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ORIGINAL ARTICLE

Carcinosarcomas of the esophagus: systematic review of a rare nosologic entity

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Summary

Purpose: *The purpose of this study was to systematically review the literature of esophageal carcinosarcomas (ECS) and report epidemiologic and clinicopathologic data for this rare entity. We also attempted to shed light to the biologic behavior of ECSs with special reference to factors that may affect disease-free (DES) and overall survival (OS).*

Methods: *A systematic literature review was performed using MEDLINE, EMBASE and the Cochrane Library databases (Search date: 12 May 2017). The search strategy referred to carcinosarcoma OR pseudosarcoma OR polypoid carcinoma OR sarcomatoid carcinoma OR spindle-cell squamous cell carcinoma OR metaplastic carcinoma OR pseudosarcomatous carcinoma AND esophagus. A total number of 103 ECS patients was identified.*

Results: *ECs most frequently occur in middle-aged as well as elderly men with a history of smoking or drinking. Middle and/or lower esophagus remains the most common location. Imaging plays a pivotal role in the management of ECS by delineating the anatomic extent of the tumor and thereby determining the appropriate therapeutic strategy. Nevertheless, immunohistochemistry is the gold standard for the diagnosis of carcinosarcomas, since it has been demonstrated that CEA, EMA, pancreatin, chromogranin A, CD56 and synaptophysin staining are highly specific markers for the carcinomatous components, while desmin, vimentin and smooth muscle/sarcomeric actin show affinity for the sarcomatous elements. Esophagectomy has been traditionally considered the treatment modality of choice. Endoscopic procedures, including mucosal resection and submucosal dissection have also been proposed. Alternative therapies, such as radio- and chemotherapy proved insufficient.*

Conclusion: *ECS is a rare tumor. Immunohistochemistry is the gold standard for the diagnosis of this disease. Esophagectomy has been traditionally considered the treatment modality of choice. Endoscopic procedures have also been proposed while potential benefit of alternative therapies, such as radiotherapy and chemotherapy remains controversial.*

Key words: *carcinosarcoma, diagnostic approach, esophagus, prognostic parameters, therapeutic management*

Introduction

Esophageal cancer remains the eighth most common gastrointestinal malignancy. While the majority of esophageal lesions worldwide are of squamous cell type, only 1.3% of cases present as carcinosarcomas [1,2]. Esophageal carcinosarcoma (ECS) is a rare malignant tumor which is biphasic in nature, composed of both carcinomatous and sarcomatous elements [3,4]. Multiple desig-

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nations assigned to the neoplastic disorder, such as carcinosarcoma, pseudosarcoma and pseudosarcomatous carcinoma reflect the controversy and differing views regarding its histogenesis and biology, as to whether the spindle cell component is epithelial or mesenchymal in origin [5]. ECS most frequently occurs in middle aged as well as in elderly men with a history of smoking or drinking. Middle and/or lower esophagus remains the most common location [1]. Presenting symptoms include dysphagia, chest pain and weight loss [6]. The more favorable prognosis associated with ECS has been attributed to early onset of symptoms due to accelerated intraluminal growth, presenting as progressively increasing dysphagia. Imaging modalities such as computed tomography (CT), endoscopic ultrasonography (EUS) and positron emission tomography (PET) play a pivotal role in TNM staging [7]. Nevertheless, immunohistochemistry is the gold standard for the diagnosis of carcinosarcoma, since it has been demonstrated that CEA, EMA, pancreatin, chromogranin A, CD56 and synaptophysin staining are highly specific markers for the carcinomatous components, while desmin, vimentin and smooth muscle/sarcomeric actin show affinity for the sarcomatous elements [8]. Despite recent research on the therapeutic strategies against ECS, surgical resection appears the only potentially curative approach. Esophagectomy has been traditionally considered the treatment modality of choice. Endoscopic procedures, including mucosal resection and submucosal dissection have also been proposed. Alternative therapies, such as radio- and chemotherapy proved insufficient [9].

The aim of this study was to systematically review the literature of ECSs and report epidemiologic and clinicopathologic data for this rare entity. We also attempted to shed light to the biologic behavior of ECS with special reference to factors that may affect DFS and OS.

