Carcinoma of the nasopharynx: The Edmonton experience

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1. INTRODUCTION

Carcinoma of the nasopharynx is a rare neoplasm in the United States and Western Europe. It is more common in southern Chinese. Southeast Asian, northern African and Eskimo populations[1,2]. In southern China, the annual incidence of carcinoma of the nasopharynx is 15 50 per 100 000[3]. The median age at which the tumour is diagnosed in southern China is between 40 and 50 years and is more common in men. The majority (95%) of the tumours are of an undifferentiated type (World Health Organization). They are not associated with cigarette smoking or alcohol. and less than 5% of these cases are squamous cell carcinoma (Grade I)[4].

The likely aetiological factors include genetic susceptibility, consumption of food with high salt content, and Epstein-Barr virus[5-7]. In "nonendemic" countries, there is a lack of association with Epstein-Barr virus and poorer survival after external beam radiation therapy[8,9]

Carcinoma of the nasopharynx is a radiosensitive tumour and radical external beam radiotherapy is the standard therapy[10-12]. Local relapse represents the major problem and is the most common cause of failure. The incidence of local relapse is 30–60%[10,12,13] and the most important prognostic factor in local failure is the extent of primary disease at the time of presentation[10,13-15].

Carcinoma of the nasopharynx is also chemosensitive, especially to platinum-based combinations[16-19]. Combined radiotherapy and chemotherapy regimens are frequently used in the management of advanced carcinomas and the response rates have generally been higher than that of other head and neck cancers. Although the overall survival has not been significantly improved, large randomised trials of adjuvant chemotherapy have demonstrated a reduction in the rate of development of distant metastases[20,21].

The survival rate for early stage disease is good; however, many patients present with advanced stages of the disease. The average 5-year survival rate reported for patients with stage III disease after radiotherapy is 46% (54% in the present series) and for stage IV disease approximately 30% (33%). The presence of bulky cervical lymph node metastases or supraclavicular lymph node metastases has been shown to be associated with an increased incidence of distant metastases, local failure after radiotherapy, and a 5-year survival rate of only 10–40%[22–25]. We report here a retrospective analysis of 172 patients with squamous cell carcinoma of the nasopharynx treated at the Cross Cancer Institute, in northern Alberta between 1975 and 1996. Candidate prognostic factors are reviewed and their impact on overall survival and disease-free survival are presented.

2. PATIENTS AND METHODS

A total of 172 patients with squamous cell carcinoma of the nasopharynx were diagnosed and treated in northern Alberta from 1975 to 1996. The charts were reviewed and data was collected from a population-based head and neck cancer registry. All the patients seen before 1987 were restaged according to the UICC TNM (1987) classification. It was not possible to restage this group of patients, as per the current 1998 recommendations, because of inadequate information.

Radiation treatment was typically delivered using a 6 MV linear accelerator. Over the period of the study. the fractionation underwent some changes with two major regimens used. In one regimen. patients were treated with a conventional fractionation using 5 fractions per week of 1.8 2 Gy. The total dose to the nasopharynx ranged from 28 Gy to 70 Gy, with a median dose of 66 Gy. All patients received whole neck irradiation of 34–50 Gy and the dose to involved cervical lymph nodes ranged from 50 Gy to 70 Gy, with surgery reserved for persistent nodal disease. In the other regimen. patients were treated with a higher dose per fraction (5 fractions per week) using a dose of 2.19–2.7 Gy per fraction. The dose to the nasopharynx ranged from 16.38 Gy to 60 Gy with a median of 47.5 Gy. All patients received whole neck irradiation of between 35 and 40 Gy, and the dose to the initially involved cervical lymph nodes ranged from 35 Gy to 70.14 Gy, with surgery reserved for persistent nodal disease.

All patients were included in the analysis, regardless of the fact that not all patients completed their prescribed

treatment, or the intention of treatments (i.e., curative vs. palliative). The following candidate prognostic variables were studied with regard to overall survival as well as disease-free survival:

- Age < 50 years versus > 50 years
- Male versus female
- T stages
- N stages :
- Ethnic origin
- Radiation dose to the primary
- Radiation dose to the nodes

Overall survival and disease-free survival were calculated using the Kaplan Meier method. The time frame involved was from the completion of radiation treatment to the date of last follow-up or death. The logrank test was used to determine the significance of the various prognostic factors and their effect on survival as well disease-free survival. The SAS computer package was used for data analysis.

