



Computed Tomography for Staging in Head and Neck and Oral Cancer How accurate are we? Are we underestimating our clinical target volume?

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Abstract

Aim: To compare radiological [Computed Tomography (CT)] tumour and nodal dimensions in head and neck and oral cancer with post-operative pathological status and explore the ramifications associated with disparity.

Materials and Methods: This prospective analytical study was conducted on a cohort of 90 patients with operable oral and head and neck cancer. Forty patients with head and neck cancer and 50 oral cancer patients were radiologically evaluated pre-operatively and assigned a clinical tumour, node and metastasis (TNM) staging, which was subsequently compared with the corresponding pathological TNM components.

Results: A significant comparative disparity was seen in 38 [42%] patients with relation to T category. Pathologically larger tumour dimensions were evidenced in both categories. Sixteen oral cancer patients and 16 patients with head and neck cancer had greater than 30% increase in tumour dimensions in the post-operative pathological staging. This did achieve statistical significance [$p=0.00$]. The specificity of CT scan in defining low-risk nodal volumes [cNo Neck] was 76% for oral cancers and 53.8% in head and neck cancer subjects. The rate of false positives for both categories was fairly high, i.e., 48% and 37.9%, respectively.

Conclusion: By theoretically extrapolating the inferences of this study to situations where radiotherapy would be the primary treatment, our findings would draw caution towards considering overtly conservative/uniform clinical tumour dimensions and estimating intermediate nodal target volumes at risk solely on the basis of CT-based evaluation.

Keywords: Advanced Head and Neck cancer, Computed tomography, Clinical target volumes, IMRT, TNM.

Introduction

Radiotherapy remains the modality of treatment in unresectable and locally advanced head and neck as well as inoperable oral malignancies^[1].

In India, this category includes 85% of head and neck cancers and 57% of oral malignancies^[2]. The new era of radiation therapy focuses on confined treatment and restricted margins. The anticipated positive outcome would be comparative to improved survival statistics due to less toxicity-related treatment breaks and better quality of life with less late tissue toxicity. But are we safe in estimating our target volumes on computer tomography (CT)-based radiological parameters alone? Are we overestimating the area of nodal involvement?

Planning CT provides the geometric integrity and relative electron density crucial for dose calculation. It remains the sole delineation for majority of patients undergoing conformal treatment. Current consensus guidelines^[3] for primary tumour delineation suggest that MRI can be used for improving soft tissue delineation in oral cavity and oropharynx. However, for optimal co-registration, this would require an RT dedicated 70 cm open bore 1.5 Tesla system, which is not available in majority of the centres^[4]. The use of FDG-PET images has been validated for more advanced tumours; however, this imaging modality also has the limitation of cost, availability and technical errors of fusion^{[5][6]}.

The current institutional study, in collaboration with the departments of Radiotherapy, Head and Neck Oncology, Oral Oncology and Pathology, was designed with the objective of throwing light on the above-mentioned issues.

Material and Methods

From November 2015 to December 2016, 40 patients with operable head and neck cancer and 50 oral cancer patients were recruited. Demographic and clinical data were collected after obtaining informed consent. The protocol was cleared by the institutional review board. All patients underwent clinical assessment and

radiological evaluation with CT scan, which along with clinical assessment formed the basis of tumour, node and metastasis (TNM) categorisations. All the enrolled patients underwent standard curative resections and pathological profiling. Comparative tabulation of clinical vs. pathological tumour, nodal and overall stage categories was done. Disparities and level of congruence between clinical and pathological TNM categorisation and staging of the enrolled patients were analysed at the institutional statistical centre.

Statistical Methods

The Fischer's exact test and unpaired 2-sided t test for ordered categorical data were used to compare patient categories. Evaluation of tumour dimensions was documented using TNM classification.

Results

Fifty patients with oral malignancy and 40 patients with non-nasopharyngeal head and neck primaries were enrolled in this study. The distribution of patients and subsites are given in Table 1.

