Ten-year retrospective study of head and neck carcinoma in situ: incidence, treatment, and clinical outcome

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Objectives. To examine the management and clinical outcome for patients with primary head and neck carcinoma in situ (CIS) and to estimate the incidence in the referral population.

Study design. A retrospective study from 2000-2009 of patients with head and neck CIS referred for treatment at Rigshospitalet. The referral area was East Denmark and Greenland with a population of 2.4 million.

Results. Fifty-five patients with primary CIS were identified: 21 oral cavity, 7 pharynx, 25 larynx, 2 nasal cavity/paranasal sinuses. The median annual incidence was 0.24/100,000. Eleven patients (20%) had T-site recurrence. The 5-year disease-specific survival rate and 5-year recurrence-free survival rate were 98% and 74% respectively.

Conclusions. The annual incidence of primary head and neck CIS was low and in accordance with previous findings reported in the literature. We recommend that CIS lesions should be treated on T-site and surveilled as T1/T2 head and neck carcinomas. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:174-178)

Head and neck carcinoma in situ (CIS) is a rare diagnosis and our knowledge about this entity is limited. Former studies from the US and Germany have shown annual incidence rates of primary head and neck CIS between 0.14-1.8/100,000.[1-4] These studies also included CIS lesions on lip where sun exposure, as opposed to the mucosa-associated CIS lesions, is a key risk factor in the pathogenesis. The diagnosis is based on cytological and architectural changes in the epithelium of the upper aerodigestive tract. A CIS lesion is defined as a full-thickness dysplasia in the viable cell layers of the epithelium. Invasion is not present.[5] Therefore regional metastases from true CIS lesions do not occur. CIS represents an in dependent entity in the spectrum of histopathological changes in the epithelium from mild dysplasia to invasive carcinoma. Different classification systems for head and neck precancerous lesions have been evaluated and recommended in the past.[6] The World Health Organization classification system has been widely accepted and is a 4-step system with the categories mild, moderate and severe dysplasia and CIS.[5] The consistency of grading systems has been extensively debated and inter-observer and intra-observer variation may affect the accuracy of the histopathological diagnosis.[7] From a clinical point of view a classification system should be able to stratify lesions according to malignant potential and facilitate the decision making in the management of the disease. Tumor models suggest a biological process of sequential intermediate stages from healthy epithelium over mild and moderate dysplasia to CIS and finally carcinoma.[8] It is widely accepted that some precursor lesions progress to carcinoma and that the degree of dysplasia is a prognosticator for progression to cancer.[9,10]

This study aimed to examine the management, patterns of recurrence, and clinical outcome in our center for patients with head and neck CIS and to estimate the incidence in the referral population.

MATERIALS AND METHODS

The study population included patients with microscopically confirmed primary head and neck CIS referred for treatment in a 10-year period from 2000-2009. The referral area was East Demark and Greenland where the treatment of head and neck cancer is centralized at Rigshospitalet. Exclusion criteria were prior head and neck cancer, lymphoma, skin cancer, cancer of unknown

Statement of Clinical Relevance

The annual incidence of primary head and neck CIS was low (0.24/100,000). The recurrence rate was 20% and the recurrences were mainly T1 or T2 carcinomas. CIS lesions should be treated on T-site and surveilled as T1/T2 carcinomas.

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Table I. Distribution of recurrences in subgroups and recurrence rate. Recurrence defined as recurrence at the same anatomical location as the primary CIS lesion after primary therapy

