Peer reviewed article

Undifferentiated carcinoma of nasopharyngeal type (UCNT): a Swiss single-institutional experience during 1990–2005

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Summary

Background: Nasopharyngeal carcinoma is a rare tumor entity in Switzerland. In contrast, it is endemic in Asian and African countries. Retrospective studies have been conducted in order to identify risk factors and prognostic determinants of nasopharyngeal carcinoma. Nonetheless, these trials were mostly conducted in regions with high prevalence for the disease and little is known about the risk factors and prognosis of nasopharyngeal carcinoma for a non-endemic population in Western Europe.

Methods: This retrospective trial was conducted to identify risk factors and prognostic determinants of nasopharyngeal carcinoma for a non-endemic population in Switzerland.

Results: Overall survival was 91%, 77% and 58% for one, three and five years, respectively. Factors with favourable prognostic value were concomitant radiochemotherapy regimens, photon radiotherapy, and a delay between diagnosis and first therapy session of less than ten weeks, respectively. Factors with unfavourable prognostic values were age over 65 years at time of diagnosis and nasopharyngeal carcinoma of WHO type I.

Conclusion: Risk factors, biological behaviour and survival are well comparable between endemic and non-endemic populations for nasopharyngeal carcinoma. Nonetheless, an aggressive diagnostic procedure and sophisticated interdisciplinary therapy are indispensable in order to achieve favourable outcome. Therefore, diagnosis and therapy of nasopharyngeal carcinoma in non-endemic populations should be limited to highly specialized tertiary centres.

Key words: nasopharyngeal carcinoma, non-endemic, prognostic factors, single-institution, survival

Introduction

Nasopharyngeal carcinoma (NPC), formerly known as Schmincke-carcinoma, is an uncommon tumor entity in Switzerland, and its age-adjusted incidence for both sexes is less than one per 100 000 per population and year. However, NPC occurs more often in Southern China and Africa with an incidence of 30–50 per 100 000 per population and year [1–5]. The reason for these geographical differences are not entirely known, but genetic susceptibility, ethnical background, and environmental factors are believed to play a key role in the cause and progression of the disease [6]. Furthermore, it is evident that the Epstein-Barr virus (EBV) plays a strong causal role in the pathogenesis of NPC [6].

No conflict of interest in relation to the article.

The location of NPC and its relationship with many delicate structures makes a complete surgical excision quite difficult. Furthermore, NPC is highly radiosensitive, and therefore, primary radiotherapy is the gold standard treatment for NPC with local control rates of 80% and 5-year survival rates of 70% [7, 8]. Due to the location of the tumor at the skull-base, fragile anatomical structures can be affected by radiotherapy, such as the brain stem, spinal cord, temporal lobes, eyes, middle and inner ears and parotid glands. Recently, intensity modulated radiotherapy (IMRT) seems to improve tumor coverage and less adverse effects than with conventional techniques are described [9, 10]. Several studies have reported the advantage of chemotherapy in combination with radiotherapy for advanced or metastatic NPC, in comparison with radiotherapy alone. The best regimen for combined chemo- and radiotherapeutic treatment, for example neoadjuvant, concurrent, adjuvant or, a combination of these, is still under inves-

tigation [11–17]. In T2b or more lesions and/or N-positive necks, concomitant chemoradiation is the standard. Furthermore, the disease seems to be diagnosed mainly at later stages with a cervical mass being the first clinical sign. Therefore, patients suffering from NPC should be investigated with aggressive diagnostic procedures, as patients with a short delay between diagnosis and treatment have a favourable outcome over patients with a delayed onset of therapy [18].

A large body of literature has been devoted to the elucidation of risk factors and prognosis of NPC [3, 19–22]. Nonetheless, most trials have been conducted in Asian and African populations where NPC is endemic. It is therefore not surprising, that most epidemiological and clinical data is available for patients from these endemic sites and the USA, where a lot of first-generation Chinese immigrants live.

The aim of this retrospective study was to characterize patients treated for NPC in a single institution in Switzerland and to identify important prognostic factors with an impact on overall survival for this non-endemic population.

