

Accuracy of Computed Tomography Pretreatment Staging and Post-treatment Recurrence in Head and Neck Cancers in Rural Western India- A Retrospective Observational Study

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ABSTRACT

Introduction: Cancers of head and neck are the most common in developing countries especially, in India. Multi-disciplinary approach and treatment are required in management of head and neck cancers which include surgeries, radiotherapy techniques and chemotherapy regimens. These can complicate the post-treatment imaging field and contribute to difficulties in image interpretation. Knowledge of these expected post-treatment changes, possible complications and the capability to identify early changes of tumour recurrence is an integral part of post-treatment surveillance and effective management.

Aim: To evaluate the effectiveness of Multi-Detector Computed Tomography (MDCT) in pretreatment staging, post-treatment response and recurrence in comparison with Positron Emission-Computed Tomography (PET-CT).

Materials and Methods: A retrospective observational study was conducted including 101 patients, undergoing pre- and post-treatment, contrast enhanced CT scan with sections from skull base to base of neck. The pretreatment imaging of primary tumour was assessed for its Tumour (T) and Node (N) stage with corresponding staging on histopathology. The imaging

observations on pre- and post-treatment scans, for outcomes on recurrence, residual disease and cure were considered. Recurrence when suspected on post-treatment CT scan was confirmed with PET-CT or biopsy. The agreement of T and N staging on pretreatment CT scan with that on histopathology was examined using quadratic weighted kappa. Sensitivity and specificity for detection of post-treatment recurrence on CT scan was determined by measuring true positive rates and true negative rates.

Results: An agreement of 0.4 and 0.58 (kappa coefficient) was found between T and N staging on CT and histopathology which suggests fair accuracy of CT in pretreatment staging of head and neck cancers. The CT had a sensitivity and specificity of 88.89% and 100% for detecting recurrence in head and neck cancers in post-treatment neck CT scan in the background of post-treatment imaging changes.

Conclusion: The MDCT is a good imaging tool in pretreatment staging of head and neck cancers. It effectively detects recurrence in the background of post-treatment changes. A standard post-treatment evaluation protocol should be followed.

Keywords: Multidisciplinary approach, Positron emission tomography, Radiotherapy

INTRODUCTION

Cancers of head and neck are the most common cancers in developing countries [1]. The highest rates have been reported from India, Sri Lanka, Pakistan, Bangladesh, Hungary and France [2]. In India, they are most common in men than women [3]. The high incidence of these cancers in India has been attributed to various factors, like use of smokeless tobacco, areca nut, low socio-economic status, poor hygiene, poor diet and viral infections [4-6]. Multi-disciplinary approach and treatment planning are required in management of head and neck cancers which include various surgical approaches of resection, neck dissection and tissue reconstruction along with different radiotherapy techniques as well as concurrent and neoadjuvant chemotherapy regimens. All of these can further complicate the post-treatment imaging field and contribute to difficulties in image interpretation. Knowledge of these expected post-treatment changes, possible complications and the capability to identify early changes of tumour recurrence are an integral part of post-treatment surveillance and effective management [7]. The importance of detection of recurrence lies in its association with high mortality and salvage rate is not more than 36%. Moreover, the prognosis as well as median overall survival after failure of first-line treatment is less than one year [8-11].

Imaging modalities like CT, PET and Magnetic Resonance Imaging (MRI) are considered as valuable modalities for initial staging as well

as for post-treatment evaluation of head and neck cancers [12]. While Contrast Enhanced Computerised Tomography (CECT) is still considered as the first line investigation available in post-treatment surveillance of patients with head and neck cancers, PET-CT has its evolving role in being more accurate as compared to CT or PET alone in post-treatment response assessment [13,14]. Even though PET-CT fusion has more promising role in post-treatment response assessment, its limited availability and cost burden makes it a complimentary investigation in doubtful cases [15].

Use of MDCT gives the advantage of rapid image acquisition for evaluation of gingiva-buccal and RMT cancers. High spatial resolution of CT can provide precise anatomic detail.

