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FULL PAPER

Tumor radiomic features complement clinico-radiological factors in predicting long-term local control and laryngectomy free survival in locally advanced laryngo-pharyngeal cancers

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Objective: To study if pre-treatment CT texture features in locally advanced squamous cell carcinoma of laryngo-pharynx can predict long-term local control and laryngectomy free survival (LFS).
Methods: Image texture features of 60 patients treated with chemoradiation (CTRT) within an ethically approved study were studied on contrast-enhanced images using a texture analysis research software (TexRad, UK). A filtration-histogram technique was used where the filtration step extracted and enhanced features of different sizes and intensity variations corresponding to a particular spatial scale filter (SSF): SSF = 0 (without filtration), SSF = 2 mm (fine texture), SSF = 3–5 mm (medium texture) and SSF = 6 mm (coarse texture). Quantification by statistical and histogram technique comprised mean intensity, standard-deviation, entropy, mean positive pixels, skewness and kurtosis. The ability of texture analysis to predict LFS or local control was determined using Kaplan–Meier analysis and multivariate cox model.
Results: Median follow-up of patients was 24 months (95% CI:20–28). 39 (65%) patients were locally controlled at last follow-up. 10 (16%) had undergone salvage laryngectomy after CTRT. For both local control & LFS, threshold optimal cut-off values of texture features were analyzed. Medium filtered-texture feature that were associated with poorer laryngectomy free survival were entropy ≥4.54, (p = 0.006), kurtosis ≥4.18; p = 0.019, skewness ≤−0.59, p = 0.001, and standard deviation ≥43.18; p = 0.009). Inferior local control was associated with medium filtered features entropy ≥4.54; p 0.01 and skewness ≤ – 0.12; p = 0.02. Using fine filters, entropy ≥4.29 and kurtosis ≥−0.27 were also associated with inferior local control (p = 0.01 for both parameters). Multivariate analysis showed medium filter entropy as an independent predictor for LFS and local control (p < 0.001 & p = 0.001).
Conclusion: Medium texture entropy is a predictor for inferior local control and laryngectomy free survival in locally advanced laryngo-pharyngeal cancer and this can complement clinico-radiological factors in predicting prognosticating these tumors.
Advances in knowledge: Texture features play an important role as a surrogate imaging biomarker for predicting local control and laryngectomy free survival in locally advanced laryngo-pharyngeal tumors treated with definitive chemoradiation.

INTRODUCTION

Cancers of larynx and hypopharynx account for one-third of squamous cell carcinomas of head and neck cancers worldwide.[1] Laryngeal preservation is one of the major challenges for these tumors as majority present at an advanced stage. Concurrent chemoradiation (CTRT) is a standard organ preservation approach in locally advanced laryngo-pharyngeal cancers where the local control rates range from 50–70%. In these tumors, salvage laryngectomy is reserved for residual/ recurrent tumor.[2] However, salvage laryngectomy in post-chemoradiotherapy setting is extremely challenging and associated with significant

morbidity and mortality.[3]Although total laryngectomy remains the gold-standard in these tumors, organ preservation protocols have replaced total laryngectomy in suitably selected stage III and IV patients of laryngo-pharyngeal cancer.Multiple randomized trials have demonstrated equivalent control rates for this approach as compared to upfront surgery.[2,4,5] However, approximately 20–40% of patients may still have to undergo total laryngectomy even after CTRT thereby mandating stringent criteria for patients selected for organ preservation protocols.[6] Cartilaginous framework involvement and exo-laryngeal disease are the most common radiological criteria used in clinics for selecting cases for total laryngectomy.[7–9] Although highly predictive, detection of cartilage erosion/lysis on contrast-enhanced CT (CECT) is less specific and subject to high interobserver variability.[10] The subjectivity of these criteria, and lack of a robust model that incorporates all the clinico-radiological parameters precludes the accurate selection of patients for larynx preservation and prediction of clinical outcomes. Therefore, there is a definite need for an innovative prognostic/ predictive tool for refining patient selection criteria for organ preservation protocols so that disease-related outcomes are not compromised.

Biologically, heterogeneity is a well-recognized feature of any cancerous tissue.[11] A high tumoral heterogeneity portends adverse biology, aggressive clinical course and suboptimal response to anticancer therapy.[12] Texture features within the tumour capture the intratumoral heterogeneity objectively using dedicated sophisticated software algorithms.

