

Pretherapeutic Assessment by Multidetector Computed Tomography for Thyroid Cartilage Invasion in Laryngeal Cancer: A Double-edged Sword

Abstract

Introduction: Almost one-fourth of head and neck cancers in India are laryngeal cancers. Both conservative and surgical therapeutic approaches are available. According to present tumor-node-metastasis staging protocol, thyroid cartilage invasion is a crucial criterion for diagnosing advanced stages of the disease. A major cartilage invasion depicts T4A stage of disease for which surgical treatment is required. **Aims:** The present study aims to evaluate the accuracy of multidetector computed tomography (MDCT) in evaluation thyroid cartilage invasion in T3 and T4 stage of laryngeal cancers. **Materials and Methods:** It is a retrospective analysis done in the Department of Radiology, Pramukhswami Medical College, Anand, Gujarat, on 22 patients of T3 and T4 stage of laryngeal cancer who presented for pretherapeutic MDCT neck evaluation. The MDCT results were retrospectively reviewed and compared with postoperative histopathological results. Statistical analysis was done for each parameter as positive predictive value (PPV) (main statistical parameter), negative predictive value, sensitivity, and specificity. **Results:** MDCT showed a PPV of 60.00% in detecting any type of thyroid cartilage invasion, 66.66% for major and 33.33% for minor cartilage invasion. Extralaryngeal spread of disease was the most specific marker for cartilage involvement. In total, 31.8% of cases were downgraded in staging by pathology. **Conclusion:** Overestimation of thyroid cartilage invasion by MDCT is a reality which should be in mind before making final therapeutic decisions. Although crucial, it should not be the sole criteria preventing while making a surgical versus conservative therapeutic call.

Keywords: *Glottic oncology, infrahyoid neck imaging, neck imaging*

Introduction

Laryngeal cancer forms 1% of all diagnosed cancers. In India, its incidence varies from 1.26 to 8.18 per 1,00,000 individuals varying in different demographic distributions. Men are invariably more affected than women, and it is the seventh most common cause of cancer in Indian men.^[1]

The association of laryngeal cancer is well established with tobacco. The present study is conducted in demographic belt in West India where tobacco consumption is higher than the national average, and hence, laryngeal cancer is an important ailment in the given demographics.^[1,2]

Laryngeal cancer is a potentially treatable disease, and it is one of the few malignancies where a surgical approach is not a primary treatment protocol and is reserved for the locally advanced disease. After the 1991 publication of the veterans

administration (VA) laryngeal trial,^[3] a paradigm shift came in the treatment protocol of laryngeal cancer. Where before that time, a total laryngectomy was the primary treatment for most patients with T3–T4 laryngeal cancer, after that trial organ preservation along with more conservative treatment such as concurrent chemoradiotherapy was started to be preferred as the first-line treatment.^[4]

Thyroid cartilage invasion has been defined as one of the crucial criteria which determine the need for total laryngectomy in a case of laryngeal cancer. According to the current American Joint Committee on Cancer guidelines, where a minor cartilage involvement defines T3 disease which may be treated with an organ preservation approach, a major thyroid cartilage erosion or destruction defines T4 disease which warrants for a more radical surgical approach. Although a number of recent trials suggest possible roles of

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chemoradiotherapy even in advanced stages, it is yet to be accepted as a primary treatment protocol in most institutions including ours.^[4-6]

In the present era, multidetector computed tomography (MDCT) forms the backbone of head and neck oncological imaging due to its superior accuracy in detection of various parameters such as soft-tissue lesions, underlying bony involvements, better depiction of nodal status, and comprehensive approach in detecting disease extension due to its multiplanar reconstructive capability. In addition, phonation and Valsalva maneuver imaging help detect the presence and extent of smaller glottic lesions.^[7]

However, MDCT has long been accused of a less accurate analysis of the thyroid cartilage involvement in laryngeal cancer by often overestimating the cartilage involvement. The MDCT results may lead to a clinicoradiological dilemma which often results in the patient being over staged and hence subjected to surgery whereas a more accurate preoperative staging could have helped treat the patient with organ preservation techniques.^[8]

The present study is conducted to address this constant dilemma and aims at analyzing the accuracy of MDCT in detecting thyroid cartilage invasion in laryngeal and hypopharyngeal cancer in a tertiary center. The MDCT results were compared with histopathological examination (HPE) results which were considered as gold standard.