Combined imaging with PET and CT has been found to be a highly sensitive technique for detection of recurrence of head and neck cancers, post-treatment. However, when PET scan is used in less than 10-12 weeks after completion of radiation therapy, a high false-positive rate occurs because of the presence of post-irradiation inflammation, edema or anatomic distortion [16,17]. The CT component of most current CT-PET systems do not have the capabilities of a dedicated CT and therefore have limited image quality [18]. MR provides superior soft-tissue contrast. Diffusion-weighted MR imaging is useful to differentiate tumour recurrence from normal post-treatment changes in the early period after treatment. CT has high sensitivity (63-100%) for differentiating recurrent tumour from

post-treatment changes, with increased accuracy in patients treated with non-surgical organ preservation treatment [12,19-27].

Aim of this study was to evaluate effectiveness of MDCT in pretreatment staging, characteristics of post-treatment changes, complications as well as sensitivity and specificity in detection of recurrence, which would allow effective post-treatment surveillance.

MATERIALS AND METHODS

This was a retrospective observational study including 101 patients with head and neck cancers undergoing pre- and post-treatment, contrast enhanced CT scan with sections from skull base to base of neck, conducted over a period of three years with mean follow-up period of 11.85 months. The study was approved by Institutional Ethics Committee of HM Patel Centre for Medical Care and Education (IEC/HMPCMCCE/87/Faculty/15/37/18).

Inclusion and Exclusion criteria: Patients of either sex with biopsy proven diagnosis of head and neck cancer involving oral cavity, oropharynx and hypopharynx, who underwent pretreatment and post-treatment CT scans, were included in the study. Patients whose pre- and post-treatment CT scans were not available, they were not included in the study.

Study Procedure

The seventh edition of AJCC cancer staging manual was followed for T and N staging [28]. From the pretreatment imaging scans, tumour characteristics for size (greatest dimension), enhancement pattern with presence or absence of necrosis were recorded and the corresponding T staging on histopathology was also noted. The pretreatment nodal status on CECT was also evaluated for size, nodal necrosis, shape of lymph node (round if longitudinal/short axis <2, and oval if longitudinal/short axis >2), margin of lymph node (smooth or ill-defined/irregular), conglomeration of lymph nodes and Perinodal Extension (PNE). A lymph node was considered positive for metastasis if short axis in jugulodigastric nodes was greater than equal to 15 mm, retropharyngeal nodes if greater than equal to 8 mm and the rest of cervical nodes if greater than equal to 10 mm, presence of necrosis, ill-defined irregular margin, and PNE irrespective of the size. The corresponding N staging and presence of PNE on histopathology were also noted.

The treatment plan was recorded including the status of surgery, radiation therapy and chemotherapy. The type of surgery whether wide excision or composite resection, type of neck dissection whether modified radical neck dissection, radical neck dissection or selective neck dissection and flap reconstruction were recorded.

The imaging observations of treatment outcome on the post-treatment scans were considered for the last available scan at the end of one year post-treatment. The outcome on post-treatment CECT such as presence of recurrence, presence of residual disease and cure were noted. Recurrence was defined as slightly expansile, infiltrative heterogeneously enhancing soft tissue lesion in head or neck with or without bony/cartilage erosion and with or without necrosis [7,29].

Residual disease was defined as persistence of primary lesion observed on pretreatment scan on post-treatment scan [30]. Cure was defined as absence of abnormal soft tissue lesion in head and neck.

Benign post-treatment changes were noted when present. Post-radiation complications and postsurgical complications were looked for in the post-treatment CT scan. Recurrence when present on post-treatment CT scan was confirmed with PET-CT or biopsy when available. Details of demography, clinical presentation, tumour site and subsite, observations of pretreatment and post-treatment images were also recorded.

