

RESEARCH ARTICLE

Survival in Head and Neck Cancers - Results of A Multi-Institution Study

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Abstract

Background: The prime output of Hospital Based Cancer Registries is stage and treatment based survival to evaluate patient care, but because of challenges of obtaining follow-up details a separate study on Patterns of Care and Survival for selected sites was initiated under the National Cancer Registry Programme of India. The results of stage and treatment based survival for head and neck cancers by individual organ sites are presented. **Materials and Methods:** A standardized Patient Information Form recorded the details and entered on-line at www.hbccrindia.org to a central repository - National Centre for Disease Informatics and Research. Cases from 12 institutions diagnosed between 1 January 2006 and 31 December 2008 comprised the study subjects. The patterns of treatment were examined for 14053 and survival for 4773 patients from five institutions who reported at least 70% follow-up as of 31 December 2012. **Results:** Surgical treatment with radiation for cancer tongue and mouth showed five year cumulative survival (FCS) of 67.5% and 60.4% respectively for locally advanced stage. Chemo-radiation compared to radiation alone showed better survival benefit of around 15% in both oro and hypo-pharyngeal cancers and their FCS was 40.0%; Hazard Ratio (HR):1.5; CI=1.2-1.9) and 38.7%; (HR):1.7; CI=1.3-2.2). **Conclusions:** The awareness about the requirement of concurrent chemo-radiation in specifically cancers of the oro and hypopharynx has to be promoted in developing countries. The annual (2014) estimate number of new Head and Neck cancers with locally advanced disease in India is around 140,000 and 91,000 (65%) patients do not receive the benefit of optimal treatment with ensuing poorer survival.

Keywords: NCDIR - informatics - multi-institutional - head and neck cancers - tongue - oral cancer - oropharynx

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Introduction

Head and Neck cancers comprise 4.3% of cancers worldwide (Ferlay et al., 2013) and the annual estimate of new cases in India is 181606 (NCDIR, NCRP, 2013). Patients invariably present in advanced clinical stage (NCDIR, NCRP(HBCR), 2013) with decreasing chances for cure. Among the head and neck cancers, those of the tongue and mouth have shown a significant increase in the incidence rates over time (NCDIR, NCRP, 2013). In a developing country there are several challenges in patient follow-up post treatment and obtaining information on recurrence and/or complications of disease are extremely difficult (Nandakumar et al., 1993). The main aim of this study was to get clinical stage specific treatment and survival information for cancers in head and neck region.

A recent publication from India (D'Cruz et al., 2015) has reported that elective neck surgery in addition to surgical treatment for the primary tumour had better survival compared to those who had the latter treatment alone. Previous publications reported broad concept of hospital based studies on Head and neck cancers (Baykara et al., 2013; Lasrado et al., 2014; Pandey et

al., 2014; Sharma et al., 2015). Other reports on survival studies in head and neck cancers in India are also from single institutions (Rao et al., 1998; Dimri et al., 2013; Gupta et al., 2013). We report the findings from pooled multi-institutional data. This was facilitated by a process of electronic data from collaborating institutions with the internet as the medium of transmission to a central repository. An earlier version of this method which constituted the basic design and framework for obtaining information was described before (Nandakumar et al., 2005).

Materials and Methods

Twelve institutions (centres) participated in the study. A standardized Patient Information Form evolved by group of oncologists with specific expertise in treating Head and Neck cancers was hosted on the website www.hbccrindia.org. Printed forms with Instruction Manual were supplied to participants. Trained staff completed the form through a combination of patient /attendant interviews, scrutiny of medical records/ other relevant documents/registers and discussions with concerned

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clinician(s). Collaborating centres were given individual login-ID and password with instructions for on-line data entry so as to electronically transmit the data to a central repository - National Centre for Disease Informatics and Research (NCDIR). The mandate and mission statements of this one of a kind centre - an outcome of the National Cancer Registry Programme of the Indian Council of Medical Research are stated in the centre's website www.ncdirindia.org.

Patients who were newly diagnosed between 1 January 2006 to 31 December 2008 with head and neck squamous cell carcinomas and treated at twelve institutions comprised the study group. The tenth edition of the International Classification of Diseases (ICD-10) (ICD-10, WHO, 2010) was followed to separate the individual organ sites of head and neck cancers and these sites were analysed separately. Accordingly, the break-up (with ICD-10 in parentheses) was as follows: anterior two-thirds tongue (C02.1-02.4, 02.8 (excludes 02.9 - tongue unspecified)); oral cavity/mouth (C03-04, C06); oro-pharynx (C01, C05, C09-10, C14); hypo-pharynx (C12-13); larynx (C32). Both TNM and clinical stage were recorded and correlation was made between the two before taking the final stage grouping. TNM based on histopathology findings (p-TNM) superseded clinical TNM (Sobin et al., 2009). Analysis was carried out separately for early stage (Stage I and II (T1N0M0 and T2N0M0)) and locally advanced stage (III to IVB). Pattern of care was examined for patients from all twelve institutions. Patients with incomplete treatment and those given only palliative/supportive care were excluded. Survival analysis was restricted to data from five centres having at least 70% follow-up information of their respective patients as of 31 December 2012. The main endpoint, overall survival was defined as that from date of diagnosis till date of death (when this was before 1 January 2013) from any cause. Patients who died on or after 1 January 2013 were considered alive. All other patients were regarded as alive and the last date of follow-up was the censored date. The number and proportion of patients with toxicity/adverse reaction (based on early and late complications) and recurrence is based on any one such reported event.