Materials and Methods

The present study was conducted in a tertiary hospital in Western India which is located in a high tobacco consumption belt.

Study design

After due Institutional Ethical Committee approval, a retrospective analysis was done for patients presenting as T3 and T4 stage of laryngeal and hypopharyngeal cancers in the tertiary teaching institute from April 2016 to March 2017.

The study comprised of patients who were clinically and radiologically diagnosed as T3/T4 laryngeal or hypopharyngeal disease and underwent laryngectomy and HPE evaluation at our institute. The postoperative HPE results were reviewed for each patient and were taken as gold standard for evaluation of the accuracy of MDCT in detecting preoperative thyroid cartilage involvement.

We excluded the patients from our study who did not undergo laryngectomy at our institute. Furthermore, the patients who had taken chemotherapy or radiotherapy before the surgery were excluded from our study.

The MDCT results were retrospectively reviewed by a single radiologist (the author) who was blind to the pathological diagnosis. The histopathological results were

obtained from the hospital's database and reviewed to be compared with MDCT results.

Multidetector computed tomography protocol and result analysis

Protocol

The study was performed with a 128 Slice Optima CT 660 (Wipro GE Healthcare Pvt. Ltd.) machine. The procedure was briefly explained to the patient, and detailed informed consent was obtained. An initial topogram of the neck was obtained, and further series were planned accordingly. With the patient in supine position, noncontrast 5 mm thick contiguous axial MDCT sections of the neck were performed from the skull base to aortic arch, subsequently followed by intravenous administration of 80 ml nonionic iodinated contrast medium (300 mg iodine/ml - iohexol) using an automated power injector. Phonation images were acquired subsequently. The axial images were reconstructed to procure sagittal and coronal reformations of high quality, with reconstructed sections as thin as 1.25 mm obtained through the region of interest.

Multidetector computed tomography analysis

The analysis aimed to establish the efficacy of MDCT comprehensively in detecting thyroid cartilage invasion in its various stages, thereby staging laryngeal cancer along with the individual accuracy of various appearances of the involved cartilage in demarcating the disease stage.

Cartilage involvement

The results of thyroid cartilage assessment were marked as no involvement, minor involvement, and major involvement.

Cortical irregularity and erosion of only inner cortex were considered minor involvement. Asymmetrical sclerosis, erosion through both inner and outer cortices, lysis, and presence of enhancing lesion on both sides of cartilage depicting extralaryngeal spread through the cartilage were considered the criteria for major cartilage erosion.^[5]

Minor cartilage involvement was seen as a depicter of T3 disease while major cartilage erosion was considered as a marker of T4 disease.^[2,4] Criteria are schematically depicted in Figure 1.

Histopathological evaluation

The histopathological results after total laryngectomy were reported as no involvement, superficial involvement, and cartilage involvement by the institute's Pathology Department.

Statistical analysis

Statistical analysis was made using Microsoft Excel and MedCalc Software. The results of MDCT in evaluating various types of cartilage involvement in comparison to the corresponding pathological diagnosis were calculated

