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ORIGINAL ARTICLE Head and Neck Cancer

Epidemiology and outcomes of nasopharyngeal carcinoma: Experience from a regional cancer center in Southern India

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Abstract

Context: Nasopharyngeal carcinoma (NPC) is a rare head and neck cancer with significant geographical variation. There are limited data on epidemiology and outcomes of NPC reported from Southern India. **Settings and Design:** Retrospective analysis. **Materials and Methods:** We analyzed our hospital data between January 2005 and December 2011 with NPC and analyzed their demographic parameters and outcomes with therapy. **Results:** A total 143 cases of NPC were identified. Median age at presentation was 35 years with male predominance. Majority (84%) of the cases had the WHO Type 3 histology. Nodal metastasis at presentation was seen in 90% of the cases, majority being bilateral. Distant metastasis was seen in 16% of the cases, most commonly at bone, lung, and liver. Concurrent chemoradiation with weekly cisplatin was offered to 84.7% of localized disease while 80% of these also received adjuvant chemotherapy. Complete remission and partial remission were achieved in 66.1% and 15.2% of the cases, respectively. Weekly cisplatin was well tolerated with Grade 3–4 toxicity seen in 22% of cases. At a median follow-up of 20 months, 2-year progression-free survival and overall survival were 67.2% and 79.5%, respectively. **Statistical Analysis Used:** SPSS software version 20. **Conclusion:** NPC is a rare head and neck malignancy in Southern India, presenting with advanced stage and more propensity to distant metastasis. It has good outcomes to concurrent chemoradiation with weekly schedule of cisplatin being well-tolerated regime. Further prospective studies to test this schedule and other novel agents in this potentially curable malignancy are warranted.

Key words: Nasopharyngeal carcinoma, Southern India, weekly concurrent cisplatin

Introduction

Head and neck carcinoma is an important public health problem mainly related to tobacco carcinogenesis. Nasopharyngeal carcinoma (NPC) is a rare head and neck cancer with an age-standardized ratio being 0.6–2.0/100,000 in males and 0.2–0.8/100,000 females worldwide.[1] However, there is significant variation in geographic distribution of the disease with the highest incidence being in Southeast Asia up to 6.4/100,000 males and 2.4/100,000 females in these regions. Chinese and Malay races appear to be at the highest risk.

India, though being an integral part of Southeast Asia, has significant geographic, racial, and cultural diversity in the population which is reflected in varied incidence of cancer in various parts of the country as well. Head and neck cancer is the leading form of cancer in males in India and ranks 5th for females. However, NPC is unequally distributed. Highest age-adjusted rates for NPC were found in Northeast States with Kohima district in Nagaland having an incidence of 19.4/100,000 population. Our center is a regional cancer center in Southern India, catering population of Karnataka and nearby states. Although leading cause of cancer in males in our center also remains head and neck cancer, NPC remains uncommon.

The disease has peculiarities in its etiopathogenesis, presentation, risk of nodal and distant metastasis, response to therapy and overall survival (OS) outcomes that stand out as compared to other head and neck cancer subsites. There are limited data on epidemiology and outcomes of NPC reported from Southern India. Furthermore, the studies reported have not addressed the therapeutic challenges faced in resource-constrained settings as ours. We tried to analyze our hospital data over last few years with regard to the disease epidemiology and outcomes with current therapy.

Materials and Methods

We retrospectively analyzed data from January 2005 to December 2011 from our hospital. We analyzed their demographic parameters including age, gender distribution, tobacco exposure, symptoms, stage at presentation, and histology according to the WHO classification. We also recorded the therapeutic options exercised in addition to primary radiotherapy (RT) including various forms of chemotherapeutic (CT) modalities including neoadjuvant, concurrent to RT, and adjuvant setting. We analyzed responses to therapeutic modalities including CT agent used. The data were analyzed with Statistical Package for Social Sciences 20 (SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, IL, USA). Progression-free survival (PFS) and OS were calculated with Kaplan–Meier method and different risk curves were compared with log-rank test.

Results

We identified 143 cases of NPC during the time frame. Median age at presentation was 35 years (10-80). Male:female ratio was 2.8:1.

Due to retrospective nature of the study, Epstein–Barr virus (EBV) titers were not measured uniformly and could not be analyzed for its prognostic significance. Fifty percent of cases (n = 72) gave history of tobacco use.

Common symptoms at presentation were neck swelling (80%, n = 114), nasal obstruction and/or epistaxis (28%, n = 40), and ear symptoms (24.5%, n = 35). Cranial involvement was seen in 15% of cases (n = 20) with most common involvement of fifth nerve. Median duration of symptoms before presentation was 6 months (1–12 months).

Histologically 84% of cases (n = 120) had the WHO Type 3 histology while only 16% (n = 23) of cases had the WHO

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Type 2 histology. None of the cases had well-differentiated keratinizing squamous cell carcinoma (SCC) in our series.

