

Original Article

A Retrospective Analysis of Disease-free Survival of 2332 Cases of Cancer of the Oral Tongue from a Single Institute in Eastern India from 1998-2017

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Background : Over half the patients of Oral Tongue Cancers in India present with locally advanced disease and Nodal Metastasis. Additionally many of them avoid surgical intervention due to fear or belief that Cancer is a Death Sentence.

Materials and Methods : A Retrospective analysis of all Oral Tongue Cancer patients treated at Mahavir Cancer Sansthan from 1998 to 2017 was done. The primary aim was to find the Disease Free Survival (DFS) rates of these patients. The secondary aim was to examine if surgical excision improved DFS rates.

Results : The mean DFS for all stages was 51 months varying from 90 months in stage 1 to 30 months in stage 4. One in every three patients survived without recurrence of disease for more than five years. The addition of surgical excision at any stage of Cancer, when possible, resulted in a significant increase in DFS.

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Key words : Oral Tongue Cancer, Disease-free Survival, Surgery, Retrospective.

Majority of patients of Oral Tongue Cancer in India present in stages three and four¹ leading to reduced disease free survival rates²⁻⁴.

The ICMR Consensus Document for Management of Tongue Cancer⁵ recommends single modality treatment for early stage Cancers and Multimodality therapy for advanced stage disease but Surgery with or without an Adjuvant Therapy is the preferred modality. Retrospective studies and randomized trials have found significantly reduced survival rates for patients treated without surgery^{6,7}. But very often patients in India are treated by Radiotherapy either due to their choice, comorbidities or locally advanced disease that make them unsuitable for Surgery⁴.

Mahavir Cancer Sansthan was established in Patna in 1998 as a Tertiary Cancer Therapy Centre. Initially it housed a Cobalt Teletherapy Machine and all patients were treated by Radiotherapy. Gradually other branches of therapy were established and Multimodality Therapy became the norm for most patients of Oral Tongue Cancers. The institute attracts

Editor's Comment :

- Average Disease free survival of patients of Oral Tongue treated at Mahavir Cancer Sansthan is 51 month and varies from 90 months for stage 1 to 30 months for stage 2.
- Surgical excision of tumour should be done whenever possible.

patients from Bihar, Jharkhand, North Bengal, Parts of Nepal and Bangladesh. It has catered to over two Lakh Cancer patients during its years of service.

The Authors did a Retrospective Analysis of Oral Tongue Cancer patients treated at Mahavir Cancer Sansthan between 1998-2017 to answer two questions: what is the disease free survival of tongue cancer patients in Eastern India and does the addition of Surgery, when possible, increase disease free survival.

MATERIALS AND METHODS

This study was approved the ICE-RMRIMS Ethics Committee.

The treatment records of all Biopsy proven patients of Oral Tongue Squamous Cell Cancers (SCC) (ICD sites C02.0-C02.3 excluding C01, C02.4, C02.8 and C02.9)⁸ were accessed and relevant data extracted. All patients who had Palliative Therapy, treatment outside the institute, incomplete therapy or incomplete follow up, incomplete treatment records or patients with histology other than SCC were excluded.

Variables examined included age, gender, WHO grade of differentiation⁹, TNM and Clinical stage as per AJCC 7th edition¹⁰, type of definitive therapy, outcome of therapy and whether any salvage therapy

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was proposed or used. The type of definitive therapy was classified into 'surgical' if it included Surgery, surgery with Radiotherapy (RT)/ Chemoradiotherapy (CRT) or Neoadjuvant Chemotherapy (NACT) with surgery with RT/CRT; and 'Non-surgical' if it included RT, CRT, NACT with CRT, Brachytherapy with RT/CRT or Brachytherapy. All Doses of Radiotherapy/ Brachytherapy were converted to Equivalent Total Dose of 2 Gy fractions using the Linear Quadratic Equation¹¹.

Outcome of therapy was divided into 'Failure' if the patient experienced recurrence of Malignant Disease or 'Censored' if no failure was experienced or patient expired before recurrence. If there were Cytological, Histological or Radiological reports giving proof of recurrence these were noted as the method of diagnosis, otherwise the method of diagnosis was classified as 'Clinical'. The site of recurrence was classified as – 'Local' if it occurred within the oral cavity; 'Regional' if it occurred within the draining nodal basin; and 'Distant' if it occurred in distant organs.