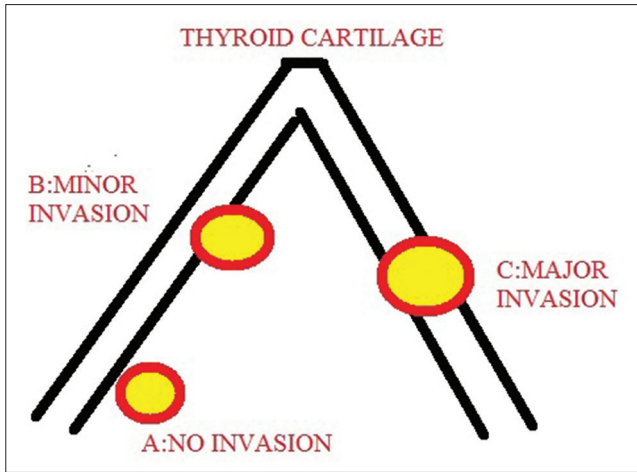


Figure 1: Schematic diagram depicting types of thyroid cartilage involvement in laryngeal cancer

in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

It is prudent to understand that this study is aimed at addressing the clinicroadiological tussle over the overdiagnosis of cartilage invasion by MDCT in laryngeal cancer and not regarding the primary pick up ability of MDCT in this situation; therefore, while analyzing the statistical data, it is the PPV and NPV of MDCT that takes the front seat rather than sensitivity and specificity.^[8]

Results

On retrospective analysis of data, we found that 61 cases of laryngeal or hypopharyngeal carcinoma had presented to our department for MDCT neck evaluation in the given time. Out of this 61, 22 cases fulfilled our inclusion criteria and were included in the study.

Demographics

The study group demographic profile is depicted in Tables 1 and 2.

Supraglottic involvement was the most common presentation seen in 72.72% patients. Most cases presented with laryngeal component of disease, only two cases (9.0%) showed hypopharyngeal involvement only with no laryngeal component [Table 3].

Cartilage involvement

A total number of cartilages involved as seen by MDCT were 15 while only 10 were pathologically confirmed to be involved.

Computed tomography (CT) found minor cartilage erosion in only three cases out of which pathology confirmed superficial erosion in one case and no erosion in the remaining two cases. Major cartilage invasion as depicted by various findings as defined in the criteria above was found in 12 cases on MDCT. Out of these, eight cases were pathologically confirmed to have major thyroid

Table 1: Age distribution

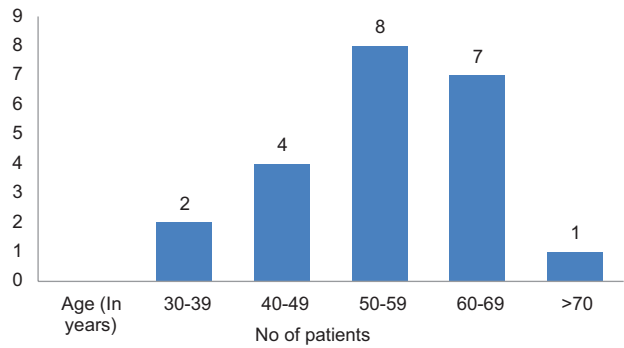


Table 2: Sex distribution and association with tobacco usage

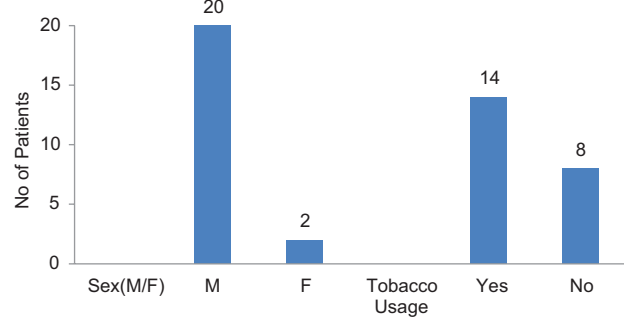
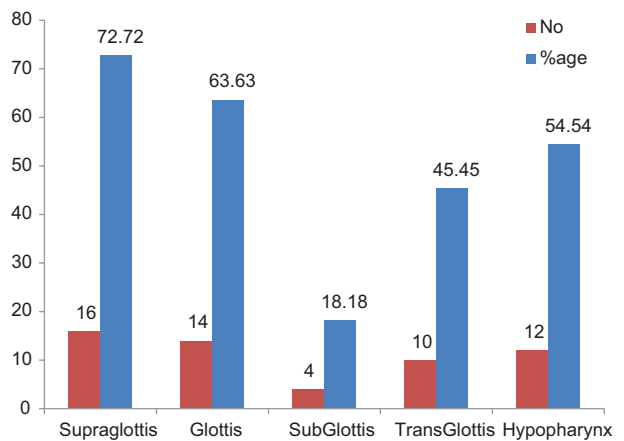


