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Comparison of Treatment Response Assessment in CT Scan by Recist and Volumetric Assessment in Patients with Cancers of Oral Cavity

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ABSTRACT

- ***Introduction***

Oral cancer is a grave problem in many parts of the world. One third of oral cavity cancers occur in India and it accounted for approximately 30% of all cancers in India. Assessment of the change in tumour burden is an important aspect of the clinical evaluation of cancer treatment. Both tumour shrinkage and disease progression are important endpoints in cancer clinical trials using chemotherapeutic drugs. The standard approach used to assess the response of solid tumors to neoadjuvant chemotherapy is RECIST. How ever it has been a common observation that RECIST which uses unidimensional measurement in imaging may not be accurate in response evaluation in oral cavity cancers owing to its complex anatomy. Hence this study was undertaken to evaluate the accuracy of RECIST and to determine if CT volumetric assessment and three dimensional assessment can better evaluate the response. There are only few studies from India in assessing response of oral cavity cancers to neoadjuvant chemotherapy. More over there is a need for more studies to be done so as to find out exactly which criteria is the better one.

- ***Objective*:**

To compare the response assessment in CT scan by RECIST, 3D and volumetric methods in borderline operable oral cancers who are receiving neoadjuvant chemotherapy using clinicopathological criteria as the reference standard.

- ***Materials & Methods***

All patients with oral cavity cancers who received neoadjuvant chemotherapy in oncology department of JIPMER and whose CT images were available in PACS were included in the study based on the inclusion and exclusion criteria. Response assessment was done only for the primary tumor by comparing the post neoadjuvant chemotherapy imaging with pretreatment imaging by three different methods namely RECIST, three dimensional assessment and volumetric assessment. In RECIST criteria, single longest measurement in the axial plane was taken. In 3 Dimensional assessment, longest diameters in three orthogonal plane in multiplanar reformatted CT image was taken. In volumetric assessment, manual delineation of tumor extent in serial 2mm axial section was done for computed volume estimation Subtraction of volumes measured at pretreatment and post treatment gave the volume changes. Percentage of reduction in the tumor measurements using the criteria were assessed. Clinicopathological downstaging/upstaging was used as the reference criteria in order to compare the other 3 criteria. The patients were categorized into progressive disease, stable disease, partial response and complete response based on the percentage response. Progressive disease and stable disease were grouped as non responders and partial response and complete response as responders The statistical analyses were performed using SPSS 19 and Medcalc Software. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for all three methods using clinico-pathological assessment as reference standard. Weighted kappa was used to assess the agreement between all three methods for categorizing the patients into progressive disease, stable disease, partial response and complete response. Bland Altman plot was used to compare the quantitative response based on CT volumetry, 3 D assessment and RECIST. To make the volumetric data in 3 dimensional assessment and CT volumetry comparable to unidimensional data of RECIST, cube root of the volumetric data was taken.

- ***Results***

Totally 28 patients with oral cavity carcinoma undergoing neoadjuvant chemotherapy were studied. The sensitivity of RECIST criteria to differentiate between responders and nonresponders was 40 %, whereas that of CT volumetry was 73.3% and 3 Dimensional assessment was 60%, whereas specificity was 100 % for all three when clinicopathological downstaging was used as the reference standard. The agreement (weighted kappa) between RECIST and clinicopathological downstaging to classify the group of patients into complete response, partial response, stable and progressive disease were 0.66, whereas that of CT volumetry was 0.83 and that of 3 Dimensional assessment was 0.73.Using Bland Altman plot, the systematic bias of using RECIST criteria when compared to CT volumetry was 5.5%. The variance of the difference between the two methods was 9.85. The absolute percentage error was 39.04%. The systematic bias of using 3 Dimensional assessment when compared to CT Volumetry was 7.38%. The variance of the difference between the two methods was 7.19. The absolute percentage error was 35.38%.

- ***Conclusion***

Sensitivity of RECIST to detect responders was significantly low as compared to CT Volumetry. There was more agreement between CT Volumetry and clinicopathological assessment compared to RECIST, in categorisation of response assessment. Hence, CT volumetry may definitely be a better method than RECIST in assessing response to NACT in oral cavity tumors. Bland Altman plot analysis showed that there was slightly better agreement between 3 Dimensional assessment and volumetry as compared to RECIST. 11. Bland Altman plot analysis showed that there was slightly better agreement between 3 Dimensional assessment and volumetry as compared to RECIST. However the difference was not significant and hence 3 Dimensional measurement cannot be used as a substitute for volumetry in response assessment and further studies with more sample size needs to be done to assess this.

Keywords:- *Carcinoma Oral Cavity, RECIST, CT Volumetry, Three Dimensional Assessment, Clinicopathological Staging.*

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CHAPTER ONE
INTRODUCTION

Oral cancer is a grave problem in many parts of the world. According to the data calculated by the Global cancer statistics, GLOBOCAN 2018, approximately 354864 new oral cavity cancer cases were reported worldwide and 177384 deaths due to this.[1] This accounted for approx. 2 % of the cancer cases world wide and 1.9 % of death from cancer cases. One third of oral cavity cancers occur in India and itaccounted for approx. 30% of all cancers in India.[2-5]

Assessment of the change in tumour burden is an important aspect of the clinical evaluation of cancer treatment. Both tumour shrinkage and disease progression are important endpoints in cancer clinical trials using chemotherapeutic drugs. The standard approach used to assess the response of solid tumors to neoadjuvant chemotherapy is RECIST (Response Evaluation Criteria In Solid Tumors).[6,7] However it has been a common observation that RECIST which uses unidimensional measurement in imaging may not be accurate in response evaluationin oral cavity cancers owing to its complex anatomy.[8-10] Hence this study was undertaken to evaluate the accuracy of RECIST and to determine if CT volumetric assessment can better evaluate the response. There are only few studies from India in assessing response of oral cavity cancers to neoadjuvant chemotherapy. Though there are other studies which compare RECIST with CT volumetry in head and neck cancers, pulmonary cancers etc. there isno other study which does the same comparison exclusively in oral cavity cancers, to the best of our knowledge.[8-11]Moreover there is a need for more studies to be done so as to find out exactly which criteria is the better one.

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CHAPTER TWO
AIMS AND OBJECTIVES

- *Objective*

To compare the response assessment in CT scan by RECIST, 3D and volumetric methods in borderline operable oral cancers who are receiving neoadjuvant chemotherapy using clinicopathological criteria as the reference standard.

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CHAPTER THREE
REVIEW OF LITERATURE

A. Epidemiology

Oral cancers are one of the foremost cause of mortality and morbidity in India and other South Asian countries from malignancies. Tobacco plays a major role in the etiology of oral cancers.[12]According to the data calculated by the Global cancer statistics, GLOBOCAN 2018, approximately 354864 new oral cavity cancer cases were reported worldwide and 177384 deaths due to this.[1] This accounted for approx. 2% of the cancer cases world wide and 1.9 % of death from cancer cases. The incidence of oral cavity cancers in men were 246420 cases and in women were 108444. According to National Institute of cancer prevention and research, one third of oral cavity cancers occur in India and it accounted for approx. 30% of all cancers inIndia and approx. 119992 new cases were reported from India and 72616 deaths.[5]

B. Anatomy

➢ *Anatomy of Oral Cavity[13]*

The oral cavity extends from the lips upto the oropharynx. It consists of vestibule and oral cavity proper. The roof of oral cavity is formed by the palate which separates the nasal and oral cavities. The floor of the oral cavity is formed by the myelohyoid. Lateral wall is formed by the cheeks. The boundary between the oral cavity and pharynx is circular and consists of the circumvallate papillae on the dorsum of tongue,anterior tonsillar pillars on the sides and the junction of the hard and soft palate superiorly. However the papillae cannot be identified on imaging

- *Cheeks*

The cheek mucosa is adherent tightly to the buccinators and hence wrinkles when the mouth is closed and stretches when the mouth is open.

➢ *Oral Vestibule:*

It is the cleft-like space between cheeks and the teeth. It is lined by the buccal mucosa. Vestibule communicates with oral cavity proper through the retromolar space. Mucosa covering the jaw alveoli reflects onto the cheeks and lips forming a sulcus known as upper and lower gingivobuccal sulcus (GBS).

➢ *Oral Cavity Proper:*

The roof of oral cavity proper is formed by the hard palate. The lateral walls are formed by the upper and lower alveolus and floor is formed by the myelohyoid muscle.

➢ *Retromolar Trigone:*

RMT is a mucosa covered fold and extends behind the last molar of mandible throughthe ramus of mandible upto the last molar of maxilla. It has a triangular shape with apex at the maxillary tuberosity and base behind the mandibular last molar. The pterygomandibular raphae lies beneath the mucosal folds. It attaches superiorly to pterygoid hamulus and inferiorly to posterior end of myelohyoid line. RMT is seen onconsecutive axial CT images from behind the maxillary last molar to the mandibular last molar. It can be seen entirely in the oblique reformatted MDCT images.

➢ *Buccal Space:*

It lies lateral to the buccal mucosa. Buccal mucosa carcinoma often spreads to this region and into the masticator space. It is bounded medially by the buccinator, laterally by the zygomaticus major and posteriorly by the masseter. Its contents are angular branch of facial artery, facial vein, buccal fat, nerves, distal part of parotid duct and lymph node. This space leads to masticator space superiorly.

➢ *Tongue*:

Tongue has oral and pharyngeal portion. The oral part of tongue forms the central partof oral cavity. It is a muscular structure, wrapped in mucous membrane. The oral tongue forms the anterior two third and the base of tongue forms the posterior two- third. Tongue has intrinsic and extrinsic muscles. It is divided into two equal halves by the midline lingual septum. Intrinsic muscles are four in number and are superior and inferior longitudinal, transverse and vertical. These are well seen on MR imaging. Extrinsic muscles arealso four in number and are the genioglossus, hyoglossus, styloglossus and palatoglossus. They are best seen on T2 weighted images. They attach the tongue to the hyoid bone, mandible and styloid process.

