



# Outcomes and Management of Head and Neck Cancer at a South Indian Cancer Centre: A Retrospective Study

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## Abstract

**Introduction** Head and neck cancers are one of the most common cancers in the Indian subcontinent. The trends of these cancers worldwide have drastically changed over the past 15 years. In spite of all the new technology and timely diagnosis, the treatment of these cancers is still a challenge. These cancers still continue to be a significant cause of morbidity and mortality worldwide.

**Objectives** To identify different patterns of care received by patients with primary head and neck cancer in a single center and analyze the outcomes of the different patterns of care received by these patients in terms of overall survival and disease-free survival.

**Materials and methods** We included 707 patients with primary head and neck cancer registered and treated in our institution from January 2015 to December 2017. The demographic details of the patient, treatment received, and outcomes of treatment were collected retrospectively from our hospital's medical registry. Descriptive analysis was performed by calculating mean and standard deviation for quantitative variables, whereas frequency and proportion were calculated for categorical variables. The mean/median overall survival and recurrence-free survival were compared across various explanatory parameters using log rank-test. A *p*-value < 0.05 was considered statistically significant.

**Results** A total of 707 patients were included in the final analysis. The median age of presentation was 60 years. In total, 50% of patients presented with stage IV disease at diagnosis and 78% had a history of smoking or other tobacco use. Oral cavity was the most common primary site. Concurrent chemotherapy with radiation therapy was the most common modality of treatment used in 49% of patients: RT was the common modality of treatment in 21% patients. Fourteen percent patients were treated by only surgery. All patients who underwent treatment were included for survival analysis,

## Keywords

- ▶ head and neck cancer
- ▶ survival
- ▶ epidemiology
- ▶ patterns of care
- ▶ outcome
- ▶ radiotherapy
- ▶ chemotherapy

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which showed that the median overall survival time was 42 months (34–49 months). The median duration of disease free-survival time was 37 months (30–43 months).

**Conclusion** In our study, most patients presented with locally advanced disease. Multimodality treatment yielded better results. Based on our study, in early-stage cancer, where single modality treatment was used, adjuvant therapy should be tailored based on nomogram.

## Introduction

Head and neck cancers (HNCs) are a heterogeneous group of cancers that arise from the mucosa of the aerodigestive tract. According to the GLOBOCAN 2018 data, 2,05,325 new cases of HNC are diagnosed in a year and 1,22,834 deaths are associated with HNC in India. Cancers of the lip and oral cavity are the second most common cancers following breast cancer. HNC constitutes 10.4% of the cancer burden and they account for 16.1% of cases in males and 4.8% of the cases in females.<sup>1</sup> Tobacco exposure and alcohol dependence are the two main causes of HNCs.<sup>2</sup> Over the past 15 years, the trends have drastically changed with increased incidence of human papilloma virus causing HNCs.<sup>3,4</sup> The majority of HNCs are diagnosed at late stages.<sup>5</sup> In spite of changes in technology, the diagnosis and management of these tumors are still a challenge. The aim of this study was to describe the modalities of treatment and outcomes in patients with head and neck cancer.

## Materials and Methods

This study was a retrospective observational study.

### Inclusion Criteria

All newly diagnosed primary head and neck cancer belonging to these sites—oral cavity, oropharynx, hypopharynx, nasopharynx, and larynx between January 2015 and December 2017 were included in the analysis. Cases with primary head and neck cancer treated during the study period and who developed recurrence or progression during follow-up were recorded. In the cases showing advanced stage of the diseases, treatment received in form of palliative radiotherapy, palliative chemotherapy was also included.

### Exclusion Criteria

Those patients who had treatment elsewhere were excluded from the study.

