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Pretreatment screening on distant metastases and head and neck cancer patients: Validation of risk factors and influence on survival

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SUMMARY

Background and purpose: Previously identified high risk factors for development of distant metastases are: three or more lymph node metastases, bilateral lymph node metastases, lymph nodes larger than 6 cm, low jugular lymph node metastases, locoregional tumor recurrence and second primary tumors. The aims of this study were to validate these specific risk factors and to investigate the impact of time (i.e. during screening or follow-up) of detection of distant metastases on survival.

Material and methods: From a total of 301 HNSCC patients with high risk factors who were scheduled for extensive treatment and underwent pretreatment screening on distant metastases using chest CT and/or whole body PET(-CT) (in some patients combined with whole body MRI), the high risk factors, the development and time point of distant metastases and survival were analyzed.

Results: Forty-four percent developed distant metastases. Multivariate analysis revealed that bilateral lymph node metastases is the strongest predictive factor. Locoregional recurrence and second primary tumor were the risk factors associated with the lowest cumulative incidence. However, if the risk factor locoregional recurrence was split into local and regional recurrences, regional recurrence became a high risk factor. The more high risk factors a patient had the lower the 5-year distant metastases free survival was. Patients with distant metastases detected pretreatment has a significant worse survival (corrected for lead time bias) compared to patients with distant metastases diagnosed during follow-up.

Conclusions: The validity of three or more lymph node metastases, bilateral lymph node metastases, lymph nodes larger than 6 cm, low jugular lymph node metastases and regional recurrence as high risk factors for the development of distant metastases was confirmed. If more high risk factors are present the cumulative incidence of distant metastases increases significantly. The detection of distant metastases by pretreatment screening worsens the overall survival as compared to distant metastases detected during follow-up.

Introduction

In patients with head and neck squamous cell carcinoma (HNSCC) distant metastases usually occur late during the course of the disease [1,2]. If distant metastases are present in general no curative options are currently available. Once distant metastases are detected, the prognosis is dismal. The median time to death from the diagnosis of distant metastases ranges from 1 to 12 months [1–7]. About 88% of the patients with distant metastases will die within 12 months [1]. Thus, the detection of distant metastases is critical for prognostication and for the choice of treatment in patients with HNSCC [3]. Detection of distant metastases may avoid futile extensive locoregional treatments with unnecessarily burden to the patient affecting quality of life and use and costs of resources, e.g. hospital stay, operating time and radiotherapy facilities. These considerations affect therapeutic decision making at initial diagnosis as well as in the management of locoregionally recurrent disease.

The reported prevalence of clinically identified distant metastases in HNSCC at presentation varies from 2% to 18% [4,8,9], but this is generally considered too low to warrant routine screening for

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distant metastases in all HNSCC patients. Besides better diagnostic techniques, selection of patients with high risk factors may increase the yield of examinations for the detection of distant metastases.

Jäckel and Rausch [9] found that screening is particularly useful in patients with advanced stage disease, local and/or regional recurrences and second primary tumors. Loh et al. [10] evaluated screening in HNSCC patients using chest CT and found T4 and/or N2 or N3 oropharyngeal, hypopharyngeal and supraglottic squamous cell carcinoma to be risk factors for the development of distant metastases: 64% of the patients with T4 and 73% of the patients with N2 or N3 disease had distant metastases detected during screening. These figures were significantly higher as compared to patients with tumors at other sites and lower T- or N-classifications [10]. Leong et al. [11] found in their series of 102 patients who underwent screening by chest X-ray and CT that of the patients with positive screening, 86% had T3 or T4 disease and 71% had N2 or N3 disease.

In a retrospective study in 101 patients with advanced HNSCC we identified risk factors for development of distant metastases: three or more lymph node metastases, bilateral lymph node metastases, lymph nodes larger than 6 cm, low jugular lymph node metastases, locoregional tumor recurrence and second primary tumors [4]. Using these refined risk factors comparable high incidences of distant metastases were found in subsequent studies on the screening for distant metastases [12,13]. Using these selection criteria, distant metastases were detected in 29–33% of the patients during initial screening (18–19%) or within 12 months follow-up after initial screening (11–14%). These studies validated the use of this set of risk factors to select patients at high risk for development of distant metastases.