➢ *Floor of Mouth:*

It is formed predominantly by the myelohyoid muscle. Myelohyoid is a U shaped sling. It extends across the myelohyoid ridges on the inner aspect of the mandible. Anteriorly, it extends from the symphysis menti and posteriorly till the last molar tooth. It is best seen on coronal plane in MR and CT imaging. The submandibular gland is located beneath the myelohyoid. Two other muscles also support the floor of mouth. They are geniohyoid and anterior belly of digastric. Geniohyoid arises from the inferior genial tubercle and inserts into the hyoid. They run above the hyoid and are paramedian in location. They appear darkly hypointense on

T2 weighted images. The anterior belly of digastric is best seenin coronal plane on the inferior surface of myelohyoid muscle.

➢ *Sublingual Space:*

It is seen lateral to genioglossus and superomedial to myelohyoid. It is fat filled. Its contents are deep part of submandibular gland, sublingual gland, Wharton's duct, neurovascular bundle supplying the tongue and anterior fibres of hyoglossus.

C. Epidemiology, Staging and Outcomes.

➢ *Risk Factors:*[12]

- Cigarette and Tobacco use
- Human Papilloma virus
- Alcohol
- Betel quid
- Genetic syndromes such as Fanconi anemia and Dyskeratosis congenita

➢ *Staging:*[14]

Table 1 Staging

T Category	T Criteria
Tx	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm with width of invasion (DOI) ≤ 5 mm
T2	Tumor ≤ 2 cm with DOI > 5 mm Or tumor> 2 cm and ≤ 4 cm with DOI ≤ 10 mm
T3	Tumor> 2 cm and ≤ 4 cm with DOI > 10 mm Or tumors> 4 cm with DOI ≤ 10 mm
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local diseaseTumors> 4 cm with DOI > 10 mm Or tumor invades adjacent structures only (eg., through cortical bone ofthe mandible or maxilla or involves the maxillary sinus or skin of face) Superficial erosions of the bone or tooth socket alone by a gingival primary is not sufficient to classify a tumor as T4
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/orencases the ICA
	DOI is the depth of invasion and not tumor thickness

Table 2 Nodal Assessment - Clinical N (CN)

CN Category	CN Criteria
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in single ipsilateral lymph node 3 cm or smaller in greatest dimension ENE (-)
N2	Metastasis in a single ipsilateral lymph node larger than 3 cm but notlarger than 6 cm in greatest dimension and ENE (-) Or metastasis in multiple ipsilateral lymph nodes, none larger than 6cm in greatest dimension and ENE (-) Or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (-)
N2a	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE (-)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (-)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE (-);

	Or metastasis in any node (s) and clinically overt ENE (+)		
N3a	Metastasis in a lymph node larger than 6cm in greatest dimension and ENE (-)		
N3b	Metastasis in any node (s) and clinically overt ENE(+)		
pN Category	pN Criteria		
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in single ipsilateral lymph node 3 cm or smaller in greatest dimension and ENE (-)		
N2	Metastasis in a single ipsilateral lymph node3 cm or smaller ingreatest dimension ENE (+) Or larger than3 cm but not larger than 6 cm in greatest dimension andENE (-) Or metastases in multiple ipsilateral lymph nodes, none larger than 6cm in greatest dimension and ENE (-): Or in bilateral or contralateral lymph node (s) none larger than 6 cm in greatest dimension and ENE (-)		
N2a	Metastasis in a single ipsilateral node, 3 cm or smaller in greatestdimension and ENE (+); Or a single ipsilateral node larger than 3 cm but not larger than 6 cm ingreatest dimension		
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE (-)		
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (-)		
N3	N3: Metastasis in a lymph node larger than 6 cm in greatest dimensionand ENE (-); Or metastasis in a single ipsilateral node larger than 3 cm in greatestdimension and ENE (+); Or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); Or in a single contralateral node of any size and ENE (+)		
N3a	Metastasis in a lymph node larger than 6cm in greatest dimension and ENE (-)		
N3b	Metastasis in a single ipsilateral node larger than 3 cm ingratestdimesnion and ENE (+); Or multiple ipsilateral , contralateral or bilateral nodes any with ENE(+); Or a single contralateral node of any size ad ENE(+)		
M category	M criteria		
cM0	No distant metastasis		
cM1	Distant metastasis		
pM1	Distant metastasis, microscopically confirmed.		
Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
III	T1, T2, T3	N1	M0
IVA	T4a	N0,N1	M0
IVA	T1, T2, T3, T4a	N2	M0
IVB	Any T	N3	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

➢ *Outcome:*[15]

The 5-year survival for Oral Cavity Squamous cell carcinoma is 60 %. But this estimate varies between 10 % to 80 % depending on the stage, age, racial factors, location and other comorbidities. Oral tongue cancers are particularly challenging in attaining locoregional control. Nodal metastasis is the most important factor which determines survival. The presence of nodal metastasis reduces survival by 50 %. Extracapsular spread is another important factor which determines survival independent of nodal metastasis.[16,17]

D. Diagnosis and Work Up:

➢ *Physical examination:*

Alteration in speech, articulation and mobility of tongue suggests possible involvement of tongue muscles or hypoglossal nerve. Poorly fitting dentures or loose teeth indicate alveolar bone invasion. Cranial neuropathies suggest nerve invasion. Trismus is a hallmark of pterygoid or masticator space invasion. Palpation of neck is useful in staging of lymph nodes.

➢ *Imaging*:

Imaging is essential to assess the extent of primary tumor, regional disease and distantdisease and to identify synchronous second primary. CT with intravenous contrast is the preferred imaging modality. CT helps in assessment of soft tissue extent as well asbony invasion and the regional nodal disease. MRI is superior for soft tissue and hardpalate and in evaluating perineural invasion. FDG PET is useful for detecting metastasis, second primary malignancy and post treatment surveillance. In assessing distal metastasis, chest X ray can be used in low risk lesions and Chest CT or FDG PET may be used in high risk cases.

E. Surgical Management:[15]

Surgery is recommended for patients with early stage tumours and surgery or definitive concurrent chemoradiotherapy is recommended for patients with advanced stage tumors.Approach to oral cavity resection are based on the location and extent of invasion. Clear three dimensional margins should be obtained. Lesions of anterior or lateral oral tongue can be resected transorally. In patients with significant posterior extent or trismus or obstructive dentition, a visor flap with lingual release may be required.

Buccal resection can be performed with a transoral approach or a lip split incision. Retromolar trigone resection usually requires mandibulectomy.FOM carcinomas can be resected transorally. These excision often requires marginal or segmental mandibulectomy. Mandibular resection is based on preoperative assessment of periosteal and cortical invasion. In managing small tumors with periosteal involvement, marginal mandibulectomy will be sufficient. Indications for performing segmental mandibulectomy are tooth loss with low mandibular height, previously irradiated bone, intra operative finding of bone invasion. Osteocutaneous- free flap reconstruction can be done along with segmental mandibulectomy. Cancers of hard palate and maxillary alveolar ridge can be resected transorally.Additional facial incision may be required in extensive disease.

F. Surgical Management of The Neck

Therapeutic neck dissection is a well established treatment for clinically node positivedisease. Selective neck dissection at levels I to IV or I to V is typically used.Radical and modified radical neck dissection are not routinely used anymore. They are reserved for advanced nodal disease, N3 and disease extending into level V or involving critical structures in the neck.In early stage tumors that are cN0, elective neck dissection can be performed if thereis greater than 20 % probability of occult nodal disease.

G. Radiation

Definitive radiotherapy can be used for oral cavity carcinoma, but is not preferred because of increased risk of osteoradionecrosis. Post operative radiation therapy is well established for locally advanced disease, pN2 to N3 disease, pN1, extracapsular spread and positive margins. Intensity modulated radiotherapy, (IMRT) has nowreplaced standard delivery of radiotherapy. Intensity modulated proton therapy is also being tested in head and neck cancers.

H. Adjuvant Chemotherapy

In advanced head and neck squamous cell carcinoma, positive margins, multiplepositive lymph nodes and extracapsular spread concomitant post operative platinum based chemotherapy and radiation is indicated.

I. Recurrence:

Recurrence rate is 30% in oral cavity cancers. For early recurrences there was similar outcomes with surgery and chemoradiotherapy. For late recurrences, surgical salvage was better compared to chemoradiation.

J. Induction Chemotherap

In case of responders, induction chemotherapy seems to improve outcome. However generally induction chemotherapy followed by surgery does not add a survival benefitor decrease distant metastasis. Cisplatin and fluorouracil can be used in induction chemotherapy. Further studies are required to evaluate the efficacy of induction chemotherapy.

K. Recist (Response Evaluation Criteria In Solid Tumors)[6,7]

In clinical evaluation of cancer treatment, assessing the change in tumor burden is an important aspect. Tumour shrinkage and progression are the end points in this assessment. RECIST is widely adopted in assessing the treatment response, to define progression and shrinkage objectively. WHO in 1981 first published tumor response criteria. In this criteria, the overall assessment of tumor burden was done by summing the product of bidimensional lesion measurement. The response to treatment was determined by evaluating the change from the baseline on treatment. However, laterin 2000, the response criteria were standardised and simplified in the form of RECIST. The key features of original RECIST was the definition of minimum size formeasurable lesions, the number of lesions to follow up, and the use of unidimensional rather than bidimensional measures for evaluating tumor burden. RECIST was updated as version 1.1. In this updated version, the number of lesion to be assessed forcalculating response were reduced from a maximum of 10 to a maximum of 5 totaland from five to two per organ. Assessment of pathological lymph node was also included. Nodes with short axis of 1.5 cm were also considered measurable and assessable as target lesions. The short axis measurements of nodes are to be included in calculating the sum of the lesions for assessing tumor response. Disease progression criteria was also clarified. In addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase was also included to guard against over calling PD when the total sum is very small. In addition to this a section on interpretation of FDG PET was also included.RECIST guideline describes a standard approach to solid tumour measurement and

definitions for objective assessment of change in tumour size in cancer clinical trials. In this criteria measurements are made at baseline before starting treatment and this iscompared with the measurements after the end of treatment to assess the response. Minimum size for measurable lesions at baseline according to RECIST 1.1 in CT is 10 mm (CT scan slice thickness should not be greater than 5 mm). While using clinical measurement it is 10 mm (this must be measurable with callipers). Thelongest diameter of selected lesion is to be measured in the plane in which the images are acquired. For body CT axial plane is the plane of measurement. In case of malignant lymph nodes, the short axis diameter must be at least 15 mm in CT scan, to be considered as pathologically enlarged and measurable, (CT scan slice thickness should not be greater than 5 mm)

- *Non-Measurable Lesions Include:*

- Small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to
- <15 mm short axis)
- Leptomeningeal disease
- Ascites,
- Pleural or pericardial effusion,
- Inflammatory breast disease,
- Lymphangitic involvement of skin or lung,
- Abdominal masses/abdominal organomegaly

In case of bone lesions, lytic bone lesions and mixed lytic-blastic bone lesions thatcan be evaluated by cross sectional imaging techniques such as CT or MRI are Considered measurable if soft tissue component meets the criteria formeasurability. However blastic lesions are nonmeasurable. Simple cysts are not to be considered as measurable. However, cystic lesions which represent cystic metastasis can be considered as measurable. Tumour lesions with prior local treatment are not considered measurable. Response criteria definitions for target lesions according to RECIST criteria is as follows: Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to 10 mm. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Progressive Disease (PD): At least a 20% increase in the sum of diameters oftarget lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters whileon study.