Texture features allow for amplification of heterogeneity within a tumor on CT images by using pre-processing techniques employing selective scale image filtration that selects image features at a particular scale. These features can be further quantified using texture parameters obtained from statistical and histogram analysis demonstrating intuitiveness to the visual/ radiological perception and linked to different components of biological heterogeneity.[13] This may have the potential to identify patients who may have inferior outcomes with standard therapeutic approaches and can help individualize therapy (personalized medicine). The predictive and prognostic role of texture analysis (TA) in locally advanced laryngo-pharyngeal cancer has not been previously investigated. Considering that texture of tumor may detect subtle pathologic changes or biologic characteristics in CT images, we studied intratumoral heterogeneity through various texture parameters on baseline CECT images in a cohort of locally advance laryngo-pharyngeal cancer patients treated uniformly with CTRT, followed up longitudinally in a single institute and correlated these features with local control and laryngectomy free survival (LFS).

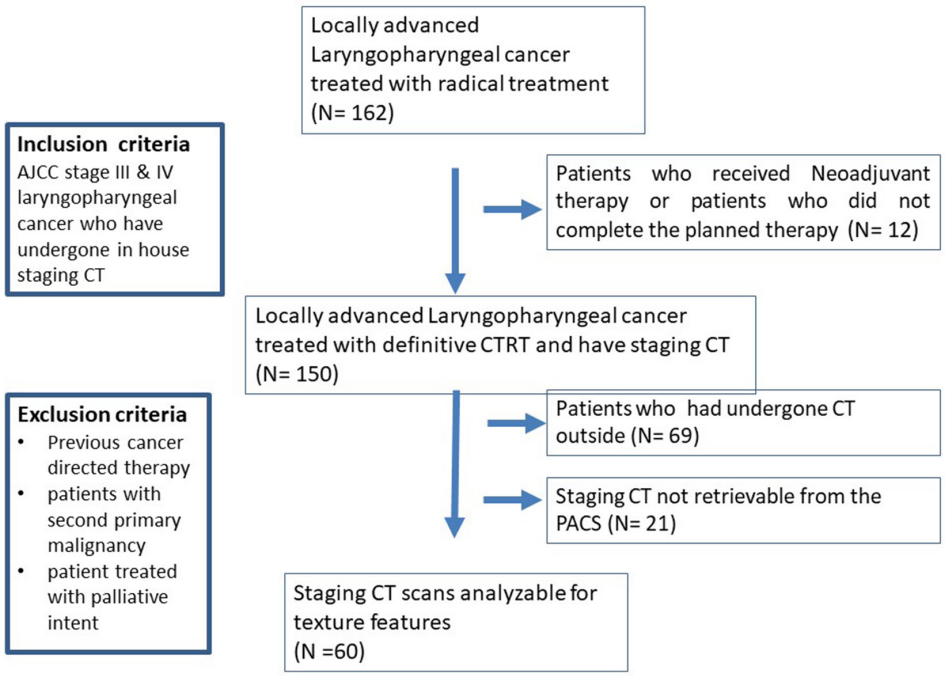
METHODS AND MATERIALS

The study was performed at a tertiary care cancer centre-after formal institutional ethics and scientific board approval. (IEC-1710)

Patients

Patients enrolled in a prospective study of organ conservation for locally advance laryngo-pharyngeal cancer between 2015 and 2017 and who had a baseline CECT scan done with a uniform imaging protocol were selected for analysis. Patients with squamous cell carcinoma of larynx and hypopharynx (excluding T1/ T2 glottic tumors) treated with definitive CTRT were included in the study. Patients with any prior cancer-directed therapy, second primary malignancy and those treated with palliative intent were excluded from the study (Figure 1).

Figure 1. Schematic shows recruitment pathway of patients for the texture analysis study.



Contrast-enhanced CT image acquisition protocol

CECT of the head and neck was performed with a 4-detector row CT scanner (Somatom emotion 16, Siemens,™ Germany) using the following CT parameters:120 kVp; 280 mAs; 0.5 mm & 3 mm section collimation; field of view:300; matrix,:512. Tube current was automatically modulated. Iodinated contrast (Iopamidol/ iohexol) at a dose of 70 ml and a concentration of 300 mg ml^{-1} was administered via the antecubital vein at a rate of 2.2 ml/s. Scans were taken after 40 s delay following administration of contrast material. Bolus tracking software was used to trigger the scanning.

Treatment and follow-up

All patients were treated with concurrent CTRT to radiation doses of 66–70 Gy to the tumor and weekly intravenous cisplatin at a dose of 40 mg/m^2 as per institutional protocol.[14] In situations, where clinical suspicion of disease progression/recurrence was suspected, relevant radiological or functional imaging was used to restage the disease. The follow-up period was designated as the total time of follow-up, starting at the date of treatment completion and ending at the date of last contact with the patient.