Patients with oral cancer were younger and were mainly women having a strong association with tobacco chewing. This also represented a higher incidence of Buccal Mucosa Primaries. Most of the head and neck subjects were male, with pyriform sinus being the most common subsite.

Table 2 documents the radiological tumour staging with relation to the gold standard: the pathological stage in patients with oral malignancies and head and neck malignancies.

Concordance of radiological data with pathological dimensions was seen in 27 out of 50 patients [64%]. Twenty-seven percent of early T1 and T2 lesions were upstaged following surgery. Ten patients with T4 lesions were down staged mainly due to false positives of bony erosion as assessed by CT scan preclinically. Early T1 and T2 lesions individually showed a concordance of 66%. On the other hand, more advanced lesions

showed a greater disparity with pathological findings in the form of down staging.

Upstaging of T2 category after surgery was more significant for head and neck subjects (37.5%). The concordance was consistently and surprisingly the same for T2 and T3 lesions. The overall concordance of radiologically evaluated tumour dimension was 62.5%.

Table 3 gives a comparison of radiological vs. pathological staging of nodes among the subjects with oral and head and neck malignancies.

Here, it was observed that a majority of patients with no nodal disease on radiological evaluation remained N0 on pathological staging (76%). However, the rate of false positives for patients with nodal disease was significant (48%). Overall, the concordance of radiological with pathological nodal stage was 46%.

In head and neck patients, the predictability of CT scan in achieving a true negative was only 53.8%. The false positive rate was 37.9%. The overall concordance of radiological with pathological nodal findings was 50%.

As observed in Table 4, the predictability of radiological staging to match pathological staging was more in stages I and II. Overall, the concordance was 38%.

The concordance of overall staging comparison in head and neck primaries was 72.5%. This was higher than that observed in oral cancer patients. The disparity between T, N and stage categorisation was significant and markedly more so for 'T' category, representing mainly tumour dimensions.

As the main intention of the study was to evaluate the impact of radiological disparity related to tumour dimensions for treatment planning, the percentage increase/decrease of clinical tumour size in comparison to pathological tumour size was separately charted out. A variation of greater than 30% was considered as significant enough to compromise clinical target delineation.

Thirty-three out of 50 patients with oral malignancies had comparatively larger tumours on pathological evaluation.

Patients with greater than 30% variation in tumour dimensions were subcategorised. Sixteen oral cancer patients had tumour dimensions greater than 30% of the clinical CT-based documented size. This was statistically significant.

Seventeen out of 50 patients had smaller tumour dimensions. However, only 5 of the 17 had greater than 30% smaller tumours. This was less significant ($p=0.042$).

On pathological evaluation, it was found that 23 out of 40 patients with head and neck primaries had larger tumours. Out of the 23 patients, 16 had greater than 30% variation, and this was significant ($p=0.000$).

Although 15 out of 40 patients had smaller tumour dimensions, only 4 had disparity greater than 30% ($p=0.038$).

Table 1: Distribution of patients and subsites with oral malignancy and non-nasopharyngeal head and neck primary malignancy

PATIENT CHARACTERISTICS	ORN(50 patients)	H & N (40 patients)
Age in years		
• <55	33	7
• 55-66	12	26
• >66	5	7
Gender		
• Female	32	3
• Male	18	37
Subsites (ORN)		
• Buccal Mucosa	23	
• Gingiva	15	
• Oral tongue	7	
• Hard Palate	1	
• Retromolar Trigone	3	
• Floor of the Mouth	1	
Subsites (H & N)		
• Pyriform sinus		15
• Postcricoid		8
• Vocal Cord		9
• AE fold		4
• Epiglottis		1
• Maxillary sinus		3

□ AE- Aryepiglottic fold,

□ H&N: Head and Neck cancer,

§ ORN- Oral Cancer

Table 2: Concordance between Radiological and Pathological ‘T’ Category in Oral & Head and Neck malignancies

