Primäres kleinzelliges Ösophaguskarzinom: Patientendaten-Metaanalyse und Review der Literatur

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1. Deutsche Zusammenfassung

1.1 Einleitung

Das kleinzellige Ösophaguskarzinom ist ein seltener, aggressiver Tumor mit schlechter Prognose. Die Prävalenz dieses Tumors beträgt etwa 2 % aller Speiseröhrentumoren (Suzuki et al., 1980). Kleinzellige Tumoren sind häufig aus der Lunge bekannt, doch sie können in sämtlichen Organen auftreten, da der Tumor neuroendokrinen Ursprungs ist und neuroendokrine Zellen überall im Körper aufzufinden sind. Er ist histologisch nicht unterscheidbar vom kleinzelligen Bronchialkarzinom, jedoch ist sein klinisches Verhalten und die Reaktion auf Chemotherapie anders. Die Histogenese dieses Tumors ist immer noch unklar und wird erforscht (Horai et al., 1978; Cook et al., 1976; Matsusaka et al., 1976). Es gibt verschiedene Ansätze zur Erklärung der Entstehung des kleinzelligen Ösophaguskarzinoms. Zum einen werden totipotente primitive Zellen als Vorläufer für verschiede Karzinome und für das kleinzellige Ösophaguskarzinom verantwortlich gemacht (Ho et al., 1984). Zum anderen besteht die Vermutung, dass der Tumor eine Folge der Metaplasie durch den Barrett'schen Ösophagus darstellt (Markogiannakis et al., 2008; Bibeau et al.; 2008). Ebenfalls werden APUD-Zellen (amine precursor uptake and decarboxylation cells) als Ursprung des kleinzelligen Tumors angesehen. (Sun et al., 2007). Ein eindeutiger Therapieansatz konnte noch nicht definiert werden, da aufgrund der Seltenheit der Krankheit keine randomisierten Studien existieren. Bisher lehnte sich die Therapie dieser Erkrankung an das Therapiemuster zur Behandlung des kleinzelligen Bronchialkarzinoms. Ziel dieser Metaanalyse bestand darin, Informationen aus internationalen Studien, die sich mit dieser Krankheit befassten, zu ermitteln und auszuwerten.

1.2 Methoden

Die Artikel wurden durch die Datenbank PubMed ermittelt. Wir verwendeten das Stichwort „small cell carcinoma of the esophagus“. Alle Artikel, die sich mit dem Thema des kleinzelligen Ösophaguskarzinoms als primären Tumor beschäftigen, betrachten wir als geeignet für unsere Metaanalyse. Wir überprüften letztlich 313 Patientenfälle auf folgende 13 auswertbare Kriterien: Alter zum Zeitpunkt der Diagnose, Geschlecht, Histologische Merkmale, Symptome, Dauer der Symptome, Risikofaktoren,

Tumorlokalisation, Tumorgröße, neuroendokrine Differenzierung, Krankheitsstadium, Lymphknotenbeteiligung, Behandlung und elektronenmikroskopische Untersuchung auf neurosekretorischen Granula. Von diesen 13 Kriterien konnte die Analyse von 7 Kriterien (Alter, Geschlecht, Histologie, Symptome, Tumorlokalisation, Tumorgröße und Krankheitsstadium) eine hinreichende Aussagekraft liefern, während die Analyse der weiteren 6 Kriterien keine adäquaten Ergebnisse brachten, weil mehr als 50 % der überarbeiteten Literatur keine ausreichenden Informationen über diese Kriterien boten.

1.3 Ergebnisse

Die Auswertung der 13 Kriterien lieferte folgende Ergebnisse: 83 % der Fälle zeigten bei der histologischen Untersuchung einen reinen kleinzelligen Tumor, in 14 % der Fällen war der Tumor ein gemischter Tumor mit Anteilen des Plattenepithelkarzinoms. Die histologische Untersuchung auf neuroendokrine Zellen war in 41,5 % der Fälle positiv. Durch Elektronenmikroskopie konnten in 41 von 61 Fällen (67,2 %) neurosekretorische Granula ermittelt werden. 59 % der Fälle zeigten eine Lymphknotenbeteiligung. Bezüglich des Krankheitsstadiums wiesen 48,2 % der Patienten ein limitiertes Krankheitsstadium auf, während 34,8 % in einem extendierten Stadium waren. Bei 57,5 % zeigten sich Schluckbeschwerden als häufigstes Symptom, neben anderen Symptomen wie Gewichtsverlust, Schmerzen in der Brust und Schluckstörungen. Verhältnismäßig wenige Patienten (ca. 3 %) merkten die Symptome früh (28 und mehr Wochen vor der Diagnose). Dafür merkten viele Patienten (ca. 27 %) die Symptome kurz vor der Diagnose (4-28 Wochen). Es gibt einen signifikanten Unterschied in der Überlebensdauer von Patienten die älter bzw. jünger als 50 Jahre alt waren. Die mediane Überlebensdauer bei Patienten, die älter als 50 Jahre alt waren, betrug 9,2 Monate, während die Überlebensdauer jüngerer Patienten unter 50 Jahren bei 17,2 Monaten lag. Ebenfalls liefern die Auswertungen der Studie einen signifikanten Unterschied in der Überlebensdauer der Patienten bezüglich des Krankheitsstadiums. Hierbei betrug die Lebensdauer eines im limitierten Stadium erkrankten Patienten 17,8 Monate, während sie für den Patienten im extendierten Stadium bei nur 4,9 Monaten lag. Die Tumorgröße und das Geschlecht beeinflussten die Überlebensdauer nicht. Sie lag hierbei median bei 9,8 Monaten. Ob der Patient eine Therapie erhielt oder nicht,

