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Prognostic features in angiosarcoma of the head and neck: A retrospective monocenter study

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ABSTRACT

Background: Cutaneous angiosarcoma of the head and neck (cAS-HN) is a rare malignancy with poor survival. Most of the histological markers and grading were not proven to be significant for prediction of outcomes in cAS-HN. This study aimed to find prognostic clinical features and histologic markers for cAS-HN.

Material and methods: We retrospectively analysed primary cAS-HN's seen in a single institution between 1980 and 2009. Clinical data and specific histologic characteristics were assessed. Outcome parameters were analysed using uni- and multivariate statistics.

Results: 80 patients (mean age 71.4 (SD 14.4) years, average follow-up time 55.3 (SD 74.4) months) were included. 5-year DSS rate was 62%. Univariate analysis revealed the extent of primary tumour (affecting more than one anatomical region), incomplete resection and initial metastatic disease as significant ($p < 0.05$) predictors for unfavourable disease specific survival (DSS) rates and time. Multivariate analysis confirmed age over 70 years, incomplete resection and initially distant metastasis influencing outcome adversely. Analysis of specific histological markers in 37 cases found patterns of growth (solid areas greater than 80%) associated with better survival ($p = 0.011$).

Conclusion: In conclusion age, number of affected regions, initial metastasis, complete initial resection and pattern of growth significantly affected mortality rates.

1. Introduction

Soft tissue sarcomas are a relatively uncommon and heterogenous group of mesenchymal tumours that represent less than one percent of all malignant tumours (Zahm, 1997). Angiosarcoma (AS) is only one percent of all soft tissue sarcomas and 60 percent of all AS affect the dermis and subcutaneous tissue (cutaneous angiosarcoma, cAS). AS are divided into sporadica AS, which most often occur in elderly persons in actinic damaged skin and into AS arising after radiation therapy or lymphoedema (Young et al., 2010). Recent molecular analyses have demonstrated that AS due to radiation therapy are biologically different tumours which show an overexpression of the myc-oncogenes in contrast to sporadic AS (Käcker et al., 2013; Mitelman and Johansson, 2014).

Previous studies have demonstrated the prognostic importance of tumour size (>5 cm), resectability, depth of growth, mitotic activity, pattern of growth, stage at initial diagnosis in AS in general – not differing between AS localization (head and neck, trunk or extremities) or aetiology (after irradiation, as sequelae of lymphoedema or sporadical) (Buehler et al., 2013; Guadagnolo et al., 2011; Ogawa et al., 2012; Perez et al., 2013; Yeang et al., 2013). Results are inconsistent and sometimes even conflicting.

In addition cAS presents a highly variable clinical presentation that often leads to delayed diagnosis and poor prognosis at the initial diagnosis. Early lesions can simulate many benign lesions, including bruises, haemangioma, infection, or inflammatory disorder. Atypical clinical presentations that have been reported

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include rosacea, rhinophyma, isolated eyelid oedema, scarring alopecia, and chronic episodic facial oedema. It may be of importance to consider the initial clinical presentation of cAS and the delay it takes to achieve the correct diagnosis (Deyrup et al., 2008a; Morgan et al., 2004).

More than half of cAS, primary and sporadic, occur in the head and neck (cAS-HN), precisely in the face and scalp, first described by Jones in 1964 (Jones, 1964). The scalp is the most common affected site in up to 48% (Albores-Saavedra et al., 2011; Rouhani et al., 2008). Until now prognostic factors in this disease are very limited. Older studies showed that histological tumour grading is of no or minimal prognostic significance (Holden et al., 1987; Morgan et al., 2004; Stewart and Treves, 1948). Distinct reliable prognostic variables for cAS, and especially cAS of the head and neck region (cAS-HN) are rare.

Recently Deyrup and colleagues presented a retrospective study and proposed a new stratification system with prognostic significance in their collection of sporadical AS (Deyrup et al., 2008a). They used epidemiologic data and histologic features as pattern of growth (vasoformative versus solid), nuclear grade (high versus low), necrosis (present or absent), cell type (epithelioid or spindled), extent of inflammatory infiltrate (minimal versus marked), and mitotic rate. Tumours were stratified into low or high risk groups based on necrosis and/or epithelioid features. They showed that most tumours invading the dermis and subcutis, higher age of patients, anatomic site of occurrence, necrosis and epithelioid features correlated with increased mortality. High risk group and age above 70 years were associated with increased mortality. The depth of tumour invasion (dermis and/or subcutis) correlated with the risk of local recurrence.

The aim our study was to clarify on the statements of Deyrup (Deyrup et al., 2008a) and to evaluate the clinical and few histological features that could predict behaviour and outcome of this fatal disease.