Based on the above criteria stage based treatment patterns were separately examined for 14053 (3071 (21.9%) in early stage and 10982 (78.1) in locally advanced stage) cases. Survival analysis was carried out independently for 4773 (1477 in early stage and 3296 in locally advanced stage) cases.

Surgical treatment: Surgery done on the primary site of tumour with or without additional surgery of the neck was considered as surgical treatment.

Radiotherapy (RT): For both early and locally advanced stage dose of radiotherapy and fractions were taken into account and only patients who received radical RT were considered as having received RT. Patients with doses below 4500cGy were regarded as having palliative treatment and excluded from the analysis except when surgical treatment for the main site was additionally done. The radiotherapy machine used and

beam (fields) arrangement were separately factored and their significance, if any, for overall survival was examined and adjusted in statistical analysis. Very few patients received radiation through IMRT, IGRT, etc and these were disregarded.

Chemotherapy(CT): Chemotherapy whether administered as neo-adjuvant, concurrent or adjuvant were all taken as chemotherapy given. Patients who received this as mono-therapy or combined with other drug(s) were grouped separately. Standard prescribed protocols in use of the respective chemotherapy drugs were followed.

Software programmes and quality checks

In-house internet based software programmes (www.hbccrindia.org; www.ncdirindia.org) were modelled for data capture, completeness and consistency check, tracking patient follow-up, updating treatment information and recording follow-up details. Checks done on data varied from date checks to verifying discrepancies in clinical information (Nandakumar et al., 2015). Lists of cases with improbable data were sent to the concerned centres for rectification. Furthermore, a 10% centre-wise random sample of cases were listed and centres asked to re-abstract the medical records for certain essential parameters.

Statistical analysis

The Kaplan Meier (Kaplan and Meier, 1958) and Cox Proportional Hazards Ratio (HR) (Cox, 1972) in the SPSS package (version 21) was used to calculate the Cumulative Survival Percent at three (TCS) and five years (FCS) and Hazard Ratio (HR) (with statistical significance) respectively. Multivariate analysis was performed using Cox Proportional Hazards Regression Model (Cox, 1972). This was specifically done for adjusting the ratio between sexes, among different types of treatments and where the dose of radiotherapy was showing a significant difference in survival.

Results

Cancer tongue

The comparison of patient, diagnostic and treatment characteristics for early and locally advanced stage is given in Table 1 and Table 2 respectively.

Early Stage (Stage I and II): Table 3 gives the three and five year cumulative survival (TCS and FCS) values among different combinations of treatment. There was no significant difference in survival in those less than 50 years and 50 or more years of age. Females showed a significantly better overall survival compared to males (Hazard Ratio (HR): 1.72 (95% CI=1.1-2.7)). Survival was somewhat but not significantly better among patients who received neck dissection along with surgery for the primary site compared to those who did not receive neck surgery. Patients who did not receive surgical treatment had poorer survival compared to patients who received surgery alone or with other combinations of treatment.

Locally Advanced (Stage III-IVB): Primary surgical treatment with radiation provided the best survival (FCS

67.5%), followed by patients who received cisplatin and 5FU in addition to surgery and radiation (FCS 61.6%). Patients who received only surgical treatment had a significant lower survival as did all other combinations of treatment. Among 216 patients who received surgical treatment 196 (90.7%) underwent surgery for the primary site with neck dissection as well.

Cancer mouth

Early Stage (Stage I and II) (Table 4): Surgical treatment for the primary tumour with neck dissection gave the best survival (both TCS and FCS being 85.7%). This was followed by patients who received surgical treatment for the primary tumour only with no neck

dissection (FCS 81.5%). Patients who received RT alone with or without CT had lower survival (FCS for RT+CT: 57.8%; FCS for only RT: 69.1%).

Locally Advanced (Stage III-IVB): The comparison of patient, diagnostic and treatment characteristics is given in Table 5. A combination of radiation with methotrexate (without surgery) gave the best survival of 67.3% (TCS) and 60.9% (FCS). Surgery plus radiotherapy with or without chemotherapy (cisplatin only or 5-fluorouracil in addition) gave comparable results. All other combinations

Table 1. Cancer Tongue (ICD10:C02.0-02.4; 02.8) Early Stage - Comparison of Patient's Diagnostic and Treatment Characteristics