The demographic details of the study population, tumor characteristics, stage (according to American Joint committee on cancer 7th edition), and treatment received were collected from the hospital's medical registry records. All patients were discussed in the institutional Tumor Board meeting (Departments involved were Radiation oncology, Medical Oncology Surgical Oncology, Palliative Care, Pathology and Radiology) and the treatment was decided. Patients treated during the study period and developed recurrence or progression during follow-up were recorded. Primary outcome of the treatment

was assessed after 2 months following the completion of treatment with history, clinical examination, imaging (CT scan neck with contrast) and was defined in terms of complete response (CR), partial response (PR), residual disease or static disease. This was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.0. The overall outcome of treatment is defined in terms of overall survival (OS) and disease-free survival (DFS). Overall survival is defined as the time from the date of diagnosis of the disease to the date of death of the patient due to any cause. Disease-free survival is defined as the time from the date of completion of treatment to the date of detection of recurrence. The follow-up strategy was for the first year, every 3 months, for the second year every 6 months, and for the third year every 12 months. These follow-ups included assessment of medical history, physical examination (complete head and neck exam; mirror and fiberoptic examination as clinically indicated), imaging (CT scan neck/MRI) done 8 weeks after completion of treatment and then yearly if the patient is symptomatic, and chest X-ray.

### Statistical Methods

Sample size was around 400 patients calculated using formula  $n = t^2 \times p(1 - p)/m^2$

Descriptive analysis was performed by evaluating mean and standard deviation for quantitative variables, whereas frequency and proportion were evaluated for categorical variables. Key outcomes included overall survival and disease-free survival. The key explanatory parameters considered for the analysis were the demographic characteristics of the patient such as age, past history of co-morbidities, disease characteristics, and treatment-related parameters. If the data were not available on any particular explanatory parameter they were considered as missing values and were excluded from the analysis while assessing the association of that factor with disease-free survival. The number of proportion of the missing values for each parameter was explicitly mentioned in the descriptive analysis. For survival analysis cases, data lost to follow-up or missing data were censored. Differences between groups in the median overall survival and disease-free survival according to possible explanatory parameters were assessed with log-rank test, and presented with Kaplan–Meier survival plots. A  $p$ -value  $< 0.05$  was considered statistically significant. The IBM SPSS version 22 software was used for statistical analysis (IBM Corp. Released 2013. IBM SPSS statistics for windows, Version 22. Armonk, NY:IBM Corp).

## Ethics

All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2013. The informed consent for this study was waived by the institutional ethics committee, G. Kuppuswamy Naidu Memorial Hospital, Coimbatore, Tamil Nadu as this is a retrospective study. The code for this study was (ECR209/INS/TN2013/RR-19 .dated 28 December 2019).

## Results

We included a total of 707 subjects. During the study period of 3 years, the incidence of primary HNC was around 250 per year (35%).

### Patient Characteristics

The age of diagnosis ranged from 27 year to 92 years with a median age being 60 years. There was a 1-year-old child diagnosed with rhabdomyosarcoma of the posterior tongue. The disease was more common in men than women (77% versus 22%) with a ratio of 3:1. Over 90% had an ECOG performance status 1 (► **Table 1**).

Approximately 62% of the subjects did not have any associated comorbidities. The most frequent co-morbidities observed were hypertension (21%), diabetes (18.8%), coronary artery disease (6.7%), and asthma (1.56%). Positive serology for significant viral infections at diagnosis included

HIV in (four patients), HCV in (two patients) and HBV in (one patient). Among patients with HIV, the most common site of HNC was found to be the oral cavity and oropharynx. A history of smoking or other tobacco use was found in 78% of patients and history of increased alcohol intake was documented in 50%.

### Tumor Characteristics

The primary tumor site were oral cavity (40%), oropharynx (24%), and hypopharynx (20%). Tongue (40%) was one of the most common subsite in the oral cavity followed by buccal mucosa (32%). In oropharyngeal tumors, the most common site were third posterior part of tongue (45%) and tonsil (19%). Pyriform fossa (73%) was the common sub-site within the hypopharynx, while cancers involving the vocal cords (70%) was the most common subsite within the larynx. Maxillary sinus was the most common PNS involved in six patients with only one patient presenting with ethmoid sinus carcinoma. In this study, 36% of patients presented with T2 disease at the time of diagnosis and cervical lymph nodes involvement was present in 63% of patients.