'Disease Free Survival (DFS)' was defined as the period from commencement of definitive therapy to first recurrence or last date of follow-up, whichever was earlier. 'Updated DFS' was defined as the period from commencement of definitive therapy to the last telephonic update when the patient could be contacted. 'Diagnosis to Treatment Initiation Time (DTIT)' was defined as the period between first examination at the institute and commencement of definitive therapy. 'Treatment Package Time (TPT)' was defined as the period between commencement and end of Definitive therapy including any Adjuvant therapy. 'Days of default' was defined as any number of days of gap in therapy from first presentation to end of therapy of more than seven days, since seven days is the kick-off repopulation time for Head and Neck Cancers¹¹.

If the patient was offered Salvage Surgery or re-irradiation he/she was considered salvageable; if the patient was offered Palliative Chemotherapy or best supportive care he/she was non-salvageable. If the records did not mention any Second Line Therapy, it was considered a missing value.

The data was stored in EXCEL spreadsheet and 'DAYS' function used to calculate the time intervals. DFS was converted into year-fractions using 'YEARFRAC' function and multiplied by twelve to obtain the same in months. Statistical analysis was done using SPSS version 20. Tests used included Chi-square, Mann-Whitney, ANOVA/Kruskal – Wallis, Kaplan-Meier and Cox Proportional Hazard. Probability levels less than 0.05 were considered significant.

OBSERVATIONS

2332 biopsy-proven Oral Tongue Cancer patients were treated at Mahavir Cancer Sansthan between 1998 and 2017. In 1771 cases were excluded for the following reasons – 290 due to Palliative Therapy, 810 for refusing treatment, 460 for having undergone treatment at other institutes, 153 due to incomplete therapy, 18 because of Histologies other than Squamous Cell Cancer, 7 because they received less than 40 Gy Radiotherapy and 38 cases because they had zero days of follow-up. This left 561 analysable cases of Oral Tongue Cancer.

The Demographic and Clinical Characteristics and results of therapy are given in Table 1.

The median follow-up, estimated using the reverse KM method¹², was found to be 18.7 months (95% CI: 16 – 21 months) and update median follow-up after telephonic contact was 26.6 months (95% CI: 20 – 33.2 months). The median DFS was 11 months (95% CI: 8 – 14 months), while updated DFS was 11.5 months (95% CI: 6 – 16.6 months). Hereon all survival analysis was done using updated DFS. Five-year DFS was 33.6%. 57.8% patients experienced recurrence within 24 months of therapy. 64% recurrences were local while 16% were nodal. Only 8% patients could be offered Salvage Therapy.

The results of univariable KM and multi-variable Cox Proportional Hazard analysis is given in Table 2. The clinical stage of disease, type of therapy (surgical *versus* non-surgical) and presence of default were found to significantly influence disease-free survival. Treatment Package Time tends to significance ($p = 0.06$) and hence should be considered an important predictor.

Figs and the attached Table compares the survival curves for 'Surgical' versus 'Non-surgical' therapy stratified by clinical stage.

DISCUSSION

The median follow-up of 19 months in our study is similar other Indian studies^{4,13} but much less than the 36-45 months recorded by foreign authors¹⁴⁻¹⁶. Probably, this indicates the time after which an Indian patient will stop surveillance due to either poverty, logistic barriers or Lack of Awareness.

The overall five year DFS of 34% is also lower than the results of other Indian and Foreign Authors^{4,13-15} but our series had a higher proportion of Stage 4A and 4B patients (44% *versus* 15-29%).

Surgical excision of the tumour was a very significant predictor of DFS at each stage of the disease. In Stages 1 and 3 the Surgery group did not