zeigte ebenfalls einen signifikanten Unterschied in der Überlebensrate. Patienten, die eine Therapie erhielten, lebten ca. 11 Monate länger als Patienten, die nicht therapiert worden sind. Sie starben bereits nach 0,8 Monaten. Die Therapieansätze hatten ebenso einen Einfluss auf die Überlebensdauer. Patienten, die zusätzlich zur lokalen auch eine systemische Behandlung erhielten, lebten im Durchschnitt nach Zeitpunkt der Diagnose noch 14,2 Monate, während die Patienten mit nur lokaler Therapie nach 7,4 Monate verstarben. Daher hängt die Prognose über die Überlebensdauer sowohl vom Alter des Patienten, als auch vom Stadium der Krankheit und von der Art der Therapie ab.

1.4 Diskussion

Das kleinzellige Ösophaguskarzinom ist ein seltener Tumor, der einen Anteil von 0,5 - 2 % aller malignen ösophagealen Neoplasmen einnimmt . Aufgrund der Seltenheit des Tumors sind Informationen über die besten therapeutischen Ansätze nicht vorhanden. Der Tumor tritt im Alter zwischen 28 und 88 Jahren auf, wobei er am häufigsten bei Patienten im Alter von 60 bis 80 Jahren auftritt. Patienten mit einem Alter unter 50 Jahren zeigten eine signifikant bessere Lebenschance als Patienten, die älter als 50 waren, jedoch waren nur 10,2 % der Patienten unter 50 Jahren. Die bessere Lebenschance bei Patienten unter 50 ist zurückzuführen auf die aggressivere therapeutische Herangehensweise bei dieser Altersgruppe, da diese Patienten in einem besseren Allgemeinzustand waren und eine aggressivere Therapie besser vertrugen. Wir ermittelten ein Verhältnis von 1,94 : 1 zwischen betroffenen Männern und Frauen, was vermutlich mit einem stärkeren Nikotin- und Alkoholkonsum bei Männern im Vergleich zu Frauen zusammenhängt, da dieser Konsum eines der Risikofaktoren für die Erkrankung darstellt. Bezüglich der Lokalisation fanden wir heraus, dass der Tumor bevorzugt im unteren und im mittleren Drittel des Ösophagus vorkommt und weniger im oberen Drittel, was sicherlich darauf zurückzuführen ist, dass sich im unteren und mittleren Drittel die Muskulatur aus glatter Muskulatur zusammensetzt, während der Ösophagus im oberen Drittel aus Skelettmuskulatur besteht. Die glatte Muskulatur beinhaltet mehr endokrine Zellen, die häufiger in kleinzellige Tumorzellen übergehen könnten. Die Symptome zum Zeitpunkt der Diagnose waren überwiegend Schluckbeschwerden, gefolgt von Gewichtsverlust und Brustschmerzen. Die mittlere

Dauer der Beschwerden lag bei 4,1 Monaten vor dem Zeitpunkt der Diagnose. Weder Tumorgröße noch Tumorlokalisation ergaben einen signifikanten Unterschied hinsichtlich der Überlebensdauer. Im Vergleich zum Bronchialkarzinom ist das kleinzellige Ösophaguskarzinom aggressiver und geht mit schnellerer und umfangreicherer Metastasierung zum Zeitpunkt der Diagnose einher. Daher ist auch die Prognose der Heilung schlechter als beim Bronchialkarzinom. Es konnte ein signifikanter Unterschied in der Überlebensdauer hinsichtlich des Krankheitsstadiums ermittelt werden. So liegt die Überlebensdauer bei einem Patienten in einem limitierten Stadium bei 17,8 Monaten im Vergleich zum Patienten in einem ausgedehnten Stadium, der eine Überlebensdauer von nur 4,9 Monaten hatte. Bei Patienten in einem ausgedehnten Krankheitsstadium konnte aufgrund des verminderten Allgemeinzustandes oft nur noch palliativ therapiert werden, weswegen die Prognose der Heilung bei diesen Patienten schlechter war. Alles in allem ist die Information über den Allgemeinzustand des Patienten von großer Bedeutung, da die Prognose und die entsprechende Therapie am Allgemeinzustand abschätzbar sind.