STATISTICAL ANALYSIS

Stata 14.2 Software was used for statistical analysis. Sensitivity and specificity for detection of post-treatment recurrence as well as PNE

on CT scan was determined by measuring true positives rates and true negative rates. Associations between patterns of recurrence and clinical, socio-demographic characteristics, pretreatment imaging features of primary lesion and nodal lesions and post-treatment complications were examined using logistic regression.

RESULTS

A total of 101 patients with head and neck cancers involving oral cavity, oropharynx and hypopharynx were included. Out of all, 68 (67.33%) had malignancy involving oral cavity, 25 (24.75%) had malignancy involving oropharynx and only eight (7.92%) had malignancy involving hypopharynx. Out of the 68 patients with oral cavity cancer, the most common primary subsite was buccal mucosa seen in 66 patients, the rest two had lip and hard palate cancers. There was a preponderance with 82 patients (81.19%) being men and mean age at first scan being 52 years [Table/Fig-1]. Tobacco consumption in form of tobacco chewing was associated in 69 (68.32%) patients with mean duration of 15 years (2.55).

Variables	Category	Frequency (%)
Age (in years)	Mean (SD)	52.35 (10.91)
Sex	Female	19 (18.81)
	Male	82 (81.19)
Type of visit	Self-referral	38 (37.62)
	Follow-up	63 (62.38)
Presence of symptoms	No	45 (44.55)
	Yes	56 (55.45)
Tobacco use	No	32 (31.68)
	Yes	69 (68.32)
Duration of tobacco use in years	Mean (SD)	15 (2.55)
Primary site of lesion on CT	Oral cavity	68 (67.33)
	Oropharynx	25 (24.75)
	Hypopharynx	8 (7.92)

[Table/Fig-1]: Demographic and clinical profile.

Out of 101 patients, 65 (64.35%) underwent local surgical resection with composite resection in 60 (92.30%), local wide excision in four (6.15%) patients and one (1.53%) patient underwent total laryngectomy with partial pharyngectomy. Out of 101 patients, radical neck dissection was performed in 15 (14.85%), modified radical neck dissection in 48 (47.52%), selective neck dissection in one (0.99%) and 37 (36.63%) did not undergo neck dissection [Table/Fig-2]. Out of 65 patients underwent 60 flap reconstruction. Chemotherapy was received by 88 patients and radiation therapy by 76 patients with mean (SD) number of cycles, dose per cycle and cumulative dose of 31 (5.0), 64 (4.4) and 1985.14 (380.0), respectively. The agreement of T staging and N staging on pretreatment CT scan with that on histopathology was examined using quadratic weighted kappa with the Cohens kappa coefficient (k) for T staging on CT compared to T staging on histopathology being 0.4 therefore level of agreement was fair.

Variable	Category	Frequency (%)
Local excision (n=101)		65 (64.35)
Type of surgical excision (n=65)	Wide local excision	4 (6.15)
	Composite resection	60 (92.30)
	Total laryngectomy with partial pharyng	1 (1.53)
Neck dissection (n=101)	None	37 (36.63)
	Radical neck dissection	15 (14.85)
	Modified radical neck dissection	48 (47.52)
	Selective neck dissection	1 (0.99)

[Table/Fig-2]: Details of surgical excision.

We studied frequency distribution of characteristics of pretreatment status of lymphnodes for nodal staging in 95 patients. Broadly on CT scan, 48 (50.52%) patients had lymphnodes labelled positive for metastasis. Out of all patients, 14.73% (n=14) showed PNE on CT scan [Table/Fig-3]. Histopathological evidence of PNE status was available in 68 of the 95 patients, which showed that 22.0% (15 out of 68 patients) had PNE.

