ORIGINAL ARTICLE

Prognostic Factors and Outcome for Nasopharyngeal Carcinoma

Terence P. Farias, MD; Fernando L. Dias, MD; Roberto A. Lima, MD; Jacob Kligerman, MD; Geraldo M. de Sá, MD; Mauro M. Barbosa, MD; Fernando B. Gonçalves, Jr, MD

Background: Nasopharyngeal cancer (NPC) is a distinct form of cancer of the upper respiratory or digestive tract in which the epidemiologic features, origin, histopathologic types, treatment, and prognosis are different from those associated with other malignant neoplasms of this anatomical area. Recent publications have demonstrated the advantage of aggressive multimodality treatment for advanced NPC.

Objectives: To evaluate the results of standardized treatment of NPC during 11 years and to identify pertinent factors for clinical outcome.

Methods: Between January 1, 1989, and December 31, 2000, 173 patients with newly diagnosed NPC were treated at Instituto Nacional de Cancer. Clinical records and radiographic studies of the patients were retrospectively reviewed. Documented data of the initial presenting symptoms, head and neck examination, radiotherapy protocols, chemotherapy regimens, and surgical technique were analyzed. To determine important prognostic factors, we correlated survival rates with age, clinical stage, tumor extent, histopathological type, and therapeutic approach. The major end point used for assessment was relapse-free survival. Survival curves were estimated by the Kaplan-Meier product-limit method. Multivariate analysis was performed using the Wilcoxon signed rank and Cox proportional hazards regression tests.

Results: Most patients (88.5%) had locoregional advanced disease, mostly (53.4%) of the nonkeratinizing subtype. Forty-seven percent of patients had clinical cervical nodal metastases at first consultation. Gross extension of the primary tumor involving the facial bones and skull base was observed in 39.3% and 20.8%, respectively. Just under 75% of patients were treated with radiotherapy (median dose, 6600 cGy), and 25.4% underwent concomitant chemoradiotherapy with adjuvant chemotherapy (cisplatin plus 5-fluorouracil) (median dose, 6800 cGy). The 5-year disease-specific survival for the 173 patients was 32.3%. The disease-specific survival for the radiotherapy group was 22.5%, compared with 61.4% for the chemoradiotherapy plus adjuvant chemotherapy group ($P=.004$). Factors associated with adverse outcomes were age older than 40 years at treatment ($P=.001$), advanced TNM stage ($P=.002$), skull base invasion ($P=.004$), and facial bone invasion ($P<.001$).

Conclusions: Compared with radiotherapy alone, concomitant chemoradiotherapy with adjuvant chemotherapy improved the treatment outcome of patients with NPC treated in our institution. Advanced age, local extension, and stage of the disease adversely affected the prognosis in our patients. Compared with reirradiation, salvage brachytherapy and radical neck dissection for local and regional residual or recurrent NPC were associated with increased rates of locoregional control and survival.

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From the Department of Head and Neck Surgery, Hospital do Câncer I, Instituto Nacional de Cancer, Rio de Janeiro, Brazil. *The authors have no relevant financial interest in this article.*

NASOPHARYNGEAL carcinoma (NPC) is prevalent among populations originating from southern China and their descendants who have emigrated to other parts of the world.[1]

Its epidemiologic features, origin, histopathological types, presentation, treatment, and prognosis differ from those of malignant neoplasms occurring in other sites of the aerodigestive tract.[2-6] Unlike most other squamous cell carcinomas of the head and neck, local recurrence and distant metastases are responsible for most of the failures after therapeutic attempts.

Contemporary major challenges in the treatment of NPC, particularly in its advanced stages, are how to improve locoregional control and prevent the development of distant metastases.[4-7] Recent evidence has demonstrated the advantage of concurrent chemoradiotherapy plus adjuvant chemotherapy (CCRT) over radiotherapy (RT) alone in the treatment of NPC.[7]

This study retrospectively evaluated the association of selected prognostic

factors with disease-specific survival rates and analyzed the effectiveness of treatment modalities used for the treatment of NPC.