1.5 Literaturverzeichnis der deutschen Zusammenfassung

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Review Article

Primary small cell carcinoma of the esophagus: patient data metaanalysis and review of the literature

Primäres kleinzelliges Ösophaguskarzinom: Patientendaten-Metaanalyse und Review der Literatur

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Abstract

We analysed the typical features of primary small cell carcinoma of the esophagus (SCCE) with emphasis on occurrence, behaviour, outcome and treatment options. This metaanalysis was aimed at collecting and analyzing information from international studies about handling this disease. This seems necessary due to the rarity of this disease. Studies were acquired from electronic databases and reference lists. We finally analysed 313 patients cases from the literature with oesophageal SCC. A data extraction was accomplished referring to 13 evaluable features that are described in the 'methods', whereof 7 were analyzed with univariate and multivariate tests. Three hundred thirteen cases were analyzed, of whose 109 patients (35%) had limited stage (LS), whereas 167 (54%) had extensive stage (ES). There is no information about the remaining 35 patients concerning the stage. Univariate and multivariate analysis showed only age (<50 years vs. >50 years, HR 1.024; 95% CI 1.000–1.041, $P<0.0001$) and disease stage (LS vs. ES, HR 4.884; 95% CI 2.572–9.27, $P<0.0001$) as significant prognostic factors. There also was a statistically significant difference in survival between those patients who received therapy compared to those who did not receive therapy besides best supportive care (11.6 months vs. 0.8 months, HR 0.093, CI 95% 0.053–0.16, $P<0.001$). In this first multivariate analysis for SCCE we show that SCCE is an aggressive type of tumour with a shorter survival rate compared to its counterpart from the lung. It is demonstrated that only disease stage (limited vs. extensive stage), age (<50 years vs. >50 years) and therapy are independent significant predictors of prognosis.

Keywords: small cell carcinoma, esophagus, oesophagus, metaanalysis

Zusammenfassung

Gegenstand unserer Untersuchungen war die Erhebung typischer Eigenschaften des kleinzelligen Ösophaguskarzinoms mit Berücksichtigung des Auftretens, des Verlaufs, der Auswirkung und der Behandlungsoptionen. Ziel unserer Metaanalyse bestand darin, Informationen aus internationalen Studien, die sich mit dieser Krankheit befassten, zu sammeln und auszuwerten. Dies scheint notwendig aufgrund der Seltenheit der Krankheit. Die verwendeten Studien wurden von elektronischen Datenbanken und Referenzlisten ermittelt. Insgesamt wurden 313 Patientenfälle mit einem kleinzelligen Ösophaguskarzinom aus der Literatur ausgewertet. Die erhobenen Daten beziehen sich auf 13 auswertbare Kriterien, die in den "Methoden" beschrieben sind, wovon sieben Kriterien mit univariaten und multivariaten Tests untersucht worden sind. Von 313 analysierten Patientenfällen waren 109 (35%) Patienten im limitierten Stadium der Erkrankung und 167 (54%) im ausgedehnten Stadium. Über die übrigen 35 Patienten sind keine Informationen bezüglich des Stadiums bekannt. Univariate und multivariate Analysen zeigten nur das Alter (<50 Jahre vs. >50 Jahre, HR 1.024;

95% CI 1.000–1.041, *P*<0.0001) und das Krankheitsstadium (LS vs. ES, HR 4.884; 95% CI 2.572–9.27, *P*<0.0001) als signifikante prognostische Faktoren. Ebenfalls gab es einen statistisch signifikanten Unterschied in der Überlebenschance zwischen jenen Patienten, die therapiert worden sind, und jenen, die außer bestmöglicher unterstützender Fürsorge nicht therapiert worden sind (11,6 Monate vs. 0,8 Monate, HR 0.093, CI 95% 0.053–0.16, *P*<0.001). In dieser ersten multivariaten Analyse für das kleinzellige Ösophaguskarzinom zeigen wir, dass diese Form des Krebses eine sehr aggressive Form ist, die mit einer kürzeren Überlebensrate einhergeht verglichen mit seinem Pendant, dem kleinzelligen Bronchialkarzinom. Es wurde gezeigt, dass nur das Krankheitsstadium (limitiert vs. ausgedehnt), das Alter (<50 Jahre vs. >50 Jahre) und die Therapie als Kriterien eigenständige, signifikante Anzeichen für eine Prognose sind.