Variables	n	Category	Frequency (%)
Size	95	<15 mm	55 (57.89)
		≥15 mm	40 (4.10)
Shape	95	Round-1 (longitudinal/short axis <2)	44 (46.31)
		Oval-2 (longitudinal/short axis >2)	51 (53.68)
Margin	95	Smooth well defined margin	83 (87.36)
		Ill-defined irregular margins	12 (12.37)
Necrosis	95	Yes	32 (33.68)
		No	63 (66.3)
Conglomeration	95	Yes	7 (7.36)
		No	88 (92.63)
PNE on CT	95	Yes	14 (14.73)
		No	81 (85.26)
Perinodal infiltration on histopathology	64	Yes	15 (22.06)
		No	49 (76.56)
CECT positivity for metastasis	95	Yes	48 (50.52)

[Table/Fig-3]: Imaging characteristics of lymph nodes on pretreatment CT scan.

*The N is 95 as rest 6 patients did not have neck lymph nodes

Out of total, 64 patients had both pretreatment CT and histopathological nodal staging available [Table/Fig-4]. The Cohens kappa coefficient (k) for N staging on CT compared to N staging on histology was 0.58, therefore level of agreement was fair.

N staging on CT	N staging on histology						Total on CT
	N0	N1	N2A	N2B	N2C	N3B	
N0	33	2	0	0	0	1	36
N1	2	5	1	3	4	3	18
N2A	0	1	0	0	1	0	2
N2B	0	1	0	0	2	3	6
N3B	0	0	0	0	0	2	2
TOTAL	35	9	1	3	7	9	64

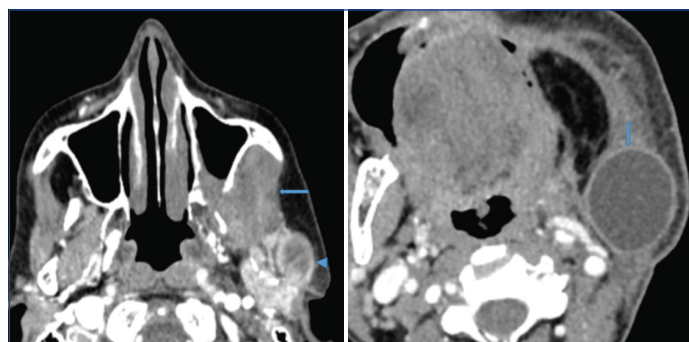
[Table/Fig-4]: N staging on CT and Histopathology.

We could follow-up 100 patients, one was lost to follow-up. Out of 34 (34%) patients were followed upto six months, 46 (46%) patients were followed upto 12 months, 12 (12%) patients could be followed upto two years and eight (8%) could be followed for >2 years.

On CT evaluation after treatment we found that out of 100 patients, 34 (34%) did not show evidence of recurrence or residual disease, 19 (19%) showed residual disease and 47 (47%) showed recurrence. Out of 47 patients who developed recurrence, 40 (85.10%) could be labelled to have recurrence without any dilemma and seven (14.89%) patients were labelled to have recurrence with dilemma. Out of these 36 (78%) patients developed in recurrence within one year. Moreover, out of 47 patients with recurrence 34 (72.36%) patients developed necrosis within the recurrent lesion and 25 (53.19%) patients developed bony erosion within recurrent lesion.

We also evaluated post-treatment changes that may or may not have contributed to dilemma in labelling recurrence. Out of 100 patients, 78 patients did not develop any post-treatment change. Thickening of platysma was present in three patients. Changes at post-operative site such as soft tissue fullness [Table/Fig-5] was present in seven patients, cortical erosion was present in one patient, mucosal irregularity was seen in one patient and edema was present in two

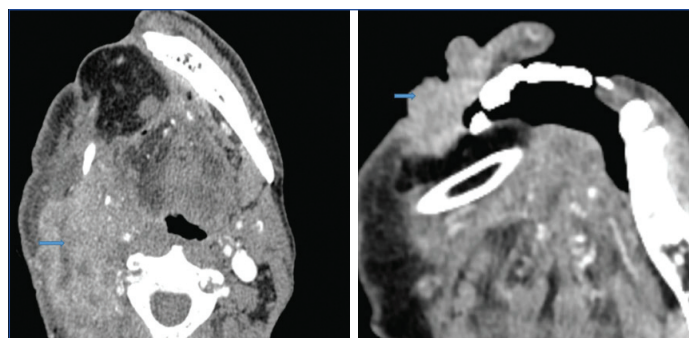
patients. Soft tissue fullness contributed to dilemma in all seven patients who were doubtful candidates for labelling recurrent lesion. None of our patients developed any post-irradiation complication. Out of 65 patients who underwent local excision, oro-cutaneous fistula developed in three (4.61%) patients, serous retention cyst [Table/Fig-6] developed in two (3.07%) patients; sinus developed in two (3.07 %) patients and oro-antral with oro-cutaneous fistula developed in one (1.53%) patient.