L. Summary of Previous Studies done on Comparison of Recist and Volumetry

Hou et al conducted a study in a group of 30 patients with head and neck cancers where they compared response assessment based on RECIST and volumetric measurements using cone beam CT.[8] It was reported that early tumor volume regression correlated with complete response, however diameter measurement with RECIST did not correlate with clinical response. They had also reported that diametermeasurements did not vary much during treatment. According to them, this was dueto the fact that the shape of tumor was not spherical and tumor regression was not symmetric and hence the long axis remained relatively stable while regression occurred in other directions. It was also reported that volume measurements had less variation than diameter measurements in locally advanced head and neck cancers. Hence one-dimensional RECIST measurement was not able to evaluate size change inmany irregular lesions.It was reported in a study conducted by V.Patil et al in a group of 24 patients with head and neck cancers undergoing chemotherapy that there was no correlation between radiological decrease in size and post operative pathological response.[9] According to them head and neck cancers had a complex shape and hence unidimensional measurements was not accurate.It was observed in a study conducted by Hadjiiski et al on a group of 36 patients with head and neck cancers that there was good correlation between automated and manualmeasurements for tumor volume change.[10] It was also reported that RECIST did not correlate well with volumetric assessment in head and neck cancers. It was reported in a study by Zhao et al in 15 patients with lung cancer that compared to unidimensional and bidimensional techniques, volumetric techniques enabled the identification of a larger number of patients with absolute changes in tumor volume ofat least 20% and 30%.[11] That is more patients were identified as progressive disease and partial response by volumetry compared to RECIST. Another study by Yankelevitz reported that some malignant pulmonary nodules had asymmetric patterns of growth which can be identified by 3D techniques better than 2D methods.[18]

A study conducted by Mayr et al where they wanted to predict outcome in cervical cancer using volume measurements in MRI reported that 3 Dimensional orthogonal assessment could estimate volume before starting RT in cervical cancer patients.[19] However after start of RT, it could not estimate tumor volume accurately.Force et al evaluated tumor response of 23 patients with thymic malignancy and 35 patients with non small cell lung cancer using CT based RECIST, WHO modified RECIST and volumetrics in Bethesda.[20] In that study it was reported that volumetric measurements identified progressive disease earlier than RECIST in advanced thymic cancers.A study conducted by Welsh et al in patients with metastatic pancreatic carcinoma and HCC in university of Iowa college of medicine USA had reported that RECIST significantly overestimated gross pathological volume, though volumetry was similar to gross pathologic volume.21 However the study had also shown that in categorising response, there was moderate agreement between RECIST and CT volumetry. They had also reported that RECIST significantly overestimated tumor

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burden compared with volumetry. In their study formula for calculating volume of an ellipsoid was used to calculate the volume of the tumorfrom the pathological measurements.

$$\text{Volume} = \pi/6 \times l \times w \times h$$

In a current update of radiologic evaluation of oncologic treatment response by Prasadet al it was stated that in considering progressive disease more than 20 % increase in unidimensional measurement corresponds to 25 % increase in the cross product and73 % increase in volume.[22] In considering partial response, more than 30 % decrease in diameter corresponds to more than 50 % decrease in cross product and 65 % reduction in volume. It was also stated that RECIST has several drawbacks. RECIST does not specify toxicity criteria. Another problem with RECIST is that unidimensional measurements may not be accurate in lesions of variable morphology,esp when the length exceeds twice the width. And treatment response with subcentimetric lesions cannot be evaluated adequately with RECIST. RECIST criteriaalso excludes necrotic and cystic areas which may also cause inaccuracies in measurement.Shah et al had conducted a study on patients with high grade glioma between 2001 and 2004 in 104 patients comparing the response assessment on MRI using 1D, 2D and 3D and Volumetry.[23] This study however showed that linear measurements correlated well with volumetric measurements. In 1D method, they used 20 % increase in the diameter as progression. In 2D methods, they used 25 % increase in area and in 3D methods, they used 65 % or 50 % increase in volume to define progression. They found that 3 D assessment did not correlate with progression free survival. It was reported in a study conducted by Warren et al in childhood brain tumors that there was less concordance between 1D, 2D and 3D in progressive disease category however, there was concordance for partial response.[24]

Lubner et al had conducted a study comparing one dimensional and volumetric measurements for response assessment in metastatic colorectal carcinoma.[25] Their study showed that both the measurements were similar in predicting response and categorising it into responders and nonresponders. However some discordance was noted between stable disease and partial responders with both unidimensional and volumetric measurements.According to a study conducted by Frauenfelder et al, in assessing therapy response inmalignant pleural mesothelioma, unidimensional measurements using RECISTCriteria showed a lower inter-rater reliability and lower inter observer agreement for tumor response classification.[26] They also found that the number of cases classified asstable disease were more for volumetry compared to modified RECIST. They also found a higher interrater reliability and interobserver agreement with volumetry.

It was reported in a study by Kimura et al on breast cancer patients that there was difference in assessing partial responders and stable disease between 2D and 1D measurements.[27] They have suggested that there should be more discussion on the exclusion of bone lesions and the exclusion of target lesions less than 2 cm to make RECIST more applicable to breast cancer.In an article by Colin Paul Spears, it was stated that an elliptical model of taking perpendicular diameters is more accurate than a spherical unidimensional model for analysis of tumor doubling.[28]Van Hoe et al conducted a study to determine the reproducibility of measurements of liver metastasis using one dimensional, two dimensional and three dimensional methods and found that three dimensional measurements are as reproducible as uni and two dimensional methods.29 They found that the reproducibility depends on the morphology and size of the lesions. In this study to compare unidimensional, two dimensional and three dimensional data, they have taken square root of the two dimensional measurement and cube root of the three dimensional measurement.A study by James et al on a large group of patients from National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) phase II and phase III studies and one Treatment Referral Center trial of the National Cancer Institute (NCI) of the United States however showed that there is good agreement between unidimensional and bidimensional measurements in assessing tumor response.30Another study conducted by Shoaib et al on comparing tumor responses as indicated by unidimensional, bidimenisonal and three dimensional methods in patients with germ cell tumor/ lymphoma has shown that there is 90% agreement between one dimensional and two dimensional measurements and 100 % agreement between two dimensional and three dimensional methods.31 This study also compared CT volumetry with actual volume in phantoms. It was shown that CT volume measurement error was 5 % or less in regular phantoms of volume 38 cc and more. In smaller objects, the partial volume effects and measurement errors become more prominent.

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CHAPTER FOUR
MATERIALS & METHODS

❖ *Study Design:*
Cross sectional study – retrospective and prospective.

A. *Study Participants*

➢ *Inclusion Criteria:*

- Patients aged more than 18 years who receive neoadjuvant chemotherapy forborderline operable oral cavity squamous cell cancers.
- Retrospective clinical, pathological and CT scan data from patients who havealready received neoadjuvant chemotherapy and have undergone surgery.

➢ *Exclusion Criteria:*

- Patients with carcinoma of tongue and carcinoma floor of mouth.
- Patients with any known contraindications to Contrast Enhanced CT scan likerenal impairment, history of allergic reaction to iodinated contrast media.
- Patients in whom both clinical and pathological response assessment data isnot available.

B. *Study Procedure:*

All patients with oral cavity cancers who receive neoadjuvant chemotherapy in oncology department were included in the study. Response assessment in CT scanwas done only for the primary tumor by comparing the post neoadjuvantchemotherapy imaging with pretreatment imaging by three different methods namely RECIST, three dimensional assessment and volumetric assessment. In RECIST criteria, single longest measurement in the axial plane was taken. In 3 Dimensional assessment, longest diameters in three orthogonal plane in multiplanar reformatted CT image was taken. In volumetric assessment, manual delineation of tumor extent in serial 2mm axial section was done for computed volume estimation using Advantage Workstation 3.2 (GE Hungary 2016). Subtraction of volumes measured at pretreatment and post treatment gave the volume changes. All the CT scans were done using Philips Brilliance 190P 6 slice multidetector CT scanner in the Departmentof Radiodiagnosis, JIPMER. It was ensured that operable patients were operatedwithin four weeks of acquiring the response assessment CT scan. Percentage of reduction in the tumor measurements using the three criteria was assessed. Clinical response was assessed by measuring two dimensional tumor size using calipers beforeand after neoadjuvant chemotherapy and by assessing the clinical stage within a week of respective CT scans. The clinical staging assessment was supplemented by radiological imaging, visual inspection in addition to measurements. Pathologicalresponse was assessed by measuring tumor dimensions in operated specimens and correlating it with pretreatment radiological measurements. Pathological staging was also used in assessing the response. Downstaging was considered as response wherever measurements were not available. The combined data from clinical measurement, pathological measurements in resected specimen and pathological staging was used to determine the final clinicopathological response of the tumor, which was used as the composite reference standard for comparison with different methods of imaging based response assessment. This was justified as many studies have shown that pathological downstaging is a surrogate marker for efficacy ofNACT and survival. [32-35] To make RECIST, CT Volumetric and 3 Dimensional data comparable, cube root of Volumetric and 3 Dimensional measurements were taken.[21,29]