Anatomical location	*Recurrence rate (%) (n/N)*	*Malignant transformation rate (%) (n/N)*	*Median progression time (months)*
Total	20 (11/55)	18 (10/55)	28 range (4-56)
Larynx	16 (4/25)	16 (4/25)	22 range (4-50)
Oral cavity	29 (6/21)	24 (5/21)	29 range (11-55)
Pharynx	14 (1/7)	14 (1/7)	28
Nasal/paranasal	0 (0/2)	0 (0/2)	–

primary or metastatic disease in head and neck. Lesions at the labial vermilion were also excluded. If the diagnosis of the lesion was changed to cancer within 2 months after the CIS diagnosis, the patient was also excluded to minimize the risk of sampling error. Patients with a histopathological CIS diagnosis were searched in the Danish National Pathology Register where all pathology reports have been registered since 1985. A search was also made in the pathology registers of the Danish Head and Neck Cancer Group and of the School of Dentistry in Copenhagen. The histopathological diagnosis was based on microscopy of H&E stained sections from formalin-fixed, paraffin embedded tissue. Data were collected from chart reviews, and patient characteristics, diagnosis, treatment, recurrence and death from head and neck cancer or other diseases were recorded. The primary treatment modality was chosen by the ENT specialist based on resectability and clinical presentation of the CIS lesion, findings during surgery and histopathological findings in biopsies or resection specimens. Patients were seen after treatment for periodic annual or midannual clinical control in an ENT or Oncology department. The identified lesions were divided into anatomical subgroups: Oral cavity, pharynx, larynx, and nasal/paranasal sinuses. If the original specimen was available, a confirmatory microscopy was performed by a pathologist (E.K. and M.H.T.). A clear margin was defined as >5 mm distance from the CIS lesion to the surrounding tissue with histological normal epithelium with no dysplasia. A recurrence was defined as CIS or carcinoma at the same anatomical site as the primary CIS lesion. At recurrence tumors were classified according to the Tumor-nodes-metastasis (TNM) classification from International Union Against Cancer (UICC) (2005). Statistical analyses were performed using STATA 11.0 (STATA Corp. Lp, College Station, TX, USA). Survival analysis was calculated by the Kaplan–Meier method. Comparisons of groups were performed by Log rank test, Chi-square test or one-way analysis of variance. For all tests significance was 2-sided and set to $P < .05$ and 95% confidence intervals (CI) were applied. Incidence rates were calculated pr. 100,000 persons based on the average of the population size in 2000 and 2009 in the referral area (www.dst.dk, www.statgreen.gl). The study was approved by the local ethical committee and the Danish Data Registry.

RESULTS

A total of 55 patients with primary CIS were identified: 21 oral cavity, 7 pharynx, 25 larynx, 2 nasal cavity/paranasal sinuses. Twenty-four patients (44%) were women and the median age was 62 years (range: 28-81 years). The median annual incidence was 0.24/100,000 persons (range: 0.08/100,000-0.47/100,000) and the median follow-up time was 59 months (range: 10-132 months). In 34 patients (62%) CIS was found in the first biopsy taken during clinical work-up. The patients who had more than 1 biopsy taken prior to the CIS diagnosis had primarily lesions in the oral cavity or the larynx. At the time of diagnosis 49 patients (89%) were past or present smokers with a median consumption of 40 pack years. Six patients (11%) had no history of tobacco consumption and had CIS lesions distributed as 4 glottis, 1 oral cavity and 1 paranasal sinuses. The patient with an oral cavity CIS lesion had a long history of oral lichen planus.

Fifty-seven patients with head and neck CIS in the pathology report were identified and in 49 cases (86%) a confirmatory microscopy of the specimen could be performed. In the remaining cases the specimen had either been collected by the patient or could not be provided. In 2 patients the diagnosis was changed from CIS to severe dysplasia and carcinoma respectively after re-examination and they were excluded from the study. In 5 patients the original slides had not been preserved and new slides were prepared from the original paraffin blocks for examination.

Eleven patients (20%) had T-site recurrence after primary therapy and the median progression time to recurrence was 28 months (range 4-56 months) (see Table I). There was 1 CIS lesion, 8 T1, and 2 T2 tumors, and the carcinomas were moderately (46%) or well differentiated (46%). At the time of recurrence no patients were diagnosed with regional neck metastases. Six patients (11%) in the cohort developed a second primary head and neck squamous cell carcinomas in other anatomical locations than the primary CIS lesion in the upper aerodigestive tract and 7 patients died from lung cancer. All but 2 patients have had regular