Table 3: Primary site of involvement



cartilage invasion, and in four cases, the cartilage was found free from the lesion or to be having only superficial erosion. There was only one false-negative case in which cartilage invasion was confirmed on HPE but missed by MDCT.

The statistical results of MDCT in detecting minor and major cartilage involvement are depicted in Tables 4 and 5.

In analyzing accuracy of individual CT appearances of a major invasion as in erosion of both inner and outer cortices and lysis, we found that these features were shown in 11 cases on MDCT out of which 8 were pathologically confirmed to be T4A disease while the rest were downgraded to T3 disease by pathology. The presence of enhancing soft tissue on both sides of the thyroid cartilage and extralaryngeal spread was seen in seven cases on MDCT out of which five were pathologically proven to be T4A disease and two were downgraded to T3 disease. Statistical results of individual morphological findings in depicting T4A staging are tabulated in Table 6. The overall results of MDCT in detecting all types of cartilage invasion are shown in Table 7.

Table 4: Statistical analysis of multidetector computed tomography results in detecting minor cartilage invasion

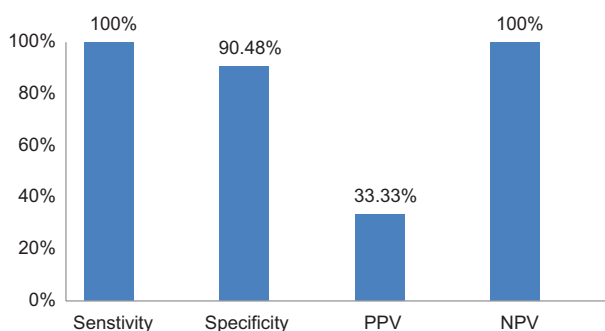


Table 5: Statistical results of multidetector computed tomography in detecting major cartilage erosion

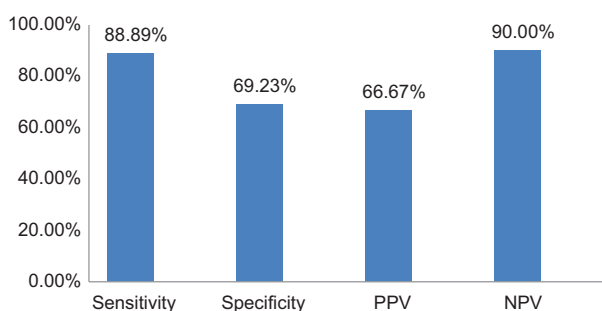


Table 6: Accuracy of individual morphological features on multidetector computed tomography in detecting T4A disease

Morphological character on MDCT depicting major cartilage involvement	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Sclerosis	2	6	1	9	18.18	85.71	66.67	40
Through and through invasion	8	10	3	1	88.89	76.92	72.73	90.91
Extralaryngeal spread	5	14	2	1	83.33	87.50	71.43	93.33

Depicted as number of cases. MDCT – Multidetector computed tomography; PPV – Positive predictive value; NPV – Negative predictive value; TP – True positive; TN – True negative; FP – False positive; FN – False negative

Multidetector computed tomography in detecting stage of laryngeal cancer

It is important to remind that while thyroid cartilage invasion is a very important criteria for T-stage detection in laryngeal cancer, it is not the only criteria for demarking these two stages, and many other CT findings play a crucial role such as the involvement of preepiglottic and paraglottic areas in T3 disease and the invasion of strap muscles, the thyroid gland, and esophagus in T4A disease. Therefore, it is worthwhile to analyze the overall capacity of MDCT in detecting the disease stage which is ultimately the actual guide for therapeutic results.