3. RESULTS

This study involved 130 male and 42 female patients. The mean age at presentation was 51.5 years. The clinical stages were: T1, 18 patients; T2, 53 patients; T3, 22 patients; T4, 61 patients; and TX, 18 patients. The nodal status was: N0, 47 patients; N1, 30 patients; N2, 56 patients; N3, 30 patients; NX, 9 patients. Five had metastatic disease at presentation.

One hundred and nineteen patients were treated with radical radiation treatment alone and 40 patients had a combined chemotherapy and radiation protocol. Eight patients received no treatment. There was inadequate information available on five patients. A total of 94 patients are now deceased and 78 are alive. Eighty-two (48%) patients had recurrent disease with 41 (24%) patients having local recurrence and 42 (24%) patients developing distant metastases. The median follow-up of the patients was 136 months. The overall 5-year actuarial survival in our series was 49% and the overall disease-free survival was 43%; for 10 years, the figures were 36% and 37%, respectively.

The median overall survival was 50 months (Figure 1), and the median disease-free survival was 33 months (Figure 2). The median survival of the patients once they had local recurrence was 13 months (Figure 3).

Univariate analysis revealed that the following prognostic variables were significant for overall survival:

1. age < 50 versus > 50 years, $p = 0.001$ (Figure 4); (when corrected for T stage, $p = 0.004$);
2. T stage, $p = 0.014$;
3. N0 versus N+ stage, $p = 0.03$; and
4. TNM stages (stage I, II vs. III vs. IV to stage IV), $p < 0.005$ (Figure 5).

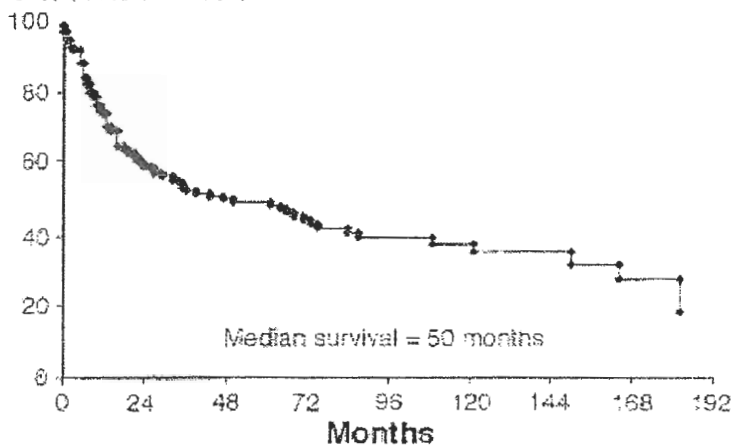The following prognostic factors were not found to be statistically significant for overall survival:

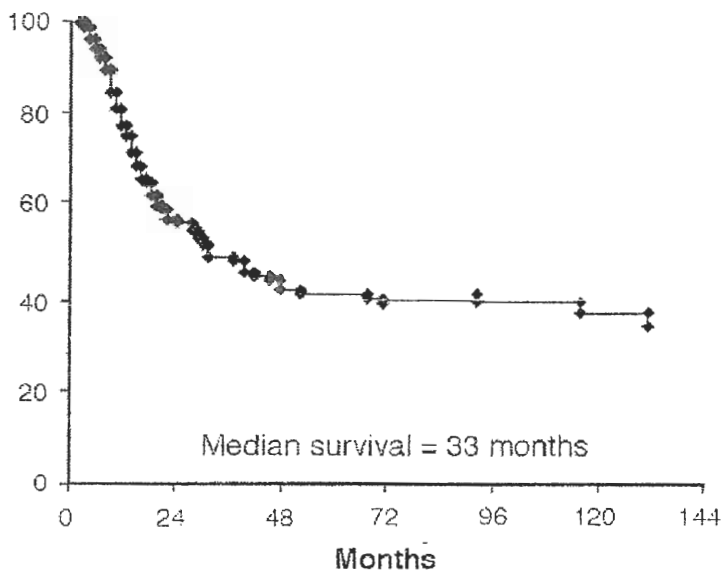FIGURE 1 *Overall survival.*

FIGURE 2 *Overall disease-free survival.*
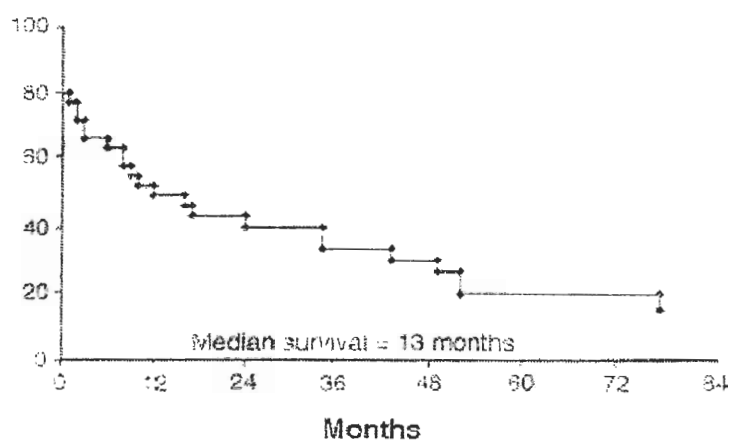
FIGURE 3 *Survival after recurrence diagnosed.*
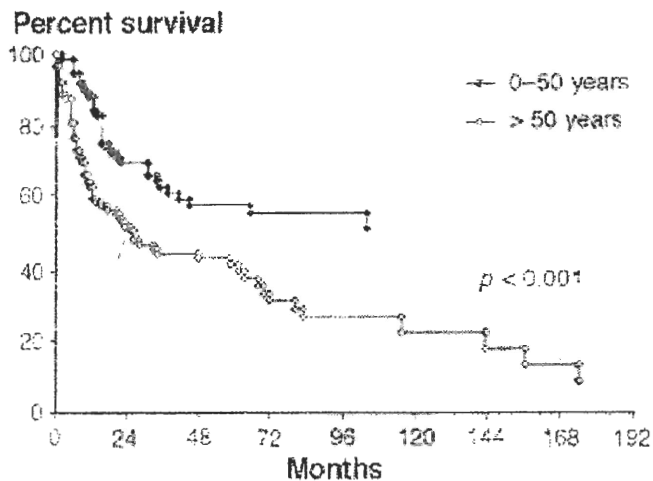
Percent survival

FIGURE 4 *Survival according to age (< 50 vs. > 50 years).*
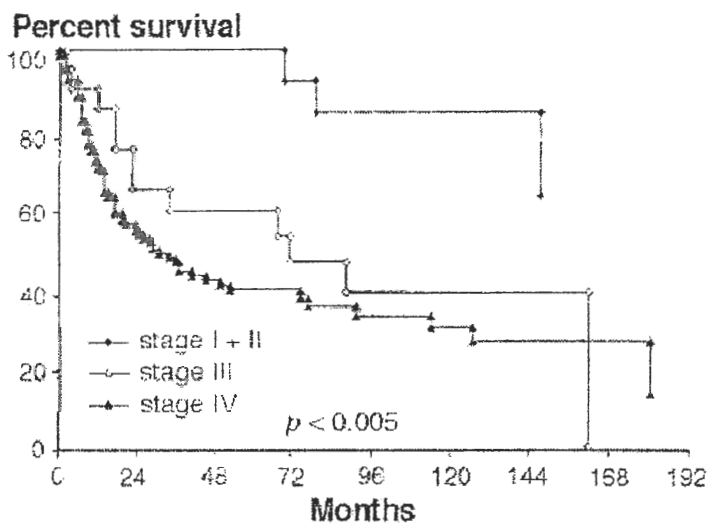
Percent survival

FIGURE 5 *Survival by stage (I + II vs. III vs. IV).*

1. various N stages (N0 vs. N1 vs. N2 vs. N3), $p = 0.148$;
2. sex of the patient (male vs. female), $p = 0.34$;
3. dose to the primary (< 5000 cGy vs. > 5000 cGy), $p = 0.21$;
4. dose to the neck nodes (< 5000 cGy vs. > 5000 cGy), $p = 0.459$;
5. treatment with or without chemotherapy in conjunction with radiation treatment, $p = 0.66$;
6. stage III vs. stage IV, $p = 0.37$; and
7. ethnic origin, Asian and Chinese decent vs. non-Asian and Chinese origin, $p = 0.26$ (Figure 6).