	Radiological ‘T’	Pathological ‘T’					Concordance
		T1	T2	T3	T4	Total	
ORAL MALIGNANCIES	T1	6	2	1	0	9	66%
	T2	4	12	1	1	18	66%
	T3	0	3	3	1	7	42%
	T4	1	7	2	6	16	37.5%
	Total	11	24	7	8	50	
HEAD & NECK MALIGNANCIES	T1	0	0	0	0	0	0
	T2	0	10	2	4	16	62.5%
	T3	0	2	5	1	8	62.5%
	T4	0	4	2	10	16	62.5%
	Total	0	16	9	15	40	

*Discordance $p=0.007$ for Oral malignancies & $p=0.009$ for Head and Neck malignancies

Table 3: Concordance between Radiological and Pathological ‘N’ categories in Oral Cancers & Head and Neck Cancers

	Radiological ‘N’	Pathological ‘N’				Total	Concordance
		N0	N1	N2	N3		
ORAL MALIGNANCIES	N0	13	3	1	0	17	76%
	N1	10	4	4	0	18	22%
	N2	6	3	6	0	15	40%
	N3	0	0	0	0	0	
	Total	29	10	11	0	50	
HEAD & NECK MALIGNANCIES	N0	7	4	1	0	13	53.8%
	N1	5	3	1	0	10	30%
	N2	6	3	10	0	19	52.6%
	N3	0	0	0	0	0	0
	Total	18	10	12	0	40	

*Discordance $p=0.18$ for Oral malignancies & $p=0.1176$ for Head and Neck malignancies

Table 4: Concordance of Radiological staging with Pathological staging in Oral Cancer and Head and Neck Cancer Patients

	Radiological Stage	Pathological Stage				Total	Concordance
		I	II	III	IV		
Oral Malignancies	I	3	0	1	1	5	60%
	II	0	5	0	1	6	83%
	III	1	4	2	11	18	11%
	IV	1	6	5	9	21	42%
	Total	5	15	8	22	50	
Head & Neck Malignancies	I	0	0	0	0	0	
	II	0	0	0	4	4	0
	III	0	3	5	1	9	55%
	IV	0	3	3	21	27	77%
	Total	0	6	8	26	40	

*Discordance $p=0.197$ for Oral malignancies & $p=0.002$ for Head and Neck malignancies

Discussion

In recent years, advances in radiotherapy technology, namely 3 Dimensional Conformal Radiotherapy and Intensity Modulated Radiotherapy, have allowed for greater volumes of focussed treatment. However, the guidelines for clinical target volumes (CTVs) for anticipated

peritumoral spread and perinodal spread have not been established. The accurate assessment of CTV plays a key role in tumour control.

The modes of assessment of primary tumour volumes are based mainly on CT-based radiological data. CTVs are created by empirical expansions of 5 to 10mm of Gross Tumour

Volumes. The nodal target volumes are again categorised by radiologically suspicious nodal involvement, and accordingly, differential doses are given to high, intermediate and low-risk areas. The documented sensitivity of CT towards tumour detection in head and neck cancer is around 68% in primary tumours^[7]. However, this does not account for tumour dimensions. The sensitivity of CT scan towards nodal detection is around 40-68%, and the ability to identify a true N0 Neck [Specificity] is around 78-92%^[8,9].

How accurate is CT scan for generating a CTV? How accurate are we in categorising a nodal region as low risk based on CT data alone?

In our trial, the overall discordance for the 'T' category was 43% ($p=0.000$), which was highly significant. For 'N' category, it was 53% ($p=0.0086$). This was comparable to the intergroup ECOG 4393/ RTOG 9614 trial, which evaluated the same in a cohort of 560 patients. Of the 501 cases in which both clinical and pathological staging was available, a disparity was found between at least 1 component tumour category in almost 50% of cases. The predictability of clinical evaluation of N0 neck to be pathologically negative was 69.7%^[10].

To assess the category of patients and the degree of impact of this radiotherapy planning, we further subcategorised patients with head and neck cancer and oral malignancies on the basis of tumour and nodal dimensions.

