



Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Unknown primary of the head and neck: A long-term follow-up



Martin Lanzer ^{a,b,*}, Sophie Bachna-Rotter ^b, Matthias Graupp ^b, Marius Bredell ^a,
Martin Rücker ^a, Gerhard Huber ^c, Sabine Reinisch ^b, Paul Schumann ^a

^a University Hospital of Zurich, Clinic for Cranio-Maxillofacial Surgery, Frauenklinikstrasse 24, CH-8091 Zürich, Switzerland

^b University Hospital of Graz, Department of General Otorhinolaryngology, Head and Neck Surgery, Auenbruggerplatz 26/28, 8036 Graz, Austria

^c University Hospital of Zurich, Clinic for Otorhinolaryngology, Frauenklinikstrasse 24, CH-8091 Zürich, Switzerland

ARTICLE INFO

Article history:

Paper received 11 December 2014

Accepted 2 March 2015

Available online 9 March 2015

Keywords:

Carcinoma of unknown primary

Recurrence

Survival

ABSTRACT

Background: A diagnosis of squamous cell carcinoma of an unknown primary (CUP) is a major burden for patients. Because the location of the primary tumor is unclear, patients remain fearful of recurrence, which aggravates the uncertain prognosis of the disease. This study evaluates factors associated with long-term recurrence-free and overall survival of patients with CUP of the head and neck. Additionally, patient survival rates are compared with those of patients with head and neck squamous cell carcinoma (HNSCC).

Methods: A total of 293 consecutive patients operated on between January 1999 and December 2009 with at least a 5-year follow-up (survival permitting), were evaluated retrospectively.

Results: Twenty-six patients with a CUP of the head and neck were identified. Patients with CUP had a low overall survival rate, comparable with that of patients with pN + HNSCC, and recurrent disease occurred with a similar likelihood as in patients with pN + HNSCC. The median recurrence-free survival in the CUP group was 28.5 months compared with 48 months in the whole of the HNSCC group. The median overall survival of the CUP group was 56 months versus 65 months for the HNSCC group. Extracapsular spread was the only independent prognostic factor for overall survival for CUP patients.

Conclusion: Patients diagnosed with CUP syndrome have a poorer prognosis for overall survival compared with other HNSCC patients. Postoperative radiotherapy diminished disease recurrence and improved overall survival. Omission of postoperative radiotherapy resulted in a very high recurrence rate (75%) for CUP patients. Based on these results we suggest postoperative radiotherapy including the oral mucosa for all patients, regardless of histopathological results, possible favorable nodal disease, or favorable lymph node ratios.

© 2015 European Association for Cranio-Maxillo-Facial Surgery. Published by Elsevier Ltd. All rights reserved.

Synopsis

Patients with CUP have a low overall survival rate, comparable to that of patients with pN + HNSCC. This study evaluates factors associated with long-term recurrence-free and overall survival of patients with CUP of the head and neck. Omission of postoperative radiotherapy resulted in a very high recurrence rate.

1. Introduction

A diagnosis of squamous cell carcinoma of an unknown primary (CUP) is a major burden for every patient. Because of the unknown location of the primary tumor, patients remain fearful of recurrences, aggravating their uncertain prognosis.

Full blood counts and biochemistry (including serum tumor markers), urine analyses, occult blood in stool tests, radiological assessments (computed tomography of the chest, abdomen, and pelvis, mammography and endoscopies in selected patients), and histopathological examinations using immunohistochemistry are necessary for the exclusion of occult primary tumors and for indications regarding the tissues of origin. Recent increases in sensitivity enable the detection of previously occult primary tumors which, coupled with advances in molecular and genetic

* Corresponding author. University Hospital of Zurich, Clinic for Cranio-Maxillofacial Surgery, Frauenklinikstrasse 24, CH-8091 Zürich, Switzerland.
E-mail address: martin.lanzer@usz.ch (M. Lanzer).

profiling of tumors, may also have contributed to the recent decrease in CUP incidence (Hoekstra et al., 2008; Urban et al., 2013; Brustugun and Helland, 2014).

The classification of CUP patients into distinct clinicopathologic subgroups was one of a few important advances during the last decades with regard to prognostication and treatment rationalization. All the different types of CUP can be classified into two broad clinicopathologic groups with distinct outcomes (Pavlidis et al., 2012); squamous cell carcinoma (SCC) involving cervical lymph nodes belongs to the subgroup with a more favorable outcome. Lately, a prognostic model was introduced, describing CUP of the head and neck region as low risk, with an expected median overall survival of 36 months (Pettrakis et al., 2013).

The different patterns of metastases within different CUP subgroups are not understood. One hypothesis posits that survival may be promising because immunological or other mechanisms that forced the involution of primary tumors might also control metastasis (van de Wouw et al., 2003). However, during this prolonged equilibrium phase a tumor may have ample time to become more malignant through the accumulation of hundreds of mutations (Dunn et al., 2002). After the tumor escapes the equilibrium state, it might evolve into a more aggressive state. Although the primary tumor in CUP is thought to be dormant, CUP patients feature early distant metastases, which may partly explain the poor prognosis (Hemminki et al., 2012). The latter pattern is not valid for the subgroup of CUP of the head and neck, which does not display early distant metastases but advanced locoregional disease.

This study evaluates factors associated with long-term recurrence-free and overall survival of patients with CUP of the head and neck. Furthermore, patient survival rates are compared with those of patients with head and neck squamous cell carcinoma (HNSCC).