At the time of diagnosis, metastatic disease was present in 1.4% of patients. Stage IV disease was documented in 50% of patients at diagnosis.

Squamous cell carcinoma was the most common histological type occurring in 87% of patients. The other histological types included verrucous carcinoma (15 patients), adenoid cystic carcinoma (five patients), nasopharyngeal carcinoma (three patients), and mucoepidermoid carcinoma (two patients). Rarer histological types included lymphoepithelial carcinoma (one patient), myoepithelial carcinoma (one patient), schwannoma of the pyriform fossa (one patient), and rhabdomyosarcoma of the posterior tongue (one patient). Around 38% of squamous cell carcinomas were graded as moderately differentiated.

### Treatment Planned

All 707 patients were discussed in the institutional multidisciplinary tumor board and their treatment was planned. In case of patients with localized, early-stage disease, single modality of treatment in the form of surgery or radiotherapy was suggested. For patients with locally advanced diseases, the treatment was suggested depending on the site, stage, and performance status of the patient. In patients having locally advanced disease, multimodality treatment was used in the form of concurrent chemoradiation (CRT) or surgery, followed by adjuvant treatment in case of operable diseases. In case of metastatic disease at the time of diagnosis palliative treatment in the form of chemotherapy or radiotherapy was suggested.

In our study population, the majority of them had locally advanced disease; so, chemoradiation (CRT) was suggested for 339 patients (48%), only RT alone for 151 patients (21%), and only surgery alone was suggested for 100 patients (14%). Surgery followed by adjuvant treatment was recommended for 74 patients (10%) and neoadjuvant chemotherapy followed by radical local treatment was suggested for 13 patients (2%) (► **Table 2**). Palliative chemotherapy was suggested for five

**Table 1** Details of demographic and clinical parameters

Parameters	Percentage
Age group	
Up to 50	20.79% (147)
51 to 70	59.83% (423)
> 70	19.38% (137)
Smoking/tobacco history	
Yes	77.51% (548)
Alcohol history	
Yes	49.50% (350)
Site	
Oral cavity	40.45% (286)
Oropharynx	23.62% (167)
Hypopharynx	19.94% (141)
Larynx	11.46% (81)
Others	4.52% (32)
Stage grouping	
I	12.73% (90)
II	13.72% (97)
III	18.81% (133)
IVA	50.50% (357)
IVB	4.24% (30)

**Table 2** Descriptive analysis of treatment planned in the study population (N = 707)

Treatment planned	Frequency	Percentages
RT + CT	339	47.95
RT	151	21.36
Surgery	100	14.14
Surgery → Adjuvant RT ± CT	74	10.47
NACT → RT ± CT	13	1.84
Others	30	4.24

patients and palliative RT for bone metastasis was recommended for one patient. In view of advanced disease and poor health palliative care was suggested for 11 patients.

### Patterns of Care Received

The type of surgery depended on the site of disease. Most oral cavity cancers were treated with surgery with or without adjuvant treatment. Wide excision and neck dissection were performed in 86% of patients. Extensive surgeries such as laryngectomy, mandibulectomy, and maxillectomy were performed in 20 patients. No postoperative complications were documented in 95% of those patients having surgery. A few complications observed included flap infection (one patient), flap vein thrombosis (one patient) and sepsis in (one patient) (► **Table 3**).

Forty nine percent (198) of patients received concurrent chemoradiation and 21% patients (85) received only RT. A radical dose of 66 Gy was administered in 33 fractions. The conventional dosage schedule was used in 85% of patients, and six patients (1.6%) were treated with a hypo fractionated schedule. Intensity-modulated radiotherapy (IMRT) technique was performed in 99% of patients. The mean RT duration was 6.2 weeks with interruptions occurring in 16% of patients. Most interruptions to radiation therapy occurred during the 5th or 6th week of treatment. The most common reasons for interruption were neutropenia (19%) and sepsis (8%). Death during treatment occurred in five patients (7.9%). During RT, grade II skin reactions were documented in 47% of patients, and grade II mucositis was documented in 70% of patients.