In patients with oral malignancies, 27% of T1 and T2 patients were upstaged. This is comparable to a larger multi-institutional study that addressed the same issue. Vincent L. Biron et al. evaluated the disparity of clinical vs. pathological staging in 560 patients with oral malignancies and found 21.9% of patients were upstaged^[11].

Taking a greater than 30% variation as a significant factor that might affect the definition of CTV, we observed that 15 out of 50 patients fall in this category. Of them, 32% was clinically significant ($p=0.008$). Five patients had a comparative decrease of >30% pathological dimensions.

In our study, 10 patients with T4 lesions were down staged due to the false positive of reporting mandibular invasion. The sensitivity of CT in defining T4 disease was around 43%, which is less than that reported in the literature^[12].

The absence of bone invasion is a significant factor that can impact the proposed treatment plan of the patient. The specificity of CT in defining patients without nodal disease was nearly 76%. However, the false positive for patients with nodal disease was 48%. This would probably indicate caution towards predicting intermediate risk CTV. If relying solely on CT data, these patients may be over treated and could have received better related normal tissue sparing in the true scenario.

In head and neck lesions, the upstaging of T2 lesions was 37.5%. The overall concordance of tumour status T category was a consistent 66% for T2 and T3 lesions. However, 16 patients had pathological tumour dimensions, which was greater than 30% of what was defined by radiological data ($p=0.005$). Four patients showed a greater than 30% smaller tumour dimension, which was not significant ($p=0.377$).

In head and neck patients, the predictability of CT towards defining a true negative neck was 53.8%. The false positive rate was also lower (37.8%). Again this data suggests that we may be at risk of underestimating primary tumour volumes and overestimating nodal regions at risk when planning based on CT-based radiological criteria alone.

There are a few considerations that impact the inferences made. One is the subjective nature of radiological reporting and lesser numbers. However, as the reporting is from a single institution, the bias/confounding element of subjective error in reporting is much less than that in prior multi-institutional studies.

The current study is being continued for accrual of 200 patients with the interim data as a basis. The additional parameters of biological prognostic factors like p53, p16 and ELF4 expressions in tumour and margins will be analysed to see which subcategory of patients may be suitable for

conservative CTVs against those in which doing so would result in target miss and compromise survival.

The comparison of clinical tumour dimensions in all categories of oral and head and neck malignancies with pathological staging revealed a clinically significant discrepancy. When planning radiotherapy treatment and defining clinical tumour volumes on CT-based radiological data alone, we may be at risk of underestimating tumour dimensions. The uniform CTV margins advocated for conformal treatment may not be appropriate for all cases of head and neck and oral cancers. We may have to use additional parameters like more advanced imaging or biological prognostic markers to better define the complete cancer treatment of patients, and their response would not be compromised by conformal radiotherapy. In oral malignancies, there is a clear risk of classifying lesions as advanced T4 on CT-based clinical information of mandibular invasion. Those patients would have been eligible for radical intent treatment if not for false positive. Reliability of CT in defining the low-risk nodal volume [N0 Neck] is fairly high. However, the false positive rate of nodal involvement in both oral and head and neck cancers is significantly high to mandate caution in defining intermediate risk nodal volume. Unnecessary treatment of these nodal regions with higher radiation doses, assuming there is nodal involvement, would compromise the normal tissue benefit of conformal treatment done without contributing to response and survival.

Conclusion

There is a considerable and significant discrepancy between clinical and pathological TNM staging, indicating that there is a need for introducing more specific radiological investigations or biological parameters in prognosticating patients with head and neck cancers. By theoretically extrapolating the inferences of this study, it would draw caution towards overtly conservative CTVs and estimating

intermediate nodal volumes based solely on CT-based evaluation.

Acknowledgments

Dr Poornachandra Tejaswi, Dr. Shubha Supriya, Dr. Niveditha, Department of Radiation Oncology
Dr. Rajasekhar Halkud, Dr Purushottam Chavan, Department of Head and Neck Oncology
Dr Rajini B.C., Dr Prakash P.M., Dr Nadimul Hola, Department of Oral Oncology
Funded by Rajiv Gandhi University of Health Sciences

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