Survival of head and neck cancer in Greenland

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ABSTRACT

Objectives. Head and neck cancer is frequent in the Inuit population of Greenland and is characterized by a very high incidence of Epstein-Barr virus associated nasopharyngeal carcinoma (NPC). However, information on the treatment and survival of Inuit head and neck cancer patients is practically non-existent. The aim of this study, therefore, was to analyse the epidemiological pattern, time course and survival of head and neck cancer patients in Greenland.

Study design. Retrospective register-based study.

Methods. The Danish Civil Registration System, the Danish Cancer Registry and hospital-based registries were used to identify all patients resident in Greenland diagnosed with head and neck cancer during the period 1994–2003. Data were analysed with regard to clinical characteristics, treatment delay and survival.

Results. A total of 125 patients were identified. The age-standardized incidence rate for all head and neck cancer cases was 28/100,000 for males and 19/100,000 for females. High incidence rates were found for NPC and oral cancers. Of all cancers, 47% were stage IV at the time of diagnosis, while 61% of all NPC's were stage IV. The median delay from date of first symptom to treatment was 248 days for all cancers. The overall crude 5-year survival rate for all sites together was 35% and for NPC 20%.

Conclusion. Survival of head and neck cancer in Greenland is very low. Delays in treatment and inadequate follow-up on treatment complications are probable causes. The improvements in treatment for NPC and other head and neck cancer cases over the last decades are yet to be seen in this Inuit population.

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Keywords: carcinoma, delay, follow-up, head and neck, Inuit, survival
INTRODUCTION

Head and neck cancer is frequent in the Arctic Inuit population, which inhabits the circumpolar regions of Alaska, Canada, Siberia and Greenland. It is characterized by a high incidence of Epstein-Barr virus associated nasopharyngeal carcinoma (NPC) and salivary gland carcinoma (1,2). Other areas that have populations with a high incidence of NPC include Southern China, South-east Asia and North Africa (3,4), while NPC is rare in areas with sizeable Caucasian populations, with incidence rates below 1/100,000 (5). The Arctic regions cover a vast territory and the population often lives in small, scattered communities far from the regional health centres, making preventive, curative and rehabilitative aspects of health care a major challenge. However, treatment outcome and survival of head and neck cancer in the Arctic populations are largely unknown.

Head and neck cancer is a local disease which often metastasizes regionally, while distant metastases are relatively rare and normally seen late in the course of the disease. It has a tendency to recur locally and regionally after treatment. As a result, treatment is focused on gaining primary local and regional control. Head and neck cancer often impairs important functions such as speaking, eating and swallowing. Follow-up is important in order to diagnose curable recurrences and to handle complications and the adverse effects of the treatment (6–9).

The largest Inuit population lives in Greenland, where approximately 90% of the population is of Inuit descent (the total population is approximately 56,000). There are 16 health districts scattered along Greenland’s 2,166,086 km² coastline, and the central hospital is located in the capital, Nuuk.

In Greenland, primary diagnosis, referral to a specialized centre and follow-up is performed by the primary sector or by ear, nose and throat (ENT) specialists visiting the remote areas once a year. Patients are transferred to Denmark for treatment at Rigshospitalet, the University Hospital of Copenhagen.

In order to investigate treatment response and survival of head and neck cancer in Inuit, we performed a population-based analysis of all head and neck cancer patients diagnosed in Greenland over a 10-year period.

MATERIAL AND METHODS

Study population

The study is retrospective. Individuals resident in Greenland and diagnosed with head and neck carcinoma between 1 January 1994, and 31 December 2003 were included. All individuals in Greenland are registered in the Danish Civil Registration System (CRS) and are ascribed a unique CRS-number. Using the CRS-number, patients diagnosed with head and neck cancer were identified from the data system at Rigshospitalet, which contains records for all patients from Greenland treated at the hospital. The diagnoses were verified by matching with histological results from the Department of Pathology, Rigshospitalet. Finally, data were compared with the Danish Cancer Registry, which covers both Denmark and Greenland. Medical files were obtained from the Department of Otolaryngology, Head & Neck Surgery and the Department of Oncology,
Rigshospitalet, Denmark, and Dronning Ingrid’s Hospital, Nuuk, Greenland. The study has been approved by the ethical committee in Greenland, the Commission for Scientific Studies in Greenland (KVUG) and by the Danish Data Protection Agency.