It was observed that out of eight cases marked as T3 disease by MDCT, four were confirmed by pathology while the other four were downgraded to T2 disease by pathology. CT demarked 14 cases to be of T4A disease out of which 11 were confirmed by pathology and 3 were downgraded to T3 disease. A total of 7 out of 22 cases were downgraded in staging by pathology [Table 8].

Representative cases are depicted in Figures 2 and 3.

Discussion

Laryngeal cancer forms about one-fourth of the diagnosed head and neck cancers in India. It has a strong male predominance as per the Indian Cancer Registries, being one of the top ten cancers to affect Indian men. In our study, we made a similar observation with 88% of the study group consisting of males. Similar observations were made by Sharif *et al.*^[9] and by Bobdey *et al.*^[11]

Laryngeal cancer is a disease of the elderly with most cases presenting between 50 and 70 years of age. The mean age in our study group was found to be 54.36 years. As depicted in literature, we also found a strong association with tobacco chewing in our study, in as many as 63.63% patients.^[1,2]

The current management protocol of advanced laryngeal cancer is guided by the American Joint Committee for Cancer which has made preoperative evaluation of laryngeal cancer, an essential requirement for the concerned oncologist, and a meticulous responsibility for the concerned radiologist. Major thyroid cartilage erosion defines T4 disease while Minor cartilage erosion defines T3 disease, both having different management protocols. It has

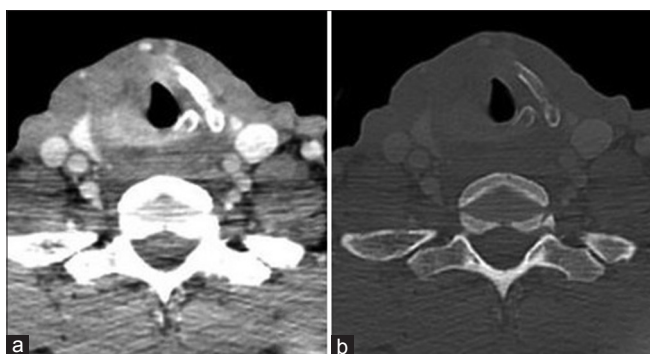


Figure 2: (a) Axial contrast-enhanced computed tomography soft-tissue window images show enhancing lesion in the right glottis eroding through the right thyroid cartilage with extralaryngeal spread. (b) Bone window image shows complete lysis of the right lamina of thyroid cartilage. Major cartilage invasion was confirmed by histopathological examination in this case

Table 7: Final statistical results of multidetector computed tomography in detecting thyroid cartilage invasion (both minor and major)

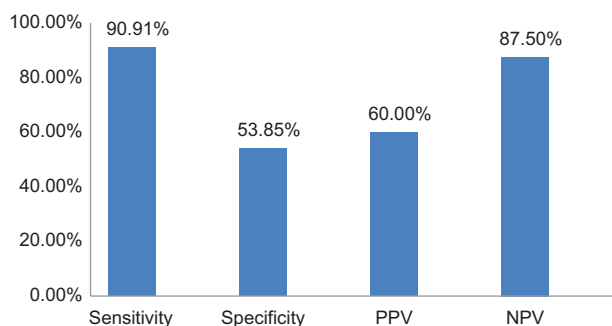
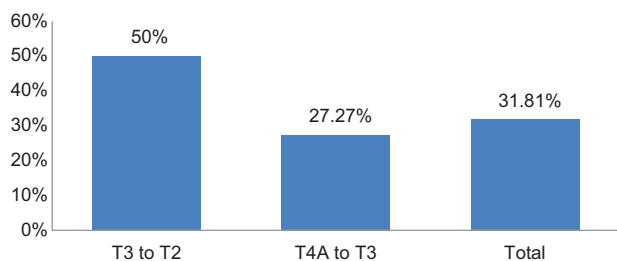