Thus in case of RECIST, percentage response was calculated as

$$Percentage\ response = \frac{Tumor\ size\ post\ chemo - Tumor\ size\ pre\ chemo}{Tumor\ size\ pre\ chemo}\ x100$$

In case of CT Volumetry and 3Dimensional assessment cube root of pre-chemotherapy volume and cube root of post chemotherapy volume were used to calculate percentage response. In case of 3dimensional assessment and pathological assessment the following formula was used to calculate volume

$$Volume = o.5 \times l \times w \times h^{36}$$

➢ *Response to Tumor was Categorized as in Recist Criteria 1.1 as follows :*

- Progressive disease (PD) (more than 20% increase in size)
- Stable disease (SD) (less than 20% increase or less than 30% decrease in size)
- Partial response (PR) (more than 30% decrease in size)
- Complete response (CR) (disappearance of lesion)

These four categories, i.e. PD, SD, PR and CR were considered to create an ordinal data set using the different methods of assessment namely RECIST, CT Volumetry, 3Dimensional assessment and Clinico-pathological assessment. Weighted kappa was used to find the agreement between the different methods of assessment as data set was ordinal.[37-40] The response outcome was further binarily classified as Responders (PR + CR) and nonresponders (PD+SD) for calculating the sensitivity and specificity of the tests.

➢ *Statistical Analysis*

Data was entered into Microsoft excel data sheet and was analysed using SPSSversion 19 software. Categorical data was represented in the form of Frequencies and proportions. Weighted kappa was used to assess the agreement between the ordinal data. Bland Altman plot was used to assess the difference between the percentage response calculated by RECIST, CT Volumetry and 3 Dimensional assessment.[41-46] Sensitivity, Specificity, positive predictive value, negative predictive value of RECIST, CT Volumetry and 3Dimensional assessment were calculated, using clinic- pathological measurements as composite reference standard.Statistical software**:** MS Excel and SPSS version 19 **(**IBM SPSS Statistics, Somers NY, USA) were used to analyse data.

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CHAPTER FIVE
IMAGE GALLERY

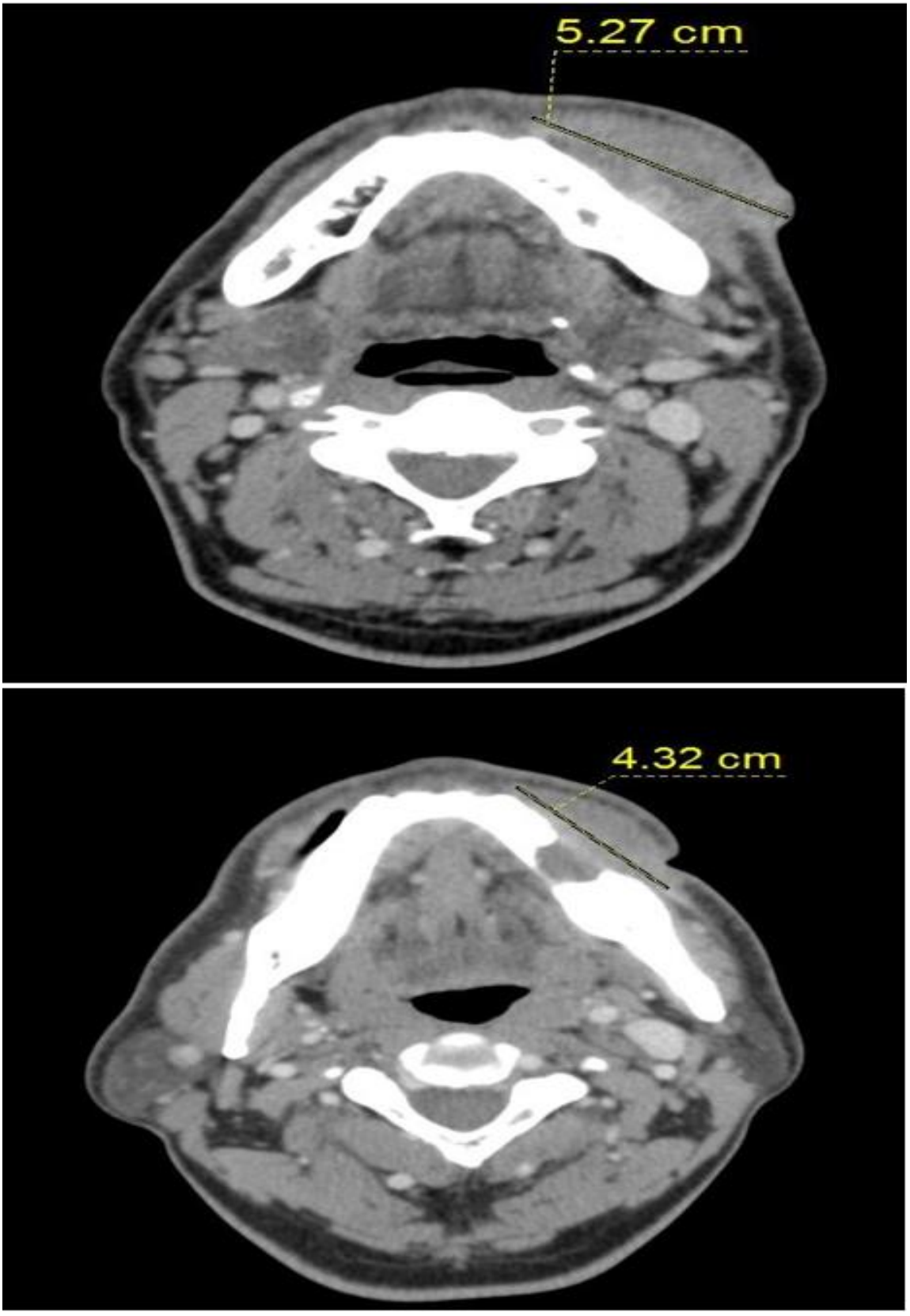

Fig 1 Axial CECT Images Pre and Post NACT Showing Single Largest Diameter Measurement as Per RECIS

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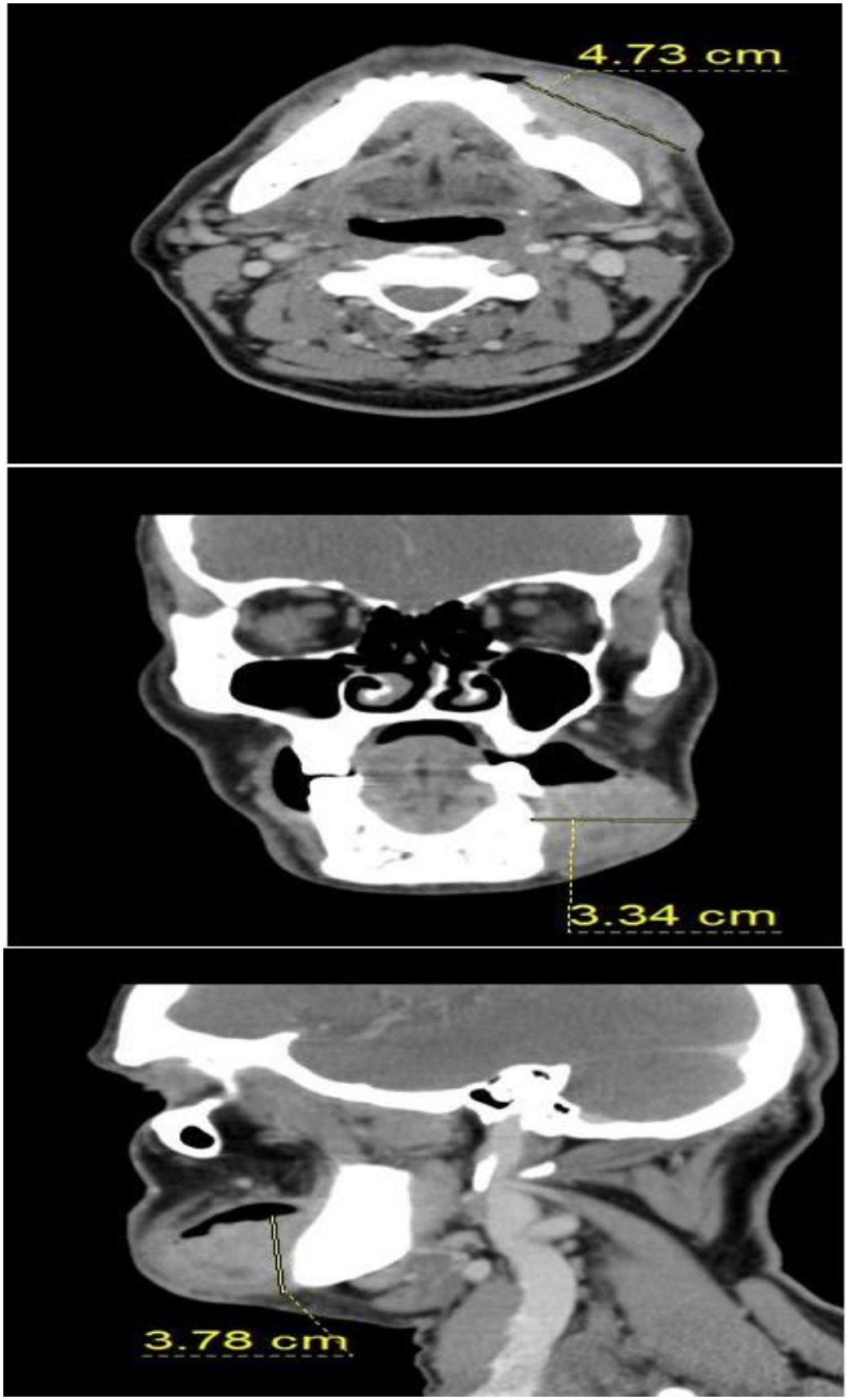

Fig 2 Multiplanar Reformatted CECT Images Showing Measurement of Largest Diameters in 3 Orthogonal Planes as per 3 Dimensional Assessment.