Introduction

Primary small cell carcinoma of the esophagus (SCCE) is a rare tumour with aggressive behaviour and poor prognosis. It was first described by McKeown in 1952 [1]. A review from Japan cites the prevalence of these rare tumours from autopsy and surgical material to be 2.1% of all esophageal tumours [2]. In the United States a lower incidence of 0.5% has been reported [3], [4]. Although most small cell cancers are located in the lung, they can occur in other sites of the body e.g. in the pharynx, rectum [5], sublingual gland, thyroid gland, pleura, liver [6], larynx [7], trachea [8], salivary glands [9], stomach [10], pancreas [11] and prostate [12] and in our case in the esophagus, since the origin celltypes of this tumour are considered to be a type of neuroendocrine cells, which can be found in many organs. The SCCE is histological indistinguishable from its counterpart from the lung, but it is generally recognized that SCCE is distinct in terms of clinical behaviour and response to chemotherapy as well as to radiotherapy, since the clinical course is much more aggressive and the response to therapy is poor because in most cases the tumour has metastasized at the time of diagnosis. Compared to a reported median survival of approximately 10–14 months and a 5-year survival of approximately 2–8% for small cell lung cancer, the survival rate of patients with SCCE is lower [13]. Considerable controversy still exists regarding its histogenesis and its existence as a specific entity [14], [15], [16]. Some investigators postulate that a totipotent primitive cell serves as the common precursor for squamous cell carcinoma, adenocarcinoma and small cell carcinoma of the esophagus [17]. There is neither information about the genetics of SCCE nor about risks associated with positive family history. One reason for the coexistence of small cell carcinoma, squamous cell carcinoma and glandular elements in the same lesion is that small cells have the potential for further differentiation into either mucin-producing or keratin-forming cells [18]. Besides, SCCE can also arise in Barrett's esophagus [19], [20]. Another viewpoint is that the SCCE's origin is from neuroendocrine cells of the submucosal gland or stratum basal, i.e. the major (amine) precursor uptake and decarboxylation cells (APUD; [21]). The presence of neurosecretory granules is not necessarily indicative of a diagnosis of SCCE. In previous retrospective reviews, argyrophilia by Grimelius staining was reported in 25% of the patients' cases and the presence of neurosecretory granules on electron microscopy was documented in 27% [22]. The incidence rate of mixed differentiation ranged between 31–37% [22], [23]. Most important, the choice of treatment remains undefined, because the rarity of the tumour has precluded prospective randomised trials and such trials are unlikely to be carried out in the future. Often, the approach of systemically combined modality is used based on data regarding small cell carcinoma of the lung.

The purpose of the study was to review the published literature and to look into the various factors that influence induction, treatment and prognosis of this rare disease.

Methods

The articles we used for analysis were detected via MEDLINE and PubMed search. We used the term "small cell carcinoma of the esophagus" for our searching. We also reviewed references which were listed in these articles to get further publications providing more information and aspects about this disease. Eligible articels were those dealing with the carcinoma of the esophagus in the manner of a primary small cell carcinoma (see list of articles in Attachment 1). We screened all eligible cases in relation to initial 13 features: age at time of diagnosis, gender, histology (pure small cell histology, mixed histology), symptoms (dysphagia, odynophagia), duration of symptoms, risk factors (smoking and/or alcohol abuse), tumour site (upper-, middle-, lower-third), tumour size, neuroendocrine differentiation, disease stage (limited stage, extensive stage), lymph node involvement (positive or negative), treatment (chemotherapy and/or radiotherapy), and electron microscopic examination of neurosecretory granules. Local treatment consisted of radiotherapy and/or surgery, whereas systemic treatment consisted of chemotherapy. Predisposing factors for the development of oesophageal cancer in general were seen as risk factors. From these 13 features the analysis of only 7 features (age, gender, histology, symptoms, tumour site, tumour size, and disease stage) could give an ad-

equate meaningfulness, whereas the analysis of the other six features did not give satisfying results because more than 50% of the reviewed publications did not provide enough information about those features. For all features the exact numbers of reported cases were given, while the histological criteria for pulmonary small cell carcinoma proposed by the World Health Organization (WHO) was used [24]. The extent of disease was considered limited (LS) if the tumour was confined to the esophagus or periesophageal tissues (including regional lymph node). Extensive stage (ES) was regarded as tumour sprouted beyond the loco regional area with distant metastasis. Argyrophilia was used for histochemical and immunochemical staining whereas electron microscopic examination was used for the ascertainment of the presence of neurosecretory granules. The staging investigation included anamnesis and physical examination, chest radiography, computed tomography of the chest and endoscopy. Altogether 313 eligible cases found in the literature were analyzed, since the rest of these studies either did not satisfy the minimal criteria in registered features or were presented collectively. Follow-up was reported in terms of time (in months) from diagnosis until death. Patients who were alive during the reported time of communication were indicated as alive.