Table 8: Accuracy of multidetector computed tomography in detecting T4A disease as compared to final histopathological results



been long established that a major thyroid cartilage erosion defines higher rate of recurrence and significantly reduces the chances of success of radiotherapy, thereby implying that only conservative measures will not suffice, and in this case, surgical treatment becomes a mandatory consideration subject to resectability.^[2-4]

A vast window has been found in depicting the accuracy of CT in detecting thyroid cartilage involvement which ranges

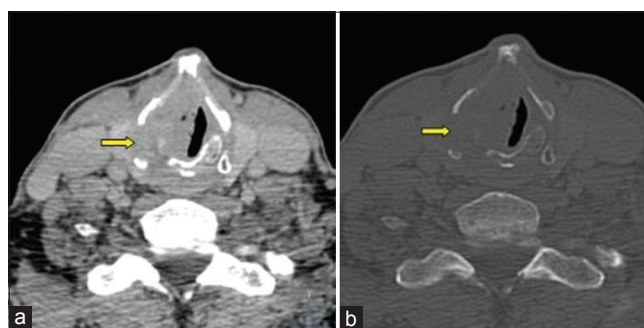


Figure 3: (a) Axial contrast-enhanced computed tomography soft-tissue window shows enhancing mass lesion eroding through the right lamina of thyroid cartilage. (b) Bone window image shows a lytic defect in the right lamina of thyroid cartilage at this level. However, on histopathological examination, major cartilage invasion was not confirmed

from 7% to 83% sensitivity and 40%–100% in the early studies conducted by Becker *et al.*^[10] Over the years and even with the advent of various techniques, the variation still remains. In a recent study, Hartl *et al.*^[11] found CT's sensitivity to be as low as 10.5% and PPV to be 13% in detecting thyroid cartilage involvement in mid to advanced laryngeal cancers.

In our study, we found that the PPV of CT was best in detecting major cartilage invasion, i.e., 66.67%, where a definite erosion of the outer cortex and extralaryngeal spread are helpful criteria for diagnosis. This was followed by the PPV for diagnosing all types of cartilage involvement, i.e., 60.00%. The major observation from this study was the poor results of CT in diagnosing minor cartilage erosion with a PPV of only 33.33%. The closest similarity with our study results was depicted by Li *et al.*^[8] who also analyzed the involvement of cartilage on similar parameters of minor, major, and overall involvement [Table 9].

Other studies which comprehensively studied both major and minor cartilage involvement together also show a large range in their results. A systemic review conducted by Adolph *et al.*,^[12] analyzed the variability of PPV of MDCT in thyroid cartilage invasion in 3 series, and showed a range of 44%–80% for PPV and 80%–100% for NPV. Koopmann *et al.*^[13] found a PPV of 76% and an NPV of 69% for MDCT in the said finding.

Analyzing individual morphological parameters, major cartilage erosion was found to be the most sensitive criteria for depicting T4 disease while extralaryngeal spread was the most specific criteria. We found a low accuracy for sclerosis in depicting cartilage involvement. Similar observation was made by Beitler *et al.*^[4] and Fernandes *et al.*^[14] who emphasized on the importance of extralaryngeal spread as a specific parameter and could not depict sclerosis as a strong parameter for depicting T4 disease.

On overall comparison of preoperative staging by MDCT to the final histopathological analysis, as many as 31.8% of cases were downgraded by pathology in T-staging.