Delineation of the region of interest (ROI) and texture analysis (TA)

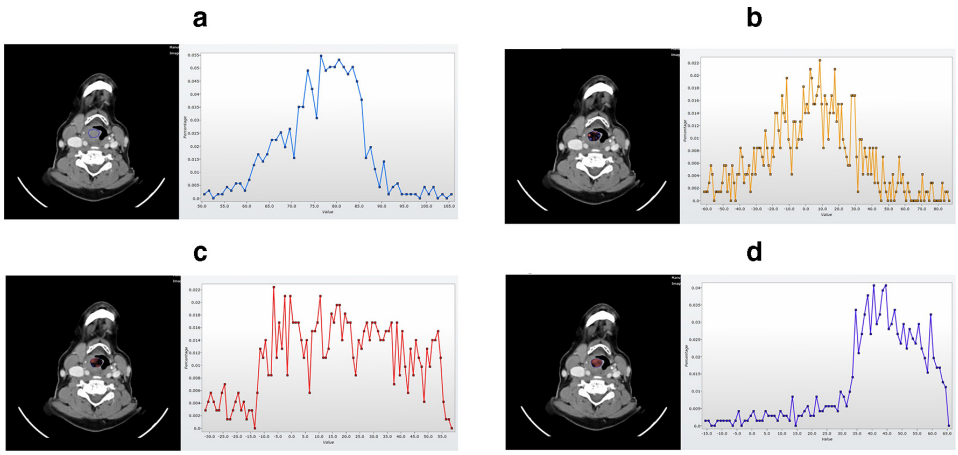
The CECT DICOM scans (Digital Imaging and Communications in Medicine) on the institutional picture archival and communication system were retrieved and pushed to the planning workstation where the commercially available TA research software TexRAD® (Feedback Medical Ltd., Cambridge, UK www.fbkmed.com) was installed for delineation of the primary tumor and TA. Delineation of the gross primary tumor was done on the slice with greatest transverse tumor dimensions. Intraluminal air regions were excluded from the analysis by thresholding out the pixels with attenuation below −50 Hounsfield unit. Furthermore, dense calcification metal and streak artefactswere also excluded by taking care of not including them within the ROIs as they would impact quantification of the texture features (Figure 2).

TA comprised of filtration-histogram-based technique where the filtration step employed a Laplacian of Gaussian (LoG) spatial band-pass filter (similar to non-orthogonal wavelet transformation) to selectively extract and enhance features of different sizes and intensity variations corresponding to different anatomic spatial scale filters (SSFs = 2,3,4,5,6), ranging from fine, medium and coarse texture scales. Heterogeneity within the ROI was quantified with and without image filtration. SSF = 2 mm corresponded to fine texture scale, SSF = 3–5 mm corresponded to medium texture scales and SSF = 6 mm corresponded to coarse texture scale. SSF = 0 corresponded to non-filtered or conventional image (as a control). Following the filtration step, quantification of textures using a statistical and histogram technique comprised of mean intensity, standard deviation, entropy, mean of positive pixels (MPP), skewness and kurtosis. At each SSF value, mean pixel intensity reflects the average brightness, standard deviation reflects the degree of variation/ dispersion from the mean, entropy reflects the irregularity or complexity of pixel intensity distribution, MPP reflects the average brightness considering only the positive pixel values, skewness reflects the asymmetry of pixel intensity distribution and kurtosis reflects the sharpness or pointedness of pixel intensity distribution. Generally speaking, a higher entropy, a higher standard deviation of the pixel distribution histogram, a higher kurtosis (visual-contrast), and a lower skewness (preponderance of dark objects which on CT could reflect lower attenuation values—hypoxic areas) are surrogates of increased heterogeneity within the ROI. A recent article via mathematical modelling and simulations highlighted what does the filtration-histogram based CTTA mean and how the features from this technique reflect visual radiological image perception and linked to different components of heterogeneity (object size, number of objects and variation in density of the objects in relation to the background ROI).[13]

Statistical analysis

Statistical analysis was done using SPSS v. 21.0. (IBM SPSS Statistics for Windows, v. 21.0, NY). Descriptive statistics were

Figure 2. Fused anatomic and texture features on (a) an unfiltered/conventional (SSF = 0) contrast-enhanced CT image of a laryngeal tumor patient and the corresponding histogram shows pixel distribution of the same patient on unfiltered CT image. (b–d) Corresponding images in the same patient after applying the filtration step: (b) fine (SSF = 2), (c) medium (SSF = 4), and (d) coarse (SSF = 6) filtered texture map and their corresponding histograms respectively showing filtered (at each SSF-value) pixel intensity distribution. SSF, spatial scale filter.



expressed as numbers and percentages for categorical variables and mean ± standard deviation or median (interquartile range) for continuous variables. LFS was defined as the time from the date of diagnosis until either laryngectomy, death from any cause (event) or the date on which the patient was last known to be alive.