Data analysis

Statistical analysis of survival for different features were carried out by the life-table method. A comparison of the survival curves was made using the log rank test. The Cox proportional hazards model with stepwise regression was used for multivariate analysis. All statistical computations performed with the Statistical Package for Social Sciences (SPSS), Version 11.0 (SPSS Inc., Chicago, USA).

Results

The patients' characteristics are listed in Table 1. In all cases, the tumour had a histology appearance indistinguishable from lung SCC. Pure small cell carcinoma were reported in 260 cases (83%) and mixed cell differentiation in 44 cases (14%) with squamous differentiation or/and in situ carcinoma. Histological testing for neuroendocrine cells (Grimelius staining, NSE, Chromogranin, Synaptophysin) was performed in 130 patients' cases (41.5%); 71 cases (22.7%) exhibited cytoplasmatic evidence for neuroendocrine differentiation. Electron microscopic examination was performed in 61 cases (19.5%) whereby neurosecretory granules were found in 41 of 61 cases (67.2%). Of 313 patients studied, in 234 cases (75%) lymph node stage was attained. Ninety-six of 234 patients (41%) had no lymph node involvement and 138 of 234 (59%) had lymph node involvement. Of 313 patients studied, in 260 cases (83%) the disease stage was attained. One hundred and fifty-one patients (48.2%) had LS, 109 (34.8%) were presented with ES, and in 53 cases (16.9%) the stage was not reported. One hundred eighty patients out of 313 (57.5 %) had either only dysphagia or no symptom. The most frequent symptom (176 of 180 patients, 97.8%) was dysphagia. For 93 patients a second additional symptom beside dysphagia was reported: 45 (14.4%) had weight loss, 9 (2.9%) had pain in the right upper quadrant, and 8 (2.6%) odynophagia. Hematemesis, dyspepsia, anorexia, cough and sore throat were only reported occasionally. For the remaining 40 patients (12.8%) no symptoms were reported. Twenty-seven patients (8.6%) experienced symptoms 4 weeks, 23 (7.3%) 8 weeks, 16 (5.1%) 12 weeks, 10 (3.2%) 16 weeks, 4 (1.3%) 20 weeks, 8 (2.6%) 24 weeks, 5 (1.6%) 28 weeks, 3 (1%) 32 weeks, and 11 patients (9.3%) more than 32 weeks before diagnosis. Information about initial treatment for 297 patients (94.9%) was available and is shown in Table 2. Statistical data for the reported features satisfying the minimal criteria are listed in Table 3. In the case of age at the time of diagnosis, the median survival for patients aged 50 years or younger was 17.2 months versus 9.2 months for patients older than 50 years ($P<0.005$, Figure 1). There also were significant differences in survival between patients with LS and those with ES ($P<0.0001$) (Figure 2). The median survival for patients with LS was 17.8 months compared to 4.9 months for ES. Both features were statistically significant in a multivariate analysis. For tumour size smaller than 5 cm the median survival was 9.8 months. For those with larger tumours, median survival was 9.2 months. There was no significant difference in survival regarding gender (male 9.7 months vs. 9.8 months for females), histology (small cell 10.2 months vs. 7.8 months for mixed cell), type of symptoms (dysphagia 9.2 months vs. 7.4 months for odynophagia), and tumour site (upper third 11.4 months, middle third 10.5 months, lower third 6.1 months). There was a statistically significant difference in survival between those patients who received therapy compared to patients who did not receive therapy besides best supportive care (11.6 months vs 0.8 months, $P<0.001$, HR 0.093, CI 95% 0.053–0.16). For patients who received antineoplastic therapy there was a statistically significant difference in survival between patients who received local-plus-systemic treatment and those who received only local treatment. The median survival for patients who received local-plus-systemic treatment was 14.2 months, whereas for those who received only local treatment the median survival was 7.4 months ($P<0.01$, HR 0.439, CI 95% 0.347–0.55). Both, univariate analysis and multivariate analysis of ES, showed that only treatment or lack of it was an independent variable for prognosis ($P<0.01$). Due to the few cases reported, no significant differences in survival for LS patients were found referring to different types of local treatments (surgery vs. radiotherapy).