Table 9: Comparison of positive predictive value of the present study with study of Li *et al.* with similar parameters of analysis

	PPV in minor thyroid cartilage erosion	PPV in major thyroid cartilage erosion	PPV in overall thyroid cartilage erosion
Present study (%)	33.33	66.67	60.00
Study by Li <i>et al.</i> (%)	30	78	63

A therapeutically important observation was that 27.27% of cases were downgraded by pathology from T4A to T3 disease which meant that >1/4th patients of the study group were preoperatively overstaged and could have been treated by organ preservation instead. This large discordance of CT and pathology highlights the clinical dilemma of why the MDCT cannot provide reliable results even with the advent of a much better technology over the years.

The answer is somewhat explained by the heterogeneity of appearance of thyroid cartilage over age or with the amount of fatty content within the marrow. The thyroid cartilage starts to ossify at adolescence and may continue up to the end of the 7th decade.^[15] The nonossified or partially ossified thyroid cartilage may create doubt regarding subtle areas of erosion, hence reducing the accuracy of MDCT. Hence, a doubtful region in the unossified cartilage may be mistaken for a minor involvement, thereby providing the lower PPV of CT for minor cartilage involvement. However, it is encouraging to know that the ossified thyroid cartilage is more likely to be involved by the tumor.^[2,8] The other striking reason remains peritumoral inflammatory changes or periostitis in laryngeal cancers which may create a false impression of cartilage involvement, especially in cases of asymmetrical sclerosis on MDCT.^[16]

All these reasons and the wide spectrum of results over time have forced both clinicians and radiologists to look beyond MDCT; however, no solution which is both accurate and practical is at hands as of now. Magnetic resonance imaging (MRI) offers a higher sensitivity of 89% and NPV of 92%–96%, but along with technical difficulties, it offers a lesser specificity and PPV in results due to being unable to differentiate between peritumoral inflammation and cartilage involvement by tumor, both of which appear as T2 hyperintensities.^[16] Fluorodeoxyglucose-positron emission tomography has a limited role in pretreatment imaging in laryngeal cancer which is mostly aimed at locating distant metastasis. Its lack of accuracy in assessing lesions of smaller sizes makes it a less likely replacement for CT or MRI in preoperative assessment of laryngeal cancer.^[17] Recent study by Kuno *et al.*^[18] comparing the results of CT with dual-energy CT (DECT) has shown promising results in thyroid cartilage involvement in squamous cell carcinomas of larynx and hypopharynx. A significant increase of PPV from 46% to 86% and specificity from 70% to 90% was shown by addition of iodine overlay images of DECT as compared to CT neck. Although this may pave the way for future diagnostics, the limited

availability of DECT makes it almost nonpractical option in today's diagnostic oncology in India.

The take-home message for the radiologist here is that detecting thyroid cartilage invasion in the given scope of diagnostic modalities today is a tough and not very rewarding exercise. A combination of expertise and meticulous assessment is required to make the best out of the present opportunities. For the clinician, it is important to remember that pretreatment thyroid cartilage invasion is though crucial but not the only criteria for detecting staging of the disease. A myriad of factors such as tumor bulk, other indicators of local spread, laryngoscopic examination findings, clinical vocal cord-related symptoms, comorbidities, and therapeutic availability and expertise should be kept in mind before making the decision regarding final therapeutic approach.

Limitations of study

Major limitation of the current study is the small sample size as only advanced stage patients were taken up for surgery at our institute. A larger prospective study is required for more efficient results.

Conclusion

A relatively low PPV for thyroid cartilage invasion in advanced laryngeal cancer depicts overestimation and overstaging of laryngeal cancer by MDCT, thereby suggesting that many patients are inadvertently subjected to laryngectomy when an organ preservation approach could have been used. Although far from perfect, MDCT offers a comprehensive and most practical preoperative diagnostic assessment as of now. It is the need of the hour to develop improved methods for differentiating between T3 and T4 stages in advanced laryngeal cancer. A multidisciplinary approach and clinicoradiological correlation seems the most rewarding option in the present times.

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Conflicts of interest

There are no conflicts of interest.

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