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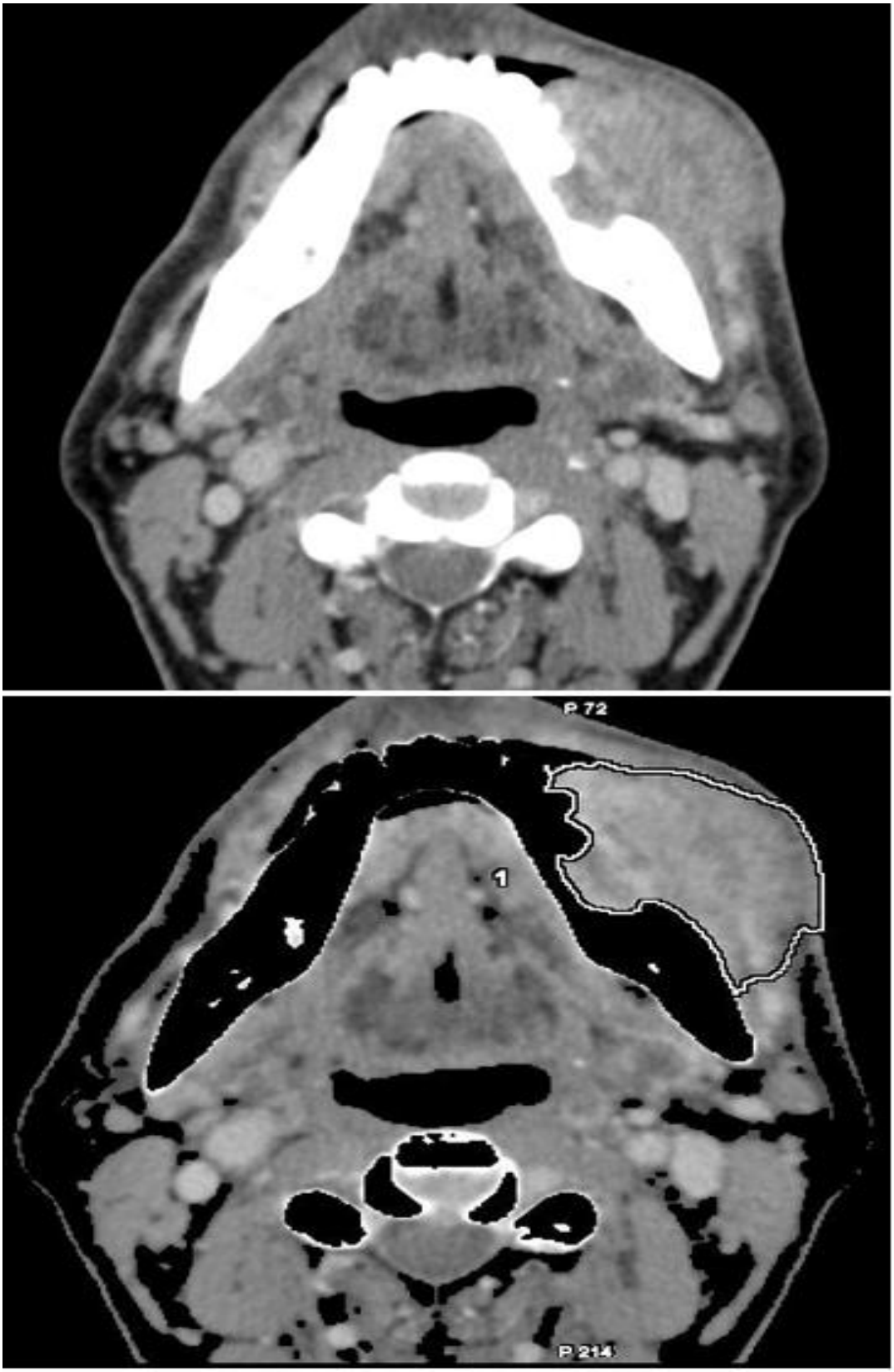

Fig 3 CECT Axial Source Image and Manual Tumor Mapped Image After bone Removal for Calculation of Tumor Volume as Per CT Volumetry.

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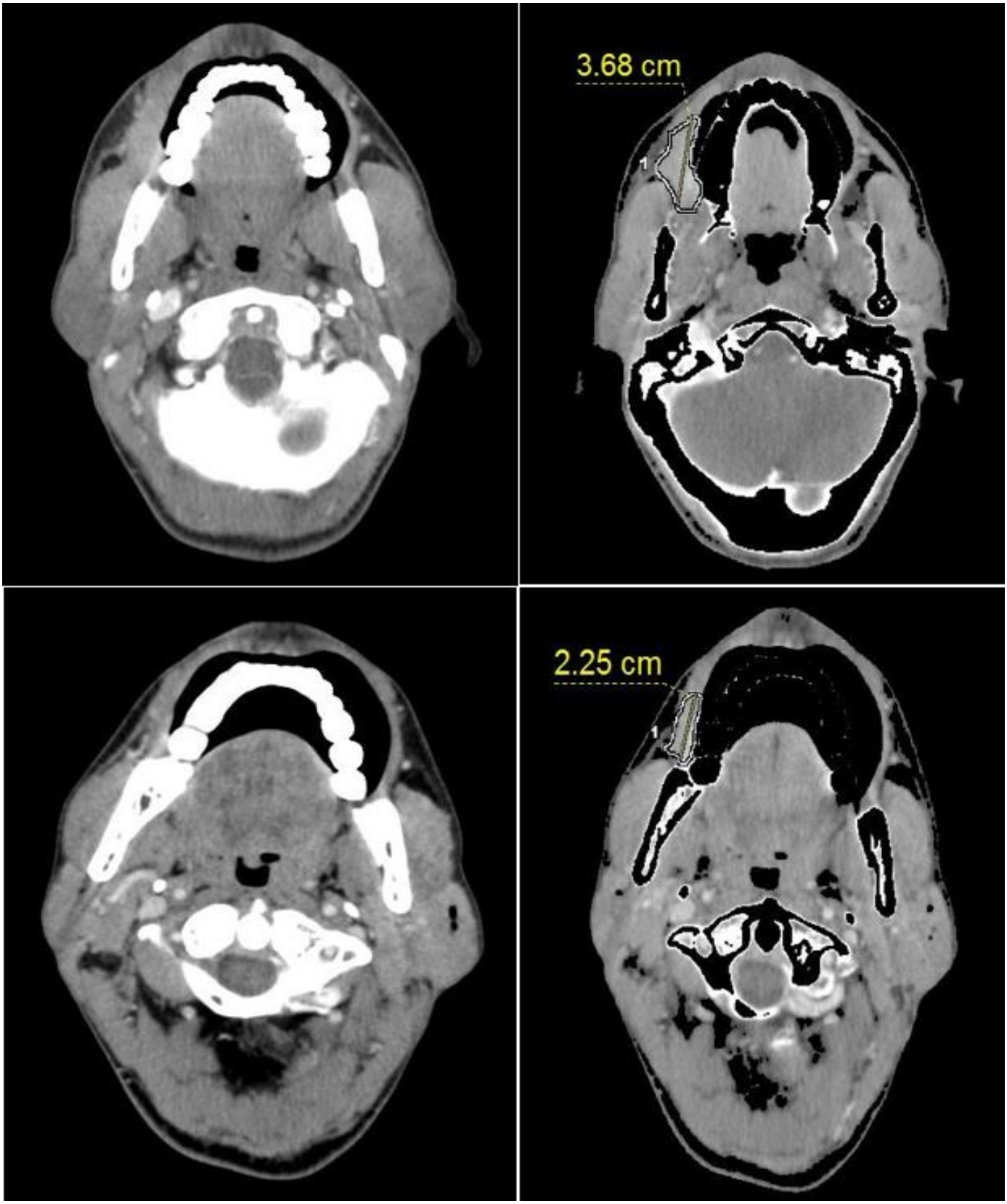

Fig 4 Axial CECT Source Image and Manual Tumor Mapped Image After Bone Removalin a Patient with Partial Response