Characteristics	M+N	M	Others
Number	222	81	146
Males	66.4	71.6	69.2
Females	33.6	28.4	30.8
Patient Characteristics			
Median Age (years)	55	55	55
Performance Status \geq 50%			
Before CDT	97.8	98.8	91.8
After (6-12 weeks) CDT	92.4	91.4	65.8
Waiting Time (<one month)			
Hospital Registration	95.5	93.8	94.5
Diagnosis/Start CDT	64.6	76.5	67.8
Follow-up Proportion	82.5	81.5	91.8
Diagnostic Characteristics			
Histology-Sub-type			
Squamous cell carcinoma	100.0	100.0	98.6
Epithelial carcinoma	0.0	0.0	1.4
Grade of Tumour			
Well differentiated	35.4	45.7	18.5
Moderately differentiated	54.7	43.2	62.3
Poorly differentiated	3.6	0.0	9.6
Unspecified	6.3	11.1	9.6
Assessment of Stage			
One Oncologist	46.2	38.3	10.3
Two Oncologists	34.6	23.5	88.3
Tumor Stage			
T1	48.4	79.0	45.2
T2	51.6	21.0	54.8
Treatment Characteristics			
Type of treatment			
S only	65.5	84.0	-
S + RT + No CT	21.1	11.1	-
S + RT + CT	9.9	2.5	-
S + No RT + CT	3.6	2.5	-
RT only	-	-	80.1
RT+CT	-	-	19.2
Completed initial CDT			
within 3 months	87.9	93.8	87.7
Early/late complications	3.6	3.7	41.8
Recurrence	10.3	12.4	30.1
Died*	22.6	18.2	48.3

All figures (except those in italics) denote relative proportion (%) of patients; Proportions may not total 100% as there could be some unknown; CDT,- Cancer Directed Therapy; RT, Radiotherapy; CT, Chemotherapy; M+N-Main+Neck Surgery; Others, All other treatment combinations; *Proportion (%) is to the total cases of Early and/or late complications and recurrence

Table 2. Cancer Tongue (ICD10:C02.0-02.4; 02.8) Locally Advanced Stage - Comparison of Patient, Diagnostic & Treatment Characteristics between Treatments

Characteristics	A	B	C
Number	82	45	303
Males	48.8	75.6	76.6
Females	51.2	24.4	23.4
Patient Characteristics			
Median Age (years)	54	52	54
Performance Status \geq 50%			
Before CDT	100.0	97.8	93.1
After (6-12 weeks) CDT	91.5	91.1	66.3
Waiting Time (<one month)			
Hospital Registrations	93.9	100.0	92.4
Diagnosis & Start of CDT	59.8	88.9	72.6
Follow-up Proportion	85.4	82.2	91.7
Diagnostic Characteristics			
Histology-Sub-type			
Squamous cell carcinoma	100.0	100.0	99.6
Epithelial Carcinoma	0.0	0.0	0.4
Grade of Tumour			
Well differentiated	19.5	13.3	21.8
Moderately differentiated	76.8	80.0	59.4
Poorly differentiated	2.4	2.2	9.9
Unspecified	1.2	4.4	8.9
Assessment of Stage			
One Oncologist	57.3	68.9	25.7
Two Oncologists	36.6	31.1	62.1
Stage			
III	47.6	37.8	45.5
IV	52.4	62.2	54.5
Tumor Stage			
T1	15.9	6.7	6.9
T2	47.6	40.0	28.7
T3	24.4	28.9	26.7
T4	12.2	24.4	32.0
Node Stage			
N0	14.6	26.7	16.8
N1	40.2	28.9	42.9
N2	45.1	37.8	32.7
N3	0.0	6.7	2.0
Treatment Characteristics			
Completed initial CDT			
within 3 months	86.6	2.2	56.8
Early/late complications	12.2	4.4	43.6
Recurrence	12.2	11.1	17.5
Died*	42.1	57.1	68.2

All figures (except those in italics) denote relative proportion (%) of patients; Proportions may not total 100% as there could be some unknown; Treatment A- Sur (Main) + Opt RT + No CT; Treatment B- Sur (Main) + Opt RT + Cis + 5Fu; Treatment C- All other treatment combinations. CDT - Cancer Directed Therapy, RT - Radiotherapy, CT - Chemotherapy; *Proportion (%) is to the total cases of Early and/or late complications and recurrence

Table 3. Cancer Tongue (ICD10:C02.0-02.4; 02.8). Three Year Cumulative Survival Percent (TCS), Five Year Cumulative Survival Percent (FCS) & Cox Proportional Hazards Ratio (HR) with 95% Confidence Interval (in parentheses) for Type of Treatment

