NASOPHARYNGEAL CANCER TREATED IN SINGAPORE

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ABSTRACT

With effect from July 1987 CT-scans of the nasopharynx became routinely available in the staging of nasopharyngeal cancer (NPC) in our department. Eighty-four evaluable cases during these first six months were studied and the results at a median follow-up period of 34 months revealed that 74% were alive at 2 years. The local relapse rate were 4% for T1; 10% for T2 and 35% for T3 tumours.

Keyword: nasopharyngeal cancer

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INTRODUCTION

Nasopharyngeal cancer is a commonly occurring cancer in Singapore where the population consists of mainly Chinese, Malays and Indians. It occurs more often in males (11.8/100,000 vs 5.2/100,000 making a male to female ratio of 2.3:1). The incidence is highest amongst the Chinese at 14.7/100,000 for males and 6.4/100,000 for females. It is less common in the Malay males and females at 3.1/100,000 and 0.8/100,000 respectively; and negligible amongst the Indian males and females at 0.6/100,000 and 0.2/100,000 respectively. There has been no significant change in incidence over the last 15 years. The age pattern has also not altered during this period. The cancer remains the most frequent one in males aged 15 to 34 years[1]. Aetiological factors including genetic[2], viral[3] and environmental[4] ones have received recent attention.

Cross-sectional imaging (CSI), including CT-scan and magnetic resonance imaging (MRI), is known to be more precise for delineation of disease extent in NPC (primary and neck) but has only been widely available in this part of the world since the mid eighties. In this series, 84 evaluable cases presenting to the Department of Therapeutic Radiology, Singapore General Hospital, during the period of July to December 1987 represents the first of a series of patients uniformly staged with computerised axial tomography (CT-scan). An analysis of this series is worthwhile as it serves to document the results of treating a sizeable number of patients according to CSI tumour delineation. Moreover, as the existing staging systems were all devised before the wide availability of CSI, we need to verify whether the currently used system is still adequate to classify tumour delineation according to data from CT or MRI and if not, should a modified working system be adopted to enhance the therapeutic and prognostic assessment of this disease.

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METHODS

The case records and CT-scans/CT-scan reports of these 84 patients were reviewed retrospectively. The median follow-up period was 34 months, the maximum was 42 months. Staging of the cases were based on Ho's Modified Staging for NPC[5] (Table I) which is more prognostically oriented than the UICC system[6] used previously in our department. The treatment techniques used during this period were reviewed and were found to be tailored according to the extent of the primary disease. The events of local recurrence and systemic spread were recorded as it was expected that with better localisation and staging, local results should improve over the previous reported results from our department[7]. As we were investigating the impact made with better imaging, we confined our discussion mainly on the primary disease in the nasopharynx.

Table I – Ho's Staging for Nasopharyngeal Carcinoma

T1 –	Tumour confined to the nasopharynx (defined as the space behind the choanal orifices and the nasal septum and above the level of the posterior margin of the soft palate in its resting position)
T2 –	Tumour extended to the nasal fossa, oropharynx or the adjacent muscles or the nerves below the base of the skull
T3 –	Tumour extending beyond T2 limits and sub-classified as follows:
T3a –	Bone involvement below the base of the skull (Floor of the sphenoid sinus is included in this category)
T3b –	Involvement of the base of the skull (The lateral and the posterior walls of the sphenoid sinus are included in this category)
T3c –	Involvement of the cranial nerve(s)
T3d –	Involvement of the orbits or laryngopharynx or the infratemporal fossa
N1 –	Node(s) wholly in the upper cervical level bounded below by the neck crease extending laterally and backwards from or just below the thyroid notch (laryngeal eminence)
N2 –	Node(s) palpable between the crease and the supraclavicular fossa, the upper limit being the line joining the upper margin of the sternal end of the clavicle and the apex of the angle formed by the lateral surface of the neck and the superior margin of the trapezius.
N3 –	Node(s) palpabe in the supraclavicular fossa and/or skin involvement in the form of carcinoma en cuirasse or satellite nodules above the clavicles.

Histologic Types

The anaplastic or poorly differentiated carcinoma accounts for 93% of all cases of NPC[1] in Singapore. This group is now classified under World Health Organisation disease classification as "UCNT" – undifferentiated carcinoma, nasopharyngeal type. In our series, 95% of cases were of such histology and 5% (4 cases) were reported to have "moderately differentiated squamous carcinoma". No attempt to review the slides was made. It has been reported that "well differentiated squamous cell carcinomas" are less radiosensitive and have poorer local control rates[8].