[Table/Fig-5]: A 60-year-old female with follow-up CT scan at one-year post-chemotherapy, left buccal carcinoma (T2N0). a) Axial section of contrast enhanced CT neck at the level of maxilla shows mildly enhancing soft tissue fullness in left retro-maxillary space, suggesting benign post-treatment change (arrow).

[Table/Fig-6]: 45-year-old female with follow-up CT scan at one-year post-treatment (surgery and radiation therapy) left buccal carcinoma (T4aN2). Axial section of contrast enhanced CT neck, shows, well-defined oval fluid density area with thin enhancing wall at operative site suggesting serous retention cyst. (Images from left to right)

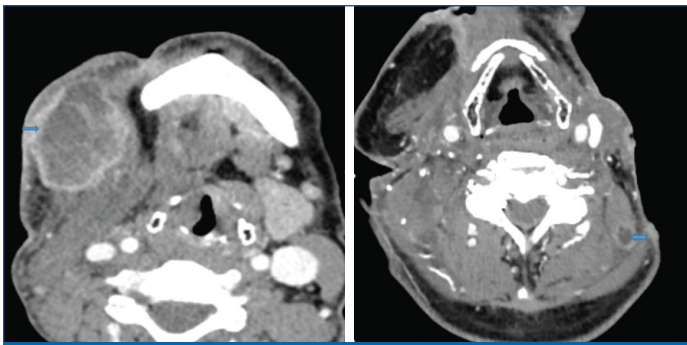
We had 68 patients in whom PET-CT and biopsy both were available to confirm the presence or absence of recurrence post-treatment. In 47 patients who were labelled to have recurrence on post-treatment CT, recurrence was confirmed in all using either PET-CT and biopsy. Based on site of recurrence we observed local recurrence in 37 (78.72%) [Table/Fig-7,8], whereas local with nodal in one (2.1%) and nodal recurrence alone [Table/Fig-9] in seven (14.89%) and regional in one (2.1%) [Table/Fig-10]. One patient (2.1%) presented with distant metastasis.



[Table/Fig-7]: A 68-year-old male with follow-up scan at one-year post-treatment (surgery and radiation therapy) right buccal carcinoma (T4aN1). An ill-defined heterogeneously enhancing area with hypodense areas is noted at flap site, suggesting local recurrence; [Table/Fig-8]: A 55-year-old male with follow-up scan at one-year post-treatment (surgery and radiation therapy) right buccal carcinoma (T4N1). a) Axial section of contrast enhanced CT neck, shows irregular, enhancing, soft tissue lesion at right angle of mouth, suggesting local recurrence. (Images from left to right)

A total of 28 patients were declared disease free on post-treatment CT evaluation and it was observed that 23 patients were confirmed to be disease free using PET-CT or biopsy; however, five patients showed presence of recurrence contradictory to our CT findings. The sensitivity and specificity of determining presence of recurrence on post-treatment CT scan was observed to be 88.89% and 100%, respectively [Table/Fig-11].

Logistic regression revealed the size of largest lymph node when greater than 15.0 mm was significantly associated with recurrence {OR:15.62 with 95% CI (1.58,154.27), p-value=0.01}. No other pretreatment nodal characteristics (conglomeration, necrosis, shape and PNE) as well as lesion characteristics (Retromolar trigone involvement, necrosis in primary lesion, supranotch/infranotch disease and bony erosion) showed any significant correlation with recurrence.