**Tumours**
Carcinomas in the pharynx, larynx, oral cavity (including the lips), salivary glands, nasal cavity and sinuses and thyroid gland were included. Cervical lymph node metastases from unknown primary tumours were also included, as 90% of these have their primary tumour in the head and neck region (10). This corresponds to the ICD-10 codes: C00-C14, C30-C32 and C73-C75. Tumours were prospectively staged and classified according to the TNM system of the UICC (International Union against Cancer), 1997 (11).

**Time course**
All patients were asked about the date of first symptom at the initial medical contact. If there was no exact date, the examiner approximated the date as either the 1st or 15th of the month of occurrence. Age was calculated as the age at the date of histological diagnosis. Treatment time was defined as the period from the first day of surgery or radiation therapy until the end of primary treatment, which could include several treatment modalities. The treatment time of thyroid carcinoma is often lengthy because repeated treatments with radioactive iodine are necessary. The date of recurrence was defined as the date of histological verification or convincing clinical features (e.g., visible tumour at the primary site). Malig-

nancy verified within 2 months after end of treatment was considered a failure of treatment rather than a recurrence. The follow-up period was defined as the time from the last day of treatment until the date of the last follow-up visit. Follow-up in both Denmark and Greenland was included. Information on death was obtained from patient files and the Medical Public Health Officer in Greenland, and was last updated 15 January 2008, which means that all surviving patients have been observed for at least 4 years.

**Statistics**
Incidence rates were calculated using the population in Greenland as a denominator, and directly age-standardized using the World Standard Population (12). Survival was estimated by the method of Kaplan and Meier and was calculated for patients who received treatment (13). The Mann-Whitney U-test was used for testing the difference between independent continuous variables within 2 groups and the Kruskal-Wallis test was used for testing the difference between independent variables within multiple groups. All test results are given as 2-sided values, and the level of significance was a p-value ≤ 0.05. All calculations were made with SPSS 15 software.

**RESULTS**
In the period 1 January 1994 to 31 December 2003, a total of 125 patients resident in Greenland were diagnosed with head and neck carcinoma. The Danish Cancer Registry and files from Rigshospitalet identified 120 and 111 patients, respectively. Five patients had
not been reported to the Danish Cancer Registry. Nine patients were not listed in the files from Rigshospitalet. The total was made up of 75 males (60%) and 50 females (40%). Eight of these patients were ethnic Danes, and the rest were of Inuit or mixed origin.

The mean age was 56 years (range 12–83) for all head and neck carcinomas. NPC accounted for one-third of all cases for both sexes, and it was the largest group among head and neck cancer cases in Greenland. The age-standardized incidence rate for all cancers was 28/100,000 for males and 19/100,000 for females (Table I). The incidence rate of NPC was 9/100,000 for males and 7/100,000 for females. The incidence of laryngeal carcinomas was low, with rates of 4/100,000 for men and below 1/100,000 for women. We found no cases of laryngeal carcinomas misclassified as other head and neck cancers. Two cases of cancer of the lip were found and both were in ethnic Danes. Staging and diagnosis are shown in Table II. Seventy-five percent of all cancers were stage III or IV at the time of diagnosis.

Table III shows that the median delay from the date of first symptom to treatment (the overall delay) was 248 days for all cancers. Tests for differences in diagnostic delay between sexes showed a non-significant trend (p=0.055), with females having a larger diagnostic delay than males. Females and males had a median diagnostic delay of 234 and 178 days, respectively. Tests for differences in diagnostic delay according to age or tumour site were not significant.

Eleven patients (9%) did not receive treatment. One died before the start of treatment, and 1 could not cooperate during radiation therapy due to dementia. Nine patients refused treatment. Six patients had no available data on treatment type or date. Three patients did not receive full treatment due to their general medical condition. Figure 1 shows the overall survival according to tumour site. Survival of the 2 patients with unknown primary tumours was less than 1 year. The overall crude 5-year survival rate for all head and neck cancer sites together was 35%. The 2 largest groups of cancers NPC and oral carcinomas had survival rates at 20% and 19%, respectively. Survival calculated from the date of histological diagnosis (n=119), including patients who were not treated, showed an overall crude 5-year survival rate for all sites at 33% and 20% for NPC alone.