**Table 3** Descriptive analysis of pattern of care received in the study population (N = 405)

Treatment planned	Frequency	Percentages
RT + CT	198	49
RT	85	21
Surgery	58	14
Surgery → Adjuvant RT ± CT	48	12
NACT → RT ± CT	4	1
Others	12	3

Concurrent chemoradiation in 339 patients and neoadjuvant chemotherapy in 13 patients was recommended. Cisplatin (40 mg/m<sup>2</sup>) was administered in 222 patients (81%) as weekly concurrent chemotherapy and weekly carboplatin was administered (AUC 2) in 17 patients. Cisplatin (75–100 mg/m<sup>2</sup>) given every 3 weeks was used in eight patients. Neoadjuvant chemotherapy was indicated for T4b and N3 nodal disease, TPF regimen was used in seven patients. Interruptions during chemotherapy were found in 45% of subjects. The most common reason for interruption was due to neutropenia in 51.1% of patients. Around three patients developed 5-fluorouracil-induced cardiac complication and one patient developed hypersensitivity to platinum. The most common acute complication of chemotherapy was found to be mouth ulcers occurring in 61.65% of the patients followed by neutropenia in 19% of patients. Palliative chemotherapy was suggested in five patients. The palliative chemotherapy regimen was cisplatin +5-fluorouracil and cisplatin and paclitaxel.

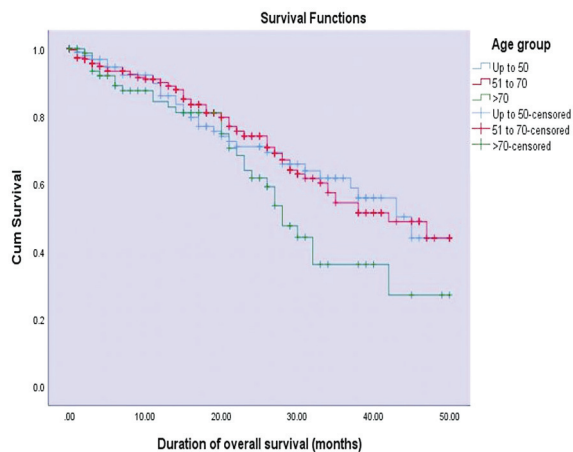
### Outcomes of Treatment

Among the 707 patients included in the study 405 patients (57%) completed their planned treatment, 244 patients (34.5%) declined treatment, 46 patients (6.5%) did not complete treatment and palliative care was provided to 12 patients (2%). Some of the documented reasons for defaulting in patients included financial constraints or decision to continue treatment at government hospitals (28.6%), followed by neutropenia in 19% of patients. Patients died, i.e., 7.9% (5) during treatment due to various reasons-sepsis (2 patients) febrile neutropenia (2 patients), cardiogenic shock (1 patient). The primary response was assessed 2 months after completion of treatment in 405 patients with clinical examination and imaging including computed tomography. Sixty-nine percent had a complete response to treatment; 22% of patients had residual disease, 6% were lost to follow-up, and 3% had progressive disease. During the course of follow-up, recurrent disease was seen in 15% of patients and 1.5% of patients developed second primary tumor. The majority of recurrences were local (76%) and distant recurrence was documented in 11 patients (24%) including lung in five patients, bone in three patients, pleura in two patients, and mediastinal lymph nodes in one patient. The median follow-up period for this study was 27 months (1 month–54 months).

### Survival Analysis

Survival analysis included 463 of the 707 patients who underwent any anticancer treatment. The median overall survival was 42 months (95% CI 34.186–49.814) and the median disease-free survival time was 37 months (95% CI 30.349–43.651). The inter-quartile range was calculated to be of 8.45. Survival was shorter in patients aged > 70 years (OS: 28 months, DFS: 27 months) than those aged < 50 years (OS: 45 months, DFS: 43 months).