METHODS

Between January 1, 1989, and December 31, 2000, 173 patients with newly diagnosed NPC were treated at Instituto Nacional de Câncer. All patients had histologically proven NPC. The pretreatment workup included complete physical examination, endoscopic examination of the nasopharynx, hematologic and biochemistry profile, computed tomography of the nasopharynx and neck, and chest x-ray films.

Clinical records and radiographic studies of the patients were retrospectively reviewed. Documented data of the initial presenting symptoms, head and neck examination, RT protocols, chemotherapy (CT) treatment regimens, and surgical techniques and approaches were analyzed.

To determine important prognostic factors, we correlated survival rates with age, clinical stage, tumor extent, histopathological differentiation, and therapeutic approach. The 2 age groups were subjects aged 40 years or younger vs those older than 40. Disease was staged according to the American Joint Committee on Cancer and Union Internationale Contre le Cancer 1997 TNM classification and stage grouping. The extent of the tumor at presentation was determined by radiological studies and clinical findings, searching for such characteristics as skull base invasion, facial bone invasion, and regional cervical metastases. Pathological differentiation was classified as 1 of 2 World Health Organization types: type I, keratinizing squamous cell carcinoma; or type II, nonkeratinizing carcinoma, including differentiated nonkeratinizing carcinoma and undifferentiated cancer, sometimes called lymphoepithelioma.

From 1989 to 1998, the treatment used was RT with doses ranging from 6250 to 7100 cGy (median, 6600 cGy) to the primary tumor and the neck in 180 to 200 cGy fractions per day 5 days a week. Since 1998, RT has been administered concomitantly with cisplatin, 25 mg/m^2 of height, on days 1 through 4, given by infusion on days 1, 4, and 7 of RT, followed by another 3 cycles of adjuvant CT starting at week 11 after the beginning of RT (cisplatin, 20 mg/m^2 per day, and 5-fluorouracil, 1 g/m^2 per day, on days 1-4 every 28 days). Concurrent RT was administered 5 times a week at 200 cGy per day up to a dose of 7000 cGy. The accumulated dose given to the primary tumor and involved neck lymph nodes ranged between 6600 and 7000 cGy.

The criteria for response, based on clinical, endoscopic, and radiological examination, were as follows: a complete response was defined as complete regression of all evidence of disease; a partial response required a 50% decrease in the summed products of the 2 largest perpendicular diameters of all measurable lesions; and stable disease was defined as no significant change in tumor size. The response after RT was assessed 3 months after completion of the treatment. Patients with a complete response to treatment were followed up every 3 months during the first year, every 4 months during the second year, and every 6 months during the next 3 years. After the fifth year of treatment, follow-up clinical examinations were made yearly.

The major end point used for assessment in this analysis was disease-specific survival. The survival curves were estimated by the Kaplan-Meier product-limit method.[8] The difference between survival curves was tested using the Mantel-Cox log-rank test. The stepwise inclusion procedure was used to determine statistically significant prognostic factors. The multivariate analysis was performed using the Wilcoxon signed rank and Cox proportional hazards regression tests.

Table 1. Stages at Presentation

Stage*	No. (%)
I	2 (1.2)
IIa	7 (4.1)
IIb	11 (6.4)
III	69 (39.9)
IVa	36 (20.8)
IVb	48 (27.7)

*American Joint Committee on Cancer and Union Internationale Contre le Cancer TNM classification. Percentages do not sum to 100 because of rounding.

RESULTS

There were 136 male (78.6%) and 37 female (21.4%) patients (median age, 49 years [range, 13-77 years]); most (71.1%) of them were of white race. Eighty-seven (50.3%) of these patients had a history of tobacco consumption, and 77 (44.5%) had a history of alcohol consumption.

