



Head and neck *in situ* carcinoma: Survival analysis of the Thuringian cancer registration database

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SUMMARY

Head and neck *in situ* carcinoma is seldom diagnosed. Our knowledge about *in situ* cancer is limited. This study describes the epidemiology and prognosis of head and neck *in situ* cancer in Thuringia, Germany. We analyzed the cancer data of the Thuringian cancer registry database from 1996 to 2005. The database contained 3821 patients with primary head and neck cancer. Thirty-four patients (0.88%) had an *in situ* carcinoma. They were evaluated for patient's characteristics, tumor stage, incidence, treatment and trends in overall survival (OS) and recurrence-free survival (RFS). During 1996–2005, the average annual incidence of head and neck *in situ* carcinoma was 0.14 per 100,000 persons. Half of the cases were localized in the larynx. The patients were treated by local excision. Six patients (18%) developed a local recurrence. Only one recurrent tumor was diagnosed in early stage (rT1), but the other five tumors in advanced stage (rT3/rT4). The median time to recurrence was 27.43 months. For all 34 patients with *in situ* carcinoma, the 5-year OS was 84% and the 5-year RFS 60.4%. OS was better for laryngeal *in situ* cancer than for oral cavity or pharyngeal *in situ* cancer ($p = 0.031$). The surveillance of patients with head and neck *in situ* carcinoma after treatment should be performed like in patients with invasive cancer, because nearly one fifth of patients developed a recurrence, predominantly in advanced stage.

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Introduction

The literature on the epidemiology of head and neck *in situ* cancer is very limited, probably because of its low incidence. Our knowledge is mainly based on two analyses of data from the US-American surveillance, epidemiology, and end results (SEER) program: for the period 1973–1977, the annual incidence rate of all *in situ* cancers of the head and neck region (anatomic sites of lip, oral cavity, pharynx, larynx, nose/paranasal sinuses) was 5 per 100,000 persons.¹ A recent update of the years 1976–1995 revealed an increase to 8 per 100,000 persons.² This increase was interpreted as a result of increased surveillance.

Head and neck *in situ* carcinoma is defined as a carcinoma that has not spread beyond the basement membrane and, therefore, metastases do not occur. Since 2005 the WHO classification applies the concept of intraepithelial neoplasia also to the head and neck region. Precursor lesions of the head and neck mucosa are classified as squamous intraepithelial neoplasia (SIN) and are graded as mild, moderate and severe (SIN 1–3).³ SIN 3 is equivalent to former carcinoma *in situ*. Each precursor lesion is associated with an ascertained risk of progression to carcinoma. Carcinoma *in situ* (or SIN 3) has the highest risk from all SIN.⁴ *In situ* lesions are typically excised.⁵ Alternatively, and especially in the larynx, they can also be treated effectively by radiotherapy.⁶

Actual data on head and neck *in situ* carcinoma is not available. Therefore, we analyzed the head and neck cancer data from the cancer registries in Thuringia 1996–2005 to give updated data on survival and prognostic factors for head and neck cancer in Germany.

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Materials and methods

The study is based on data of the Thuringian cancer registry database from 1996 to 2005. This registry is a population-based registry collecting data from the five Thuringian cancer databases in the Thuringian towns: Nordhausen, Gera, Suhl, Jena and Erfurt. These five databases register all cancer cases of the federal state Thuringia in the eastern part of Germany. For this study, the data was merged together in one database in Jena. The registration of new cancer cases is obligated by federal law. The Thuringian cancer registry covers about 98% of all head and neck cancer patients in Thuringia.⁷ Follow-up is assured by periodic clinical follow-up data from the ENT departments. In case patients miss follow-up examinations for more than one year, the general practitioner or the local registrar office of Deaths is contacted.

New cases of head and neck cancer were classified according to the International Classification of Diseases for Oncology (ICD-O)⁸ and selected according to the following inclusion criteria: cancer from the lip (separated from oral cavity because of much better prognosis), oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, salivary glands, and nose/paranasal sinus. Patients who were treated for recurrent disease only, lymphoma, skin cancer, metastasis in the head and neck region of other origin, and carcinoma of unknown primary were excluded. Duplicate records of patients removed. By this, 3821 patients with primary head and neck cancer were identified. Carcinoma *in situ* (CIS) is histologically defined as a high-grade squamous intraepithelial neoplasia without invasion through the basal membrane.³ Thirty-four patients (0.88% of all patients) with CIS were found in the database. Primary treatment presented in this presentation is defined as the first course of cancer-specific treatment performed to treat the primary tumor. Subsequent therapy to treat recurrences is defined as re-treatment.