Material and methods

Population and characteristics

Between 1990 and 2005, 34 patients with histologically proven NPC were treated at the Department of Otolaryngology, Oncology and Radio-Oncology at the Kantonsspital Lucerne, a tertiary hospital in Switzerland. This review was done in accordance to the guidelines of the local ethics committee.

From the total of 34 patients, 29 (85.3%) were Caucasians, three (8.8%) were North Africans, and two were originally from Asia (5.9%). All the patients were Swiss citizens.

Clinical and pathological workup

Workup included a full head and neck examination, routine blood chemistries, a flexible fiberoptic endoscopy and a computer-assisted tomography (CT), or in case of bone erosion a supplementary magnetic resonance imaging (MRI). Symptoms at the stage of presentation included ear involvement (e.g. otalgia, unilateral serous otitis media), an enlarging neck mass, epistaxis or nasal congestion. Histological diagnosis was performed from biopsy material of the primary site of the tumor and/or nodal excision tissue.

NPC was classified according to following World Health Oranisation (WHO) types: type I for keratinizing differentiated carcinoma, type II for non-keratinizing carcinoma, and type III for undifferentiated carcinoma. The distribution of the different histological subtypes in the current study is shown in table 1. All patients were staged according to the TNM- and the UICC 2002 staging sys-

Table 1

Distribution of histopathological types according to WHO classification.

	n =	%
WHO type I	**6**	**18%**
WHO type II	**4**	**12%**
WHO type III	**24**	**70%**

Table 2

Distribution of T- and N-stage according to TNM classification.

	N0	**N1**	**N2**	**N3**	**Total**
Tis	0	0	0	0	**0**
T1	4	3	0	0	**7**
T2	2	3	3	0	**8**
T3	2	0	8	0	**10**
T4	5	0	4	0	**9**
Total	**13**	**6**	**15**	**0**	**34**

Table 3

Distribution of Tumor stages according to UICC 2002 classification and status of patients.

		Status			
		alive n =	**dead n =**	**censored n =**	**Total n =**
UICC 2002	Stage 0	0	0	0	**0**
	Stage I	3	1	0	**4**
	Stage IIA	1	1	0	**2**
	Stage IIB	5	0	1	**6**
	Stage III	4	6	3	**13**
	Stage IVa	5	3	1	**9**
	Stage IVb	0	0	0	**0**
	Total	**18**	**11**	**5**	**34**

tem [23, 24]. The T- and N-Stage and the UICC 2002-tumor stages of the study population are shown in table 2 and 3.

Radiotherapy and chemotherapy

All patients received megavoltage radiation therapy. From 1990–1998, an *adjuvant* chemotherapy with cisplatin was offered. After 1998, all patients received a *concurrent* radiochemotherapy using cisplatin 100 mg/m^2 i.v. on day 1, 22, and 43.

With regard to radiotherapy, there was a change in the treatment technique: The first group was recorded between 1990 and 1998, the second group between 1998 and 2005. In the first period, the primary tumor and anterior neck were treated with strictly opposing photon fields (6 MV) up to a dose of 45 Gy, the posterior neck with a mixture of photons and electrons up to 9 Gy. The upper mediastinum was treated with anterior fields, blocking the spinal cord before 45 Gy. In the second period, a strictly 3-D planning was done with up to 8 photon fields (mediastinum included) and doses up to 50 Gy for the spinal cord, covering non-involved neck lymphatic with 54–56 Gy and involved lymphatic up to 60 Gy (or more) and the primary tumor up to 70–72 Gy (5–6 x2 Gy per week). Feeding tubes were routinely used during radiation in the second treatment period.

Follow-up and statistical analysis

All patients were followed for a minimum of three years after completion of radiation therapy. After treatment, the patients were followed bimonthly for the first year, quarterly for the second year, and biannually thereafter.

Overall survival rates were analyzed in relation to various patient and tumor characteristics. Patients in whom loco-regional control was not achieved at their first follow-up visit were considered as failures. Patients who died without evidence of loco-regional or distant disease were censored at the date of death.