Most (88.5%) of these patients had locoregional advanced disease, mostly (53.4%) of the nonkeratinizing carcinoma subtype. Forty-seven percent (82/173) of patients had clinical cervical nodal metastases at first consultation. Gross involvement of facial bones was observed in 68 patients (39.3%) and gross invasion of the skull base in 36 (20.8%). Histologically, 81 (46.8%) patients had type I keratinizing squamous cell carcinoma, and 92 (53.2%), type II nonkeratinizing squamous cell carcinoma. Patients' disease stages are given in **Table 1**.

The outcome of patients with NPC in our institution was analyzed at the end of December 2000, after a minimum follow-up of 16 months and a median follow-up of 45 months (RT group median, 21 months; CCRT group median, 19 months).

One hundred twenty-nine patients (74.6%) were treated with RT (median dose, 6600 cGy), and 44 (25.4%) underwent CCRT (cisplatin plus 5-fluorouracil; median dose, 6800 cGy). Fifty-seven patients (33.0%) had local residual disease or recurrence of their tumors, and 27 (15.6%) had regional nodal residual disease or recurrence of their metastases. Distant metastases were observed in 34 patients (19.7%), including metastases to the bones in 23 (67.7%), lungs in 7 (20.6%), and brain in 4 (11.8%).

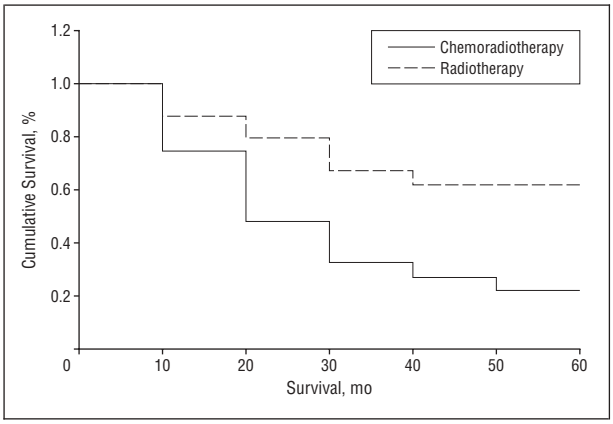
Fifteen (26.3%) of 57 patients with local persistent or recurrent disease underwent salvage reirradiation with doses increased up to 8200 cGy. Complete response was observed in 1 patient (6.7%) and partial response in 2 (13.3%). They remained disease-free or disease-static for a maximum of 21 months after RT, but all died of their tumors before 24 months.

Ten (17.5%) of 57 patients with local persistent or recurrent disease underwent salvage brachytherapy using intracavitary intubation with doses increased up to 10 250 cGy. Two patients (20.0%) had complete response and 2 other patients (20.0%) had partial response of their tumors. Both patients who had complete response after salvage brachytherapy are alive with no evidence of local disease after 28 and 43 months. One

Table 2. Analysis of Prognostic Factors

Variable	5-Year Disease-Specific Survival, %	*P* Value (Wilcoxon Test)	*P* Value (Cox Test)
Histopathological type			
Keratinizing	14.8	.10	NS
Nonkeratinizing	30.4		
Invasion of the skull base			
Yes	3.5	.004	.31
No	29.4		
Age >40 y			
Yes	16.8	<.001	.001
No	44.0		
Stage			
I	100.0	.002	.001
IIa	85.7		
IIb	54.5		
III	30.4		
IVa	25.0		
IVb	25.0		
Bone infiltration			
Yes	8.8	<.001	<.001
No	34.2		

Abbreviation: NS, not significant.



Comparison of 5-year disease-specific survival between the therapeutic groups.

patient who had partial response is alive with persistent but static local disease after 17 months.

One (1.8%) of 57 patients with persistent disease underwent salvage surgery (medial maxillectomy and palate split) for a stage IIa NPC. This patient is alive and free of disease after 17 months.

