

ORIGINAL ARTICLE

Impact of different therapeutic regimens on survival of patients with nasopharyngeal carcinoma

Nikolaos Christodouloupoulos¹, Nicholas Mastronikolis¹, Evangelos Tsiambas², Eleni Jelastopulu³, Despoina Spyropoulou⁴, Spyridon Lygeros¹, Gerasimos Danielides¹, Stylianos Mastronikolis⁵, Theodoros A. Papadas¹

¹Department of Otorhinolaryngology-Head and Neck Surgery, University of Patras Medical School, Patras, Greece; ²Department of IHC & Molecular Biology, 401 GAH, Athens, Greece; ³Department of Public Health, School of Medicine, University of Patras, Patras, Greece; ⁴Department of Radiation Oncology, Medical School, University of Patras, Patras, Greece; ⁵Department of Medicine, School of Health Sciences, University of Crete, Heraklion, Greece.

Summary

Purpose: Nasopharyngeal carcinoma (NPC) demonstrates specific histo-genetic features that affect its biological behaviour. Our aim was to investigate the correlation between different therapeutic approaches and survival of patients with NPC in southwestern Greece based on specific clinico-pathological features.

Methods: Seventy-two NPC patients (n=72) were treated between 1990 and 2014 at the University Hospital of Patras. Patient demographics, tumor histology, use of tobacco and alcohol, exposure to mutagenic agents, chosen treatment and survival were recorded. All patients were treated with radiotherapy (RT), chemotherapy, surgery or their combinations.

Results: In the patients who used immobilization mask during RT, the 5-year survival rate and overall survival were higher than the rest of patients (57% and 6 years vs. 13.6% and 3.36 years, $p=0.0001$, respectively). RT with mask combined with chemotherapy increased survival rates compared to RT without chemotherapy conventional regimen ($p=0.0001$). Additionally, patients who received chemotherapy demonstrated a 5-year survival of 51.6% compared to

those without chemotherapy (11% $p=0.0014$). (*The 5-year survival rate group of patients refers to the percentage of people who will be alive 5 years after diagnosis. It does not include those who die from other diseases. Sometimes, this includes all people with a specific cancer type. Researchers call this an overall rate. In contrast, overall survival provides information for the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the overall survival is one way to see how well a new treatment works).

Conclusions: In the majority of examined NPC cases treated with the use of immobilization RT mask along with chemotherapy, a significantly better prognosis compared to conventional RT-chemotherapy treatment was observed. Thus, chemotherapy offers an advantage to patient survival as an adjuvant treatment regimen in conjunction with RT.

Key words: nasopharyngeal carcinoma, radiotherapy, chemotherapy, epidemiology, survival

Introduction

Nasopharyngeal carcinoma (NPC) is a unique head and neck epithelial malignancy arising from the nasopharynx at the most superior part of pharynx. NPC is highly invasive and usually develops

metastasis with clinical and epidemiologic characteristics distinct from those of other head and neck epithelial cancers. Every year approximately 86,500 new cases of NPC are diagnosed and about

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD. 17 Patriarchou Grigoriou E' Street, Ag. Paraskevi, 153 41 Athens, Greece.

Tel: + 30 6946939414, E-mail: tsiambasecyto@yahoo.gr

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50,000 deaths occurred because of it [1]. NPC is a rare entity in Western Europe and the United States of America with a probability of occurrence of 0.5-2/100,000 people/year, while it is much higher in South China, reaching 25/100,000 people/year [2]. Areas such as Southeast Asia, the Middle East, North Africa and the Arctic have an intermediate incidence. Populations migrating from high risk areas for NPC to low risk areas still have an increased incidence, but this has been significantly reduced over the past thirty years, mainly due to changes in lifestyle and eating habits [3]. The likelihood of NPC occurrence is greater in males than in females with a ratio of 3:1, respectively. In high-risk populations, the incidence of NPC is greatest at the age of 40-59 years. There has also been a significant potential for increased incidence for adolescents and young adults in areas such as Southeast Asia, South Africa and the United States. In most low-risk populations and the likelihood of NPC increases proportionally with age. Epidemiological studies have demonstrated that the underlying pathogenesis is multifactorial including alcohol consumption, smoking, food containing nitrosamines (i.e. salted food) [4], Epstein-Barr virus infection (its genome can be identified in 80% of the cases) and genetic predisposition including specific HLA types and microRNAs [5,6]. The World Health Organization (WHO) classified NPC into keratinizing and non-keratinizing squamous cell carcinoma (SCC), the latter being subdivided into differentiated and undifferentiated types [7]. Currently, an additional category has been included, as basaloid SCC. Non-keratinizing carcinoma accounts for 75%, while keratinizing for 25% of the cases of NPC. The specific clinical and biological profile of NPC, its difficult anatomic location and the fact that it is highly sensitive to radio-chemotherapy, limit the role of surgery as a therapeutic option. Thus, the mainstay of treatment is based on external beam RT with or without chemotherapy according to the disease stage. During the last two decades advances in radiotherapy techniques have allowed precision in tumor targeting, both increasing the dose delivery at the tumor and reducing the side