2. Materials and methods

We retrospectively evaluated patients who presented to the Department of Otorhinolaryngology and Head and Neck Surgery (ENT) at the Medical University Hospital Graz, Switzerland, for treatment of HNSCC between 1 January 1999 and 31 December 2009, and who had at least a 5-year follow-up (survival permitting). This study was approved by the institutional ethics committee (EK-Nr. 21-020 ex 09/10).

The inclusion criteria were a diagnosis of SCC and operative treatment at the locoregional metastatic site with/without adjacent adjuvant radiotherapy or radiochemotherapy. Patients with histological findings other than SCC, distant metastasis before neck dissection, or who received primary treatment outside the ENT department were excluded.

The study variables examined were: age; sex; tumor location, stage, size, and grade; neck lymph node status; histological factors (blood vessel invasion [hemangiogenesis], lymph vessel invasion [lymphangiogenesis], extracapsular spread [ECS], and perineural invasion); resection margin (a positive resection margin was defined as <5 mm (Loree and Strong, 1990; Meier et al., 2005)); and adjuvant therapy (postoperative chemotherapy and/or adjuvant radiotherapy). Perineural invasion was defined as present 'within the body of the tumor' and 'ahead of the invasive front'.

Patients with a histologically proven SCC from one or more affected lymph nodes of an unknown primary underwent panendoscopy, biopsies of the lingual and palatine tonsils, and received a positron emission tomography scan for exclusion of primary tumors of other origins. If all diagnostic examinations were negative, the tumor remained classified as CUP. We performed a neck dissection involving level I–V. At this stage, prophylactic tonsillectomy was performed bilaterally for diagnostic reasons. Postoperative radiotherapy was advised for every patient and

administered to all patients who consented to the adjuvant therapy. If administered, each patient received 60 Gy in the metastatic tumor region, the oral cavity, and the oropharynx of the affected side. For some patients, radiochemotherapy was performed with cisplatin (100 mg/m² on days 1, 22, and 43) as the adjuvant chemotherapeutic agent. Indications for radiochemotherapy for patients treated after 2005 were based on the EORTC and RTOG trials (Bernier et al., 2005).

Data were collected and processed by building a database of information regarding patient characteristics (sex, age), tumor characteristics (location, size, lymph node status), operative parameters (date, type of resection, resection margin, type of neck dissection, number of levels excised, number of lymph nodes excised, number of positive lymph nodes, excision of non-lymphatic structures), histopathological diagnostic findings (hemangiogenesis, lymphangiogenesis, ECS, perineural invasion), postoperative therapy, location and time of recurrence, and overall survival. Patient data were analyzed using the SPSS software (SPSS Inc., Chicago, IL, USA).

Descriptive statistics were computed for each variable. Univariate Cox regression analysis was used for each variable, and odds ratios and *p*-values were calculated. Multivariate Cox regression analysis was used for each predictor variable identified as statistically significant (*p* < 0.05) in the univariate analysis. We used a forward step-wise (likelihood ratio) procedure. Kaplan–Meier curves were calculated using the log-rank test for statistical evaluation of significance.

3. Results

In total, 293 patients were included in this study (Table 1). Of these, 267 patients had HNSCC. For 26 patients, the origin of the primary tumor remained inconclusive after all the diagnostic examinations were conducted, including biopsies and prophylactic tonsillectomies (CUP group). The median age was 62 years for the CUP group and 64 years for the HNSCC group (Table 1). In both groups, most patients were men. Staging was unfavorable in the CUP group compared with the HNSCC group, with all but three patients presenting with stage IV disease (*p* = 0.004). Nevertheless, in both patient cohorts stage IV disease was present in the majority (88.5% versus 53.2%, respectively) of patients (Table 1). The tumor grade was equal in both groups: most tumors displayed a low (poor or un-) differentiated histological grade. The median lymph node ratio (LNR) was higher in CUP patients. Histopathological factors (perineural invasion, lymphangiogenesis, hemangiogenesis, ECS, and conglomerate lymph nodes) were not significantly different between groups. Most CUP patients (57.7%) received postoperative radiotherapy or combined radiochemotherapy (11.5%). Eight CUP patients refused radiotherapy, it is noteworthy that only one of these patients had an ECS and was considered to be at a very high risk for recurrence. The recurrence rate did not differ between CUP and HNSCC patients. Of the 26 CUP patients, four (15.4%) experienced a recurrence in the oropharyngeal region, four (15.4%) experienced a lymph node recurrence, and three patients (11.4%) suffered from distant metastasis. Local recurrences occurred in three cases in the ipsilateral root of the tongue, and in one case at the ipsilateral pharyngeal wall. A majority of the 166 HNSCC patients remained disease free (62.2%). For HNSCC patients, local recurrence, lymph node recurrence, or distant metastasis occurred in 41 (15.4%), 22 (8.2%) and 38 (14.2%) patients, respectively. Nine patients with CUP survived the follow-up period (34.6%) compared with 110 patients with HNSCC (41.2%).

Perineural invasion was the only independent prognostic factor for recurrence-free survival in CUP patients (*p* < 0.001) in

Download English Version:

<https://daneshyari.com/en/article/3143195>

Download Persian Version:

<https://daneshyari.com/article/3143195>

[Daneshyari.com](https://daneshyari.com)