Type of Treatment	No of Patients	TCS	FCS	Unadjusted HR 95% (CI)	Adjusted* HR 95% (CI)
Early Stage					
S (M+N) + No RT + No CT	145	91.6	89.2	1.0	1.0
S (M) + No RT + No CT	68	85.2	83.2	1.74(0.84 - 3.62)	1.71(0.82 - 3.56)
S (M+N) + RT + No CT	47	83.8	79.8	1.64(0.70 - 3.84)	1.62(0.69 - 3.78)
No S + RT + CT	28	74.8	70.9	3.36(1.48 - 7.61)	3.13(1.38 - 7.1)
No S + RT + No CT	117	62.6	55.4	5.04(2.88 - 8.81)	5.07(2.90 - 8.86)
Other combinations	44	74.2	68.8	2.89(1.39 - 6.00)	2.66(1.28 - 5.55)
Sex					
Females	143	88.5	82.7	1.0	1.0
Males	306	75.2	71.8	1.72(1.11 - 2.67)	1.74(1.12 - 2.7)
Total	449	79.5	75.3	-	-
Locally Advanced Stage					
S + RT + No CT	82	68.9	67.5	1.0	
S + RT + Cisplatin + 5Fu	45	66.8	61.6	1.25 (0.67 - 2.34)	
S + No RT + No CT	31	56.9	42.3	2.16 (1.14 - 4.10)	
S + RT + Only Cisplatin	29	55.2	48.3	2.10 (1.11 - 3.98)	
No S + RT + Other Drugs	45	51.4	46.4	2.23 (1.28 - 3.88)	
S + RT + Other Drugs	18	43.2	27.8	2.96 (1.51 - 5.78)	
No S + RT + Only Cisplatin	59	35.6	28.8	3.44 (2.10 - 5.65)	
No S + RT + Cisplatin + 5Fu	9	30.0	15.0	4.84 (1.98 - 11.82)	
No S + RT + No CT	51	24.6	17.9	4.73 (2.88 - 7.78)	
No S + No RT + Other Drugs	10	13.0	13.0	4.38 (1.89 - 10.15)	
Other combinations	45	39.3	33.6	3.24 (1.89 - 5.56)	
Total	424	48.5	42.8	-	

S – Surgery, M+N-Main+Neck, RT – Radiotherapy, CT – Chemotherapy, Other Drugs – without cisplatin; * Type of Treatment is adjusted with Sex

Table 4. Cancer Mouth- (ICD10:C03-04, C06). Three Year Cumulative Survival Percent (TCS), Five Year Cumulative Survival Percent (FCS) & Cox Proportional Hazards Ratio (HR) with 95% Confidence Interval (in parentheses) for Type of Treatment

Type of Treatment	No of Patients	TCS	FCS	Unadjusted HR 95% (CI)
Early Stage				
S (M+ N) + No RT + No CT	28	85.7	85.7	1.0
S (M) + No RT + No CT	48	89.4	81.5	1.11 (0.34 - 3.7)
S (M + N) + RT + No CT	38	81.6	73.4	1.97 (0.62 - 6.27)
No S+ RT + No CT	192	75.0	69.1	2.30 (0.83 - 6.35)
No S + RT + CT	67	68.3	57.8	3.45 (1.21 - 9.85)
Other combinations	41	72.3	69.5	2.66 (0.87 - 8.08)
Total	414	76.7	70.3	
Locally advanced Stage				
S (M) + RT + No CT	139	65.6	60.4	1.0
No S + RT + MTX	156	67.3	60.9	0.87 (0.6 - 1.26)
S (M) + RT + Only Cisplatin	35	65.7	56.0	1.16 (0.67 - 1.99)
S (M) + RT + Cisplatin + 5Fu	37	61.6	58.8	1.01 (0.57 - 1.79)
No S + RT + No CT	449	51.8	43.6	1.55 (1.16 - 2.07)
S (M) + No RT + No CT	48	50.6	46.0	1.62 (1.02 - 2.58)
No S + RT + Only Cisplatin	190	50.2	44.5	1.56 (1.12 - 2.16)
No S + RT + Other Drugs	95	48.8	39.4	1.71 (1.18 - 2.47)
No S + RT + Cisplatin + 5Fu	59	43.4	38.8	1.82 (1.19 - 2.80)
Other combinations	182	37.8	30.1	2.39 (1.73 - 3.31)
Total	1390	53.2	46.1	-

S-Surgery, RT – Radiotherapy, CT – Chemotherapy, M+N- Main+Neck

of treatment had significantly lower survival. (Table 4)

Cancer Oro-pharynx

Early Stage (Stage I and II) (Table 6): The proportion of patients who received surgical treatment was 7.7%. There was no statistically significant difference in survival between patients who received RT alone or RT and CT (95% CI=0.8-2.5).

Locally Advanced (Stage III-IVB): The comparison of patient, diagnostic and treatment characteristics is given in

Table 5. Cancer Mouth- (ICD10:C03-04, C06) - (Locally advanced Stage). Comparison of Patient, Diagnostic & Treatment Characteristics between Treatments