effects from irradiation of uninvolved tissues [8]. The timing of the chemotherapy has been a matter of significant debate; however, the use concomitant platinum-based chemo-radiation favors the prognosis of advanced disease [9]. Important prognostic factors for survival are stage, WHO type and age at diagnosis [10]. In the current study we focused on the impact of different treatment strategies in NPC patients' survival in the non-endemic area of South-Western Greece.

Methods

Patients

This clinical retrospective study was conducted at the University Hospital of Patras, Greece, which is the main tertiary care unit of the Southwestern Greece. The cancer registry maintained by the Department of Pathology was retrospectively reviewed from 1990 up to 2014. Seventy-two patients (72) with histologically proven NPC and all clinically staged according to WHO Classification were included in the study. The study was conducted according to World Medical Association Declaration of Helsinki guidelines. Patients had not received previous treatment, had no distant metastases and were treated with curative intent. All of them underwent a thorough clinical examination, fiberoptic nasopharyngoscopy and biopsy for histopathological diagnosis. A complete blood count and biochemical profile, CT and/or MRI studies were also performed. Patients were categorized according to the WHO and TNM classification systems based on their medical reports and radiological images [7, 11].

Concerning therapeutic strategies applied in the examined NPC patients' group, all patients were treated with RT, chemotherapy, surgery or their combinations. In fact, all patients except one received RT (71/72) with or without the use of immobilization masks. These masks are made of special thermoplastic material and applied when the patient is going to be irradiated in mobile areas of the body (e.g., head and neck). They intend to immobilize the irradiated areas enhancing the precision of radiation beam to the target throughout the course and also to reduce the possibility of healthy tissue irradiation. Irradiation with the immobilization mask was performed in 45 patients (72.6%) while the remaining 26 (27.4%) were irradiated without a mask. The mean total radiation dose given to patients was

Table 1. Treatment methods

	Radiotherapy (total n=71)	
	Without mask (n=26)	With mask (n=45)
Chemotherapy (n=66)	13	38
Surgery (n=10)	2	1
Chemotherapy plus surgery (n=7)	4	3
No chemotherapy (n=6)	5	1
No surgery (n=62)	2	2

about 6.102 Gy (max 7.625 Gy -min 3,184 Gy) and was administered on a 7-week period, i.e. 35 sessions with an average dose per session of 180 Gy. In addition, 66 (90.3%) of the patients received chemotherapy either in combination with RT or not, while 6 patients (9.7%) did not receive chemotherapy. Chemotherapy included cisplatin in combination with 5-fluorouracil. After therapy, all patients were monitored regularly for recurrence at our outpatient clinic. Therapy-based patients' categorization is demonstrated in Table 1.

Statistics

All data concerning the treatment regimens were correlated with patients' survival. The analysis was performed using the Kaplan-Meier and log rank (Mantel-Cox) test with 95% confidence intervals (95% CI). Overall survival was defined as the time from the day of the histological diagnosis to the last follow-up visit or patient's death. The Kolmogorov-Smirnov analysis was used to verify that the data is in a normal distribution. Student's t-test was also used to compare data between two groups and the chi-square test (χ^2) when considered as necessary. Statistical analyses were performed using the SPSS statistical program (IBM SPSS Statistics v20, Chicago, IL, USA) and Prism v5.0.0 (GraphPad, San Diego, CA). A value $p < 0.05$ was considered statistically significant.