Statistical analysis

All statistical analyses were performed using SPSS statistical software for Windows (SPSS 15.0, Chicago, Illinois, USA). Incidence rates were calculated per 100,000 persons based on the yearly estimations of habitants living in Thuringia (Statistical Bureau of Thuringia: <http://www.statistik.thueringen.de>). Overall survival (OS) and recurrence-free survival (RFS) rates were calculated by the Kaplan–Meier method and the significance of difference among survival curves was calculated by the log-rank test. Comparisons of subgroups were performed by Mann–Whitney–U-test. For all statistical tests, significance was two-sided and set to $p < 0.05$.

Results

We identified 34 cases fulfilling the selection criteria. 29 patients were male and 5 patients were female. The age at diagnosis

ranged from 45 to 91 years (median 64.5 years). Most tumors were localized in the larynx ($n = 17$; 15 glottic tumors, 2 supraglottic tumors). Other localisations were lip ($n = 3$), oral cavity ($n = 5$), oropharynx ($n = 5$), hypopharynx ($n = 2$), and paranasal ($n = 2$). All patients were treated by local excision of the tumor. An *in situ* cancer was never found in the nasopharynx and in salivary glands.

The absolute numbers of registered patients with *in situ* carcinoma in the different head and neck subsites from 1996 to 2005 and the calculated crude incidence rates are given in Table 1. The annual incidence varied between 0.04 and 0.30 (mean 0.14) cases per 100,000 persons. The incidence for male patients was 0.245 and for female patients 0.004. Concerning subsites, the highest incidence had larynx *in situ* cancer with 0.07 (glottic 0.062; supraglottic 0.008). The incidence for *in situ* cancer of the lip was 0.012, of the oral cavity 0.021, of the oropharynx 0.021, of the hypopharynx 0.008, and of the paranasal sinuses 0.008.

The median follow-up time for all patients was 33.17 months (range: 1.30–108.00). The median follow-up time for patients alive was 37.07 months (1.30–108.00). Six patients got a tumor recurrence. Twenty-eight patients were recurrence-free. Seven patients are dead and 27 are alive (24 without tumor recurrence and 3 with recurrence). The 5-year OS rate was 84.0% (Fig. 1A). The mean OS time was 79.82 months (CI 63.84–95.79 months). The 5-year RFS rate was 60.4% (Fig. 1B). The mean RFS time was 72.87 months (CI 57.83–87.92 months). All female patients were alive 5 years after treatment, i.e. the 5-year OS rate was 100%, whereas the 5-year OS rate for the male patients was only 81.8% (log-rank test not applicable because all female patients alive). The female patients were older than the male patients at time of diagnosis, but the difference was not significant (on average 71 years versus 63 years, respectively; $p = 0.233$). The 5-year RFS was not significantly different between female and male patients ($p = 0.831$). OS and RFS were not different between patients < 65 years (median age of study group) and patients ≥ 65 years ($p = 0.908$ and $p = 0.221$, respectively; Fig. 1C and D). OS was significantly better in patients with larynx *in situ* cancer than in patients with oral cavity or pharynx cancer; $p = 0.031$; Fig. 1E), although the patients with laryngeal cancer were in average older than patients with oral cavity or pharynx cancer (65 years versus 60 years, respectively; $p = 0.05$). The 5-year RFS was not significantly different between laryngeal and oral cavity/pharyngeal *in situ* cancer ($p = 0.638$; Fig. 1F). When comparing the laryngeal subsites, interestingly, the two patients with supraglottic *in situ* cancer were alive after 5 years, whereas the 5-year OS rate for glottic *in situ* cancer was 90% (log-rank test not applicable; Fig. 1G). The RFS was not significantly different between supraglottic and glottic *in situ* cancer ($p = 0.564$; Fig. 1H).

Six patients suffered a local tumor recurrence with invasive head and neck cancer. The median time from primary treatment to tumor recurrence was 27.43 months (range: 14.47–55.73 months). The follow-up intervals of these six patients varied

Table 1
Absolute number of patients with head and neck *in situ* cancer per year and calculated incidence.

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	Total
Lip	0	0	0	1	0	1	0	0	1	0	3
Oral cavity	0	0	1	0	0	1	1	0	2	0	5
Oropharynx	1	0	1	0	0	0	1	0	1	1	5
Hypopharynx	0	0	1	0	0	0	0	1	0	1	2
Larynx	0	1	2	1	2	3	2	0	2	4	17
Paranasal	0	0	0	0	1	0	0	0	0	1	2
Male	1	1	3	1	3	5	4	1	4	6	29
Female	0	0	1	1	0	0	0	0	2	1	5
Total	1	1	4	2	3	5	4	1	6	7	34
Habitants in Thuringia in millions	2.49	2.48	2.46	2.45	2.43	2.41	2.39	2.37	2.36	2.33	2.42
Crude incidence	0.04	0.04	0.16	0.08	0.12	0.20	0.17	0.04	0.26	0.30	0.14

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