Characteristics	A	B	C
Number	139	156	1,095
Males	59.7	59.0	63.0
Females	40.3	41.0	37.0
Patient Characteristics			
Median Age (years)	60	61	60
Performance Status \geq 50%			
Before CDT	93.5	98.1	90.4
After (6-12 weeks) CDT	87.1	92.3	69.8
Waiting Time (<one month)			
Hospital Registration	96.4	98.1	94.6
Diagnosis & Start of CDT	95.7	96.2	61.6
Follow-up Proportion	77.7	69.9	85.4
Diagnostic Characteristics			
Histology-Sub-type			
Squamous cell carcinoma	100.0	100.0	98.3
Epithelial carcinoma	0.0	0.0	1.7
Grade of Tumour			
Well differentiated	23.0	37.8	30.0
Moderately differentiated	67.6	37.2	46.8
Poorly differentiated	3.6	1.3	4.6
Unspecified	5.8	23.7	18.4
Assessment of Stage			
One Oncologist	51.1	94.2	51.7
Two Oncologists	38.9	5.1	42.7
Stage			
III	18.7	44.9	39.4
IV	81.3	55.1	60.6
Tumor Stage			
T1	4.3	2.6	3.8
T2	17.3	21.8	24.0
T3	5.0	30.8	20.1
T4	70.5	39.1	46.5
Node Stage			
N0	38.8	17.9	21.1
N1	33.8	55.1	47.0
N2	24.5	20.5	24.9
N3	0.0	0.6	1.4
Treatment Characteristics			
Completed initial CDT			
within 3 months	73.4	91.7	87.9
Early/late complications	12.2	10.9	31.2
Recurrence	14.4	18.0	16.0
Died*	54.3	36.4	59.1

All figures (except those in italics) denote relative proportion (%) of patients; Proportions may not total 100% as there could be some unknown; Treatment A- Sur (Main) + Opt RT + No CT, Treatment B- No Sur + Opt RT + Methotrexate, Treatment C- All other treatment combinations, CDT - Cancer Directed Therapy, RT - Radiotherapy, CT - Chemotherapy; *Proportion (%) is to the total cases of Early and/or late complications and recurrence

Table 7. The proportion of patients who received surgical treatment was 6.7% (Table 6) with most of the others receiving radiation alone or a combination of radiation and chemotherapy (RTCT). The latter had a significantly better survival compared with radiation alone (FCS 40.0% and 25.5%). There was no survival difference in the types or combinations of drugs used for chemotherapy.

Cancer Hypo-pharynx (Table 6)

A combination of RT with CT resulted in significantly better survival than RT alone in both early (Stage I and II) and in locally advanced (Stage III-IVB) disease. The use of cisplatin alone or in combination with 5-FU and/or use of other drug combinations in chemotherapy did not significantly alter the survival. The comparison of patient, diagnostic and treatment characteristics for locally advanced stage is given in Table 8.

Cancer larynx

Early Stage (Stage I and II): Over 88% (88.7%) of patients received only radiation as the mode of treatment with another 7.7% receiving radiation with either surgery and/or chemotherapy. There was no difference in survival between those who received RT alone and other combinations of treatment.

Locally Advanced (Stage III-IVB) (Table 9): Surgery followed by radiation or radiation combined with cisplatin and 5-fluorouracil gave comparable survival figures. Surgery alone had a non-significant lower survival. All other combinations of treatment had lower survival. Out of 119(31.1% of all laryngeal cancers) laryngeal cancers that had laryngectomy, 29 did not receive any other treatment and 51 received radiation. There was no statistically significant difference in the FCS between these two groups and those that had no surgical treatment but had received RTCT. The remaining 39 laryngectomy patients who had other combinations of treatment had significantly poorer survival.

Table 10 provides comparisons in survival with other studies where near comparable survival based on specific anatomical sites of head and neck cancers were available. The FCS in the present study is higher than that observed in other reports.

Table 11 indicates the proportion of patients who received the different kinds of treatment in each of the organ sites of head and neck cancer that gave better survival compared to other combinations of treatment. This proportion is listed for a) the complete data from 12 institutions and b) from institutions where data was used for survival analysis.

Discussion

In India head and neck cancers as a whole account for 25.9% of all cancers in males and 7.4% in females (NCDIR, NCRP, 2013). Locally advanced cancers (Stage III-IV) were the predominant proportion (62.4% - 87.7%) in all these anatomical sites.

There have been several reports on survival in head and neck cancers from single institutions in India (Rao et al., 1998; Dimri et al., 2013; Gupta et al., 2013). This multi-

Table 6 Cancer Oropharynx (ICD10:C01,05,09-10,14) & Hypopharynx (ICD10:C12-13). Three Year Cumulative Survival Percent (TCS), Five Year Cumulative Survival Percent (FCS) & Cox Proportional Hazards Ratio (HR) with 95% Confidence Interval for Type of Treatment

Type of Treatment	No of Patients	TCS	SB\$	FCS	SB\$	Unadjusted HR 95% (CI)
Cancer Oropharynx						
Early stage						
RT + CT	47	77.9		60.2		1.0
RT	85	59.4	18.5	52.8	7.4	1.42 (0.80 - 2.52)
Other combinations	11	100		75.0		0.48 (0.15 - 1.56)
Total	143	68.9		57.0		-
Locally advanced stage						
RT + CT	322	50.8		40.0		1.0
RT	174	33.8	17.0	25.5	14.5	1.54 (1.23 - 1.94)
Other combinations	123	40.2		35.3		1.3 (0.99 - 1.71)
Total	619	43.8		34.9		-
Cancer Hypopharynx						
Early stage						
RT + CT	36	71.5		68.7		1.0
RT	31	48.4	23.1	41.9	26.8	2.16 (1.04 - 4.49)
Other combinations	16	62.5		49.2		1.74 (0.73 - 4.17)
Total	83	61.1		54.7		-
Locally advanced stage						
RT + CT	198	46.8		38.7		1.0
RT	116	29.4	17.4	23.4	15.3	1.65 (1.25 - 2.19)
Other combinations	166	34.0		29.8		1.41 (1.08 - 1.83)
Total	480	38.1		32.0		-

