIA, IIIB, IVA and IVB, respectively. The anatomopathological stages of the series were as follows: stage 0 in 11 (18.0%) of the cases, stage I in 10 (16.4%), stage IIA in 21 (34.4%), stage IIB in 10 (16.4%) and stage III in 9 (14.8%). There were 17 (27.9%) patients who showed positive lymph nodes and the mean size of measured lymph nodes was 13.0 (SD 8.8), the median of the affected lymph nodes was 0.98 (SD 1.9) and a ratio of affected/examined lymph node greater or equal to 0.20 was found in 11 (18.0%) of the cases. The follow-up median was 29 months (range: 7-167) and during it 30 (49.2%) showed recurrence. The recurrence was diagnosed through clinical evaluation on 3 (10.0%) patients, endoscopy on 3 (10.0%), ultrasonography on 2 (6.7%), thoracic CT on 10 (33.3%), abdominal CT on 6 (20.0%), cerebral CT on 1 (3.3%), bone scintigraphy on 1 (3.3%) and PET on 4 (13.3%). Out of all of them, in 20 (66.7%) cases the recurrence diagnosis was confirmed histologically, 3 (10.0%) cytologically and 7 (23.3%) through PET. The overall survivals and DFI on a 5-year period was 53.5% and 42.0%, respectively. The survival curves by stage were statistically different for both instances –$p = 0.001$ and $p = 0.002$, respectively– and are depicted in figure 2.

Recurrence risk factors

The analyzed risk factors for the development of recurrence are shown in table I. From the univariate analysis, pN+, pTNM and the pathological response to neoadjuvancy can be seen as risk factors with statistical significance. When the multivariate analysis was run, it was found that the presence of compromised lymph nodes (pN+) (p = 0,003; *odds ratio* [OR] 8,167; confidence interval [CI] 2,034-32,789) was the only factor with statistical significance.

Disease free interval and recurrence pattern

For those patients that had recurrence ($n = 30$), the median DFI was 10.5 months (range 7-68) and 90% of them, were diagnosed before of 2 years. The recurrence pattern was then evaluated and it showed 3 (10%) cases locally, 8 (26.6%) regionally (4 mediastinic, 3 cervical and 1 abdominal) and 19 (63.3%) distantly (8 pulmonary, 4 hepatic, 3 peritoneal, 2 osseous, 1 pleural and 1 cerebel-