Information on follow-up after discharge was available for only 61 patients. The median and mean time from discharge to date of first follow-up visit was known in 58 of 114 treated cases (51%) and was 95 days and 170 days, respectively. We only had information on subsequent follow-up for 30 of these patients. For them the median follow-up time was 476 days (range 64–4,813 days; mean 864 days). Twenty-eight patients had a verified recurrence, and 8 of these received palliative treatment. However, it must be emphasized that this number is a minimum due to the lack of data on follow-up for most of the patients. Thirty-five patients with NPC received treatment, of whom 23 have reports of follow-up and 16 had verified recurrences. After 4 years of observation, 5 patients with NPC were alive, 2 of whom had verified recurrences.
### Table I. Numbers and incidence of head and neck cancer per 100,000 persons-years in Greenland in the period 1994-2003.

|                | Males | Females |
|----------------|-------|---------|
|                | n     | %       | Age mean | Crude rate | AS* rate | n     | %       | Age mean | Crude rate | AS rate |
| Nasopharynx    | 23    | 32      | 59       | 8          | 9        | 18    | 36      | 48       | 7          | 7       |
| Oropharynx     | 8     | 11      | 53       | 3          | 2        | 4     | 8       | 68       | 2          | 2       |
| Hypopharynx    | 5     | 7       | 62       | 2          | 2        | 1     | 2       | 81       | <1         | <1      |
| Larynx         | 9     | 13      | 66       | 3          | 4        | 1     | 2       | 64       | <1         | <1      |
| Salivary gland | 6     | 8       | 59       | 2          | 2        | 7     | 14      | 40       | 3          | 2       |
| Oral cavity    | 16    | 22      | 60       | 6          | 6        | 10    | 20      | 62       | 4          | 4       |
| Thyroid        | 3     | 4       | 42       | 1          | <1       | 9     | 18      | 44       | 3          | 3       |
| Unknown Primary| 2     | 3       | 63       | <1         | <1       | 0     | 0       | 0        | 0          | 0       |
| All cancers    | 72a   | (100)   | 59       | 25         | 28       | 50    | 100     | 51       | 19         | 19      |

*Age-adjusted using world standard.

Three males did not have available information on age at time of diagnosis.

### Table II. Head and neck cancer in Greenland, staged by UICC 1997.

|                | I  | II | III | IV | Total |
|----------------|----|----|-----|----|-------|
| Nasopharynx    | 0  | 0  | 1   | 2  | 41    |
| Oropharynx     | 0  | 3  | 25  | 3  | 50    |
| Hypopharynx    | 0  | 1  | 20  | 2  | 40    |
| Larynx         | 1  | 10 | 20  | 4  | 30    |
| Salivary gland | 6  | 50 | 1   | 8  | 33    |
| Oral cavity    | 1  | 4  | 6   | 13 | 14    |
| Thyroid        | 7  | 58 | 1   | 8  | 12    |
| Total          | 15 | 13 | 15  | 13 | 54    |

*All papillary carcinomas.

Five men and 2 women lacked information for staging. Two patients with unknown primary tumours were not staged.

### Table III. Time course in days for all head and neck cancer cases.

|                | n   | Diagnostic delay* | Treatment delay* | Overall delay* | Treatment days* | Recurrence* |
|----------------|-----|-------------------|------------------|---------------|-----------------|-------------|
|                |     | Mean              | Median           | Range         | Minimum         | Maximum     |
|                | 106 | 106               | 101              | 101           | 107             | 28          |
| Mean           | 269 | 43                | 40               | 855           | 0               | 846         |
| Median         | 207 | 207               | 248              | 2126          | 24              | 2150        |
| Range          | 2086| 855               | 2126             | 1710          | 0               | 1710        |
| Minimum        | 24  | 0                 | 24               | 1710          | 0               | 1710        |
| Maximum        | 2110| 846               | 2150             | 1710          | 96              | 1992        |

*Day of first symptom to histological verification.

Histological result to treatment day 1.

First symptom to treatment day 1.

Treatment day 1 until discharge from treating hospital.

Discharge to recurrence. Missing values represent patients with no observed recurrence at follow-up (n=23) or no information on follow-up (n=74).

Some patients were operated for clinically evident malignant tumours in Greenland before histology was determined.