Results

From the 72 patients with NPC presented in the Otorhinolaryngology Department in a 25-year period, 57 were male (79.2%) with an average age of 56.7 ± 15 years (85-18) and 15 were women (20.8%) with an average age of 52.9 ± 14.9 years (73-16). Mean age was similar according to gender ($p = 0.38$). Smokers accounted for 65.3% of all patients. Specifically, 53.3% of women and 68.4% of men were smokers with average pack-years of 49.84 and 83.95, respectively. The main presenting symptoms were neck lump (45.8%; 33/72 patients),

epistaxis 22.2% (16/72), serous otitis media 19.4% (14/72), nasal obstruction 5.5% (4/72), facial pain and otalgia each one at 4.2% (3/72) and trigeminal neuralgia or headache 2.7% (2/72). In terms of alcohol consumption, women were consuming much less (6.6%) in comparison with men (42.1%). Twenty-three out of 72 patients (31.9%) were exposed to various environmental factors, which are thought to play an important role in carcinogenesis. Such factors were mainly the pesticides (21 patients – all farmers), exhaust fumes (1 patient) and ammonia (1 patient); patients were exposed to these factors because of their work. According to the TNM system, 19 out of 72 patients (26.4%, 13 men and 6 women) were diagnosed with NPC stage I, 5 patients (6.9%, 3 men and 2 women) with stage II, 31 patients (43.1%, 25 men and 6 women) with stage III cancer and 17 patients (23.6%, 16 men and 1 woman) with stage IV cancer.

We observed that there was a very large difference in survival among the groups: there were 19 (38.8%) deaths in the irradiation mask group vs. 18 (81.8%) deaths in non-mask group. The median survival of patients using mask during irradiation was 6 ± 2.28 , while non-masked patients had median survival of 3.36 ± 2.65 years. Comparison of the median survival of the two groups showed statistically significant difference indicating that the use of the mask increased the life expectancy by 79%. Finally, a 5-year survival rate of 13.6% was observed for patients without mask, while in masked patients it was 57.1%. To evaluate the impact of chemotherapy in the examined patients, they were divided into groups depending on whether or not they received chemotherapy and what effect chemotherapy had on their survival. A statistically significant difference between the patients who received and those who did not receive chemotherapy was detected ($p = 0.0014$) (Figure 1A-C). Also, the 5-year survival

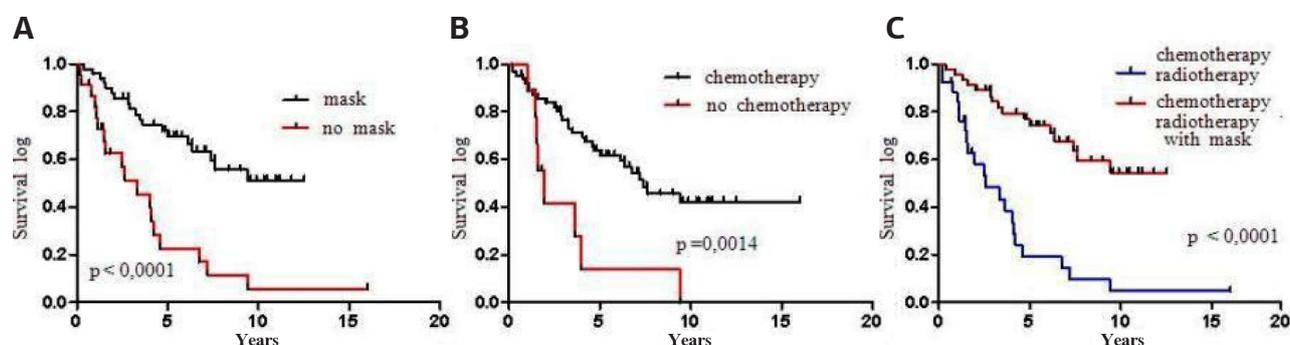


Figure 1. Combined overall survival analyses of the examined NPC patients. **A:** Patient survival using irradiation mask (black) when irradiated were compared to those who did not use a mask (red). **B:** Comparison of overall survival between patients receiving chemotherapy (black) or not (red). **C:** Comparison of overall survival between subjects who received either radiotherapy or chemotherapy or a combination of them (blue) to those who received radiotherapy with mask and chemotherapy (red).

rate in patients who did not receive chemotherapy was 11%, while in those receiving chemotherapy this figure was 51.6%. Thus, chemotherapy offers a significant advantage to patient survival.

We then tested the overall survival of patients who received RT using mask and chemotherapy compared to those who received either chemotherapy or non-masked RT or a combination of them. We noted that patients who had a combination of RT with mask and chemotherapy (group 1) had better survival than those receiving either mask-free RT or chemotherapy (group 2) or a combination of them. The 5-year survival rate in group 1 was 61% (28/46), while in group 2 a dramatic decrease in the 5-year survival to 11.5% was noted (3/26).