Treatment Methods

During that period computer planning and treatment simulation was not yet available, and as we had not taken delivery of the new 6MV linear accelerator, the patients were all treated on the telecobalt machine. The field sizes and treatment technique were based on the extent of the disease as shown on CT-scan. The neck was electively treated even in the absence of lymph nodes as the rate of occult metastatic disease in the neck is high. It has been shown that Ho's stage 1 (T1N0) patients who relapse in the neck had significantly poorer overall results[9].

The dose to the primary was prescribed to the 80% isodose when a 3-field technique was used for the primary site. A minimum dose of 55 Gray was prescribed. The tumour dose at the 90% isodose would be 12.5% more. If parallel opposed lateral fields were used, then the prescribed dose was a minimum 60 Gray. The neck dose ranged between 55 to 60 Gray mid-plane dose with additional electron boosts to clinically involved nodes. The treatment fractionation was either 1.8 or 2 Gray daily, 5 days a week. The doses attained can be considered optimum as we were attaining doses of at least 60 Gray to the tumour in 6 to 7 weeks in almost all patients.

Apart from a chest X-ray, no other routine investigation for metastatic work-up was done. In view of the low pick-up rate of systemic disease by bone scan[10-12], we only further investigated patients who had symptoms and signs suggestive of metastases or for "N3" nodal disease[12]. Furthermore, even in the presence of metastases, the local control of the disease was considered relevant as local treatment contributed to the better quality of life of the patients by controlling their presenting symptoms.

RESULTS AND DISCUSSION

The age-sex distribution of this study group is shown in Table II.

Table II – Age-sex distribution of the patients in the study

Age Group (yrs)	<40	40-59	>60	Total
Male	17	31	11	59
Female	11	12	2	25
Total	28	43	13	84

About 85% of the patients in this group were under 60 years and one third of the patients are under 40 years of age. As mentioned earlier, this disease occurs more often in males than females, and at a ratio of 2.4:1 in this study is comparable to the national ratio. The age groups that are most commonly afflicted are those in the economically active age groups hence making NPC a social as well as a serious medical problem for the local population.

The staging system used was the Ho's Staging for NPC as shown in Table I. With the introduction of CT-scans of the primary site and neck, the extent of disease in the nasopharynx was better defined and the following findings were observed.

Table III – Patient distribution by Ho's T-stage

T1	–	28 (33%)
T2	–	30 (35%)
T3abcd	–	26 (32%)

Table IV – Patient distribution by Ho's Clinical N-stage

N0	–	30 (36%)
N1	–	22 (26%)
N2	–	21 (25%)
N3	–	11 (13%)

Table V – Relationship between Ho's T and N staging

T/N	N0	N1	N2	N3	Total
T1	11	6	5	6	28
T2	8	11	8	3	30
T3	11	5	8	2	26

In our series, 63% of the cases had clinically detected lymph nodes. This is a little lower than the usually reported figure of 70 to 80% [13,14]. An earlier series from the same department had clinically positive nodes in 81% of cases[7].

The T and N stages in the study group were fairly evenly distributed as noted in Tables III and IV and therefore probably representative of a larger population. However, there does not appear to be any correlation between the nodal status (N) and the T staging as noted in Table V. That is, with even more extensive primary disease, the nodal involvement rate was no different. This is probably because of the rich lymphatic supply of the nasopharynx allowing the spread to the neck nodes to occur very early in the course of the disease. In fact, the paradoxical relationship between T and N stages is apparent in our series as also noted in a larger CT scanned series from the Chinese University of Hong Kong in which N0 stage was 2 times more frequent than N3 nodal involvement in patients with Ho's T3 stage[13].

The introduction of routine CT-scanning for NPC has resulted in more accurate treatment localisation of especially the primary disease. The results are shown in Table VI.

Table VI – Relapses (overall) at minimum 2 years follow-up

Local (Primary)	–	14%
Cervical (Regional)	–	15%
Distant (Systemic)	–	15%

Unfortunately, the patients who relapsed systemically were not further investigated locally as it did not alter the management of these patients. Therefore we could not estimate the relationship between local recurrent disease to systemic spread.