One patient with a diagnostic delay at 23,671 days was excluded. The patient had a slow-growing tumour on the right parotid area since childhood. Histology showed carcinoma ex pleomorphic adenoma.
Table IV. Literature review on survival of nasopharyngeal cancer and its stages.

| Author (reference) | No. of patients | Nationality | Time period | Endpoint | Stage I–III % | Stage IV % | 5-year survival % | Classification |
|--------------------|----------------|-------------|-------------|----------|---------------|------------|-------------------|----------------|
| Bentzen (14)       | 47             | Inuit Greenland 1965-1985 OSa | 11          | 89       | 20            | UICC 1978  |
| Lanier (16)        | 31             | Alaska Natives Alaska: Inuit, Indians, and Aleuts 1966-1976 OS – | –          | –        | 48            | –          |
| Johansen (15)      | 149            | Danish       1963-1991 OS | 40          | 60       | 43            | UICC 1982  |
| Lee (4)            | 2070           | Chinese, Hong Kong Inuit, Greenland 1996-2000 OS  | 72          | 28       | 75            | UICC 1997  |
| Current study      | 42             | Inuit Greenland 1994-2003 OS | 39          | 61       | 20            | UICC 1997  |

a Overall survival.
b Alaska Natives: Inuit, Indians, and Aleuts.

Table V. Stage according to UICC 1997 and median survival. Greenland 1994–2003 and SEER* data.

| Stage | Greenwood | SEER | Greenwood median survival (weeks) |
|-------|-----------|------|----------------------------------|
| n     | Stage I–II | Stage III–IV | Stage unknown | Stage I–II | Stage III–IV | Stage unknown | (weeks) |
|-------|------------|-------------|---------------|------------|-------------|---------------|---------|
| %     | %          | %           | %             | %          | %           | %             |         |
| C. oris* | 25          | 20          | 68            | 12         | 17869       | 49            | 44      | 7       | 11     | 48-59 |
| Nasopharynx | 42         | 10          | 88            | 2          | 2819        | 22            | 67      | 11      | 21     | 68    |
| Oropharynx | 13         | 23          | 69            | 8          | 5301        | 28            | 65      | 7       | 45     | 45    |
| Salivary gl. | 13         | 54          | 39            | 8          | 4058        | 51            | 30      | 19      | 99     | 112   |

a SEER, Surveillance Epidemiology and End Results, United States National Cancer Institute. Data from 1988-2001, on all races from 12 regions in USA.
b Exclusive lip
c Tongue 48, floor of mouth 50, gum and other mouth 59.
DISCUSSION

The present study documents significant delays in the diagnosis and treatment of head and neck cancer patients from Greenland. Late disease stage at diagnosis and corresponding poor survival rates were found irrespective of disease site. Table IV shows that the overall survival rate for NPC among Inuit in Greenland was low compared to populations living in both high- and low-incidence areas and has not improved over the last 20 years (4,14–16). At the time of admission, NPC tumours were at advanced stages but were comparable to those recorded in other studies (15). However, even at the same stage, the size of the tumour may vary considerably. Thus, the advanced disease of NPC may still be part of the explanation for the poor survival rate in Greenlanders.

Oral carcinomas, the second-largest group of head and neck cancer in Greenland, were diagnosed with 29% in stages I–II and 71% in III–IV. The overall 3-year survival rate was 29%. A study performed on Danish patients with oral carcinomas treated at the same oncology centre at Rigshospitalet in the period 1992–1996 found that 43% were diagnosed in stage I–II and 57% in stage III–IV, with a 3-year overall survival rate of 42% (17). For this group of cancers, the low survival rate among Greenlanders may be explained by the difference in stages at the time of admission compared to Danish patients. Another Danish study on cancers of the larynx, pharynx and cavum oris, with 52% of cancers in stage I–II and 58% in stage III–IV, found an overall 5-year survival rate at 50% (18). In the present study, these sites distributed with 20% in stages I–II, 80% in stages III–IV and an overall 5-year survival rate at 23%. Table V compares staging and survival data from Greenland to data from the SEER program, United States National Cancer Institute on selected cancers (19).

Laryngeal cancer was found with a low incidence. An earlier study on cancers in Greenland in the period 1988–1997 found a similar low age-standardized incidence at 3/100,000 for men and less than 1/100,000 for women (20). Alcohol and tobacco consumption in Greenland are among the highest in the world. The annual alcohol intake peaked in 1987 at 22 L/person and has since declined to 12 L/person (2007) (21). A health survey from 1993–1994 found that 79% of the population smoked regularly (22). Lung cancer, another cancer in the respiratory tract strongly associated with smoking, occurs with an increasingly high incidence, especially among women. As misdiagnosis of laryngeal cancers is highly unlikely due to the obvious clinical symptoms, we do not yet have any explanations for the low incidence of laryngeal cancers in this population.