Correlations between texture features were assessed by Spearman's rank correlation test. Possible interactions were explored between CT texture parameters considered for the Cox regression model in relation to local control and LFS. Kaplan–Meier analysis was performed to determine the relationship, if any, between CT texture features of the tumor, and 2-year local control & LFS. For analysis, each texture parameter at different filter values (fine, medium, and coarse) was dichotomized with respect to the threshold cut -off value. Multivariate cox-proportional hazard model was performed to assess whether any of the univariate texture parameters were predictors of local control or LFS independent of the conventional clinical predictors like the tumor stage, age or site of disease (larynx or hypopharynx). A p-value of less than 0.05 was considered to indicate a significant difference.

RESULTS

Patient demographics, clinical factors and clinical outcome

A total of 162 patients diagnosed with locally advanced laryngopharyngeal cancer treated with radical intent were screened for the study, of which 12 patients had either received neoadjuvant chemotherapy or had not completed the planned therapy. Of the 150 patients who had received definitive CTRT, only 60 patients who met the inclusion criteria and whose staging CT images were retrievable were found to be suitable for extracting the texture features for the above study (Figure 1). Laryngeal primaries were 32 (52%) while hypopharyngeal primaries were 28 (48%). The median age for the entire cohort was 56 years (Interquartile range 49–64). The demographic features of the cohort are described in Table 1.

Median follow-up for the entire cohort was 24 months [95% confidence interval (CI): 20–28 months]. At last follow-up, 18/60 (30%) had died of which 17 had died due to disease progression or relapse and 1 died of other causes (aspiration pneumonia). Three (5%) patients were lost to follow-up. The estimated 2 year local control and LFS rates were 63.6% (95% CI: 49–75%), and 80.5% (95% CI: 66–89%) respectively (Figure 3). The mean local control was 25 months (95% CI 23.6–24.4 months). The mean LFS was 30.2 months (95% CI 29.2 and 31.3 months). Disease relapse/ progression was observed in 28/60 (47%) patients. Patterns of disease failure was local in 10 (16%), locoregional in 8 (13%), regional in 6 (10%) and distant in 4 (7%). Salvage laryngectomy was performed in 10 (16.6%) patients.

On univariate analysis, age <60 years was associated with better LFS (p = 0.002), while laryngeal tumors had better local control as opposed to the hypopharyngeal tumors (71% vs 58.6%,p = 0.0001). None of the other clinical parameters had any significant association with the above clinical outcomes of LFS and local control.

Table 1. Patient demographics and treatment characteristics (n = 60)

Age	
Median	56 (IQR:49–64 years)
Mean	56 (Range:26–78 years)
Site	
Larynx	31 (51%)
Hypopharynx	29 (49%)
Smoking	
Yes	44 (73%)
No	16 (27%)
T Stage	
T1 &T2	12 (20%)
T3&T4	48 (80%)
N Stage	
N0	27 (45%)
N1	8 (13%)
N2	25 (42%)
N3	0
AJCC Stage (seventh edition, 2010)	
Stage III	33(55%)
Stage IV	27 (45%)
Grade of Tumor	
Well differentiated	7 (11%)
Moderately differentiated	13 (22%)
Poorly differentiated	16 (27%)
Not specified	24 (40%)

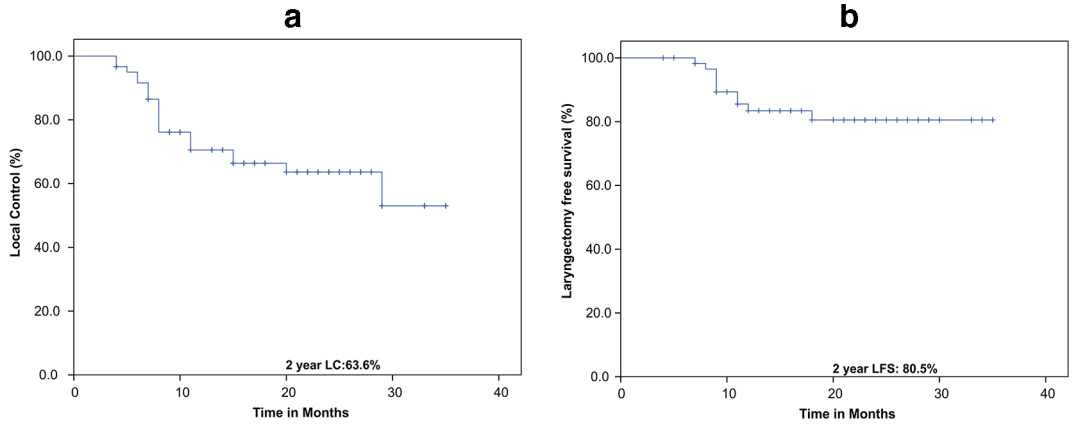
IQR, Interquartile range.