Analysis of stage at presentation is shown in Table 1. Ninety percent (n = 129) of the cases had nodal metastasis at presentation with only 27.9% (n = 40) having unilateral nodal disease. Among the upfront metastatic cases, most common sites of metastasis were bone 66.7% (n = 8), lung 33.3% (n = 4), and liver 33.3% (n = 4).

Out of the total case studies, 30% (n = 43) did not complete planned therapy, of which 14% (n = 20) did not receive any form of therapy due to early death or loss to follow-up even before starting therapy while 5.5% (n = 8) developed progressive disease (PD) on therapy. Four cases of metastatic disease received palliative CT with cisplatin and 5-fluorouracil while one case expired shortly after palliative RT to bone. Thus, total 118 cases were offered therapy for localized disease. Concurrent CTRT was given to 84.7% (n = 100) of cases while 15.3% (n = 18) cases received RT alone. Eighty percent of these cases (n = 80) who received CTRT also received adjuvant CT. Additional neoadjuvant CT was given to 11% (n = 13) of cases in an attempt to decrease larger RT field for the upfront disease and related toxicity. RT dose used for the primary was 70–72 Gy while that for the involved neck nodes was 66–70 Gy. CT agents used were cisplatin with or without 5-fluorouracil in majority of cases including palliative setting. Dose and schedule for concurrent CT used was cisplatin 40 mg/m^2 weekly (85%) or carboplatin area under the curve 2 (15%) weekly. Four patients also received concurrent nimotuzumab with RT under clinical trial setting.[2] Adjuvant CT was given with three cycles of adjuvant cisplatin at 80 mg/m^2 on day 1 plus fluorouracil at 1000 mg/m^2 daily, days 1–4, given every 4 weeks. Median number of CT cycles received in combination with RT was 4 (2–6). Acute Grade 3–4 toxicities were noticed in 22% (n = 26) of treated cases (n = 118) mainly being mucositis (15.3%, n = 18), cutaneous toxicity (16.9%, n = 20), nausea/vomiting (11.8%, n = 14), and myelosuppression (11%, n = 13) including 7.6% (n = 9) of cases developing febrile neutropenia.

Table 1: Stage at presentation

Stage	Number of patients (%)
AJCC-stage	
I	2 (1.4)
II	22 (15.4)
III	59 (41.3)
IV	60 (41.9)
T-stage	
T1	30 (20.9)
T2	48 (33.6)
T3	29 (20.3)
T4	36 (25.2)
N-stage	
N0	14 (9.8)
N1	40 (27.9)
N2	66 (46.2)
N3	23 (16.1)
M-stage	
M0	131 (84)
M1	12 (16)

AJCC=American Joint Committee on Cancer

Among those who received RT/CTRT (n = 118), complete response was seen in 66.1% (n = 78) while partial response, stable disease, and PD were seen in 15.2% (n = 18), 6.8% (n = 8), and 11.9% (n = 14), respectively. Relapse posttreatment was seen in 24.5% (n = 35) cases of which 42.8% (n = 15) were locoregional recurrences while 57.2% (n = 20) were distant metastasis. Among recurrent metastatic disease, 80% (n = 16) were bone metastasis while 15% (n = 3) and 10% (n = 2) lung and liver metastasis were seen, respectively.

In intention to treat analysis, at a median follow-up of 20 months (2–68 months), estimated PFS 2 years was 67.2% [Figure 1]. Corresponding estimated OS at 2 years was 79.5% [Figure 1].

Discussion

NPC constitutes of a rare form of head and neck malignancies. It has many peculiarities which stand out from the other carcinomas in head and neck region and requires particular attention.

It has a unique etiopathogenesis than that of other head and neck cancer subsites. It is mainly associated with EBV infection, along with some genetic and dietary factors including preserved smoked foods contributing to the genesis in endemic areas while well-differentiated forms may be associated with smoking. Due to retrospective nature of our study, EBV titers could not be measured. However, 50% of cases had a history of tobacco use.

The tumor can affect pediatric to geriatric age groups. In low-risk regions, the disease incidence is found to increase with age; while in high incidence areas, there is a bimodal distribution noted with a small peak in adolescent and young adults and a larger later peak at around 50–55 years of age.[3] Median age in our population was 35 years which is quite low as compared to the other parts of the world as well as those from Northeast India.