Statistical analysis was carried out using SPSS 14.0 for Windows. Statistical comparisons were made using Mann-Whitney test for two independent variables. Chi-square test was applied where appropriate. The method of Kaplan and Meier was used to plot outcome. Survival analyses were performed using generalized Wilcoxon test (Gehan method). A p-value of less than .05 was considered to be statistically significant.

Results

Patients

Between 1990 and 2005, a total number of 34 patients (24 males, 10 females; sex ratio of 2.4:1 ($p < 0.05$)) were evaluated for a previously untreated NPC. The mean age of the patients at the time of diagnosis was 54.4 years (range 20.2–84.1 years).

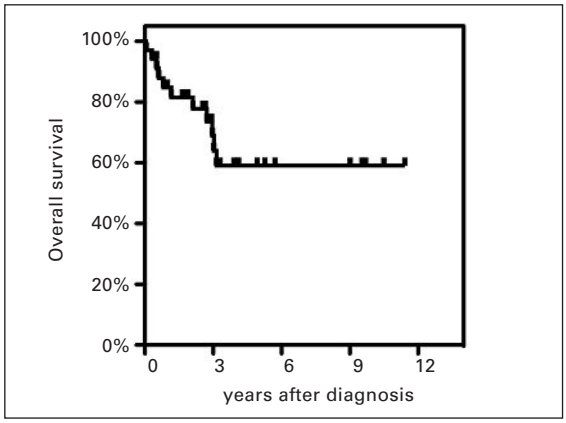


Figure 1
Overall survival.

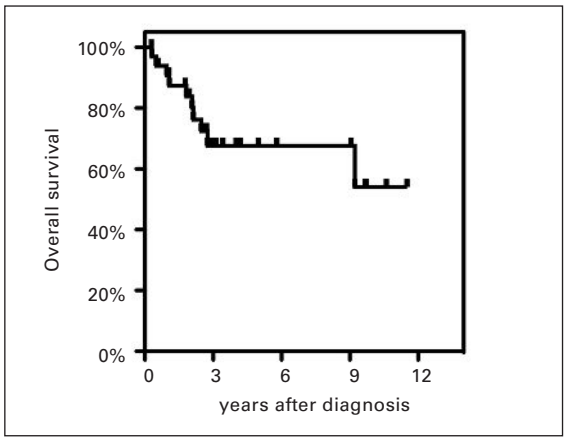


Figure 2
Disease-free survival.

Histological assessment

The most prevalent WHO histology type was type III (n = 24, 71%), followed by WHO type I (n = 6, 18%) and WHO type II (n = 4, 11%) ($p < 0.001$).

Staging

The most prevalent T-stage was T3 (n = 10, 29%). Nodal staging was performed by clinical examination and imaging (CT or MRI). A total of 21 (62%) patients presented with positive neck nodes. The most prevalent N-stage was N2 (n = 15, 44%). The most prevalent tumor stage, according to UICC 2002, was stage III (n = 13, 38%).

Follow-up

The median follow-up time among the 18 living patients was 3.72 years (range: 1.05–11.51 years). Five patients were discarded due to loss of follow-up. The median follow-up time among five censored patients was 2.70 years (range: 0.54–10.24 years). 14 patients of the latter group (77.8%) had a minimum of 2-year follow-up, six (33.3%) had at least 5 years of follow-up, and two (11.1%) had more than 10 years of follow-up.

Survival rates

For the entire population, the 1-, 3- and 5-year overall survival rates were 91%, 77% and 58%, respectively (fig. 1). A total of eleven patients died during the observation period. Seven of these patients died of nasopharyngeal cancer, four patients died of intercurrent diseases. Deaths due to secondary primaries or therapy complications were not reported. Overall, 18 patients are alive

and disease-free at the end of the study period. Five patients were discarded due to loss of follow-up.