Ten (37.0%) of 27 patients with regional cervical residual or recurrent disease underwent salvage radical neck dissection. All but 2 patients (80.0%) remained free of disease for a maximum of 63 months after surgery.

Complications of the treatment used and the presence of comorbidities also played a role in the outcome of our patients. Most patients (78.2%) experienced slight trismus after the completion of RT treatment, which did not interfere with their daily life, but 3 patients with severe trismus could not open their mouth more than 1 finger's breadth, significantly interfering with oral intake. Other minor complications such as choanal stenosis (24.0% of patients) and saddle nose (17.8% of patients) were observed. Sphenoid osteoradionecrosis developed in 2 patients, and maxillary osteoradionecrosis was observed in 3 other patients who underwent salvage reirradiation. Massive nasal bleeding occurring late (3 months) after RT occurred in 1 patient. Rupture of the carotid artery in 1 patient with locoregional progression of the disease after CCRT and salvage radical neck dissection also occurred, leading to his death.

Among the cohort of 173, 15 patients (8.7%) died of causes other than the NPC or its treatment during the period. Four patients died of pneumonia, 3 of malnutrition, 3 of cerebrovascular infarction, 2 of gastrointestinal hemorrhage, 1 of myocardial infarction, 1 of pulmonary infarction, and 1 of sputum impaction.

The 5-year disease-specific survival rate for the 173 patients was 32.3%, and the 5-year disease-specific survival rates for the groups of patients according to their stages were 100% for stage I, 85.7% for stage IIa, 54.5% for stage IIb, 30.4% for stage III, 25.0% for stage IVa, and 25.0% for stage IVb. The prognostic association of stage with the outcome of patients in our study was statistically significant ($P=.002$, Wilcoxon test; $P=.001$, Cox test) (**Table 2**).

To assess the prognostic association of each therapeutic modality (RT vs CCRT) with outcome, we compared the groups according to their 5-year disease-specific survival rates. The difference was statistically significant (RT group, 22.5%; CCRT group, 61.4%; $P=.004$). A comparison between the therapeutic groups is shown in the **Figure**.

A comparison between the 2 therapeutic groups in each stage of the disease was also performed. Concomitant chemoradiotherapy plus adjuvant chemotherapy improved the 5-year disease-specific survival of patients in all stages except those with IIa and IVa, who underwent RT as the only modality of treatment. Nevertheless, the 5-year disease-free survival improvement achieved in the CCRT group compared with the RT group was statistically significant only among patients with stage III disease ($P=.05$). A comparison of 5-year disease-specific survival according to the disease stage is given in **Table 3**.

Among the other factors of possible prognostic association analyzed in our study, age older than 40 years, invasion of the skull base, and invasion of facial bones adversely affected the disease-specific survival rates of patients ($P=.001$, $P=.004$, and $P<.001$, respectively). The only factor in our study that did not correlate with prognosis was the histopathological type of NPC ($P=.10$). An analysis of prognostic factors is given in Table 2.

COMMENT

Nasopharyngeal carcinoma usually runs asymptomatically for long periods, precluding early diagnosis. In most cases, the diagnosis is made based on locoregional advanced disease symptoms, such as cranial nerve involvement or cervical nodal metastases.[9,10] Most (88.5%) of our patients were classified as having stages III and IV of the disease at first consultation, with cervical nodal metastases as the most common (47.4%) clinical presentation.

Nasopharyngeal carcinomas are sensitive to RT and CT.[11,12] The RT and CT sensitivity of these tumors and

the difficulties and complexity of current surgical approaches have led to the conservative management of NPC, with surgical therapy left for salvage of residual or recurrent locoregional disease.

Although NPC is a radiosensitive tumor, long-term survival for patients with advanced disease remains poor.[4,13,14] According to recent studies,[15,16] with RT alone, the 5-year survival rate for stage IV disease ranges between 28% and 35%.