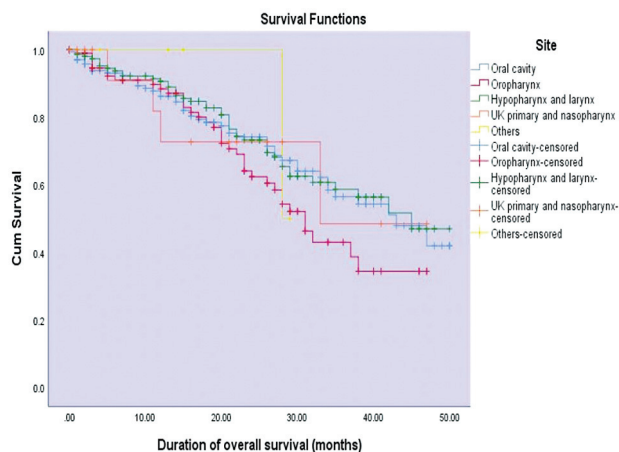
The median overall survival time according to varying patient age groups was found to be 45 months in 50 years, 42 months in 51 to 70 years, and 28 months in > 70 years. The



**Fig. 1** Kaplan–Meier curves of duration of overall survival (months) across various age groups ( $p$ -value = 0.100).

difference in the duration of overall survival distribution and age group groups was discovered to be statistically not significant ( $\rightarrow$  Fig. 1).

The median overall survival at the time of diagnosis was found to be 42 months in patients who had stage I and II disease, 45 months in stage III disease, and 37 months in stage IV disease. Similarly, the median DFS was evaluated to be 42 months in early stage I and II disease, 30 months in stage III disease, and 35 months in stage IV disease. Cancers of the hypopharynx and larynx had a median survival of 45 months, followed by 43 months for oral cavity, 33 months for nasopharynx, and unknown primary tumor with neck as the secondary site: 31 months for oropharynx and 28 months for malignancies involving paranasal sinus, ear and nasal cavity ( $\rightarrow$  Fig. 2). Similarly, hypopharynx and larynx had median DFS of 42 months followed by 38 months in the oral cavity, 33 months in the nasopharynx, and unknown primary tumor; and 26 months in the oropharynx. Patients treated with CRT had a median survival period of 38 months. Treatment with CRT was associated with a DFS of 31 months compared with other combined modalities, which had a DFS of 33 months.



**Fig. 2** Kaplan–Meier curves of duration of overall survival (months) across various sites of head and neck ( $p$ -value = 0.100).

## Discussion

Our institution data on patients diagnosed with head and neck cancer between January 2015 to December 2017 showed that the disease was more common among men with a median age of diagnosis of 60 years. Around 54.7% of patients presented with a stage IV disease at the time of diagnosis. Association with history of smoking or any kind of tobacco use was found in 77.5% of patients in the study. The strong association between tobacco and several HNC has been well established by Wynder et al and several other studies in the literature.<sup>6,7</sup>

A report from south Indian population shows that the trend is emerging showing that there is a definite increase in the number of patients presenting with tongue cancers.<sup>8</sup>

Oral cavity was the most common site involved followed by oropharynx and hypopharynx. Concurrent chemoradiation was the most common modality of treatment used. All patients who underwent treatment were included for survival analysis which showed that median overall survival was 42 months and the median DFS was 37 months. Decreased survival was found in patients more than 70 years of age, with cancers of the oropharynx and having stage IV disease.

This study was a retrospective observational study in which data were collected from a hospital-based cancer registry. Cancer registries are good sources of information on the demographics, tumor characteristics, and stage at diagnosis.<sup>9</sup> Benefit of any treatment in oncology can be defined in two ways—the patient either live longer (OS) or live better (q quality of life). OS is a universally accepted measure of benefit and is the most commonly used measure.<sup>10</sup> Because we wanted to compare the outcomes of the different patterns of treatment in our institute, overall survival was considered as the primary end point. Disease-free survival is a surrogate end point and is most commonly used to assess the benefit of adjuvant treatment.