The overall survival of HNSCC patients with distant metastases detected by pretreatment screening is significantly lower than patients with negative screening [12,14]. Brouwer et al. [12] found a significantly better overall survival in patients who developed distant metastases during follow up compared to those with metastases at the time of pretreatment screening. Of the patients with distant metastases detected during follow-up, 60% survived longer than 12 months after initial treatment [12]. However, Haerle et al. [14] could not confirm this difference in overall survival. A survey in The Netherlands revealed that the majority of head and neck surgeons would refrain from extensive treatment if a HNSCC patient would develop clinically manifest distant metastases within 12 months [15]. Screening for distant metastases is helpful to select patients who are good candidates for extensive treatment.

The aims of this study were to validate these specific risk factors each and to confirm the impact of time (i.e. during screening or follow-up) of detection of distant metastases on survival.

Material and methods

Patients who underwent pretreatment screening on distant metastases from 1997 till 2011 were retrospectively included in this study. Inclusion criteria were: (1) HNSCC, (2) candidates for extensive treatment with curative intent (surgery and/or radiotherapy with or without chemotherapy), (3). at increased risk for distant metastases (i.e.: $\geqslant$3 lymph node metastases (n = 43), bilateral lymph node metastases (n = 97), lymph node metastases of $\geqslant$ 6 cm (n = 37), low jugular lymph node metastases (n = 33), locoregional tumor recurrence (n = 83) and second primary tumors (n = 89)), as assessed by palpation, CT, MRI, and/or ultrasound-guided fine-needle aspiration cytology. Most patients were also included in previous studies on the accuracy of chest CT (n = 109) PET (n = 73) [12,13]. The other patients underwent screening as a routine procedure using PET and CT (n = 47), PET–CT (n = 52) or whole body MRI (n = 20). The high risk factors, the development and time point of distant metastases and survival from a total 301 HNSCC patients were analyzed.

Of these patients 234 were male, the mean age was 61 years (range 33–86). Primary tumor sites were the oral cavity (n = 78), oropharynx (n = 118), hypopharynx (n = 33), larynx (n = 70), cervical esophagus (n = 6), lymph node metastases of an unknown primary tumor (n = 16), nasopharyngeal (n = 3), neopharyngeal (n = 1). Twenty-four patients had more than one synchronous primary tumor in the head and neck area. Six patients had a synchronous (primary) lung or hepatocellulair tumor. These patients were not excluded because they did not develop distant metastases during screening or follow-up.

In case of negative pretreatment screening on distant metastases patients were treated with curative intent (despite high risk factors) and patients with positive screening by palliative treatment. Patients with high risk factors and negative screening were not treated differently from other patients not diagnosed with distant metastases.

Imaging techniques

Spiral CT scans were obtained with a third-generation Siemens Sensation 64 (Siemens AG, Erlangen, Germany) after intravenous biphasic administration of contrast medium (Ultravist, Schering AG, Berlin, Germany). Contiguous axial scanning planes were used with a 5-mm slice thickness. Radiological criteria for lung metastases were: smoothly defined and subpleurally located lesions, multiple and located at the end of a blood vessel; for bronchogenic carcinoma, solitary, spiculated, and centrally located lesions; and for mediastinal lymph node metastases, a short axial diameter of more than 10 mm.

FDG-PET was performed after patients had fasted for 6 h with ample access to water. At 60–90 min after the intravenous administration of 250–370 MBq FDG, imaging of trajectory knee-skull base was performed using a dedicated full ring BGO PET scanners (CTI/Siemens ECAT HR+). From 2007, patients were also scanned with a Gemini 64TF (Philips) PET–CT scanner. Any focal abnormality, suspicious for malignancy was reported.

See for more details on scoring criteria our previous studies [12,13].

Data analysis

The results of the clinical diagnostic work-up at presentation and follow-up were analyzed. Follow-up was performed by regular (each 4–6 weeks in the first year) visits to the outpatient clinic. The median follow up for patient alive at the end of follow up was 38 months (range 0–167). Detection of distant metastasis in follow up was confirmed by imaging, in case of clinical suspicion in the outpatient clinic. During follow-up the dates of the detection of distant metastases, and death were recorded. Overall survival was defined as the time of screening (during pretreatment initial diagnostic work-up) until death. In this way survival was corrected for lead time bias of the detection of distant metastases by adding the time of initial diagnostic work-up to the survival after detection of distant metastases. Distant free survival was defined as time of screening until distant metastases were diagnosed. Time interval between diagnosis of distant metastases and death was calculated. CT- and FDG-PET-scans were evaluated by different attending staff radiologists and nuclear medicine physicians, respectively, according to common clinical practice.

Statistical analysis

For each separate risk factor the cumulative incidence of distant metastases at 5 year was calculated. Estimates of survival