For disease-free survival, we were unable to demonstrate a significant difference in the tested candidate prognostic factors of sex, T stage, various N stages, or stage III versus stage IV disease. Dose to the primary (< 5000 cGy vs. > 5000 cGy), dose to the neck nodes (< 5000 cGy vs. > 5000 cGy), and treatment with or without chemotherapy also had no statistically significant effect upon disease-free survival. There was, however, a significant difference
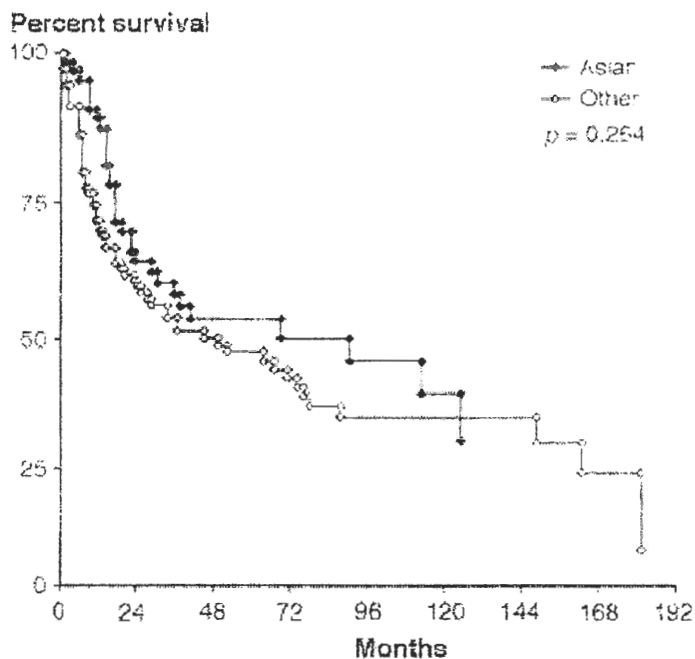
Percent survival

FIGURE 6 *Survival by ethnicity (Asian vs. non-Asian).*

between N0 versus N+ disease ($p = 0.03$) and stage ($p = 0.002$).

4. DISCUSSION

The optimal management for patients with advanced squamous cell carcinoma of the nasopharynx remains an unsettled issue. Advanced carcinoma of the nasopharynx, when treated with radiation treatment alone, is associated both with significant incidence in the rate of distant metastases and local recurrences. The control of primary nasopharyngeal carcinoma by external beam radiation treatment is dependent upon the primary volume and the dose of radiation[26]. Interruptions or prolongations of treatments have been shown to adversely affect the outcome of carcinoma of the nasopharynx when treated with radiotherapy[27].

There are several radiosensitive structures in close proximity to the nasopharynx (e.g., brain stem, spinal cord, temporal lobes, visual apparatus, audio vestibular system, and the pituitary gland) and some centres have used an intracavity boost using remote high dose rate systems[28-30] in an attempt to further improve the therapeutic ratio.

The use of neo-adjuvant and adjuvant chemotherapy has shown high initial response rates, but has not demonstrated improvement in overall survival consistently. The routine use of neo-adjuvant and adjuvant chemotherapy in the management of advanced carcinoma of the nasopharynx, therefore, remains an unresolved issue as several large clinical trials have shown[31-38].

Age was found to be a significant factor affecting overall survival in our series. Thus patients who are less than or equal to 50 years of age had a 5-year survival of

57% as opposed to 42% for those above 50 years of age (Figure 4). When corrected for T stage, age remains significant ($p = 0.004$), but the effect of age has not been universally seen[38,39].

It appears that the biology of carcinoma of the nasopharynx may be different in those patients from southern China, where 95% of the patients present with non-keratinising and undifferentiated histological sub-types (World Health Organization type II and III disease) versus WHO type II and III nasopharyngeal carcinoma in the western world[40]. In the present series, when we compared the overall survival and disease-free survival in patients of Chinese or Asian origin versus the patients from the rest of the world, there was no significant difference noted in outcomes.

At other sites in the head and neck region, most local recurrences occur within the first 2 years. However, in the nasopharynx late recurrences are common[41]. We have noted recurrences continuing to occur for at least 5 years; Chua et al.[42] reported that 63% of the recurrent disease was diagnosed within the first 2 years and 96% within 5 years, which we believe confirms the value of 10-year survival statistics in patients with this disease.

In our series, the patients who developed local recurrence had a median survival of 13 months (Figure 3), which is similar to other reports[43–45], however at the Cross Cancer Institute, patients with local recurrence after radical treatment were rarely treated with re-radiation.

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