CT texture analysis and clinical outcome

The texture parameters derived from histogram analysis and LoG filtration algorithm are depicted in the Supplementary Table 1. The collinearity between different texture parameters with and without filtration and at different filtration levels for all the AJCC Stage III and Stage IV patients of laryngo-pharyngeal cancers are summarized in Supplementary Table 2. Spearman's rank correlation did not show any strong correlation between most of the texture parameters either on unfiltered or filtered images. However, only mean showed a very strong positive correlation with MPP on unfiltered CT images as this maybe due to lack of many negative pixel values (negative Hounsfield unit).

Univariate analysis of texture parameters at different filtration levels were analyzed to study their association with local control and LFS (Table 2). Our analysis showed that entropy was consistently (across the different filter scales) significant predictor of local control and LFS with higher values of entropy linked to a poorer outcome. (*e.g.* fine texture scale, >4.29; medium texture scale, >4.54) (Figure 4 and Table 2). Other texture parameters that predicted for both poor LFS and local control were kurtosis

Figure 3. Kaplan–Meier survival curves representing (a) LC, (b) LFS. LC, local control; LFS, laryngectomy free survival



(LFS: medium texture scale >4.18, p = 0.001 and local control: fine texture scale of >−0.27, p = 0.01, Table 2) and threshold value of skewness (LFS: medium texture scale <- 0.59; p = 0.001 and local control: medium texture scale <−0.12, p = 0.02). Additionally, medium texture filter standard deviation >43.18, p = 0.009, and coarse texture filter entropy >4.44, p = 0.03; kurtosis >−0.85, p = 0.03 and skewness <0.58, p = 0.01, were significant predictors of inferior LFS.

Multivariate analysis showed a higher medium filter entropy to be an independent predictor for both inferior local control [Hazard ratio (HR): 1.8 (95% CI: 1.25–2.57; p = 0.001)] and LFS [HR: 5.98 (95% CI: 2.59–13.81; p = 0.0003)] while a higher MPP was independent predictor for better LFS only [HR: 0.97; 95% CI (0.95–0.99), p = 0.002] (Table 3). Although the HR value of 0.97 was statistically significant (p = 0.002), the 95% CI was touching unity, therefore, statistically MPP should not be considered a clinically significant predictor for LFS in contrast to entropy.

At our institute (Tata Memorial Centre, Mumbai, India), only patients with T stage between T1 and T3 (any N stage) are usually considered for radiotherapy-based organ conservation protocols. Patients with T4a disease (gross cartilaginous erosion) are generally not considered for laryngeal preservation due to inferior outcomes in multiple series.[15,16] However, for a relatively small subset of T4a patients, CTRT is considered, either because the patients are unwilling or unfit for surgery or because of limited exo-laryngeal disease not involving the cartilaginous framework. Texture features were able to identify a subset of T4a patients who may be offered organ preservation protocol who otherwise based on traditional clinico-radiological features would have undergone total laryngectomy (Table 4).

DISCUSSION

We observed that CTTA can be used to predict the local control and LFS in patients diagnosed with locally advance laryngopharyngeal cancer treated with chemoradiotherapy-based organ conservation protocols. More specifically, baseline entropy at medium filter was found to be an independent predictor of disease-related outcomes (local control & LFS) after adjusting for all the clinical variables.