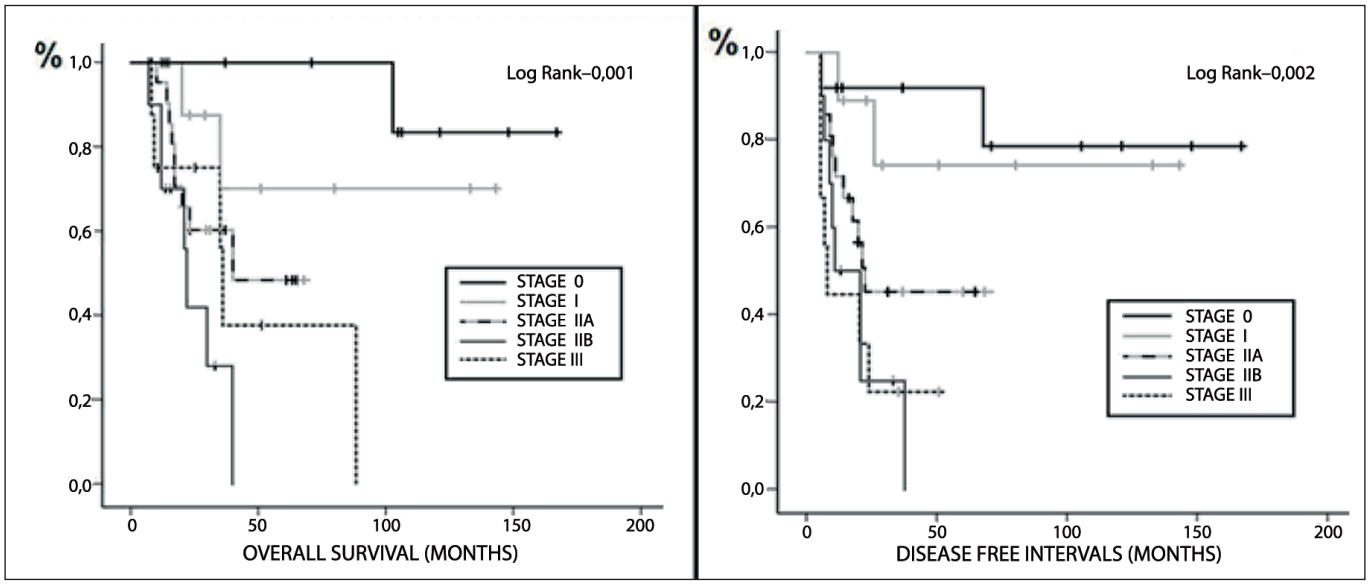

Fig. 2. Curves on overall survival and disease free intervals (DFI) by stages.

lar). The median for the DFI was 24 months (range 8-68) for the local recurrence, 8 months (range 7-26) for the regional recurrence and 11 months (range 7-38) for the distant recurrence. Table II shows the recurrence pattern according to the analyzed variables. It is shown that the histological type is the only statistically significant variable related to the recurrence pattern, indicating that the adenocarcinomas show a higher metastasis percentage distantly.

Management of patients with recurrence and their survival

Ten (33.3%) patients were indicated chemotherapy; 4 with recurrence in the mediastinic lymph nodes with survivals of 1, 7, 15, and 34 months, 3 with recurrence in the cervical lymph nodes with survivals of 5, 9 and 82 months and the other 3 with recurrences on the abdominal, pleural and peritoneal lymph nodes with survivals of 15, 11 and 1 month, respectively. Three patients were indicated metastasectomy with curative intention; 1 of them with unique cerebellar metastasis, whose survival was 2 months and 2 with pulmonary metastasis: one with a 2 month survival, but the cause death different from the neoplasm and the other one remains disease free after 16 months of follow-up. The rest of the patients were managed palliatively. None of the 4 patients with mixed recurrence had a survival greater than 4 months. The post-recurrence survival curve is shown in figure 3 and the median is 7 months. After the diagnosis of recurrence was reached, there were 6 (20.0%) patients that showed a survival greater than 12 months; table III shows the characteristics and the treatments implemented on them.

DISCUSSION

Even after curative surgery, recurrence in esophageal cancer, continues to be high and the literature mentions many associated factors. Our results indicate that the presence of compromised lymph nodes as one of, or even the main risk factor of recurrence, which has already been reported by several authors (4,11,29,30) in the literature. Other risk factors described are the presence of dysphagia, pT, the pTNM stage and those without a response to neoadjuvancy (1,2,27,31). In our experience the last two were statistically significant, only in the univariate analysis, maybe due to an insufficient number of patients. The impact prognosis of the response to the neoadjuvant treatment remains a broadly discussed subject in the literature. Meguid et al. (27) corroborated that those patients with a complete pathological response would have a lower risk of recurrence.

Based on observations that the lymphatic and hematogenous extension occur independently and that local recurrence would be within the context of the persistence of neoplastic cells in relation to the primary tumor (1,32,33), we defined the recurrence pattern in local, regional and distant recurrences. There is no consensus on this matter, some have classified it this way (1, 2,6,7,10) and others have defined local-regional recurrences (local recurrence and concomitant lymph nodes) and mixed (lymph node recurrences and at a concomitant distance) as independent groups (2,3,31,34). Since we consider the number of

Table I. Prognosis factors associated to recurrence development. Univariate analysis