Discussion

Seventy-two patients were enrolled in this study with the most common symptoms being neck lymphadenopathy (45.8%) epistaxis (22.2%), otitis media with effusion (19.4%), nasal congestion or obstruction (5.5%), and severe pain in the head and neck area (6.9%). The above symptoms are among the most common and have been found with similar frequency in other studies [12]. The mean age of our NPC patients was 55.9 years and it was observed that those who were below that mean had a better overall survival than those over that age. This observation is confirmed by another study with patients from USA and is attributed to increased toxicity of chemotherapy and RT in elderly patients compared to younger patients [13]. Toxicity such as of leucopenia and gastrointestinal complications are better tolerated from younger patients who can easily recover. Male patients were 79.17% (57/72) and women 20.83% (15/72); the men/women ratio was 3.8:1.

After diagnosis, NPC patients have been treated to inhibit tumor growth and, if possible, to completely eliminate it. The first treatment line for NPC includes primary tumor RT with a good 5-year survival along with neck irradiation to prevent or treat metastases in the neck lymph nodes [14]. Most patients also received a chemotherapy, which has been shown to increase OS of patients [15]. In particular, patients enrolled in the study received a total radiation dose of 6.102 Gy on average over a 7-week period and the average dose per session was 180 Gy. The irradiation of the patients was done either using a mask (72.6%) or without it (27.4%). At the same time, patients received cisplatin in combination with 5-fluorouracil (90.3%) while 9.7% of patients did not receive chemotherapy. Finally, 10 patients with neck nodal metastases were surgically treated since neck dissection has

been shown to result in a higher 5-year survival rate. Depending on the treatment followed, it has been shown that there is also an effect on the OS of patients [16].

In this study, the potential treatment schemes received by the patients were: RT in combination with chemotherapy (23.6%), or not (6.9%), and RT with immobilization mask in combination with chemotherapy (63.9%) or without (4.2%). Initially we observed that the use of chemotherapy offers better 5-year OS to all patients regardless of stage, which is also confirmed by other studies [8]. Similarly, it was observed that the use of immobilization mask during RT offered the patients a better 5-year OS at all stages of disease. Finally, patients receiving chemotherapy in combination with RT using a mask in all stages exhibited statistically significant better 5-year OS. The above fact suggests that the best treatment for NPC is radiotherapy using a mask in combination with chemotherapy, as confirmed by similar studies [17-19].

In order to determine the survival advantage of each treatment, we divided patients according to the stage of disease and the treatment they received. It was noted that in patients with WHO stage II and III disease, who were the major part of our cohort, the use of a radiation immobilization mask in combination with chemotherapy offers better 5-year and overall survival compared to the rest of patients receiving non-masked radiotherapy with or without chemotherapy. For WHO stage I, the small sample of patients (n=5) did not allow a reliable analysis for definite conclusions. Following a similar reasoning for the TNM system, it was observed that for stage I and III patients the use of the radiation immobilization mask in combination with chemotherapy offered to patients a better 5-year and overall survival compared to the patients received radiation therapy without mask, with or without chemotherapy. Stage II patients were very few and could not be used for survival's statistical analysis. Stage IV patients had no difference in survival whether using the immobilization mask or not, most likely because the disease had evolved sufficiently and could not be effectively treated.

The precise placement of the patient, with no deviations of even a few millimeters, during the RT session has proven a major issue in order to have reproducibility in the radiation performance at the point where the tumor develops, adding thus to the effectiveness of treatment. Novel molecular data regarding the genetic landscape of NPC rise and development and also the application of sophisticated and accurate diagnostic and treatment methods are promising aspects for targeted approaches [6,20].

In conclusion, we observed that patients with NPC at early stages had a better overall survival when RT was delivered using an immobilization mask in combination with chemotherapy compared to the other patients who received radiotherapy without a mask, with or without chemotherapy. The survival advantage observed in the above-mentioned patients is probably due to the fact that the radiation is delivered at each session on the affected site without deviations, resulting in a better disease treatment. In cases where no

mask was used, there might be a deviation of the point at which radiation targeted due to involuntary movements of the patient during the session and ultimately leading to less effective treatment of disease.

Conflict of interests

The authors declare no conflicts of interest. No financial support was granted.

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