Measuring spatial heterogeneity in a tumor by non-invasive CT texture parameters has now gained momentum as a means to extract subtle microscopic information from the primary tumor imaging and the surrounding apparently normal appearing tissue for not only differentiating benign from malignant lesions, but also for response assessment to therapy, predicting or prognosticating in cancers and as a surrogate imaging biomarker for biological correlates of aggressiveness of tumor-like hypoxia, genomic instability and increased proliferative capacity.[17,18] In general, it is hypothesized that spatial heterogeneity within the tumor may be due to aberrant blood supply (some areas have higher vascular supply while other areas have hypoxic voids and areas of necrosis) resulting in hypoxia and ultimately leading to aberrant tumor metabolism, oxidative stress leading to promotion of prosurvival pathways, genomic instability and therapy resistance.[19–21] Image TA has been shown to pick up these biological abnormalities and is prognostic/predictive across various tumor sites like colorectal cancers, non-small cell lung cancers and renal cell carcinomas etc.[22–24]

Although few studies have addressed spatial heterogeneity in primary head and neck cancer as an imaging surrogate for prognostication, there are no published studies that have focused on tumor heterogeneity as a biomarker in laryngo-pharyngeal cancers treated uniformly with definitive CTRT. Studies in a heterogeneous cohort of head and neck cancer patients treated with neoadjuvant chemotherapy have shown histogram parameters like entropy and skewness to be independently predictive of poor overall survival and second-order texture parameters like gray-level run-length features, gray-level non-uniformity, run-length non-uniformity *etc* to be significant predictors for local control in patients treated with concurrent CTRT.[25,26]

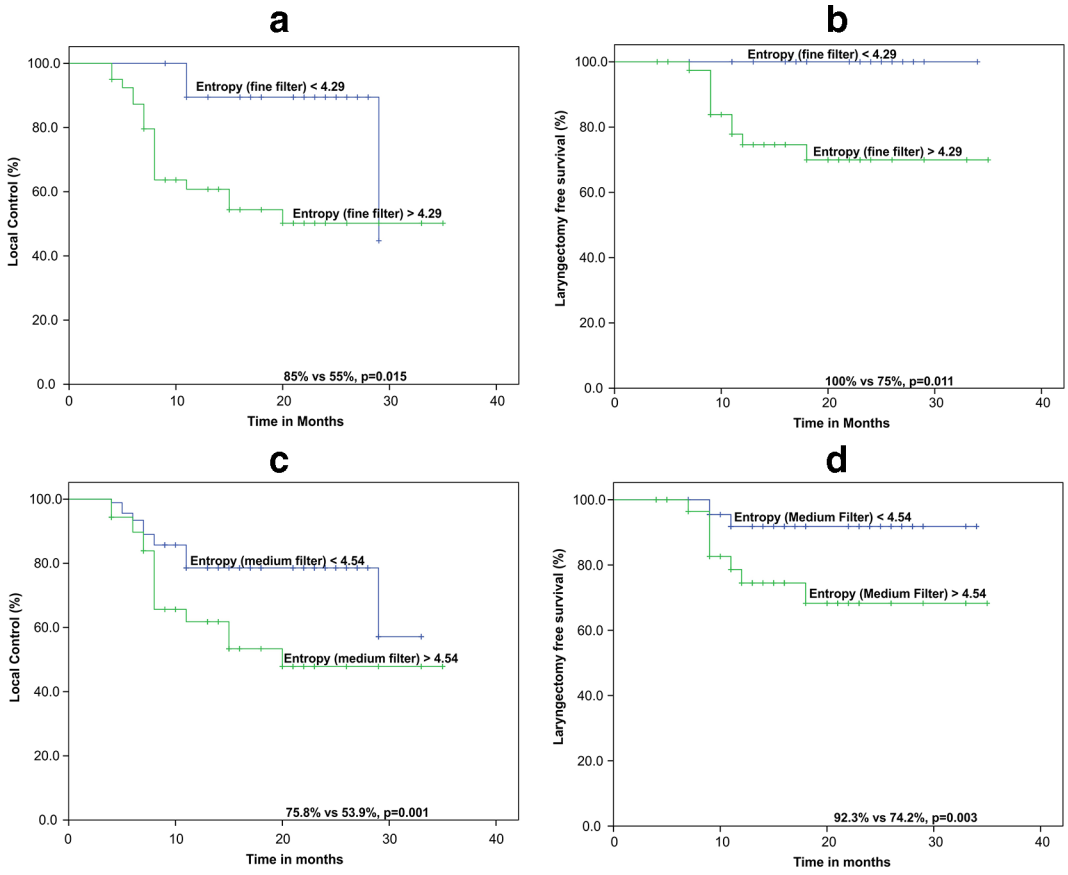
We employed the widely published and validated filtration histogram technique while investigating the association of heterogeneity with local control and LFS in our patient cohort who were treated with CTRTas a part of organ preservation protocol.[27] Although relatively simple (important for eventual understanding and adoption in routine clinical practice), this method is intuitive in assessing heterogeneity in various malignancies. This approach has been validated to predict clinical outcomes