Table 1: Patient characteristics (all percentages pertain to the number of patients of 313)

Feature	number (percent) of reported cases	
Age [years] (median, range)	60 (31–89 y.)	291 (92.9%)
Gender		
Male	192 (61.3%)	291 (92.9%)
Female	99 (31.6%)	
Tumour site		
Upper third	11 (3.5%)	
Middle third	107 (34.2%)	224 (71.6%)
Lower third	98 (31.3%)	
Mid-lower third	7 (2.2%)	
Upper-lower third	1 (0.3%)	
Tumour size [cm] (median, range)	8.5 (1–16 cm)	
1–2 cm	14 (14%)	160 (51.1%)
2–5 cm	57 (18.2%)	
5–10 cm	65 (20.8%)	
10–16 cm	24 (7.7%)	
Predisposing factors		
Smoking	30 (9.6%)	
Alcohol	2 (0.6%)	99 (31.6%)
Smoking and alcohol	50 (16%)	
Non-smoking/non-drinking	14 (4.5)	
Achalasia	3 (1%)	

Table 2: First line treatment for SCCE

Treatment of reported cases	number (percent)
First line treatment	311 (99.4)
Best supportive care	31 (9.9)
Chemotherapy	102 (32.6)
Platin based therapy	46 (14.7)
Non-platin based therapy	56 (17.9)
Operation	84 (26.8)
Radiotherapy	25 (8)
Chemotherapy + Radiotherapy	34 (10.9)
Operation + Radiotherapy	7 (2.3)
Operation + Radiotherapy + Chemotherapy	14 (4.5)
Bronchial stent + Radiotherapy + Chemotherapy	2 (0.6)
Bronchial stent	7 (2.2)
Bronchial stent + Chemotherapy	1 (0.3)
Laser treatment + Chemotherapy	1 (0.3)
Afterloading + Chemotherapy	2 (0.6)
Afterloading	1 (0.3)

Table 3: Cox univariate and multivariate analysis of overall survival

	Univariate analysis			Multivariate analysis		
Variable	P-value	HR*	(95% CI**)	P-value	HR	(95% CI)
Disease stage	<0.0001	3.218	2,406–4.30	<0.0001	4.884	2.572–9.27
Age (years)	0.976	1.012	0.834–.212			
<50	<0.0001	1.024	1.000–1.041	0.028	0.520	0.290–0.9
>50	0.018	0.609	0.404–0.91	0.046	0.489	0.189–0.89
Tumor size	0.429	0.974	0.913–1.04			
Gender	0.270	1.160	0.891–1.50			
male	0.428	0.321	0.019–5.343			
female	0.534	0.423	0.022–4.992			
Histology	0.609	1.100	0.764–1.58			
small cell	0.984	1.004	0.838–1.202			
mixed	0.371	1.012	0.986–1.039			
Symptoms	0.199	0.995	0.987–1.00			
Odynophagia	0.611	1.131	0.703–1.820			
Dysphagia	0.597	1.231	0.782–1.785			
Tumor site						
Upper 1/3	0.752	1.330	0.227–7.786			
Middle 1/3	0.654	1.239	0.213–6.987			
Lower 1/3	0.713	1.329	0.245–7.231			