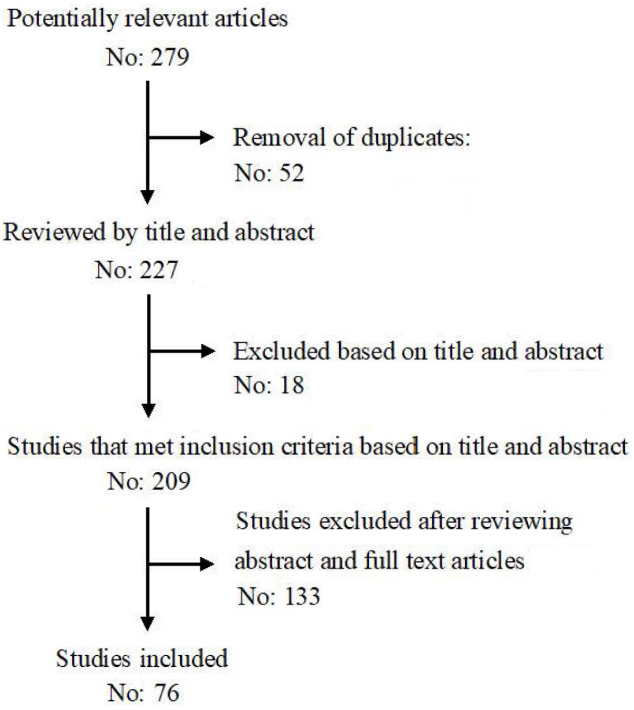

Figure 1. Study flow chart.

Methods

A systematic literature review was performed using MEDLINE, EMBASE and the Cochrane Library databases (Search date: 12 May 2017). Phrase searches, adjacent free text terms and medical subject headings were initiated. The search strategy referred to carcinosarcoma OR pseudosarcoma OR polypoid carcinoma OR sarcomatoid carcinoma OR spindle-cell squamous cell carcinoma OR metaplastic carcinoma OR pseudosarcomatous carcinoma AND esophagus. The reviewed clinical series and case reports were included if they reported surgical treatment options and also analyzed oncological outcome on individual patients. Additional meticulous analysis resulted in 74 case reports consisting of 74 patients and 2 case series including 29 patients. A total number of 103 ECS patients were identified (Figure 1).

Data extraction was performed using a standard registry database. Epidemiologic as well as clinicopathologic data including age, sex, clinical features, location, tumor size, stage, type of surgical intervention, administration of neoadjuvant or adjuvant treatment, tumor recurrence or metastasis and survival were registered in each case. Data was presented as counts with percentages or medians with interquartile ranges. The American Joint Committee of Cancer Staging Manual (6th Edn) was used for the pathologic staging, as the vast majority of patients were reported before 2013.

Statistics

Statistical analyses were performed using the R environment for Statistical Computing. Study variables were assessed for normality using the Shapiro-Wilks test. On normally distributed variables, Student's *t*-test and x^2 or Fischer's exact test were applied to quantitative and qualitative data, respectively. Non-parametric statistical models Wilcoxon rank-sum and Kruskal-Wallis have also been performed. Survival analysis was performed for disease-specific-survival (DSS), DFS and OS using Kaplan-Meier curves and their differences were evaluated using the log-rank test. Adjusted hazard ratio (HR) was calculated for tumor-related death using a Cox proportional hazards multivariate model including size, tumor location, UICC stage, adjuvant and neoadjuvant treatment administration. In addition, HR was reported with 95% confidence intervals. Only variables that met the proportional hazards assumption and demonstrated a p value lower than 0.1 on univariate analyses were selected for inclusion in multivariate models. The level of statistical significance was set at 0.05.

Results

Pooled analysis included 103 patients gathered from case reports and case series published from 1997 to 2014 (Figure 1) The median age of affected patients was 62 years, ranging from 26 to 86 years. Male to female ratio was 8.4:1 (92 male, 11 female). The most common tumor location was middle esophagus (56.9%), followed by lower esophagus (23.5%) and upper esophagus (19.6%) (Table 1). Tumor size ranged from 1.5 to 18 cm (mean 7.4±4.1). TNM classification, UICC stage (recalculated according to AJCC 6th edition) and treatment strategies are depicted in Table 2. Moreover, among 74 patients with available clinical data on diagnosis, 66 (89.2%) were symptomatic, whereas 8 (10.8%) reported absence of clinical signs. Tumor size was positively correlated with clinical presentation, with a mean size of 8.2 cm among symptomatic patients and 5.3 cm among non-symptomatic cases (p=0.04).