Table 2. Univariate Kaplan–Meier analysis of texture parameters at different filtrations levels and their association with local control and laryngectomy free survival

Texture parameters at different filtration levels	Threshold cut-off value	Median LC		P -value	Threshold cut-off Value	Median LFS		P- value
		Number of patients above threshold	Number of patients below Threshold			Number of patients above threshold	Number of patients below Threshold	
Unfiltered(SSF 0)								
Entropy	≥3.30	43	17	0.004	≥4.52	4	56	0.01
Mean	≥64.39	21	39	0.012	-	-	-	-
MPP	≥64.39	15	45	0.02	-	-	-	-
Fine Filter (SSF 2)								
Entropy	≥4.44	35	24	0.04	≥4.29	35	25	0.01
Skewness	<0.11	22	38	0.04	-	-	-	-
Kurtosis	≥−0.27	36	24	0.01	-	-	-	-
Medium Filter (SSF 3)								
Entropy	≥4.39	37	23	0.01	≥4.24	41	19	0.01
Kurtosis	-	-	-	-	≥4.18	2	58	0.001
Skewness	<−0.12	33	27	0.02	<- 0.59	18	42	0.001
SD	-	-	-	-	≥44.16	38	22	0.01
Medium Filter (SSF 4)								
Entropy	≥4.57	32	28	0.02	≥4.57	35	25	0.006
Skewness	<−0.005	36	24	0.02	<−0.005	36	24	0.03
SD	-	-	-	-	≥43.18	39	22	0.009
Medium Filter (SSF 5)								
Entropy	≥4.65	26	34	0.02	≥4.44	34	26	0.01
Coarse Filter (SSF 6)								
Entropy	-	-	-	-	≥4.44	36	24	0.03
Kurtosis	-	-	-	-	≥-0.85	42	18	0.03
Skewness	-	-	-	-	<0.58	12	48	0.01

MPP, mean positive pixels; SD, standard deviation; SSF, spatial scaling factor.
SSF which ranges between object radii of 2–6 mm and classified as fine, medium and coarse filters.
SSF-2: fine filter; SSF3,4,5: medium filter; SSF6: coarse filter

Figure 4. Kaplan–Meier curves of fine filter value (SSF2) of threshold entropy (median 4.29) shows a statistically significant difference in (a) Local control (p = 0.015) and (b) laryngectomy free survival (p = 0.011). Kaplan–Meier curves of medium filter value (SSF3–5) of threshold entropy (median 4.54) shows a statistically significant difference in (c) local control (p = 0.001) and (d) laryngectomy free survival (p = 0.0003). SSF, spatial scaling factor.



in various published oncological studies and may have clinical relevance.[23] In our study, we found tumors that demonstrated greater spatial heterogeneity at both fine and medium filter levels were associated with poorer local control, while greater heterogeneity at all three filter levels was associated with poorer LFS (Table 2). These findings have been observed in other tumor types, where greater heterogeneity was associated with poorer clinical outcomes.[25,28–30]

Table 3. Multivariate cox proportional hazards regression analysis of texture parameters with clinical parameters as dependent co-variates for local control and laryngectomy free survival

Parameters	Local control			Laryngectomy free survival		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (years)	0.992	0.970–1.014	0.461	0.976	0.941–1.012	0.185
T stage T1,T2 *vs* T3,T4	0.629	0.333–1.189	0.154	0.468	0.19–1.151	0.098
AJCC Stage IV *vs* III	1.158	0.649–2.067	0.619	0.942	0.418–2.123	0.886
Subsite Hypopharynx *vs* larynx	1.120	0.624–2.010	0.704	0.547	0.246–1.220	0.141
Entropy (medium filter)	1.800	1.257–2.578	**0.001**	5.982	2.590–13.813	**0.0003**
MPP (medium Filter)	0.998	0.989–1.007	0.723	0.969	0.949–0.988	0.002

CI, confidence interval; HR, hazard ratio; MPP, mean positive pixels.