Variable	percent	P value
Gender :		
Male	417	74.3
Female	144	25.7
Age (mean ±SD) :		
Male	48 ±14	0.148
Female	49.6 ±11	
Median age * gender		
Grade of Differentiation :		
Well Differentiated	153	56
Moderately differentiated	107	39
Poorly differentiated	13	5
Clinical T Stage :		
T1	61	11
T2	189	35
T3	104	19
T4	191	35
Clinical N Stage :		
N0	279	51
N1	144	27
N2a	38	7
N2b	57	10
N2c	21	4
N3	5	1
Clinical Stage :		
1	53	9.7
2	168	30.8
3	86	15.8
4	239	43.8
Stage * Differentiation		
0.119		
Type of therapy :		
Surgery	32	5.7
Surgery + RT ^β	162	28.9
Surgery + CRT ^γ	72	12.8
NACT + Surgery + RT/CRT ^δ	20	3.6
Radiotherapy	113	20.1
Chemoradiotherapy	115	20.5
RT + Brachytherapy	29	5.2
NACT + RT/CRT	16	2.9
Brachytherapy	2	0.4
Therapy * Stage 1/2		
0.088		
Therapy * Stage 3/4 ^ε		
0.03		
Outcome of therapy :		
Failure due to recurrence	300	53.5
No recurrence	261	46.5
Site of Recurrence :		
Local	191	63.9
Regional(Nodal Basin)	47	15.7
Distant	24	8.0
Local + Regional	35	11.7
Others	2	0.6
Method of diagnosis of recurrence :		
Cytology :	60	20
Histopathology	44	15
Radiology	34	11.4
Clinical	159	53.2
Others	2	1
Diagnostic mode*type of therapy ^ν		
<0.01		
Salvage Therapy :		
Applicable	155	51
Not Applicable	25	8
Not Recorded	123	40.6
Salvage*Type of therapy		
0.19		

β - Radiotherapy, γ - Chemoradiotherapy, δ - Neoadjuvant Chemotherapy, ε - this difference can be explained by number T4b (inoperable patients) who were given RT/CRT, ν - clinically diagnosed recurrences were commoner among patients with non-surgical therapy

Variable	p value	
	univariable	multi-variable
Clinical Stage of disease	< 0.01	0.018
Default in treatment – yes/no	< 0.01	< 0.01
Type of therapy – surgical/non-surgical	< 0.01	< 0.01
Treatment Package Time(TPT)	0.284	0.06
Grade of differentiation	0.685	0.766
Age	NA	0.407
Gender	0.144	0.134
Clinical T stage	< 0.01	0.505
Clinical N Stage	< 0.01	0.617
Diagnosis – Treatment Initiation(DTI)	< 0.01	0.394

attain median survival on a maximum follow up 140 months. An equal proportion of early stage and late stage patients underwent surgical therapy (H = 2.322; p = 0.50) and Radiotherapy (H = 3.040; p = 0.37). Similar results have been recorded by other authors^{6,14,17,18}. A randomized trial comparing Surgery and Radiotherapy versus Chemoradiotherapy found increased survival in the surgical arm which failed to reach statistical significance but it included Advanced Tongue Cancer patients only⁷. Therefore, we suggest that surgery should be a part of the therapeutic regime whenever possible.

The median 'Diagnosis to Treatment Initiation' time (DTI) and 'Treatment Package Time' were 28 days (Interquartile range: 16-51 days) and 62 days (Interquartile range: 47-76 days), respectively. A systematic review of both intervals found threshold values from 20-120 days and 77-100 days respectively¹⁹. Since the values in our series was within the threshold range and neither was found to affect survival.

Figures (1-5) — Survival Curves of Oral Tongue cancer patients stratified by clinical stage and type of therapy with