However, with improvements in modern radiation techniques, the intent of treatment in HNC has been more inclined toward cure with functional preservation. This could explain why CRT was the major modality of treatment preferred for locally advanced HNC in our study population. More than 50% of the study population presented with stage IV disease at the time of diagnosis. Similar presentations were found in the retrospective study performed by Roy et al.<sup>11</sup> The outcomes and epidemiology of HNC were evaluated from a cancer registry, and it was found that 49% of the study population had stage IV disease at the time of presentation.<sup>12</sup> This can be attributed to illiteracy and lack of awareness among the general population regarding the disease. In developing countries such as India, the majority of the people presented with advanced disease at the time of diagnosis. Therefore, HNC in developing countries contribute to a significant mortality and morbidity.<sup>13</sup>

In our study, the primary response was assessed 2 months after completion of treatment in 405 patients. It showed that 69.3% of patients had a complete response to treatment; 22.2% had residual disease, 2.7% had a progressive disease, and 5.6% were lost to follow-up. Steinbichler et al in Austria performed a study on persistent disease following



first line treatment in HNC. Out of the 741 patients studied, 76% had complete response to treatment, 24% had persistent or residual disease.<sup>14</sup>

Out of the 707 patients, survival analysis was performed for 463 patients who underwent treatment at our center. The median overall survival was evaluated to be 42 months and the median disease-free survival time was evaluated to be 37 months. The median overall survival and disease-free survival were found to be decreased in patients of age > 70 years (OS-28 months, DFS-27 months) when compared with those < 50 years (OS-45 months, DFS-43 months). However, this difference was not found to be statistically significant.

Both median OS and DFS were found to be decreased in cancers of oropharynx when compared with cancers of the oral cavity, hypopharynx, and larynx. In our study, laryngeal cancers are found to have better survival when compared with other sites. These results were in accordance with study by Cadoni et al and Kambiz et al, where the median survival time was higher for laryngeal cancers and reduced survival was associated with increasing age of diagnosis and advanced tumor stage.<sup>15,16</sup> In both of these studies, the 4-year overall survival for all HNC sites was around 60%. Cancers involving nasal cavities, paranasal sinuses, and ears had very poor survival rate. HPV positivity was more commonly found in oropharyngeal cancers among non-smokers.<sup>17,18</sup> HPV 16 positivity was associated with an increased risk of HNC, especially oropharyngeal cancers.<sup>19</sup> Future studies should include HPV data to observe its impact on the multimodality treatment.

In our center, single modality of treatment was recommended for early-stage localized diseases. Multimodality of treatment including surgery, chemotherapy, and radiation therapy had a slightly better survival than CRT. However, this difference was not statistically significant.

Accelerated radiation and hypofractionation are effective methods of increasing therapeutic benefits of radiation. A meta-analysis on the role of chemotherapy in HNC (MACH-NC) showed that hypofractionated RT with concurrent chemotherapy was the best modality.<sup>20</sup>

Latest update of (MACH-NC) is that overall survival was not increased by addition of induction or adjuvant chemotherapy. Efficacy of induction chemotherapy decreases with poorer performance status.

It has been shown that hypofractionated RT can achieve similar tumor response to conventional fractionated RT in HNC although with some increased toxicity.<sup>21</sup>

Similarly, randomized RTOG trials showed hyperfractionated RT had better local control and overall survival compared with conventional fractionation in HNC.<sup>22,23</sup>

The strength of the study was the number of patients, data being collected from a hospital-based cancer registry, treatment of all patients being decided by a multidisciplinary team of medical professionals.

## Limitations

The maximum duration of follow-up observed in our study was only 50 months and the last patient recruited was in

December 2017. Due to limitations in time and resources, a 3-year or 5-year survival analysis could not be performed. This would have given us more scientific and meaningful conclusions on the outcomes of HNC.

In this study, we have not assessed the HPV status. Recently, we started testing HPV status for all oropharyngeal cancers for its future potential implications. We are also planning for clinical trials including dose escalation strategies in locally advanced head and neck cancer particularly in non-responders.

## Conclusion

In our study, most patients presented with locally advanced disease. Multimodality treatment yields better results. Based on our study in early-stage cancer where single modality treatment was used, adjuvant therapy should be tailored based on nomogram.

### Funding

None.

### Conflict of Interest

None declared.

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