The disease is 2–3 times more frequently seen in males than in females.[1] Male:female ratio found in our series was 2.8:1 which is in keeping with the same. The Chinese study also found similar male preponderance.[4]

In NPC, due to its location, diagnosis is delayed until the disease manifests by spreading to surrounding structures. Common symptoms reported are nasal obstruction, headache, ear symptoms, and neck swellings. Cranial nerves III, V, VI, and VII are most commonly affected because of para-cavernous sinus tumor invasion. Hoppe *et al*. had reported neck swellings (71%), nasal symptoms (54%), ear symptoms (51%),

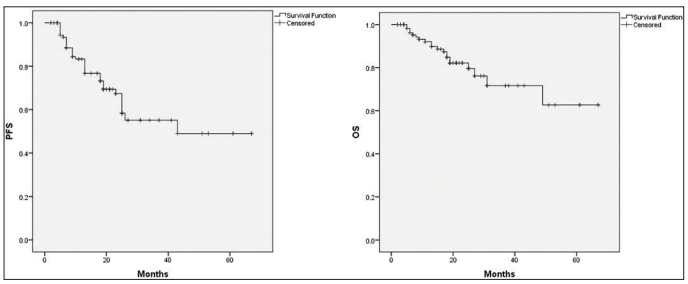

Figure 1: Progression-free survival and overall survival by Kaplan–Meier method

and cranial involvement (12%) in their series.[5] Fifteen percent of our cases presented with cranial nerve involvement.

NPC tends to show higher risk of lymphatic and hematogenous spread. In various series, 60% to 85% of cases have nodal metastasis at presentation; more than 50% being bilateral.[5] Neck masses were the presenting feature in 80% of our cases too. NPC may present with metastasis at baseline in 10%–40% of cases which is very high as compared to other head and neck subsites where it is seen in 5%–24% of cases. We found 16% of cases with metastasis at presentation. The most frequent sites of distant metastases reported by Altun *et al*. were bone (75%), lung, liver, and distant nodes which are similar to our metastatic presentations.[6]

SCC accounts for up to 98% of malignancies of nasopharynx. The WHO has given histological classification of NPCs as mainly three types with recent addition of basaloid variety in 2005 as a separate entity. Type 1 is more frequently seen in low-risk regions while Type 3 with poor differentiation is most frequently associated with EBV and has favorable prognosis than the other two subtypes. In our series, we found majority of cases (84%) being poorly differentiated Type 3 carcinomas. The study from China reported Type 3 cancers in 91% of their population.[4]

NPC is mainly treated by RT. Many advances in RT techniques and schedules are attempted to improve outcomes of the disease starting from intracavitary brachytherapy, intensity modulated RT to simultaneous modulated accelerated RT, all showing some promise with most significant benefit seen with addition of CT, especially in intermediate (Stage II) and advanced (Stage III, IVA, IVB) cases.

The benefit of concurrent and adjuvant CT in addition to RT alone was demonstrated in meta-analysis of CT-NPC meta-analysis with significant improvements in 10 years PFS and OS, 53.2% versus 38.5% and 57% versus 43.1%, respectively.[7] In our series, 84.7% of the cases received concurrent CTRT, out of which 80% also received adjuvant CT.

Cisplatin is the most effective agent in this setting. However, carboplatin had lesser toxicity and had shown similar efficacy to cisplatin in a study by Chitapanarux *et al*.[8] We used carboplatin in 15% of the concurrent CTRT cases due to low glomerular filtration rates. Novel-targeted agents such as cetuximab and nimotuzumab are still investigational in this setting.[2]

Weekly schedule of platinum as concurrent CT was followed for all our patients. It has already shown good efficacy with relatively low acute toxicity in SCC cervix. Majority of data regarding its comparison with 3 weekly cisplatin concurrent with RT in NPC is retrospective. The largest randomized study using weekly cisplatin with RT was by Chan *et al*. who compared CTRT to RT alone and found increased but acceptable toxicity profile of weekly schedule with 4.6% Grade 4 mucositis and 12.6% Grade 3 leukopenia.[9] Randomized controlled trial by Lee *et al*. in NPC showed similar efficacy and Grade 3–4 toxicity profile with 3 years PFS of 64.9% versus 63.8% in the two arms and similar Grade 3–4 toxicities.[10] Our population also tolerated weekly cisplatin schedule well.

Lack of awareness still remains a major hurdle in cancer management in India, which adds on to delayed presentation to health-care facility in our setting. This may be reflected by 83% of cases accounting for Stage III/IV in our series after a median duration of symptoms being 6 months. Even those who reach health-care facilities, many are lost to follow-up even before starting therapy or on therapy due to social, economical, and cultural reasons. In our study, up to 30% of cases could not complete planned therapy with majority of the reasons being those apart from PD or death. Furthermore, median duration of follow-up was only 20 months which highlights poor follow-up posttherapy. While there are ongoing efforts to improve RT and CT usage in the disease, the importance of optimal counseling and social support cannot be overemphasized in current state to improve outcomes of this potentially curable malignancy.

Conclusion

NPC is a rare form of head and neck cancer presenting with advanced stage and more propensity to metastasize to distant organs. The disease has good response and outcomes to concurrent CTRT with or without additional adjuvant or neoadjuvant CT. Concurrent weekly schedule of cisplatin is well tolerated in majority of the population. Further prospective studies to test this schedule and other novel agents in this potentially curable malignancy are warranted.

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Conflicts of interest

There are no conflicts of interest.

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