2. Materials and methods

2.1. Patients

Patients with angiosarcoma in the head and neck region (cAS-HN), treated in our skin and head and neck cancer center between 1980 and 2009, were identified consecutively in a retrospective manner from our institutional database.

This study was approved by the local Ethics committee (Ethical committee of the Westfalian Wilhems-University Muenster, Approval-No. 2006-088-f-S), was conducted in accordance with the Guidelines for Good Clinical Practice (GCP) and in compliance with the Declaration of Helsinki. All participating patients or their relatives (in deceased cases) gave their written informed consent to participate in the study.

Inclusion criteria for this study were sporadical cutaneous angiosarcoma of the head and neck (cAS-HN) and complete database with histopathological secured diagnosis of cAS-HN. Exclusion criteria were incomplete datasets concerning the assessed variables, patients suffering from multiple cancers of the head and neck, patients after other malignancies in the head and neck or after already performed cancer or lymph node surgery (e.g. neck dissection). Patients with cAS-HN arising in lymphoedema or after radiation were also excluded from the study. In summary, we assessed only patients with primary sporadical cAS-HN and without history or treatment of other head and neck cancers. All patients received complete appropriate staging, including ultrasound diagnostics of relevant lymph node levels and abdomen and also radiological imaging by either CT or MRI of head, neck, thorax and abdomen. All patients were initially treated surgically (resection of the primary tumour) with curative intention. In total 80 patients were eligible for inclusion in this study.

2.2. Methods

With a specially developed data entry form the characteristics of all cases were analysed.

In all cases the following relevant epidemiological and clinical parameters were assessed: age at the time of first diagnosis (divided into two groups: $\leq$70 years versus >70 years), sex, primary tumour site in general (face or scalp) and more detailed (scalp, lower third of the face, midface including the nose, upper third of the face, ear and periauricular, tumour including more than one of the above mentioned regions of the face or scalp, tumour of more than one region in the face and the scalp), extent and dimension of the primary tumour (one region versus two or more regions; $\leq$5 cm versus >5 cm in diameter), initial locoregional or distant metastasis, resection status (R0 = histopathological tumour free (i.e. negative) resection margins, R1 = microscopically positive margins, R2 = macroscopically positive margins), minimal safety margin ($\geq$1 cm versus <1 cm), adjuvant radiation (yes/no), adjuvant chemotherapy (yes/no), comprehensive treatment protocol (surgery, surgery + radiotherapy, surgery + adjuvant chemotherapy, surgery + combined radio-chemo-therapy). Outcome and course of disease were analysed concerning tumour recurrence (local relapse, occurrence of distant metastasis), concerning overall survival status and time and concerning disease specific survival status and time.

Histological examinations and re-evaluations were performed by two experts in dermatopathology (HJS, CH) independently and blinded from each other. Diagnosis was proven in formalin fixed and paraffin embedded representative biopsies and excisions using conventional H&E staining as well as a panel of immunohistological stainings with antibodies against different vascular markers (CD31, CD34, Podoplanin).

In cases of adequately archived tumour material, the following histological parameters were analysed retrospectively: According to the FNCLCC system tumour differentiation (Score 1: sarcoma closely resembling normal adult mesenchymal tissue, Score 2: sarcoma for which histologic typing is certain, Score 3: Embryonal and undifferentiated sarcoma, sarcomas of uncertain type), mitosis count (Score 1: 0–9/10 HPF (high power fields), Score 2: 10–19/10 HPF, Score 3: $\geq$20/10 HPF) and microscopic tumour necrosis (Score 0: no necrosis, Score 1: $\leq$50% tumour necrosis, Score 2: >50% tumour necrosis). These 3 Sub-Scores were summed up to build a total score value, from which the histological grade according to the FNCLCC system is deduced (Grade 1 = total score 2 or 3, Grade 2 = total score 4 or 5, Grade 3 = total score 6–8). The infiltration depth (dermis, subcutis, fascia or deeper), percentage of solid areas (<–80%, $\geq$80%, Fig. 1) and cell type (epithelioid versus spindled cells) were evaluated. A risk stratification according the proposals of Deyrup (Deyrup et al., 2008a) was derived from the parameters tumour necrosis and cell type: the low risk histologic group (LRHG) is defined by absence of necrosis and epithelioid cells, the high risk histologic group (HRHG) displays epithelioid morphology and/or necrosis.

2.3. Statistical analysis

To assess significance of differences concerning disease specific survival (between patients having died due to their cAS-HN and patients without tumour dependent death at the end of their follow-up period) Chi-square test and Fisher's exact test were applied for categorical variables, for metric parameters Kolmogorov–Smirnov (KS) test was used as non-parametric test in not