Table VII – Local relapse rate according to T-stage

T1	–	4%
T2	–	10%
T3	–	35%

With CT-scanning of the nasopharynx, the local relapse data (Table VII) in this series bears out the impact of this investigation in both staging of the disease as well as its treatment resulting in very encouraging local control of early disease at minimum of 2

years follow-up. Compared to previously published data from our department [7] it appears that with routine CT-scans of the nasopharynx and neck, we are able to plan radiotherapy treatment more accurately, resulting in better overall results.

Table VIII shows the T-staged survival of our data reported in 1976. It shows that with staging using the UICC TNM system[6] (Table IX) without CT-scanning, the T-stage makes little impact on the results. Presumably under-staging of the disease occurred frequently, resulting in rather discouraging results of T1 and T2 cases as compared to our current series. In fact, the results for all the T-stages in the previous study ranged between 30% to 37%. Broad comparison of these two staging systems will show that the UICC T1 and T2 are about equivalent to Ho's T1; UICC T3 corresponds to Ho's T2 and the UICC T4, to the T3abcd of Ho's staging.

Table VIII – 1976 survival data at 4 years follow-up (UICC Staging)

T1	–	7/19 (37%)
T2	–	20/58 (35%)
T3	–	3/10 (30%)
T4	–	6/16 (37%)

Table IX – UICC 1974 T-Staging for Nasopharyngeal Cancer

Tis	– Pre-invasive carcinoma (Ca-in-situ)
T0	– No evidence of primary disease
T1	– Tumour limited to 1 region in nasopharynx
T2	– Tumour extending into 2 regions of nasopharynx
T3	– Tumour extending beyond nasopharynx without bone involvement
T4	– Tumour extending beyond nasopharynx with bone involvement

Even with "equivalent" stage to stage comparison, the results with CT-scan staged patients was dramatically improved although the treatment techniques and total doses reached were fairly similar in both the current and previous series. Despite the fact that CT-scanning has resulted in the up-staging of the disease stage in many cases, it cannot be disputed that the impact of this investigation in the management of this cancer has been positive. Hence routine CT-scanning is absolutely essential for the proper staging and treatment of NPC.

CONCLUSION & FUTURE DIRECTIONS

We have found that although our current staging system (Ho's), has a better correlation with prognosis than the UICC/AJC systems, it was still inadequate as far as classifying CSI data is concerned. For example, parapharyngeal involvement, which is commonly documented by CSI, was not included in any of the stages in Ho's system. Parapharyngeal involvement currently is classified as T2 disease using Ho's staging. However, we have found this to be inappropriate as T2 patients who had posterior nasal cavity involvement only, did very much better than those with parapharyngeal involvement which were all staged as T2 disease. Hence parapharyngeal disease should be considered as a more advanced stage and we propose that it should be classified as T3 disease. Moreover the other sites of involvement like the base of the skull, cranial nerves, orbit, infratemporal fossa, cavernous sinus, middle cranial fossa, carotid sheath and laryngopharynx should not be classified as T3 disease which, rather unconventionally, is the highest T stage in the Ho's system. Another unconventional feature of Ho's system is the 5 group staging instead of the usual four [5]. This makes comparison with others very difficult if not impossible. On the other hand, the UICC/AJC T4 covers too wide a range of local disease not all of which reflect poor prognosis.

As for nodal classification, Ho's N3 which refers to palpable nodes in the supraclavicular fossa appears to be accurate because such nodes are often associated with a higher chance of distant metastases [11]. On the other hand, Ho's N-staging completely ignores the nodal size and the impact of bilateral lymph nodes which the UICC/AJC system addresses. Accumulated data [15] show that bulky nodes do worse even if they are of the same Ho's staging which is dependent on where the node is found in the neck [15]. The UICC/AJC nodal staging for neck disease does appear more appropriate for NPC.

We would, therefore at this juncture, like to propose a more conventional working staging system which combines the strong points of both Ho's and the UICC/AJC systems. We feel that because of the ready availability of CSI today, NPC demands a staging system that will be more accurate in assessing and staging of the disease. We hope that it would be considered for use by as many centres as possible and feedback be given to us, as our aim is to establish a staging system more in tune with modern practice of radiotherapy of nasopharyngeal cancer.