[Table/Fig-9]: A 45-year-old female with follow-up CT scan at 1-year post-treatment (surgery and radiation therapy) left buccal carcinoma (T4a N2). Axial section of contrast enhanced CT neck, shows, large irregularly marginated peripheral enhancing with central hypodense, soft tissue lesion in left IB region, suggesting nodal recurrence.

[Table/Fig-10]: A 54-year-old male with follow-up scan at 1-year post-treatment (surgery and radiation therapy) right buccal carcinoma (T4aN2). Axial section of contrast enhanced CT neck, shows round, peripherally enhancing, centrally hypodense lesion in left posterior paraspinal muscles, suggesting local-regional recurrence. (Images from left to right)

Recurrence	PET CT or biopsy		Total
	+VE	-VE	
Recurrence	40 (88.89)	0	40
No recurrence	5 (11.11)	23 (100)	28
Total	45	23	68

[Table/Fig-11]: Sensitivity and Specificity of CT as compared to PET/CT or Biopsy.

DISCUSSION

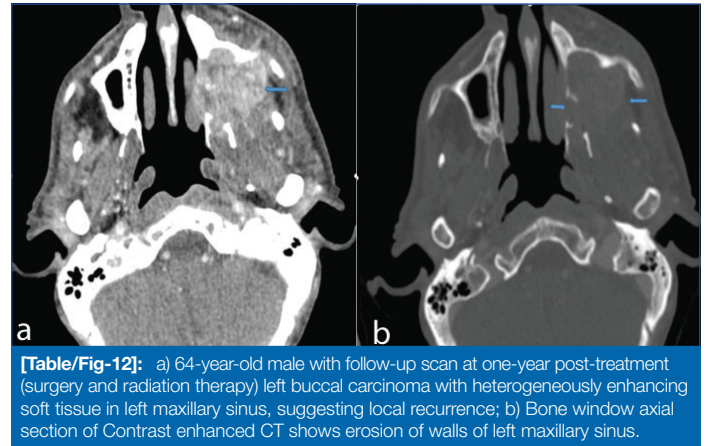
In the present study, the kappa coefficient (k) was found fair enough with value of 0.4 and 0.58, respectively for T and N staging derived on CT when compared with histopathology. Therefore, T and N staging based on CT imaging in a radiological report may help in prognostication of disease. Our observations are in line with Dammann F et al., in his prospective study of 79 patients having primary squamous cell carcinoma of oral cavity and oropharynx staging was performed utilising CT, MRI and FDG PET. They reported that CT was a good imaging tool for staging a primary lesion, with PET beneficial in equivocal cases [19]. However, another study by Veit-Haibach P et al., concluded that combined PET/CT was more accurate in assessing overall TNM stage than CT alone [31].

In our study, though soft tissue spread and bony erosion impacted the treatment planning however did not show any correlation with tumour recurrence. The lymphatic dissemination of SCC is an important prognostic indicator. Several CT characteristics like size, shape of node, presence of necrosis and PNE can suggest presence of metastasis. We observed necrosis and conglomeration to be the most reliable criterion for metastasis which is similar as concluded by Arya S et al., whereas Yousem DM et al., reported more accurate detection of metastasis by CT in presence of central nodal necrosis and extra-capsular spread [32,33]. Yamazaki Y et al., studied 1076 lymph nodes with preoperative FDG-PET and CT. FDG-PET detected metastatic lymph nodes ≥ 10 mm more accurately, and had fewer false-positives than CT [34].

In our study, PNE was identified on CT in 14.73%, whereas histopathology showed that 22.0% had PNE thus CT had a sensitivity of 33% and specificity of 98% for detecting PNE which is in line with a study performed by Prabhu RS et al., which included 432 patients who underwent neck dissection for head and neck cancer and had sensitivity and specificity of 43% and 97.7%, respectively on CT [35]. A study performed by Aiken AH et al., was a blinded inter-observer study which included 111 patients with pre-operative CT imaging, followed by pathological evaluation with criteria including lymph node necrosis, irregular borders/stranding, gross invasion for predicting PNE. The sensitivity and specificity was found to be 68% and specificity of 88%, respectively by the blinded reviewers as compared to sensitivity and specificity of 46% and specificity of 95%, respectively in the original reports. A higher sensitivity in this study could be due to higher sensitivity of reviewer and criteria for determining PNE [36].