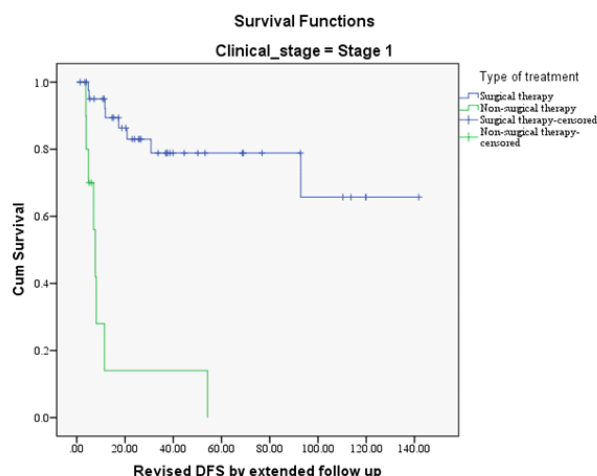


Fig 1

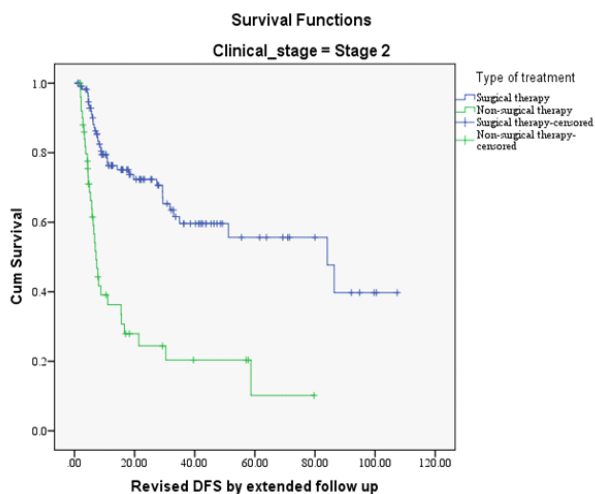


Fig 2

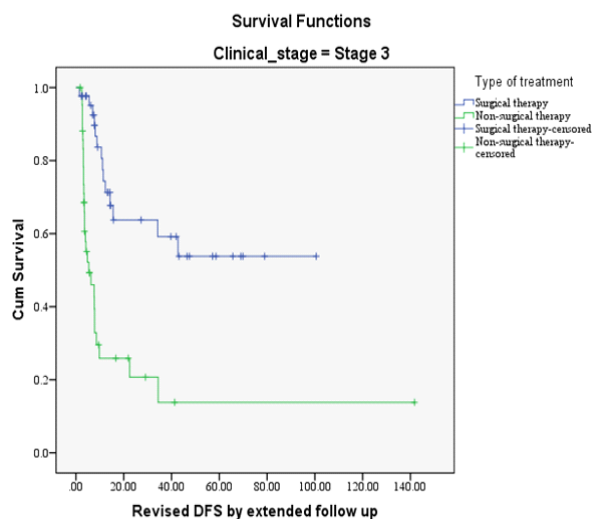


Fig 3

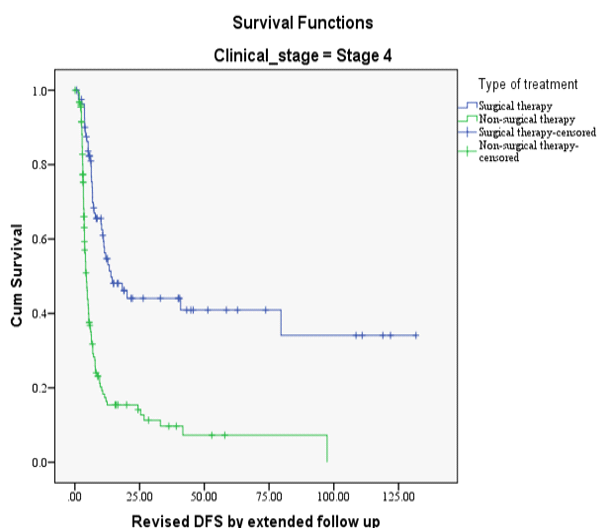


Fig 4

	Stage 1	Stage 2	Stage 3	Stage 4
Surgical Therapy	**	84.1	**	13.9
Non-surgical Therapy	7.7	7.2	5.4	4.5

Fig 5

The mean duration of default was 9 days (95% CI: 5-15 days) and although only 7.3% patients defaulted it was a very significant independent predictor of the outcome. 83% defaults occurred during radiotherapy reducing the planned to administered EQD 2 by 10-60%.

All other predictors including age, gender, clinical T and N stages and grade of differentiation were not significant. While clinical T and N stages were found significant in univariable analysis they were insignificant

on multivariable analysis, probably because they get subsumed in the clinical stage.

Limitations of the Study :

This is a retrospective study done on hospital records accumulated over a 19 year period and therefore suffers from all the disadvantages of any such study²⁰. Not all records were meticulously maintained and when found incomplete, such records had to be excluded. The authors have tried to eliminate sources of bias by strictly adhering to the inclusion and exclusion criteria and making all Radiotherapy regimes as comparable as possible.

There was no Cytological or Histological Proof of 52% of recurrent Tumours and this was commoner in patients undergoing non-surgical therapy ($p < 0.01$). Probably, most of these patients were of advanced stage and when they failed either the clinician felt it unnecessary to pursue a Biopsy for just palliative Therapy or the patient refused biopsy/FNAC or financial constraints forced the patient to Abandon Therapy.

Conclusions :

- (1) The mean disease-free survival of a Tongue Cancer patient in Eastern India for all stages is 51.4 months, varying from 90 months in Stage 1 disease to 30 months in Stage 4 (mean DFS has been quoted since median DFS for stage 1 patients was not reached at the conclusion of this study).
- (2) One in three patients experience disease-free survival for five years or more.
- (3) 60% patients are likely to experience recurrence of Cancer within 24 months of Therapy.
- (4) The addition of surgical excision of the disease

makes a very significant difference in the outcome ($p < 0.01$).

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Conflict of Interest : None

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