Marcial et al[16] reported a 96% complete response of T1 tumors treated with RT, 88% for T2, 81% for T3, and 74% for T4 tumors. Nevertheless, the 5-year survival rate of all these patients was 40%.

Qin et al[17] reviewed the survival of 1379 patients with NPC, most with stage III and IV disease, treated with RT alone and found 5-, 10-, and 20-year survival rates of 46%, 29%, and 17%, respectively. Failure is usually caused by locoregional disease (40%-80% of patients) and distant recurrence (15%-50% of patients).

The overall worldwide 5-year survival rate ranged from 32% to 62% among series involving more than 9500 patients with all stages of NPC.[14,17-24] Our 32.3% 5-year disease-specific survival rate is in line with these results.

The usual dose of RT is 6500 to 7500 cGy in 180 to 200 cGy fractions per day 5 days a week. The dose of irradiation is crucial for achieving locoregional control and improving survival.[23] Accelerated hyperfractionated RT may also improve local control rates in patients with advanced NPC. Wang[25] reported improvement in local control of patients with NPC with N2 and N3 disease with accelerated hyperfractionated RT, compared with patients treated with conventional RT.

Most (74.6%) of our patients were treated with conventional RT (median dose, 6600 cGy). Radiotherapy was an effective therapeutic strategy only for early-stage NPC. The high rate (76.7% of patients) of residual or recurrent disease in the RT group (except among patients with stage I and IIa disease) indicated that our RT protocol, 6600 cGy in conventional fractionation, was not sufficient to adequately control NPC, particularly in its advanced stages.

Nasopharyngeal carcinoma is also a chemosensitive tumor.[26] Although randomized clinical trials using induction CT have not shown any survival benefit compared with RT alone,[27-29] some patients with stage IVc disease treated with CT alone achieved complete response of their tumors.[26] In addition, the combination of CT and RT is an attractive therapeutic option because of a possible synergy between them, particularly when cisplatin-based regimens are used.[23]

The Intergroup Study of North America demonstrated the advantage of CCRT over RT alone.[7] Early studies of the Radiation Therapy Oncology Group[20,30,31] presented the results of treating 124 patients who had locally advanced, inoperable, or unresectable stage III and IV tumors (including 27 patients with NPC) with concomitant single-agent cisplatin and RT, demonstrating a complete response rate of 89% and an overall survival of 55% for patients with NPC. Hong et al[32] reported a 70% 5-year overall survival and an 81% distant metastases-free rate for stage IV NPC treated with induction CT followed by RT.

Table 3. Comparison of 5-Year Disease-Specific Survival According to Disease Stage

Stage	Concomitant Chemoradiotherapy Plus Adjuvant Chemotherapy	5-Year Disease-Specific Survival, %	*P* Value
I			
Yes	1	100.0	NA
No	1	100.0	
IIa			
Yes	...	...	NA
No	7	85.7	
IIb			
Yes	2	100.0	.10
No	9	44.4	
III			
Yes	24	57.6	.05
No	45	18.7	
IVa			
Yes	...	...	NA
No	36	25.0	
IVb			
Yes	17	54.5	.23
No	31	16.2	

Abbreviations: ellipses, absence of patients; NA, not applicable.

Huncharek and Kupelnick[33] published a meta-analysis evaluating the effect of integrating CT with external beam RT in locoregional advanced NPC. They identified 6 randomized controlled trials enrolling more than 1500 patients that compared standard radical external beam RT (control arm) with RT plus CT delivered adjuvantly, neoadjuvantly, or concurrently with radiotherapy. The outcomes of interest were disease-free or progression-free survival and overall survival. They observed that the addition of CT to RT increased disease-free or progression-free survival by 37% at 2 years, 40% at 3 years, and 34% at 4 years after treatment.[33]