The trend of women having longer diagnostic delays than men in this study is surprising, and we do not have any explanation hereof. In a Danish study on delays in treatment of cancers in the pharynx and larynx, the median patient delay (symptom to first health care contact) and median delay in diagnostic procedures (first healthcare contact to histological verified diagnosis) were 75 and 18 days, respectively (23). The corresponding median delay from symptom to diagnosis was 207 days in Greenland, and is likely to be the main reason for the advanced tumours found. The median delay from diagnosis to treatment was 46 days in the Danish study, which is similar to our findings and reflects an equal course of treatment planning for both Danish and Greenlandic patients.
Due to the rapid tumour growth in head and neck cancer cases, where significant changes can be seen after 4 weeks of delay, Danish guidelines from 2007 require that all patients with a reasonable suspicion of malignancy in the head and neck should be referred to an ENT specialist and start diagnostic procedures within 48 hours (24). Late diagnosis of head or neck cancer in patients does not seem to be limited to Greenland. A recent study found that head and neck cancer in Alaska Natives is more often diagnosed at an advanced stage when compared to the diagnosis of non-Hispanic whites in Alaska (25). While such a difference may be explained by a number of factors, including socio-economic differences, access to health care and a different cancer pattern, it indicates that disparities in head and neck cancer survival rates may be a general Arctic problem.

Only 26% of treated patients had reports on 2 or more follow-up visits after the end of treatment. This indicates problems with handling complications of treatment in Greenland leading to a high morbidity and possibly a higher mortality. Since data were collected retrospectively, follow-up information may have been lost from the local district hospitals, leading to an overestimation of the magnitude of the problem. However, the overall impression is that of a follow-up program which did not match international or Danish recommendations during the period 1994–2003. The lack of a permanent ENT specialist in Greenland for most of this period and an infrastructure hampering adequate follow-up are probably the main reasons.

The overall survival of head and neck cancer patients is often influenced by co-morbidity caused by alcohol and tobacco use (cardiovascular diseases, chronic lung diseases and concurring cancers such as lung cancer). The population in Greenland has a lower life expectancy compared to Denmark and most Western countries. Possible explanations for this are the high level of alcohol intake (though similar to Danish conditions), cigarette smoking and violent deaths (accidents and suicides), while tuberculosis and other infectious diseases are now more rare causes of death (26). Long-term morbidity from extensive surgery and radiation therapy is particularly high among patients treated for head and neck cancer (18). Advanced disease stage and limited options for support and treatment during follow-up are probably the main reasons for the low overall survival rate in Greenland, but the lifestyle, exemplified by a lower life expectancy, may also contribute. Access to health care is free of cost in Greenland, so we therefore do not expect economic factors to play a direct role in the receipt of cancer treatment.

Human papilloma virus (HPV) is associated with cervical cancers and the development of oropharyngeal carcinomas and a small minority of oral cavity cancers (27). There is an increased risk of tonsillar cancers (subsite of oropharynx) among husbands of women with a history of cervical dysplasia or cancer (28). As Inuit women have high rates of cervical cancers, one could expect to find HPV-associated head and neck cancer cases in the Inuit populations, but this needs to be investigated in future studies. HPV vaccines against cervical cancer could potentially prevent some oropharyngeal cancers, but this has not yet been proven. The HPV vaccine is part of the child vaccination program in Greenland.

To improve the survival rates of head and neck cancer in Greenland, focus should be on
prevention, early detection and rehabilitation. Lowering alcohol consumption and tobacco use is essential.

The establishment of a centralized register of family relations could enable a clinical screening of first-degree relatives. Studies investigating the genes associated with NPC are recommended to identify family members at risk. Prospective surveys on causes and distribution of patient and professional delay in Greenland are important to identify cultural, demographic and infrastructural issues.

There is a great need for follow-up programs adjusted to the conditions in Greenland. The use of new technologies such as telemedical consultations should be considered. Since 2005, ENT specialists based in Nuuk have organized follow-up procedures and enabled faster diagnosis of recurrences, and hopefully this will improve the treatment outcome in the future.

The survival of head and neck cancer patients in Greenland is low and has remained unchanged over the last 20 years. Demographic problems and the lack of specialists cause delays in treatment and inadequate follow-up on treatment complications. The improvements in the treatment of NPC and other head and neck cancers over the last decades are yet to be realized for the Greenlandic population.

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