Post-treatment changes are affected by the treatment method, such as the type of surgery, reconstruction, neck dissection, and radiation therapy.

Tumour recurrence may be hard to identify on clinical examination alone, therefore imaging is essential. Most commonly tumours have been found to recur within the first two years. On CT recurrence may be seen as an infiltrating, slightly hyper-attenuating mass with enhancement, progressively enlarging mass, with or without associated bone destruction [Table/Fig-12a,b] [7].



[Table/Fig-12]: a) 64-year-old male with follow-up scan at one-year post-treatment (surgery and radiation therapy) left buccal carcinoma with heterogeneously enhancing soft tissue in left maxillary sinus, suggesting local recurrence; b) Bone window axial section of Contrast enhanced CT shows erosion of walls of left maxillary sinus.

Our study showed a recurrence rate of 47%. Schwartz GJ et al., in their study showed a recurrence rate of 28% whereas Mucke T et al., in their study showed 23.9% [8,10]. Based on site of recurrence we observed local recurrence in 82.9% whereas local with nodal in 2.1% and nodal recurrence alone in 12.7% and regional in 2.1%.

Our study found CT an effective tool for evaluation of pretreatment and post-treatment status in head and neck cancers with sensitivity and specificity for detection of recurrence being 88.89% and 100%, respectively, which is comparable to study conducted by Lell M et al., who studied 331 patients with head and neck cancers who underwent CT after treatment with diagnosis being correlated with histology with sensitivity and specificity being 86% and 80%, respectively [29]. Bransetter IV BF et al., studied 65 consecutive patients with each patient with PET alone, CT alone and PET/CT combined with a minimum follow-up of six months and biopsy as reference standard. They found that PET/CT was more accurate than PET or CT alone for depiction of malignancy in head and neck with a sensitivity of 98% and specificity of 92% [14]. Previous studies have shown the higher accuracy of PET/CT in staging head and neck cancer and in identifying tumour recurrence [16,23-28].

Lowe VJ et al., have demonstrated sensitivities and specificities, respectively, of 38% and 85% for conventional imaging and 100% and 93% for PET imaging confirming that PET performs significantly better than conventional imaging in detecting recurrent disease [37].

Therefore, although combined PET/CT has a higher sensitivity, CT alone is a good imaging tool with PET/CT reserved for selective cases where is a diagnostic dilemma. Further a baseline CT scan after 3-6 months' therapy would be helpful as it would allow treatment induced changes to be detected and differentiated from recurrence on follow-up scan. We recommend that a stringent post-treatment evaluation programme to be followed including a base line post-treatment CT scan performed at 3-6 months' postcompletion of therapy. Further, standardisation of post-treatment imaging guidelines could help accurate and early detection of recurrence even before it clinically becomes evident thus allowing timely intervention.

Limitation(s)

The retrospective nature of this study is associated with several inherent biases. The limitation of our study lies in the duration of follow-up for each patient, a longer duration of follow-up may have

added further value for predicting disease free survival. Another limitation lies in lack of adherence to a standardised post-treatment imaging protocol the reasons of which may be limited economic resources and patient compliance or early deaths.

CONCLUSION(S)

Our study concludes that MDCT is a good imaging tool in evaluation of pretreatment as well as post-treatment status in head and neck cancers. Pretreatment T and N staging can help to provide a fair judgement of prognosis. MDCT can effectively detect recurrence in the background of complicating post-treatment benign changes and CT alone can be a good tool in post-treatment neck evaluation identifying recurrence and complications with PET/CT reserved for selective cases.

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