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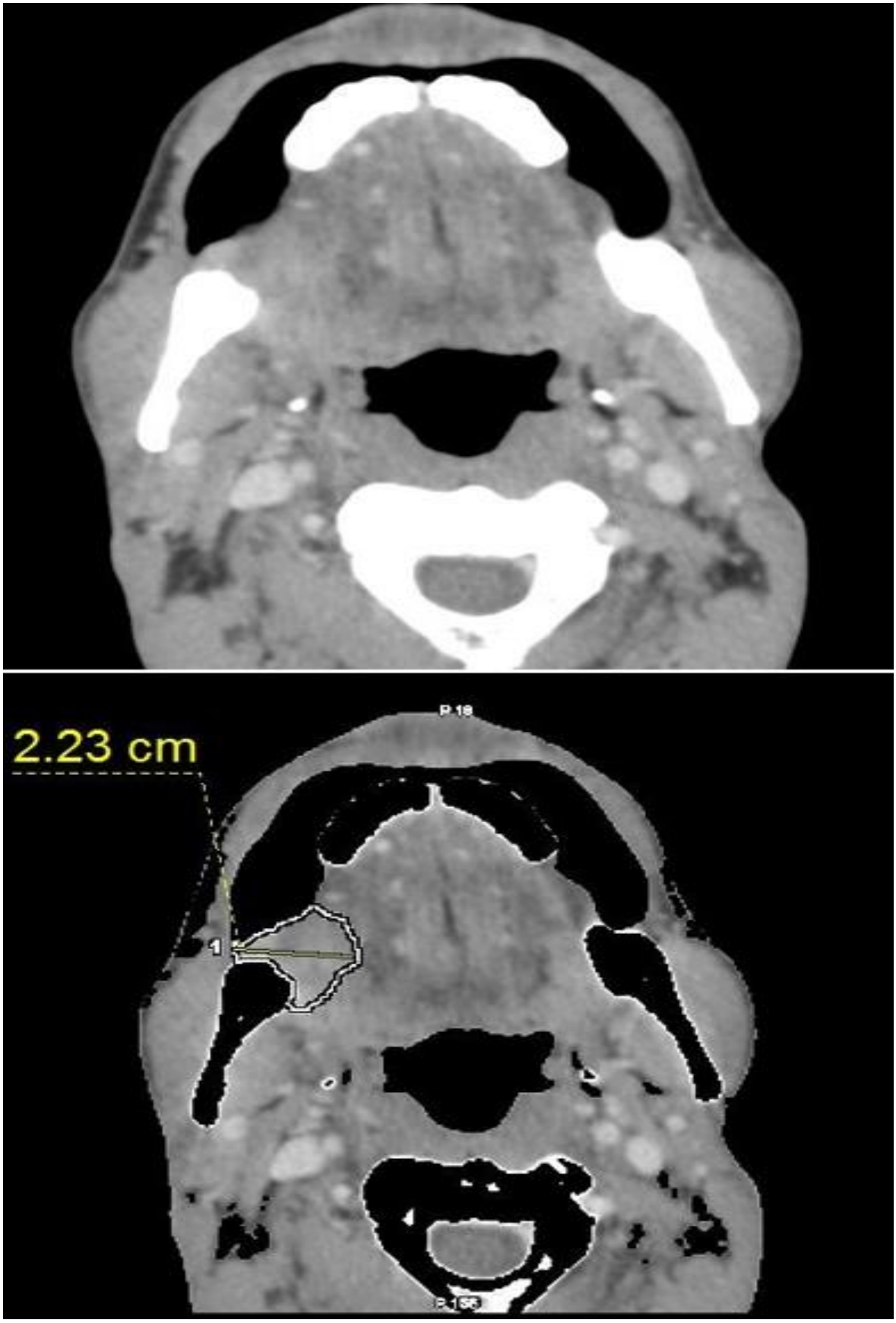

Fig 5 Axial CECT Source Image and Manual Tumor Mapped Image after Bone Removal in a Patient With Progressive Disease

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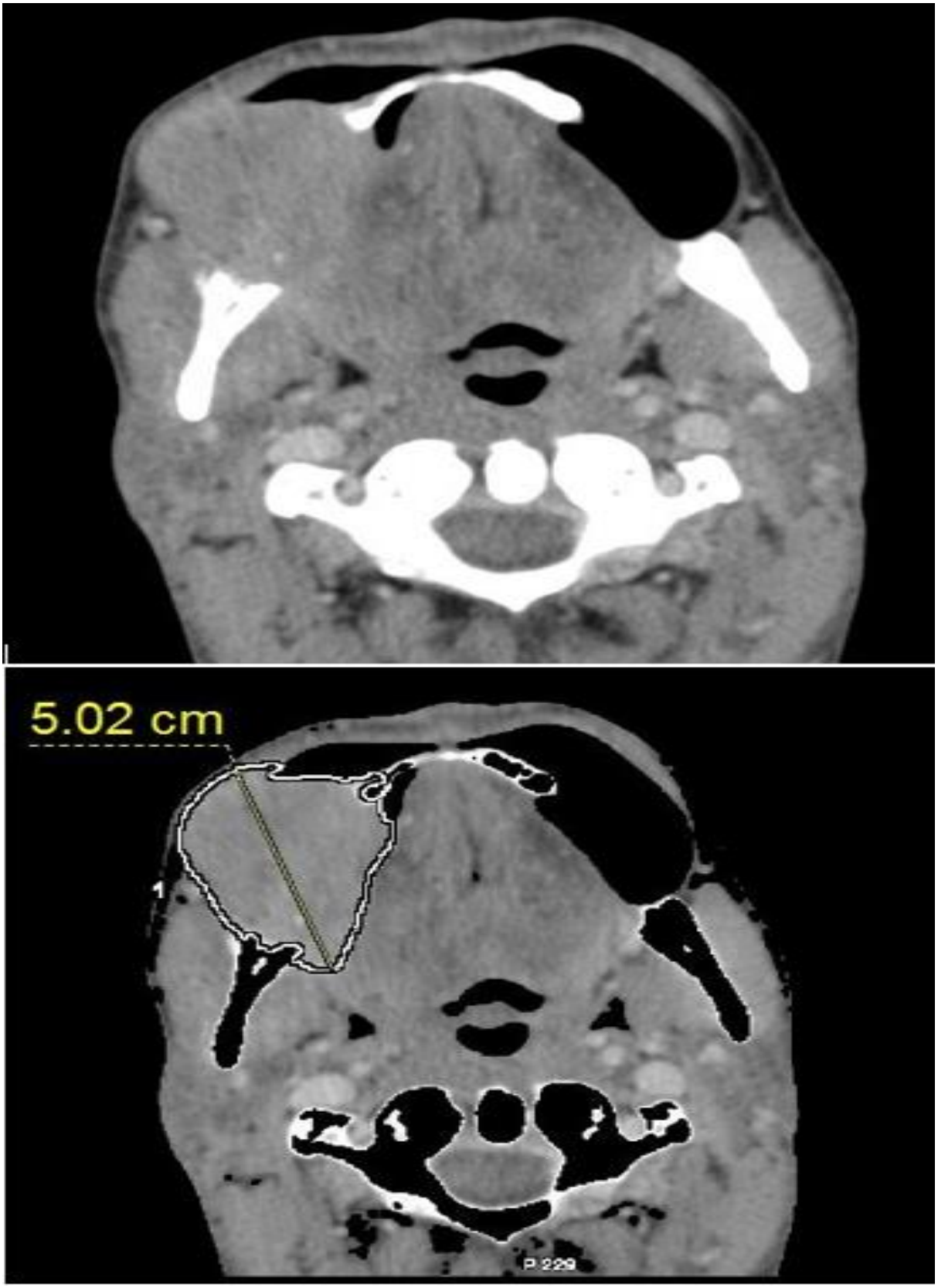

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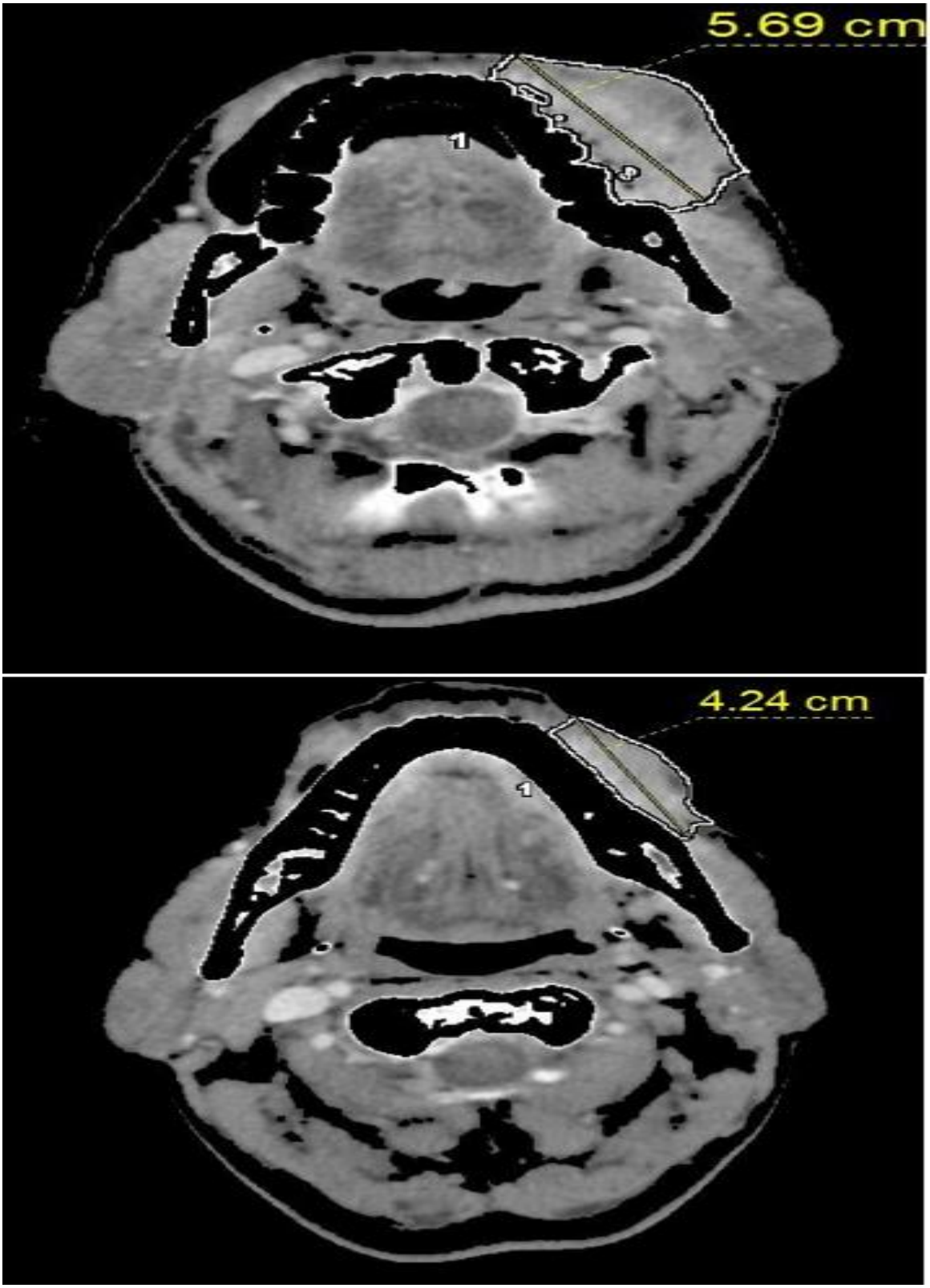

Fig 6 Axial CECT Images After Bone Removal pre and Post NACT Showing Stable Disease as per RECIST and Partial Response as per Volumetr