Table 4. CT texture analysis for T3/T4 tumors

	T3	T4
Number of patients	33	12
Local failure	11 (33%)	6 (50%)
Locally controlled	22 (67%)	6 (50%)
Predictive value of texture parameters (Medium filter entropy)	8/11 with local failures (72.7%)	3/6 patients with local failures (50%)

After adjusting for the clinical and radiological factors, the texture features that were strongly associated with disease-related outcomes in multivariate analysis were entropy and MPP. The most significant cut-off values across multiple filters for various texture parameters were obtained by an inbuilt statistical tool provided with the software. Medium filter entropy was found to be a predictor for inferior local control and LFS respectively on multivariate analysis independent of other clinical features including tumor stage, site of disease and age of the patient (Table 3). Entropy represents overall tumor complexity and is hence probably the best marker for heterogeneity, and therefore intrinsic aggressiveness.[13] MPP is the average brightness of positive pixel values of the image which gets accentuated with an increase in mean vessel density within the tumor, hence correlating strongly with neoangiogenesis.[31] Although studies investigating various texture parameters in head and neck cancers have not reported any clinical significance of MPP, studies in lung, colorectal cancer and soft tissue sarcomas have been equivocal. In fact certain studies have shown a negative correlation of MPP with angiogenesis in lung cancer and hypoxia in colorectal cancer exhibiting KRAS mutations where lower MPP may confer improved outcomes.[23,24] Similarly higher MPP values have been associated with poorer clinical outcomes in terms of overall survival in soft tissue sarcomas.[32] On the contrary, a higher MPP value correlated with better outcomes in our cohort of patients where a higher value predicted for better LFS on multivariate analysis although its clinical significance may be blunted given that the HR was close to 1.0 (Table 3). The divergent results may be a reflection of differences in the patterns of angiogenesis in different malignant histological subtypes or due to distorted vasculature within the tumor which could be the reason for poorer response to therapy and therefore inferior outcomes. We also analyzed other texture parameters in this study. Although these parameters, (kurtosis, skewness, standard deviation) were significant at various filter levels on univariate analysis but were not found to be significant on multivariate analysis, hence their independent predictive value was not conclusive. Based on our observations, high tumor entropy correlated best with both local control and LFS. Therefore, we propose tumor entropy at medium filter level as a direct surrogate for tumor heterogeneity and a texture parameter worth considering for selecting patients for organ preservation protocols using CTRT.

One of the strengths of the study was that the texture parameters were measured in baseline CECT images from a cohort of locally advance laryngo-pharyngeal cancer uniformly treated with CTRT. Moreover, features were extracted from images that were acquired from the same CT machine with a uniform acquisition protocol and reconstruction algorithm. Finally, tumor delineation was done by a single operator, thereby reducing the operator-variability in the tumor margin delineation which otherwise would have increased in multi-observer tumor margin delineation. However, a previous study has demonstrated via test–retest analysis of CTTA in lung cancer that there is a high intraclass correlation between operators and within the same operator.[33] Filtration-histogram technique of CTTA employs the LoG filtration to generate a set of derived images (fine, medium and coarse texture maps) where the Gaussian part of the filter smoothens the image (reducing the impact of photon noise existing on CT) and Laplacian part of the filter amplifies and enhances subtle features not apparent to the naked eye. Due to the filtration step, one could get away with quantification of texture using the computationally less-intensive statistical and histogram metrics which are more intuitive (having a biological-rationale,reflecting the different components of radiologic image heterogeneity, less complex and more reproducible), thereby obviating the necessity for the use of more complex feature extraction process which might be a barrier to adoption in practice.[34] Our study was designed to outline the tumor in its maximum cross-sectional area, since outlining the tumor margins on all the CT slices can lead to ambiguity as tumor margins are not well delineated even with contrast enhancement, and eventually be time-consuming which may not be practical if adopted in clinical practice. Although, multi-slice/ volume analysis may better represent heterogeneity across the entire tumor but a previous study has demonstrated single-slice analysis to be comparable to multi-slice/ volumetric analysis in terms of prognostication in primary colorectal cancer on CT and thereby raises the question about the additional clinical utility of undertaking multi-slice tumor delineation.[29] Although the study undertaken was retrospective in nature, the encouraging results of the present analysis need to be validated in a larger cohort of patients within the framework of a well-designed prospectively Phase II study.

CONCLUSION

CT-based image texture features (higher entropy), generated within the software programme using cohort data may help in selecting cases over and above the traditional clinical parameters for organ conservation protocols in patients diagnosed with locally advanced laryngo-pharyngeal cancer. Considering the shift towards definitive chemoradiation as the preferred modality for organ preservation in locally advanced larynx and hypopharyngeal cancers, image texture features being non-invasive and probably less prone to subjective variation, can complement the clinicoradiological parameters as a predictive and prognostic tool in these patients and for selecting appropriate cases for these protocols.

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CONFLICT OF INTEREST

SS, JSG, KJ, RM, NM, AB, SK, SGL, TG, VM, JPA do not have any conflict of interest.

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markets the TexRAD texture analysis software employed in this study.

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