		Recurrence (n = 30)	*Without recurrence (n = 31)*	*p*
Age		60.4 (SD ± 8.9)	59.1 (SD ± 10.4)	0.641
Gender M/F		9/1	6.75/1	0.722
ASA	I	4 (66.7%)	2 (33.3%)	0.338
	II	13 (56.5%)	10 (43.5%)	
	III	13 (40.6%)	19 (59.4%)	
Transfusion	Yes	15 (51.6%)	15 (48.4%)	0.900
	No	16 (48.4%)	16 (51.6%)	
Minimal invasive surgery	Yes	6 (46.1%)	7 (53.8%)	0.806
	No	24 (50.0%)	24 (50.0%)	
Anastomosis	Cervical	10 (52.6%)	9 (47.3%)	0.717
	Intrathoracic	20 (47.6%)	22 (52.4%)	
Complications	None	20 (57.1%)	15 (42.9%)	0.702
	I	0 (0.0%)	1 (100%)	
	II	4 (44.4%)	5 (55.6%)	
	IIIA	1 (50.0%)	1 (50.0%)	
	IIIB	2 (50.0%)	2 (50.0%)	
	IVA	3 (33.3%)	6 (66.7%)	
	IVB	0 (0.0%)	1 (100%)	
Histological type	Adenocarcinoma	14 (45.1%)	17 (54.8%)	0.523
	Squamous carcinoma	16 (53.3%)	14 (46.7%)	
Location	Supracarinal	10 (58.8%)	7 (41.2%)	0.417
	Infracarinal	12 (52.2%)	11 (47.8%)	
	Esophageal-cardial	8 (38.0%)	13 (61.9%)	
Stage pTNM	0	2 (18.2%)	9 (81.8%)	0.006
	I	2 (20.0%)	8 (80.0%)	
	IIA	11 (52.4%)	10 (47.6%)	
	IIB	8 (80.0%)	2 (20.0%)	
	III	7 (77.8%)	2 (22.2%)	
pT	0	4 (28.6%)	10 (71.4%)	0.890
	1	3 (27.3%)	8 (72.7%)	
	2	15 (68.2%)	7 (31.8%)	
	3	7 (58.3%)	5 (41.7%)	
	4	1 (50.0%)	1 (50.0%)	
pN	0	16 (36.4%)	28 (63.6%)	0.001
	1	14 (82.4%)	3 (17.6%)	
Pathological response to the neoadjuvancy (n = 49)	Total	2 (18.2%)	9 (81.8%)	0.025
	Partial	11 (52.4%)	10 (47.6%)	
	No response	12 (70.6%)	5 (29.4%)	

patients to be insufficient and because of the discrepancies in the classification systems, our objective was not to compare the survival according to the types of recurrence patterns. On this, Kato et al. (31) mention that those patients with mixed recurrence would be the ones that show the worst prognosis and the best would be for those with local-regional recurrence.

The DFI median is similar to other publications (1,3), with the exception of local recurrence, with only 3 patients with this type of recurrence. Of these, two had

Table II. Factors associated to the recurrence pattern

		Local (n = 3)	*Regional (n = 8)*	*Distant (n = 19)*	*p (Pearson χ^2)*
Histological type	Adenocarcinoma	1 (7.1%)	1 (7.1%)	12 (85.7%)	0.049
	Squamous carcinoma	2 (12.5%)	7 (43.8%)	7 (43.8%)	
Location	Supracarinal	2 (20.0%)	3 (30.0%)	5 (50.0%)	0.165
	Infracarinal	0 (0.0%)	5 (41.7%)	7 (58.3%)	
	Esophageal-cardial	1 (12.5%)	0 (0.0%)	7 (87.5%)	
Anastomosis	Cervical	0 (0.0%)	2 (20.0%)	8 (80.0%)	0.3
	Intrathoracic	3 (15.0%)	6 (30.0%)	11 (55.0%)	
Pathological response to the neoadjuvancy (n = 25)	Total	1 (50.0%)	0 (0.0%)	1 (50.0%)	0.138
	Partial	0 (0.0%)	4 (36.4%)	7 (63.6%)	
	No response	1 (8.3%)	2 (16.7%)	9 (75.0%)	
pN	Positive	2 (14.3%)	4 (28.6%)	8 (57.1%)	0.713
	Negative	1 (6.3%)	4 (25.0%)	11 (68.8%)	