RT – Radiotherapy, CT – Chemotherapy, SB\$ – Survival Benefit between RT alone and RT + CT

centric observational study provides results on stage and treatment based survival as part of an expanded exercise of hospital based cancer registries - named Patterns of Cancer Care and Survival Study (POCCS). Because of variations in types of cancer directed treatment and outcome in individual organ sites of head and neck, the results of this study are given by single anatomical sites rather than head and neck cancers as a whole.

A recent report (D’Cruz et al., 2015) suggests that for early stage cancers (especially of the tongue) therapeutic neck dissection significantly benefitted survival when compared with patients who had surgery for the primary site alone without neck dissection. This study showed an improved survival in patients who had simultaneous neck node dissection along with the primary tumour compared with those without, but was not statistically significant. In the absence of surgical treatment, patients who received a combination of RT and CT have shown better survival than patients who received RT alone. We could not ascertain the reasons for patients not undergoing surgery or not receiving CT, but we envisage that this could be due to issues un-related to the medical condition of the patients.

Rao et al. (1998) have reported an observed overall five year survival of 31 and 21.3% respectively for Stage III and IV (locally advanced) cancer of anterior tongue. The five year cumulative survival in this report for locally advanced disease was 42.8%. Surgical treatment in the form of glossectomy followed by radiation gave the best results. This study has additionally underscored the importance of the combination of cisplatin and 5FU along with surgical treatment and radiotherapy. Patients who

had surgery and radiotherapy along with cisplatin only (without 5FU) have fared poorly compared to those who received 5FU in addition.

As for cancers of the tongue, surgical treatment in the form of mandibulectomy with its variants was the mainstay for locally advanced carcinomas of the mouth. In the absence of surgery, radiation with methotrexate gave similar results. This is an unusual result and would require further investigation.

The improved survival with RTCT as opposed to RT alone for locally advanced cancers of the oro and hypopharynx has been demonstrated in earlier reports. Our study has confirmed this for locally advanced cancers of both these sites and for early stage hypo-pharyngeal cancer. What is indeed perplexing is that only 52% of patients with oro-pharyngeal and 41.3% of cancers of the hypo-pharynx have received this benefit with others receiving RT alone or other combinations of treatment with ensuing poorer survival.

This paper has once again highlighted that for laryngeal cancers can be treated in ways other than surgery and therefore with organ preservation and good quality life without affecting survival.

This study reports results from a large observational study combining data from several major cancer hospitals in different parts of India and is not a randomized one. It provides an overview of comparative survival with various treatment modalities. Since patients were categorized purposively rather than randomly into different treatment groups, survivor figures reflect the combined effects of criteria therapeutic categorization

and the therapeutic categories themselves. Some criteria for dividing patients could be objective e.g. stage of the disease and for the parameters available in the dataset, the effect measurements can be adjusted. Some of the criteria may be considered subjective and those cannot be taken into account in analysis. All the patients who received cancer directed treatment in the participating institutions were included. Exclusion criteria were based on scientific logic. Thus, there was no selection bias. There is the possibility of some patients having received additional treatment elsewhere the details of which could not be quantified. Because of the challenges of patient follow-up

in the Indian setting, progression or event free survival or patterns of relapse could not be ascertained. Recurrence and complication proportions could be an underestimate and information on late toxicity has not been provided.

Strengths and opportunities: This study may be considered as a pioneering effort of NCDIR where the feasibility of a multi-centric hospital based clinical cancer registry has been explored with the help of dynamic data capture, checks and analysis through the internet. As a result of this endeavour, therapy related survival could be worked out that may lead to formation of an evidence based oncological practice guideline suitable for Indian

Table 7. Cancer Oropharynx - Locally Advanced Stage. Comparison of Patient, Diagnostic & Treatment Characteristics between Treatments