Surgical procedures were conducted in 62 patients, with the most common technique being the 3-incision McKeown operation on 46 patients (63.9%), followed by an Ivor Lewis esophagectomy on 9 patients (12.5%), a transhiatal esophagectomy on 3 (4.2%) and a tumor enucleation on 4 patients (5.6%). Alternative therapeutic approach included 5 palliative operations (6.9%) and administration of definite chemo/radiotherapy in 2 patients (2.8%), whereas 3 patients remained without any treatment (4.2%). All Ivor-Lewis esophagectomies were performed for lower esophageal tumors and all transhiatal esophagectomies for ECS located in the middle esophagus. Surgical treatment strategy did not appear to be correlated with tumor size.

The median follow-up time was 12 months (IQR 8-24). At the end of the follow up period, 47 patients had died (45.6%), 43 were alive (41.7%) and 13 were lost to follow-up (12.6%). Among the deceased, 33 died of disease progression (70.2%) and 6 from irrelevant causes (12.8%), while in 8 patients the cause of death was not reported (17%). Among patients still alive at the end of the studies, 36 were free of disease (83.7%), 3 experienced local recurrence (7%) and 4 were registered with unknown disease status (9.3%). Subsequent

Table 1. Patient demographics

Demographics	*n*	*%*
Tumor location (n=102)		
Upper esophagus	20	19.6
Middle esophagus	58	56.9
Lower esophagus	24	23.5
pT (n=94)		
T1	42	44.7
T2	31	33.0
T3	16	17.0
T4	5	5.3
pN (n=93)		
N0	55	59.1
N1	35	37.6
N2	3	3.2
pM (n=93)		
M0	74	79.6
M1	19	20.4
UICC Stage (n=92)		
I	28	30.4
II	34	37.0
III	10	10.9
IV	20	21.7
Neoadjuvant therapy (n=99)		
None	90	90.9
Chemotherapy	2	2.0
Radiotherapy	2	2.0
Chemo/Radiotherapy	5	5.1
Adjuvant therapy (n=98)		
None	76	77.6
Chemotherapy	8	8.2
Radiotherapy	7	7.1
Chemo/Radiotherapy	7	7.1
Treatment strategy (n=72)		
Ivor Lewis esophagectomy	9	12.5
McKeown esophagectomy	46	63.9
Transhiatal esophagectomy	3	4.2
Tumor enucleation	4	5.6
Palliative surgery	5	6.9
Definite Chemo/Radiotherapy	2	2.8
No treatment	3	4.2

Table 2. Treatment strategy stratified by tumor location

Location	*Ivor-Lewis*	*McKeown*	*Transhiatal*	*Enucleation*
Upper esophagus	0	5	0	2
Middle esophagus	0	31	3	2
Lower esophagus	9	10	0	0

Table 3. Kaplan-Meier survival and log-rank p values

Factor	*Overall survival*	*Disease-specific survival*	*Disease-free survival*
Symptoms	0.16	0.10	0.08
Location	0.21	0.15	0.72
Treatment strategy	0.04	0.03	0.03
Size	0.80	0.79	0.88
T+	<0.01	<0.01	0.12
N+	0.33	0.14	0.22
M+	0.23	0.15	0.03
Stage	<0.01	<0.01	<0.01
Adjuvant therapy	0.99	0.69	0.25
Neoadjuvant therapy	0.53	0.76	0.88

Table 4. Multivariate Cox model

A. Disease-specific survival	*Adjusted hazard ratio*	*95% CI*	*p value*
Tumor size	1.06	(0.94-1.18)	0.36
Location=middle+	0.31	(0.11-0.82)	0.02
Location=lower esophagus	0.69	(0.20-2.38)	0.55
Stage II+	4.49	(1.01-20.1)	0.05
Stage III+	29.6	(4.84-181.1)	<0.01
Stage IV+	6.45	(1.47-28.3)	0.01
Adjuvant therapy	1.05	(0.44-2.47)	0.92
Neoadjuvant therapy	1.93	(0.36-10.4)	0.44
B. Disease-free survival	*Adjusted hazard ratio*	*95% CI*	*p value*
Tumor size	1.00	(0.88-1.13)	0.97
Location=middle	0.83	(0.12-5.61)	0.84
Location=lower	0.87	(0.12-6.40)	0.89
Stage II	3.20	(0.62-16.39)	0.16
Stage III+	20.38	(2.22-187.2)	0.01
Stage IV+	7.04	(1.32-37.5)	0.02
Adjuvant therapy	1.06	(0.33-3.41)	0.92
Neoadjuvant therapy	2.61	(0.46-14.92)	0.28