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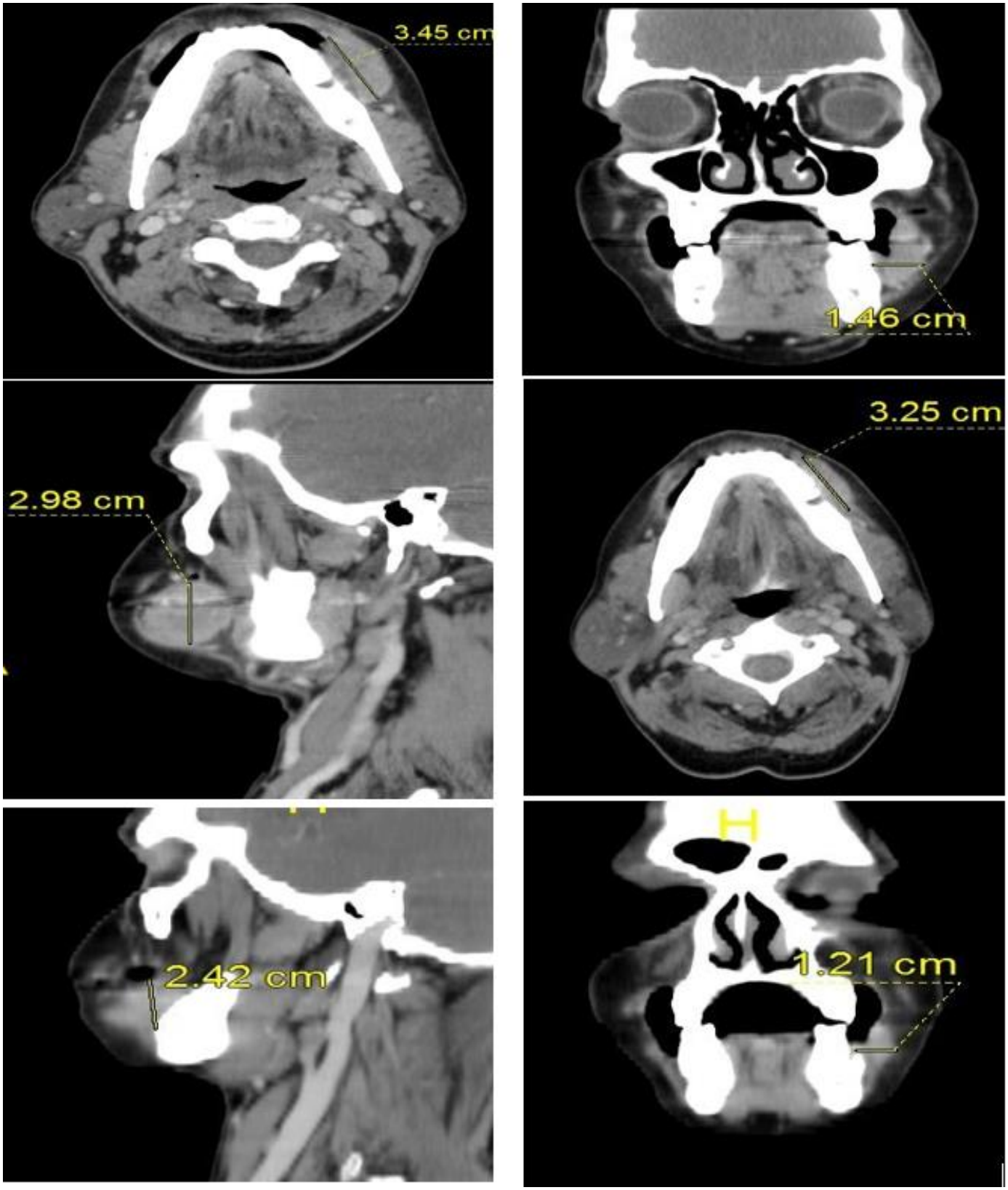

Fig 7 Multiplanar Reformatted Images pre and Post NACT Showing Stable Disease as per 3Dimensional Assessment

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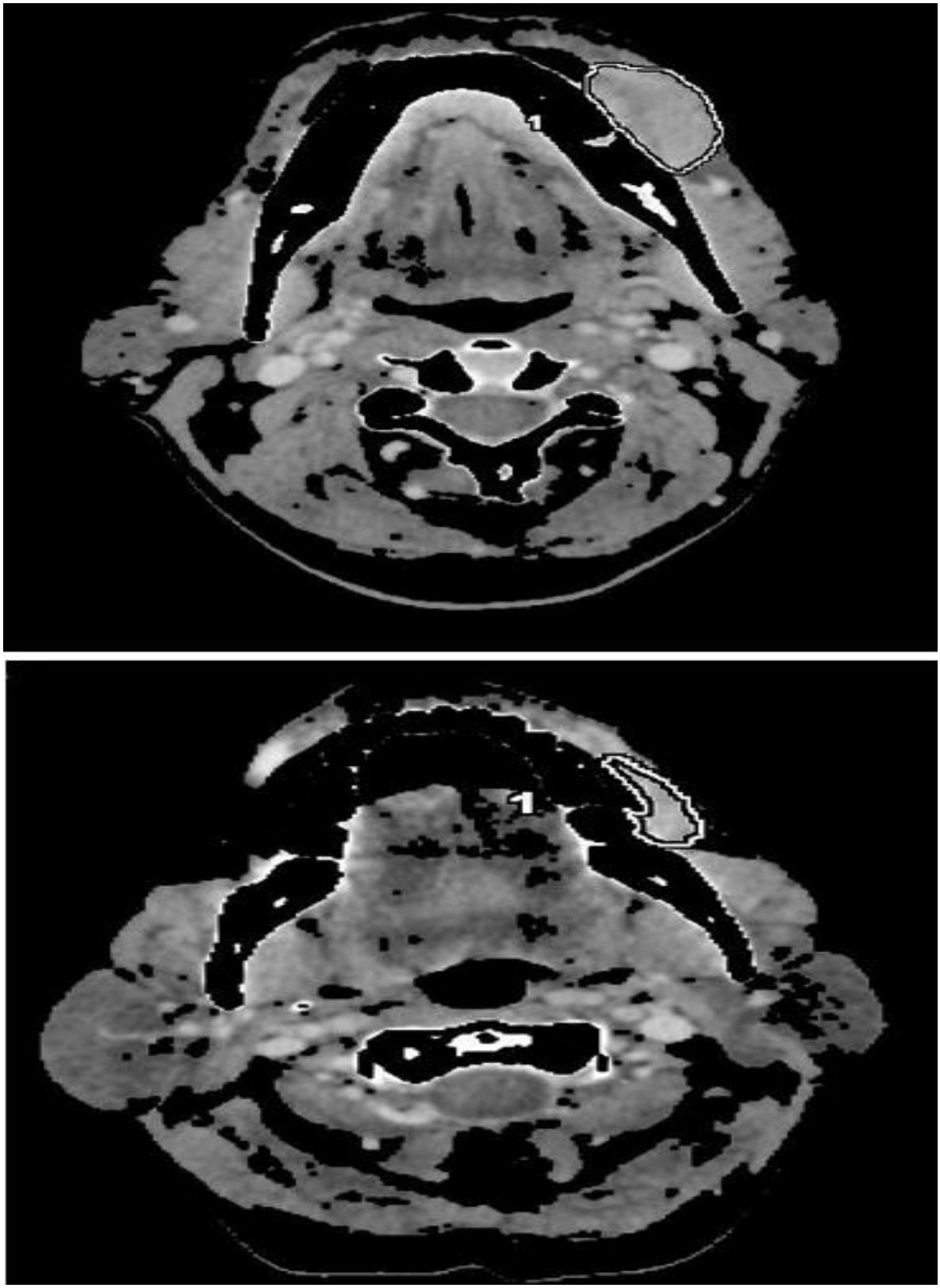

Fig 8 Axial CECT Images After bone Removal, pre and post NACT in the Same Patient Showing Partial Response as per CT Volumet

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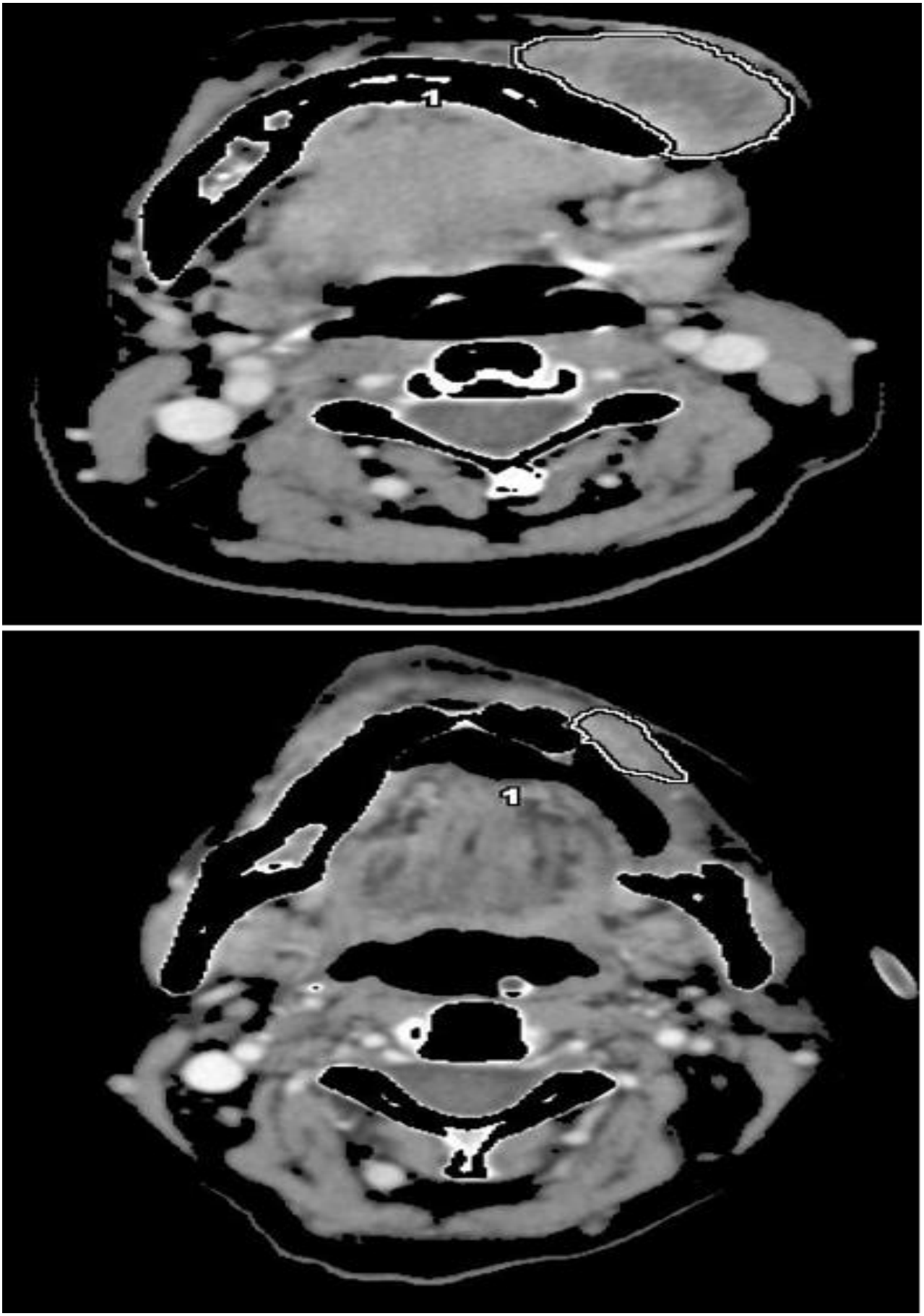