Characteristics	RT+CT	RT	Others
<i>Number</i>	322	174	123
Males	91.6	90.8	80.5
Females	8.4	9.2	19.5
Patient Characteristics			
Median Age (years)	56	62	61
Performance Status \geq 50%			
Before CDT	92.9	89.1	86.2
After (6-12 weeks) CDT	77.0	62.6	64.2
Waiting Time (<one month)			
Hospital Registration	93.8	95.4	91.7
Diagnosis & Start of CDT	73.9	62.1	62.6
Follow-up Proportion	86.0	87.9	77.2
Diagnostic Characteristics			
Histology-Sub-type			
Squamous cell carcinoma	96.0	97.1	99.2
Epithelial carcinoma	4.0	2.9	0.8
Grade of Tumour			
Well differentiated	16.8	17.8	20.3
Moderately differentiated	46.9	47.7	44.7
Poorly differentiated	18.3	14.9	13.0
Unspecified	18.0	19.5	22.0
Assessment of Stage			
One Oncologist	55.3	51.1	56.1
Two Oncologists	35.1	35.7	30.1
Stage			
III	43.5	54.0	37.4
IV	56.5	46.0	62.6
Tumor Stage			
T1	1.6	4.6	6.5
T2	29.8	24.7	22.8
T3	41.0	44.3	38.2
T4	15.8	16.1	22.8
Node Stage			
N0	14.9	23.6	20.3
N1	31.7	32.8	22.8
N2	37.0	32.8	35.8
N3	4.7	0.6	11.4
Treatment Characteristics			
Completed initial CDT			
within 3 months	94.4	97.7	74.8
Early/late complications	27.0	20.1	22.8
Recurrence	13.9	15.5	14.6
Died*	60.5	69.8	52.4

All figures (except those in italics) denote relative proportion (%) of patients; Proportions may not total 100% as there could be some unknown; Others- All other treatment combinations, CDT - Cancer Directed Therapy, RT - Radiotherapy, CT - Chemotherapy; *Proportion (%) is to the total cases of Early and/or late complications and recurrence

Table 8 Cancer Hypopharynx - Locally Advanced Stage. Comparison of Patient, Diagnostic & Treatment Characteristics between Treatments

Characteristics	RT+CT	RT	Others
<i>Number</i>	198	116	166
Males	77.3	83.6	74.1
Females	22.7	16.4	25.9
Patient Characteristics			
Median Age (years)	55	63	56
Performance Status \geq 50%			
Before CDT	87.4	81.9	91
After (6-12 weeks) CDT	68.7	63.8	74.1
Waiting Time (< one month)			
Hospital Registration	91.4	92.2	95.2
Diagnosis & Start of CDT	78.3	69.0	59.6
Follow-up Proportion	57.6	72.4	65.7
Diagnostic Characteristics			
Histology-Sub-type			
Squamous cell carcinoma	97.5	98.3	97.6
Epithelial carcinoma	2.5	1.7	2.4
Grade of Tumour			
Well differentiated	16.2	13.8	12.7
Moderately differentiated	48.0	40.5	48.8
Poorly differentiated	14.1	18.1	24.7
Unspecified	21.2	27.6	13.9
Assessment of Stage			
One Oncologist	45.5	47.4	46.4
Two Oncologists	36.3	35.4	43.4
Stage			
III	50.0	52.6	25.3
IV	50.0	47.4	74.7
Tumor Stage			
T1	3.5	0.9	2.4
T2	31.8	31	15.1
T3	39.4	36.2	38.0
T4	14.6	12.9	31.3
Node Stage			
N0	22.2	20.7	18.1
N1	32.8	30.2	23.5
N2	29.8	25	33.1
N3	4.5	5.2	12.0
Treatment Characteristics			
Completed initial CDT			
within 3 months	92.9	100	78.3
Early and/or late complications	27.3	19.0	22.3
Recurrence	17.2	12.0	16.2
Died*	45.6	75.0	67.3

All figures (except those in italics) denote relative proportion (%) of patients; Proportions may not total 100% as there could be some unknown; Others- All other treatment combinations, CDT - Cancer Directed Therapy, RT - Radiotherapy, CT - Chemotherapy *Proportion (%) is to the total cases of Early and/or late complications and recurrence

Table 9. Cancer Larynx (ICD10:C32) (Locally Advanced stage). Three Year Cumulative Survival Percent (TCS), Five Year Cumulative Survival Percent (FCS) & Cox Proportional Hazards Ratio (HR) with 95% Confidence Interval (in parentheses) for Type of Treatment.

Type of Treatment	No of Patients	TCS	FCS	Unadjusted HR 95% (CI)
S + RT + No CT	51	73.9	64.8	1.0
No S + RT + Cisplatin + 5Fu	71	77.2	63.8	0.93 (0.49 - 1.74)
No S + RT + No CT	93	60.2	48.3	1.7 (0.98 - 2.94)
S + No RT + No CT	29	57.9	46.5	1.77 (0.89 - 3.51)
No S + RT + Other Drugs	20	50.8	45.2	2.01 (0.93 - 4.36)
No S + RT + Only Cisplatin	33	50.2	41.7	2.16 (1.12 - 4.17)
S + Other combinations	39	71.1	52.4	1.24 (0.63 - 2.44)
No S + Other combinations	47	55.1	44.1	1.89 (1.03 - 3.47)
Total	383	64.3	52.8	-