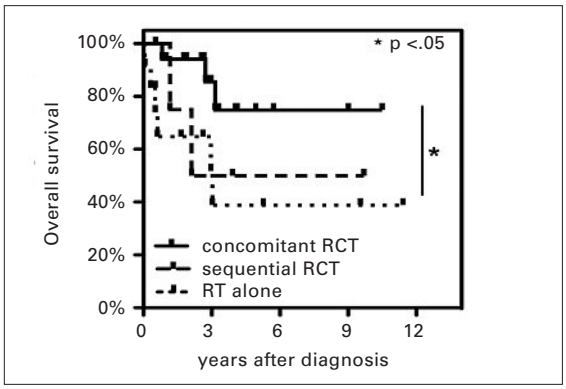
The actuarial tumor control rates for the whole series were 81%, 71%, and 71% at 1-, 3-, and 5 years, respectively (fig. 2). A total of ten patients suffered from tumor recurrence with a median time to recurrence of 0.73 years (0.00–9.23 years). Eight of these failures presented as concomitant local, neck and distant failure, one patient presented with isolated local failure and one with isolated neck failure. Three of these failures appeared within one year of therapy and nine within three years. One patient suffered from distant recurrence after more than five years of follow-up.

Impact of different parameters on survival

Chemotherapy

The form of combined radiochemotherapy regimen was found to be a strong determinant for survival: During the years 1998–2005, all 17 patients had a performance status that allowed concomitant radiochemotherapy, whereas during 1990–1998 five patients were treated with sequential radiochemotherapy (adjuvant chemotherapy) and 12 patients with radiotherapy only (six patients with T1/2 N0 lesions, and six patients with a bad performance status). The survival rates at 1-, 3- and 5 years were 100%, 94% and 73% and 100%, 50% and 50%, and 74%, 64%, and 38% for concomitant radiochemotherapy, sequential radio-chemotherapy, and radiotherapy alone, respectively ($p < 0.05$ for concomitant radiochemotherapy vs radiotherapy alone in pair wise comparison) (fig. 3).

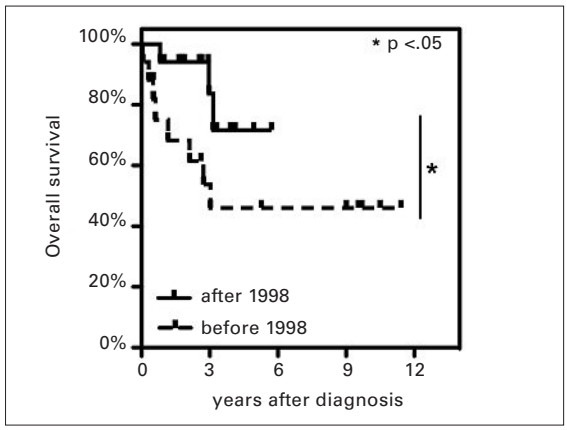
Figure 3
Therapy regiment.



Radiotherapy

The form of the radiotherapy regimen was also found to be a determinant for survival: 17 patients received radiotherapy treatment before 1998 compared to 17 patients with radiotherapy treatment after 1998. Analysis of deaths in the two groups revealed a higher proportion of events in the group treated before 1998 (8 events compared to 3 events, $p < 0.05$). The survival rates at 1-, 3- and 5 years were 81%, 61% and 45% for treatment before 1998, compared to 100%, 93%, and 70% for treatment after 1998 ($p = 0.058$) (fig. 4).

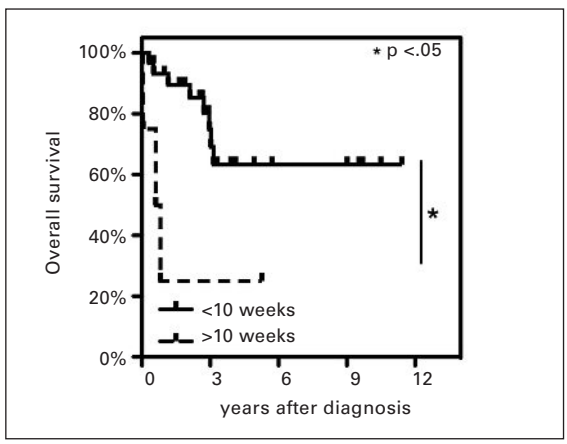
Figure 4
RT regiment.



Time to treatment

30 patients (81%) received the first therapy session within ten weeks after diagnosis with a survival rate of 93%, 85%, and 62% at 1-, 3- and 5 years compared to four patients (12%) where treatment was delayed by more than ten weeks after diagnosis with survival rates of 75%, 25%, and 25% at 1-, 3- and 5 years ($p < 0.05$) (fig. 5).