showed a DFI greater or equal to 24 months and these correspond to squamous tumors with preoperatory radiation. All the local recurrences of our series have been in cases with intrathoracic anastomosis, for which we deem essential the resection margins of the primary tumor (proximal, distal and circumferential) (35-38). Tam et al. (39) recommend a free tumor proximal section margin greater than 5-7 cm, that in supra and infracarinal tumors could be achieved safely, through a subtotal esophagectomy with cervical anastomosis. After many years of debate, the lymph node dissection in two or three fields continues to create controversies in the esophageal cancer surgery (40). We, differently from the oriental trend, did dissection on 2 fields, based on studies that show a low impact of the cervical dissection (41-43). On this study we can provide our experience indicating that all the recurrences on cervical lymph nodes were by squamous carcinoma and that the recurrence pattern of the adenocarcinomas was mainly distant (44). At the time of the diagnosis, the chemotherapy and mainly the neoadyuvant chemotherapy gains importance for the control of subclinical micrometastasis (45).

The general prognosis for patients with recurrence is bad and for their management there exists a variety of accepted guidelines, like exclusively chemotherapy o radiotherapy, chemoradiotherapy, surgery with or without adjuvancy and the palliative treatment. In our study, 4 of the 6 patients that had a post-recurrence survival greater than 12 months, were subject to chemotherapy. This supports other authors that say there should be a group that responds to chemotherapy, improving their expectations (11), albeit with very low curative possibilities. For the management of lymph node recurrences, current studies show encouraging results with chemoradiotherapy and lymphadenectomies (9,11-16,34). Similarly, cases with good results have been published in the past few years, for resections in single pulmonary recurrences and within the context of patients with good general conditions. We contribute one case with these characteristics with a DFI of 22 months, which supports other authors that propose a prolonged DFI as a favorable factor to consider when faced with this behavior (46,47).

We conclude that recurrence of esophageal cancer, despite the R0 surgery, is very frequent. We believe it is necessary to have more studies to evaluate the results of

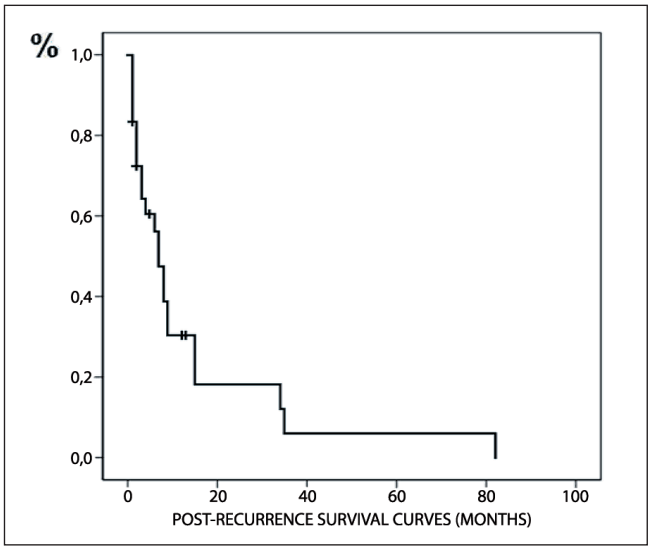

Fig. 3. Post-recurrence survival curves.

Table III. Characteristics of patients with recurrence and survival greater than 12 months

Location (histological type)	*Recurrence place (pattern)*	*Disease free interval (DFI)*	*Management*	*Survival (present state)*
Supracarinal (Squamous)	Anastomosis (Local)	68 months	Palliative Dilatation	35 months (deceased)
Supracarinal (Squamous)	Mediastinal lymph nodes (Regional)	6 months	Chemotherapy	34 months (deceased)
Infracarinal (Adenocarcinoma)	Pulmonar single (Distant)	22 months	Lobectomy	16 months (alive)
Infracarinal (Squamous)	Mediastinal lymph nodes (Regional)	7 months	Chemotherapy	15 months (deceased)
Infracarinal (Adenocarcinoma)	Abdominal lymph nodes (Regional)	21 months	Chemotherapy	15 months (deceased)
Infracarinal (Squamous)	Cervical lymph nodes (Regional)	7 months	Chemotherapy	82 months (deceased)

different treatments and similarly, more studies to evaluate the tumor biology of the esophageal cancer so as to reach the best approach when we are faced with these patients.

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