* HR: hazard ratio
** CI: confidence interval

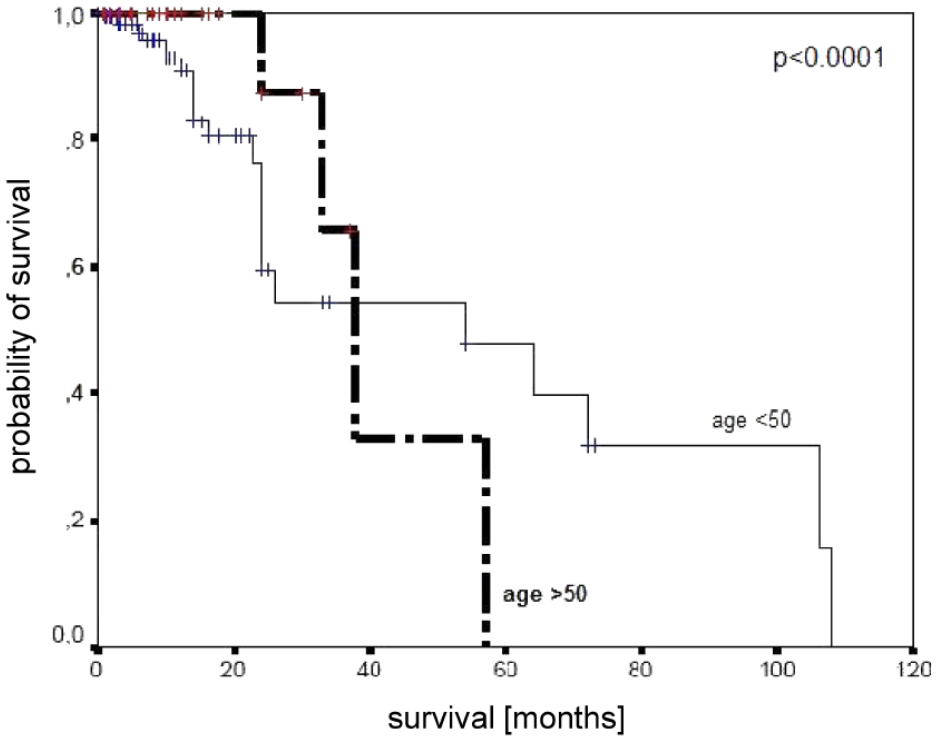

Figure 1: Survival probability, depending on age <50 years versus >50 years, is shown.

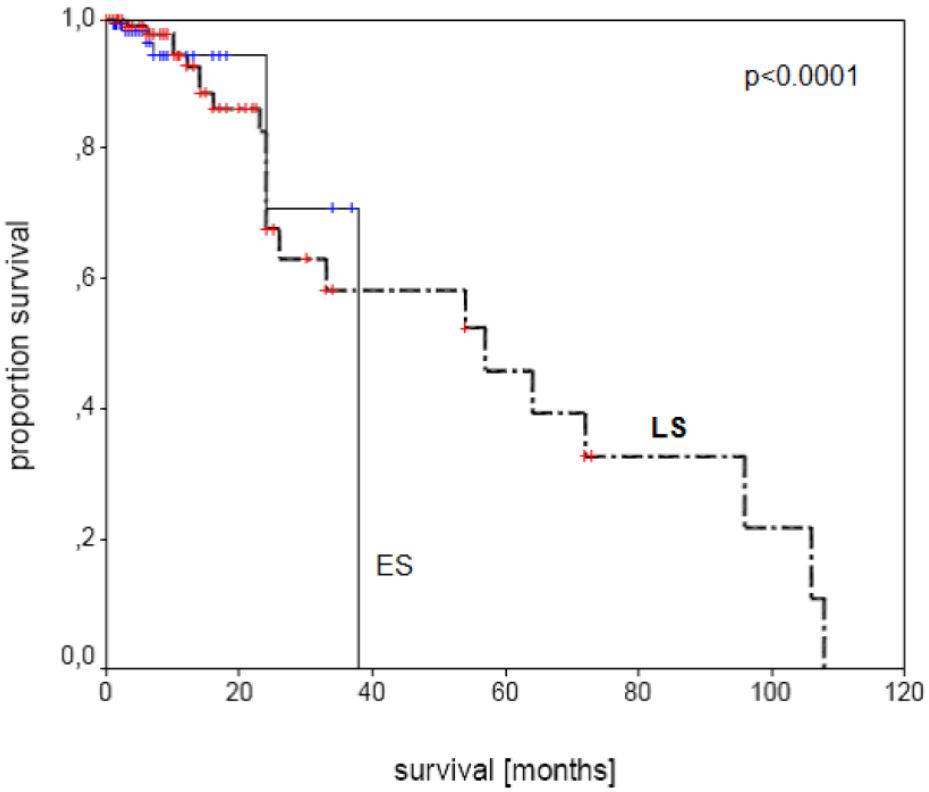

Figure 2: Survival probability, depending on localized stage (LS) versus extended stage (ES), is shown.

Discussion

SCCE is a rare tumour ranging between 0.5% up to 2.4% of malignant oesophageal neoplasms [3], [25] and therefore information about the best therapeutic approach is not available. Here we present an individual patients' data metaanalysis in respect of the reviewed published literature. The disease has been described in patients ranging in age between 28–88 years, but most commonly it occurs during the sixth to eighth decades of life [26]. This matches to our median age of 60 years. Age <50 years was associated with a statistically significant better overall survival at the time of diagnosis, but only 10.2% of the patients were younger than 50 years. The reason for this observation may be attributed to more aggressive therapy in cases of younger patients. Every patient younger than 50 years received a multimodal therapy with at least two different modalities. The clearest case of this fact were two patients who were treated with chemotherapy and syngeneic bone marrow or an autologous bone marrow transplant followed by radiotherapy. One patient achieved an overall survival of 36 months [27]. The other was disease-free 38 months after transplantation [28]. In a retrospective review of 199 patients, Casas et al. reported a male-to-female ratio of 1.57:1 [22]. Our ratio was slightly higher with a relation of 1.94:1. A study of 21 cases from China even reports a male-to-female ratio of 3.2:1 [29]. The male dominance could reflect the higher incidence of typical risk factors for esophageal cancer in general. Certain risk factors were not exactly specified and other risk factors beside smoking and alcohol, in rare cases also reflux and Barrett syndrome, were not named. So the typical risk factors for a small cell carcinoma of the lung, ergo alcohol and smoking, can be transferred to our case of the esophagus. In contrast to former series described [22], [26], we found a predominance of SCCE in the middle third of the esophagus followed by the localization in the lower third of the esophagus, but the low differences suggest that the tumour can be found in the lower and middle third in the same proportion. In the upper esophagus SCCE is rarely found (<5%). This correlates with the different nature and the type of muscle cells in the upper esophagus in relation to the lower and middle third (skeletal muscles in the upper third, smooth muscles in the middle and lower third). Symptoms present at the time of diagnosis were predominantly dysphagia, followed by weight loss and chest pain. Mean duration of symptoms was 4.1 months. Neither tumour size nor site of the tumour in the esophagus showed statistical differences in terms of different median survival in any group. Due to the small number of patients who have been reported on, the importance of factors such as argyrophilia or the presence of neurosecretory granules has not been evaluated. With regard