Concurrent chemoradiotherapy plus adjuvant CT has been used since 1998 in our department, which is why only 25.4% of our cohort of patients underwent this type of treatment. Most patients (95.5%) had advanced-stage NPC (stages III and IV). The addition of CT to standard radical RT in our group of patients increased the 5-year disease-specific survival by 22.5% to 61.4% ($P = .004$), which is similar to several results reported in the literature.[11,20,30,31]

When we compared the outcome of patients for each stage, CCRT was associated with better outcomes compared with RT not only for advanced NPC stages (III and IVb) but also for patients staged IIb, although the difference was statistically significant only among patients with stage III (Table 3). Concurrent chemoradiotherapy for NPC seems to be promising for early stages of NPC too. Because of the small number of patients in the CCRT group, particularly those in early stages of NPC, our single-institution experience deserves further investigation in larger prospective trials.

The nasopharynx is an anatomical site particularly amenable to reirradiation. The feasibility of reirradiation at this site is especially important because the tumors arising in the nasopharynx are generally nonresectable. The management of locally persistent and

recurrent NPC is limited by the RT dose that can be safely given by reirradiation using external RT. The use of brachytherapy[32,34,35] and surgery[36,37] has generally resulted in better outcomes compared with external reirradiation.[21,38] Using brachytherapy, therefore, a high RT dose can be delivered to the mucosa of the nasopharynx and to tumors lying immediately beneath the mucosa.[23] In our study, 15 patients with local persistent tumors received reirradiation with conventional RT with doses increased up to 8200 cGy, and 10 patients with local residual tumors underwent salvage brachytherapy with doses increased up to 10250 cGy. Patients who underwent salvage brachytherapy had a 20.0% rate of complete response compared with 6.7% among those who received conventional RT. In addition, only the patients salvaged by brachytherapy remained alive and free of disease 24 months after reirradiation. Although patients in our series had a better salvage rate with brachytherapy, compared with external reirradiation, the difference was not statistically significant ($P = .06$), probably because of the small number of patients. One patient with local residual disease amenable to a limited resection is alive and well 17 months after salvage surgery.

Nasopharyngeal carcinoma has a tendency to metastasize. Ahmad and Stefani[39] in an autopsy study of 256 men with NPC found that up to 38% of patients had distant metastases. According to the literature, the frequency of metastases is 4.4% to 7% at diagnosis[39,40] and 20% to 27% after RT.[40] Distant metastases were diagnosed in 19.7% of our patients, mostly (67.7%) to the bones. Regional metastases were present at first consultation in 47.4% of patients. Among the 10 patients (3.7%) who had recurrence in the neck, 80.0% were successfully salvaged by radical neck dissection, remaining free of disease for a maximum of 63 months.

The statistically significant prognostic factors with a negative effect on survival in this series were age older than 40 years, gross invasion of facial bones and skull base, and advanced stage at treatment. Hong and coworkers[32] did not find a prognostic correlation with the American Joint Committee on Cancer and Union Internationale Contre le Cancer TNM staging system. Lin et al[22] found that local extension of NPC to the nasal mucosa was an independent prognostic factor in predicting the outcome of treatment. Sham et al[10] found that the extension of NPC to the paranasopharyngeal space was an important adverse prognostic factor in local control and survival.

CONCLUSIONS

Prognostic factors associated with an adverse effect on locoregional control of disease and on disease-specific survival included advanced stage, invasion of surrounding bony structures, and age older than 40 years.

Salvage brachytherapy and radical neck dissection for local and regional residual or recurrent NPC were associated with increased rates of locoregional control and survival compared with reirradiation.

In our group of patients, CCRT improved locoregional control of NPC compared with RT alone. These results are in line with recent reports in the literature supporting aggressive multimodality therapy for advanced stages of NPC.

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Corresponding author and reprints: Fernando L. Dias, MD, Department of Head and Neck Surgery, Hospital do Câncer I, Instituto Nacional de Cancer, Av Alexandre Ferreira, 190 Lagoa, Rio de Janeiro, RJ 22470-220 Brazil (e-mail: fdias@inca.gov.br).

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