+ indicates statistically significant result compared to baseline (Location: upper, Stage: I)

univariate analysis using log-rank test indicated that treatment strategy, T parameter and TNM stage were independent predictors of OS, DSS and DFS. Moreover, patients who received palliative radio/chemotherapy presented increased mortality rate compared to patients subjected to a palliative tumor enucleation (p=0.03). Similarly, advanced T stage as well as TNM stage were statistically associated with lethal outcome (p<0.01). Nevertheless, tumor location, size, presence of symptoms on diagnosis, lymph node involvement or patient's treatment with adjuvant or neoadjuvant chemotherapy did not significantly affect OS (Table 3). Moreover, tumors located in the middle esophagus had significantly less disease-specific deaths compared to those of the upper esophagus (Table 4).

Discussion

Carcinosarcoma is a rare tumor with an incidence of 0.1-1.5% among all esophageal malignancies [8]. In 1865, Virchow investigated an uncommon biphasic malignant neoplasm consisting of carcinomatous and sarcomatous components and named it as 'carcinosarcoma'. Since then, it has also been known as sarcomatoid carcinoma, pseudosarcoma or spindle cell carcinoma. In 1992, Ro et al. proposed the histological criteria of carcinosarcoma including the concurrent presence of malignant epithelial and spindle cell elements with parallel existence of transitional areas and the sarcomatoid component express of an epithelial phenotype [10]. Therefore, ECS presents polypoid

configuration usually composed of invasive and/or *in situ* squamous carcinoma cells surrounding the base and surface of an exophytic tumor and sarcomatous spindle cells forming the body of the polypoid mass [7]. The oncogenesis of the lesion is still unclear and both metaplastic and collision hypothesis have been proposed. The metaplastic project involves individual elements derived from a single common ancestor cell. On the contrary, the collision aspect involves two individual stem cells that independently and simultaneously undergo malignant transformation [8,11].

Molecular analysis revealed that the two components of carcinosarcoma possess different genetic mutations, mainly involving the p53, cyclin D1, p16, MDM2 and CDK4 genes. P53 gene mutations exist in both the sarcomatous and carcinomatous component. Nevertheless, the type of mutation differs [12]. Cyclin D1 gene amplification is frequently detected in carcinosarcoma, particularly in the sarcomatous element. Moreover, it has been demonstrated in the esophagus that the two components exhibited cyclin D1 gene amplification and p16 homozygous deletion by differential polymerase chain reaction and fluorescence *in situ* hybridization [13]. Certain studies have elucidated that MDM2 and CDK4 were strongly implicated in the pathogenesis of both carcinoma and sarcoma. In addition, CDK4 overexpression was observed in laryngeal squamous cell carcinoma, which was significantly correlated with tumor size and an advanced stage [8,12-14].

Carcinosarcoma has been found in such diverse organs as the uterus, breast, thyroid, lung and upper gastrointestinal system [15]. In the esophagus, our statistical analysis confirmed that the most common tumor location was middle esophagus (56.9%), followed by lower (23.5%) and upper (19.6%) esophagus. Further investigation also elucidated that ECS most frequently occurs in middle-aged men with a history of smoking and/or alcohol abuse [1]. The clinical presentation of ECS is similar to that of squamous cell carcinoma with dysphagia as the most prominent and frequent symptom. The more favorable prognosis associated with carcinosarcoma against other esophageal neoplasias has been attributed to early onset of clinical signs due to accelerated intraluminal growth, presenting as progressively increasing dysphagia, which leads to relatively prompt diagnosis [6]. Relevant appearance of early symptoms was confirmed in our survey as among 74 patients with available clinical data on diagnosis, 66 (89.2%) were symptomatic, whereas 8 (10.8%) reported absence of clinical signs.