to the small tumours of the lung, the oesophageal variety behaves aggressively and is associated with rapid and widespread metastases at time of diagnosis, therefore the prognosis for constant healing is worse compared to its counterpart from the lung, but compared to the small cell carcinoma of the lung, a significant survival difference has been observed between LS and ES disease. One reason of bad prognosis for disease at ES could be that most of the patients had either been in very poor condition at the time of diagnosis and thus received no specific antineoplastic therapy, or were treated only with palliative surgery. In none of the articles the performance status of patients was clearly documented, which is an important factor for the beginning of treatment. The provision of treatment in cases of ES or the addition of systemic treatment in cases of LS is also influenced by performance status. Therefore, the performance status is a very important factor in the selection of treatment. Also, due to the small number of patients, evaluation of possible differences in the therapeutic results of different applications of chemotherapy has not been carried out. A lot of options have been exercised in the treatment of SCCE, but it is still not possible to compare the efficiencies because of the small number of patients and the lack of controlled trials. In Japan, a 78-year-old man with SCCE was treated with a carboplatin (CBDCA) plus etoposide (VP-16) combination of chemotherapy and radiation leading to complete remission without recurrence [30]. Another 60-year-old Japanese patient was treated with 5-fluorouracil plus cisplatin (CDDP) and surgery leading to disappearance of the tumor without recurrence [31]. Dealing with extrapulmonary SCC, there is an arising conformance in the literature that chemotherapy should be the basis of treatment. Our review confirms this fact, also because it is verified that small cell carcinoma in general is susceptible to antineoplastic chemotherapy. SCCE is histologically identical to its counterpart from the lung, its aggressive behavior and chemosensitivity are similar [19]. Lack of antineoplastic therapy is associated with a statistically significant shorter survival which is shown in cases where patients received only best supportive care. In any case the practicability of any kind of active treatment is the best prognostic factor. Therefore systemic treatment must be an integral part of treatment in view of the high rate of distant metastasis at diagnosis or later in the course of the disease. Local tumour control also seems to be important. A patient reported by Law et al. survived 72 months after he has been treated by surgery followed by chemotherapy and, after recurrence, by radiotherapy. Radiotherapy alone used on patients with esophageal SCC has shown disappointing results and should rarely be used as the sole treatment modality [32], [33]. In their review of 107 patients [34], Lieberman et al. found out that the longest median survival time (28 months) was obtained in cases of patients treated by esophagectomy in combination with chemotherapy. Kuo et al. suggested that for patients with limited disease, curative resection followed by chemotherapy can provide long-term survival and can be considered as primary treatment for selected patients [35]. The fact that patients could have mixed histology implicates that these tumours do not have chemo- and radiosensitiveness like pure SCCE and therefore should be treated by radical en bloc esophagectomy. In general, the appropriate selection of patients who were treated with combined regimens has to be noticed in order to be able to prove sufficiently that those who received multimodality treatment have lived longer than those given only one form of treatment. Since SCCE should be considered a systemic disease, we recommend that chemotherapy combined with local treatment, probably additional radiotherapy, should be used as standard treatment for LS as well as for ES of SCCE, as in the case of intrathoracic SCC of the lung, because it may produce long term remission and possibly long term survival. In the ES the optimal prognostic factor is the application of treatment depending on performance status. However, our study did not reveal any optimal treatment protocol. At the sight of lack of randomized trials, the selection of the best therapeutic approach to tackling this rare illness can be made easier by classifying the illness in prognostic subgroups.

Notes

Competing interests

The authors declare that they have no competing interests.

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Attachments

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1. 000180_List-of-Articles.pdf (64 KB)
   List of articles used for "Primary small cell carcinoma of the esophagus: patient data metaanalysis and review of the literature"

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