Figure 5
Time to treatment.



WHO histology type

The WHO histology type of the tumor was another strong determinant for survival. The survival rates at 1- and 3 years were 50% and 33%, and 100% and 71%, as well as 100% and 84% for tumors of WHO type I, II and III, respectively. (5-year survival rates were not available due to short follow-up period in the group of WHO type II). Pairwise comparison revealed significant differences in survival rates between type I and III ($p < 0.05$) (fig. 6).

Age

The patient's age group at the time of diagnosis (<45 years, n = 10; 45–65 years, n = 13; >65

Figure 6
WHO type.

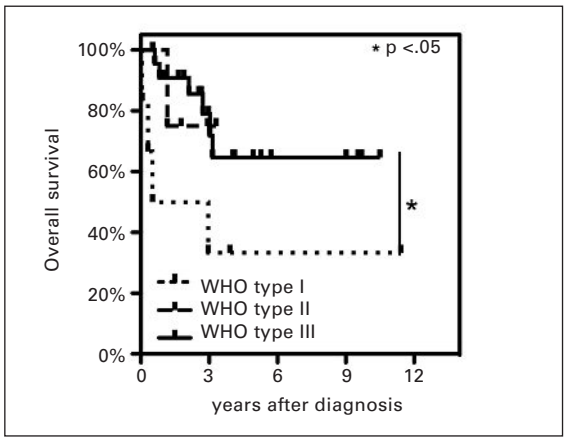
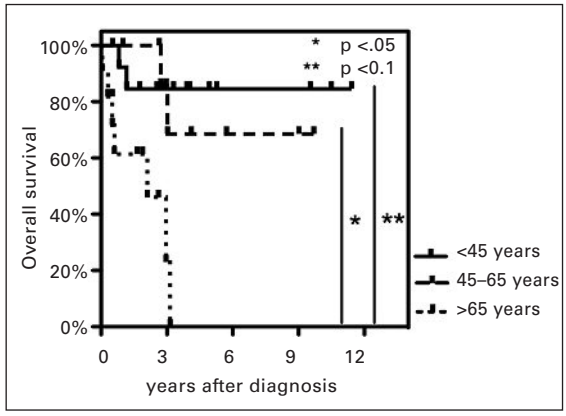


Figure 7
Age groups.



years, n = 11) was found to be further determinant for survival. The survival rates at 1- and 3 years were 100% and 100%, and 100% and 84%, as well as 71% and 43% for patients less than 45 years, 45 to 65 years and patients over 65 years, respectively (5-year survival rates were not available due to short follow-up period in the latter group). Survival rates were significantly decreased in the age group older than 65 years in pairwise comparison with the group younger than 45 years at diagnosis ($p = 0.006$), and the group 45–65 years ($p = 0.023$), respectively (fig. 7). Survival rates were equal in both male and female patients suffering from NPC. Survival rates were 96%, 74%, and 59% for males, and 80%, 80%, and 55% for females for 1-, 3- and 5-year overall survival, respectively.

TN-stage

In order to compare the results with those of other published series, integrated T- and N-stage categories were used [25, 26]. Patients in these groups were further characterized as to the absence (N0) or presence (N+) of cervical metastases at time of treatment. Three-year overall survival rates for the mentioned groups were 83%, 83%, 86% and 60% for the groups T1–2 N0, T1–2 N+, T3–4 N0, T3–4 N+, respectively.

Discussion

NPC is a unique entity in head and neck malignancies: its sensitivity to radiotherapy and chemotherapy and its survival characteristics render the disease inimitable. Most of the literate arises from Asia, as described previously. In the current work, we describe important prognostic factors for patients suffering from NPC in a non-endemic region. The limitation of this work is the small sample size and its retrospective character, however, the study population was found to be representative in means of age, sex, histology type, and tumor stage compared to other epidemiological reports for NPC in high-prelevance regions such as Asia and Africa. Furthermore, recurrence rates and survival after standard treatment in our series was comparable with reports from endemic sites, indicating that NPC at non-endemic sites share similar biological features compared to the better understood disease from endemic regions [5, 21, 26].