S-Surgery, RT – Radiotherapy, CT – Chemotherapy

Table 10. International Comparison of Survival Rates

Authors	Study type/Year	Treatment	N	TCS (%)	FCS (%)
Early Stage					
Cancer Tongue					
D'Cruz AK et al (2015)	Randomised trial (2004-2014)	Therapeutic surgery	243	67.5	
		Elective surgery	253	80	
D'Cruz AK et al (2009)	Retrospective study (1980-1994)	Wait and watch	359	62	60
		END		69	60
Yuen AP et al (1997)	Retrospective study (1980-1994)	Wait and watch	30		55F
		END	33		86F
Yuen AP et al (2009)	Randomised trial	Observation	35		87F
		END	36		89F
Haddadin KJ et al (1999)	Retrospective study (1980-1996)	No Neck dissection	53		59.7D
		NKDM	37		44.8D
		NKDS	47		80.5D
Matsuzuka T et al (2014)	Retrospective study (1987-2007)	Wait and watch	52		84
		SNNS	29		96
Huang SF et al (2008)	Retrospective study (1995-2002)	Observation	56		75.1
		MRND	37		79.6
		SOND	287		87.2
Present study	Observational study (2006-2008)	Surgery (M)	68	85.2	83.2
		Surgery (M+N)	145	91.6	89.2
		Overall	449	79.5	75.3
Locally Advanced stage					
Oral cavity/Mouth					
Razak et al (2010)	Observational study (1986-2005)	S	26		38.5
		S+RT	28		30.6
Present study	Observational study (2006-2008)	S +RT	139	65.6	60.4
		S+RT+CT	98	67.7	62.0
		Overall	1390	53.2	46.1
Oropharynx					
Denis et al (2004)	Randomised trial	RT	113		16
		RT+CT (Carboplatin+5FU)	109		22
Present study	Observational study (2006-2008)	RT	174	33.8	25.5
		RT+CT	322	50.8	40.0
		Overall	619	43.8	34.9
Larynx					
Forastiere AA et al (2003)	Randomised trial	RT	173		56
		RT+CT(Cis)	172		54
		RT+CT(Cis+5FU)	173		55
Present study	Observational study (2006-2008)	S +RT	51	73.9	64.8
		RT+CT(Cis+5FU)	71	77.2	63.8
		Overall	383	64.9	52.8

Three year cumulative survival percent (TCS), Five year cumulative survival percent (FCS), END-Elective Neck Dissection, F Disease Free Survival, NKDM-Metachronous Neck Dissection, NKDS-Synchronous Neck Dissection, D Disease related survival, SNNS-Sentinel Node Navigation Surgery, MRND- Modified Radical Neck Dissection, SOND- Supraomohyoid Neck Dissection, (M+N)-Main+Neck, S-Surgery, RT – Radiotherapy, CT – Chemotherapy, Cis- Cisplatin; *Present study site of cancer (ICD10) may not be same for other author's studies.

Table 11. Proportion (%) of Patients Who Received Treatment with more Favourable Survival for (a) Patterns of Care (POC) and (b) Patterns of Survival (POS) sets of data

Specific treatment	Early Stage		Locally Advanced Stage		
	POC	POS	Specific treatment	POC	POS
Tongue					
S (M+N) + No RT + No CT	33.6	32.3	S + RT + No CT	27.6	19.1
S (M) + No RT + No CT	21.5	15.1	S+ RT + Cisplatin + 5Fu	3.1	10.5
S (M+N) + RT + No CT	14.9	10.5			
Total	70.1	57.9	Total	30.8	29.5
Mouth					
S (M+ N) + No RT + No CT	24.4	6.8	S (M) + RT + No CT	21.8	10
S (M) + No RT + No CT	17.2	11.6	No S + RT + MTX	3.7	11.2
S (M + N) + RT + No CT	17.4	9.2	S (M) + RT + Only Cisplatin	5.8	2.5
No S+ RT + No CT	21.0	46.4	S (M) + RT+ Cisplatin +5Fu	1.0	2.7
Total	80.0	73.9	Total	32.3	26.4
Oropharynx					
RT	51.9	59.4	RT+CT	24.4	52.0
RT+CT	19.1	32.9			
Total	71.1	92.3			
Hypopharynx					
RT + CT	30.4	43.4	RT + CT	20.4	41.3
Larynx			S (M) + RT + No CT	5.5	13.3
			No S + RT+ Cisplatin+ 5Fu	4.8	18.5
			No S + RT + No CT	18.8	24.3
			S (M) + No RT + No CT	6.3	7.6
			No S + RT+ Other Drugs	3.8	5.2
			Total	39.2	68.9

S-Surgery, RT – Radiotherapy, CT – Chemotherapy, M+N-Main+Neck

population for site specific cancers.

In conclusion, this study has shown the importance of separating out individual anatomical sites of head and neck squamous cell carcinomas rather than giving the picture as a whole. Secondly, in the context of a developing country the need to promote awareness about the requirement of concurrent chemo-radiation in the cancers of the oro and hypopharynx has been highlighted. Thirdly, surgical treatment in locally advanced cancers of the anterior tongue and mouth is the mainstay of an effective therapeutics though additional RT and/or CT do have their benefit. This data has shown that such optimal treatments are given in only a little over one-third (35.7%) of patients with locally advanced disease. The annual (2014) estimate number of new Head and Neck cancers with locally advanced disease in India is around 140,000 and if one extrapolates, then 91,000 (65%) patients every year do not receive the benefit of optimal treatment with ensuing poorer survival.

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