Table X – Proposed New Staging for Nasopharyngeal Cancer [16]

T-Staging

T1a	– Disease confined to one subsite of the nasopharynx
T1b	– Disease at more than 1 subsite of the nasopharyngx
T2	– Disease involving the paranasopharynx and/or the posterior nasal fossa
T3	– Disease involving one or more of the following regions: parapharynnx, oropharynx, anterior nasal cavity, sphenoid sinus, ethmoid sinus, maxillary antrum and base of skull
T4	– Disease involving orbit, infratemporal fossa, laryngo-pharynx, bony extension above floor of sphenoid including intracranial extension and/or cranial nerve palsies

N-Staging

N1	– Single ipsilateral node involved, 3cm or less
N2	– Node(s) more than 3cm but not more than 6cm or bilateral[5] nodal involvement
N3	– Any node greater than 6cm or presence of supraclavicular lymph nodes

Stage 1	– T1aT1b N0
2	– T2 N0 N1
3	– T3 N0 N1 N2
4a	– T4 N0 N1 N2 N3
4b	– M1 (Distant Metastases)

The above staging system is now being tested prospectively as well as retrospectively to assess its accuracy in prognosticating the disease outcome for NPC. It has also been presented as a poster at Royal College of Radiologists Annual Scientific Meeting 1991, in Dublin, Eire by the author.

REFERENCES

1. Lee HP, Day NE, Shanmugaratnam K. Trends in cancer incidence in Singapore 1968-1982. WHO-IARC Publication No. 91 1988
2. Huang DP, Lo KW, Choi PHK, Ng AYT, Tsao SY, Yiu GKC, et al. Loss of heterozygosity on the short arm of Chromosome 3 in NPC. Cancer Genet Cytogenet 1991; 54:91-9
3. Tsao SY, He YS, Cheng PMN, Ho S, Leung SF, Chang RS. Epstein Barr virus in oropharyngeal and nasopharyngeal secretions of patients with NPC and control subjects. Intervirology 1991; 32:209-15.
4. Armstrong RW, Armstrong MJ, Yu MC, Henderson BE. Salted fish and inhalants as risk factors of NPC in Malaysian Chinese. Cancer Res 1986; 43:2967-70

5. Ho JHC. Stage classification of nasopharyngeal carcinoma – A review. In: de The G, Ito Y, eds. Nasopharyngeal carcinoma: Etiology and Control. IARC Scientific Publication No 20, 1978

6. Hermanek P, Sobin L H. eds. UICC-TNM Classification of malignant tumours. 4th Fully rev. ed. New York: Springer-Verlag 1987: 20-1

7. Khor TH, Tan BC, Chua EJ, Chia KB. NPC results of radical radiotherapy in 103 patients. Ann Acad Med Singapore 1976; 5:21-3

8. Mesic JB, Fletcher GH, Goepfert H. Megavoltage irradiation of epithelial tumours of the nasopharynx Int J Radiat Oncol Biol Phys 1981; 17:447-53

9. Lee AW, Sham JS, Poon YF, Ho JCH. Treatment of stage 1 NPC: Analysis of patterns of relapse and the results of withholding elective neck irradiation. Int J Radiat Oncol Biol Phys 1989; 17:1183-90

10. Leung SF, Metreweli C, Tsao SY, Van Hasselt CA. Staging abdominal ultrasonography in NPC. Australas Radiol 1991; 35:31-2

11. Sundram FX, Chua ET, Goh ASW, Toh HJ, Khor TH, Chua EJ. Bone scintigraphy in NPC. Clin Radiol 1990; 42:166-9

12. Leung SF, Stewart IET, Tsao SY, Metreveli C. Staging bone scintigraphy in NPC. Clin Radiol 1991; 43:314-5

13. Lindberg RD. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972; 29:1446-9

14. Skinner DW, van Hasselt DW, Tsao SY. NPC – Modes of presentation. Ann Otorhinolaryngology 1991; 100:544-51

15. Teo P, Tsao SY, Shiu W, Leung WT, Tsang V, Yu P, et al. A clinical study of 407 cases of NPC in Hong Kong. Int J Radiat Oncol Biol Phys 1989; 17:515-30

16. Yang ETL, Tsao SY, Chua EJ. Proposed new staging for NPC. Poster presentation at Royal College of Radiologist Scientific Meeting 1991, Dublin