We were able to clearly identify important prognostic factors for NPC in this single-institutional treated cohort. Factors for unfavourable prognostic behaviour were increased age at time of diagnosis, advanced TN-stage and NPC WHO type I. The latter finding correlates with the results found in a European study featuring ten countries and involving 2.054 patients: the overall 5-year survival rates for differentiated and undifferentiated were 40 and 50%, respectively [27]. Venkitaraman R [28] found that poorly differentiated carcinoma (WHO type III) fared significantly better than carcinoma with squamous histology (WHO type I and II), with 5-year disease-free survival of 56% and 44%, respectively. In our work, the disease was diagnosed at later stages, with a cervical mass being the most common presentation. This is in correlation with the findings of d'Espiney Amaro C et al. [29]. Other unfavourable prognostic factors, such as a poor performance status [30], different genetic mutations [31] were not analyzed due to the retrospective character of this study.

On the contrary, important prognostic factors for favourable prognosis were identified: a short interval between time of diagnosis and onset of radiotherapy was found to be a strong and important determinant for survival. This correlates with previous work from Kwong DL et al. [18] for an endemic population and highlights the urgency for aggressive diagnosis and sophisticated therapy at highly specialized institutions. In this work, patients with delayed time to treatment were statistically not significantly suffering from advanced disease compared to the other group. Furthermore, photon radiotherapy regiments with strict 3-D plans were found to be strongly superior over older radiation regiments. The dose distribution of modern photon radiotherapy regiments is much more homogeneous, especially in the posterior

deep part of the neck and allows higher total dose in primary tumour region and/or neck nodes. Therefore, the total dose in macroscopic tumor regions could be increased to nearly 70 Gy, without experiencing increased complication rates of neurological late toxicity of the spinal cord. Recent studies show improved tumor coverage and spared normal tissues by using IMRT instead of conventional techniques [9, 10]. In our study, the use of concomitant chemotherapy showed significantly better survival rates than sequential chemoradiotherapy or radiotherapy alone. Other authors have also reported the same results [32, 33]. However, in our series, the benefit for survival in figure 3 was twofold: Firstly, new imaging technologies render a better definition of the lesion in the group treated during 1998–2005 compared to the older group. The primary is optimally assessed with CT and MR imaging for staging. Intracranial invasion should particularly be assessed with contrast MR imaging. Recent studies advocate PET/CT and head-and-neck MRI as initial radiographic workup [34]. Secondly, and even more important, patients in the group 1998–2005 were given a total dose of 70 Gy to the primary, whereas the patients within the group 1990–98 were only given a total dose of 45 Gy. A dose of 70–72 Gy to the primary tumor and metastatic lymph nodes seems to be widely accepted. In case of residual primary lesion, a boost dose of 8–24 Gy will be added [35]. However, higher radiation doses contribute to a higher incidence of radiation-related complications. Whether chemotherapy should be performed by using cisplatin only, or in combination with another agent, since it shows good curative results and less adverse effects, remains unclear. It is evident that concurrent chemotherapy increases the morbidities, such as grade 3–4 hematologic and mucosal toxicities [28]. The role of EBV-associated with NPC is manifold: there are geographical variations in the prevalence of EBV-associated NPC. There is an intermediate risk of NPC in southern France where a lot of migrants of Maghrebian origin live, while the risk of NPC is low in Northern Europe, such as Scandinavia [36]. The positive role of EBV associated with increased survival [37] was not further analyzed in our small samples size due to its retrospective character.

Conclusion

In conclusion, we identified important prognostic factors in terms of survival in a small patient population suffering from NPC treated in a single institution in a non-endemic site. Risk factors, biological behaviour and survival are comparable between endemic and non-endemic populations for NPC. Nonetheless, aggressive diagnostic procedures and sophisticated interdisciplinary therapy regimes performed by experienced otorhinolaryngologists, oncologists and radiooncologists are absolutely mandatory in order to achieve favourable outcome. Therefore, we suggest that diagnosis and therapy of NPC in non-endemic populations should be limited to highly specialized tertiary centres.

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