Nevertheless, immunohistochemistry is the gold standard for the diagnosis of carcinosarcoma. There are highly specific markers for the carcinomatous components such as CEA, EMA, pancreatin, chromogranin A, CD56 and synaptophysin. As for the sarcomatous elements, desmin, vimentin and smooth muscle/sarcomeric actin are extremely sensitive markers too [8,16,17]. Imaging plays a pivotal role in the management of ECS by delineating the anatomic extent of the tumor and thereby determining the appropriate therapeutic strategy as well as contributing to post-treatment surveillance. On endoscopic examination, the lesion is depicted as a bulky, polypoid, gray-white mass with smooth, lobulated or scalloped margins [8]. Mucosal ulceration or a pedicle may also be present. Imaging methods such as EUS, CT and PET play an important role in TNM staging, which seems to be the most critical determining factor for treatment decisions [18,19]. Staging workup to elucidate potential regional or distant lymph node metastasis is mainly evaluated with EUS, which seems to be superior compared to CT and PET [9].

Therapeutic approach of primary ECS is a reflection of tumor location, type, grade and stage. ECS less than 11-20 mm in size that are limited to the mucosa/submucosa demonstrate a low frequency of lymph node and distant metastasis, and thus might be managed with local excision including endoscopic treatment. Therefore, endoscopic mucosal resection (EMR) as well as endoscopic submucosal dissection (ESD) have been proposed [20]. In addition, endoscopic treatment might also be considered in particular in patients with a high risk of perioperative complications due to advanced age or serious contraindications to major surgery [8]. As endoscopy is usually deemed unsuitable, surgical approach appears the only attractive alternative. In referral centers, protocols wherein ECS patients undergo upfront surgery if resectable or neoadjuvant chemoradiotherapy followed by surgical procedure if borderline resectable have been proposed [21].

Surgical resection is the treatment of choice for carcinosarcoma when feasible. The surgical treatment of ECS depends on the location of the tumor, the depth of invasion, lymph node metastases, evaluation of pre-operative status as well as the culture and beliefs of associated individuals and institutes [24]. The most common surgical approaches to accomplish ECS resection include transhiatal, Ivor Lewis, and McKeown esophagogastrectomy [25]. Indeed, in our study, the 3-incision McKeown operation appeared to be the most common, applied on 46 patients (63.9%), followed by Ivor Lewis esophagectomy on 9 patients (12.5%), transhiatal esophagectomy on 3 (4.2%) and tumor enucleation on 4 patients (5.6%) among surgical procedures

conducted in 62 patients. Anthracycline-based chemotherapy combined with platinum or taxanes has been administered either in the adjuvant setting or with palliative intent in unresectable or metastatic ECS.

Actually, conflicting results about prognosis have been published. An older Chinese paper reported four patients who were all alive "free of disease" after 3 years of surgical resection and another study reported a 3-year OS of 62.8% [26,27]. In addition, two recent retrospective surveys showed quite good prognosis for ECS patients, with a 3-year OS over 50% and 5-year OS over 40% [24]. Nevertheless, the concept of better prognosis was not supported by two recent Japanese studies that reported a similar prognosis for ECS patients and esophageal squamous cell carcinoma patients. Kuo et al. suggested a relationship between early lymphatic spreading, distant metastasis and poor prognosis [25]. Sano et al. reported an even lower survival in ECS T1 patients than in esophageal squamous cell carcinoma T1 patients [28]. Both reviews reported a poor prognosis in their pools of ECS patients. In our analysis T parameter and TNM stage were independent predictors of OS, DSS and DFS. Finally, tumor location, size, presence of symptoms on diagnosis, lymph node involvement or patient's treatment with adjuvant or neoadjuvant chemotherapy did not significantly affect OS.

Conclusion

In conclusion, ECS is a rare tumor most frequently diagnosed in middle aged as well as in elderly men with a history of smoking or drinking. Middle and/or lower esophagus remains the most common location whereas immunohistochemistry is the gold standard for the diagnosis of carcinosarcoma. Nevertheless, imaging plays a crucial role in the management of ECS by delineating the anatomic extent of the tumor and thereby determining the appropriate therapeutic strategy. Esophagectomy has been traditionally considered the treatment modality of choice. Endoscopic procedures have also been proposed while potential benefit of alternative therapies, such as radiotherapy and chemotherapy remains controversial.

Conflict of interests

The authors declare no conflict of interests.

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