Fig 9 Axial CECT Images after Bone Removal pre and post NACT Showing Partial Response by CT Volumetry. The Pathology Report Showed Complete Response post NACT

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CHAPTER SIX
RESULTS

❖ *Totally 28 Patients With Oral Cavity Carcinoma Undergoing Neoadjuvant ChemotherapyWere Studied.*

➢ *Demographic data*

- *The mean age was 50.5 years. Majority of patients were in the age group 45 to 55 inour study population.*

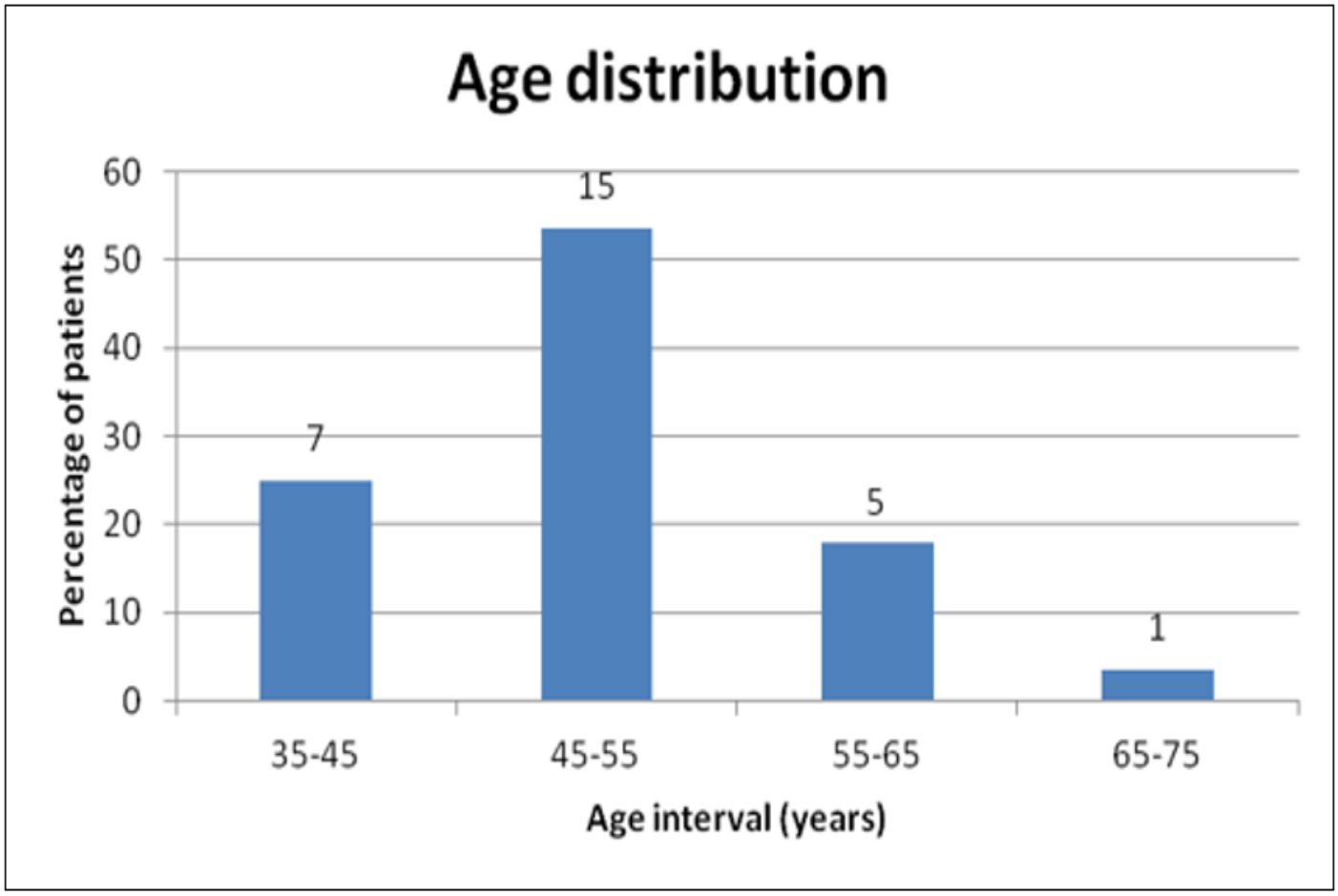

Fig 1 Shows age Distribution of the Patients Undergoing Study

➢ *Gender distribution.*

- *In our study, 3/4th of the subjects were male and 1/4th were females as shown in thegender distribution in Figure 2.*

Table 1 Gender Distribution in Study Subjects

Gender	Frequency	Percentage
Female	7	25
Male	21	75
Total	28	100

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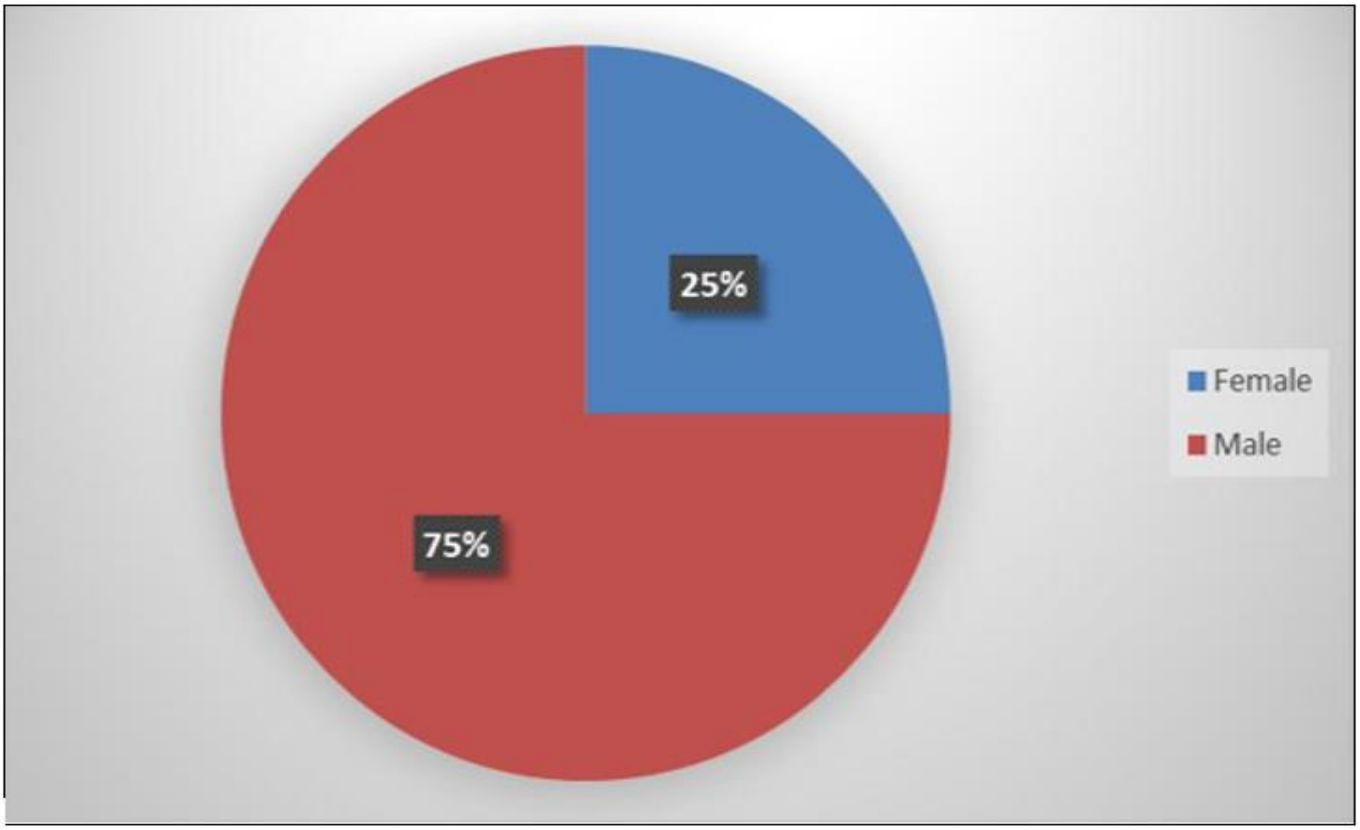

Fig 2 Gender Distribution in our Study

- *Tumor Location*

- *Buccal Mucosa was the Most Common site of Tumor in our Study as shown in Figure 3.*

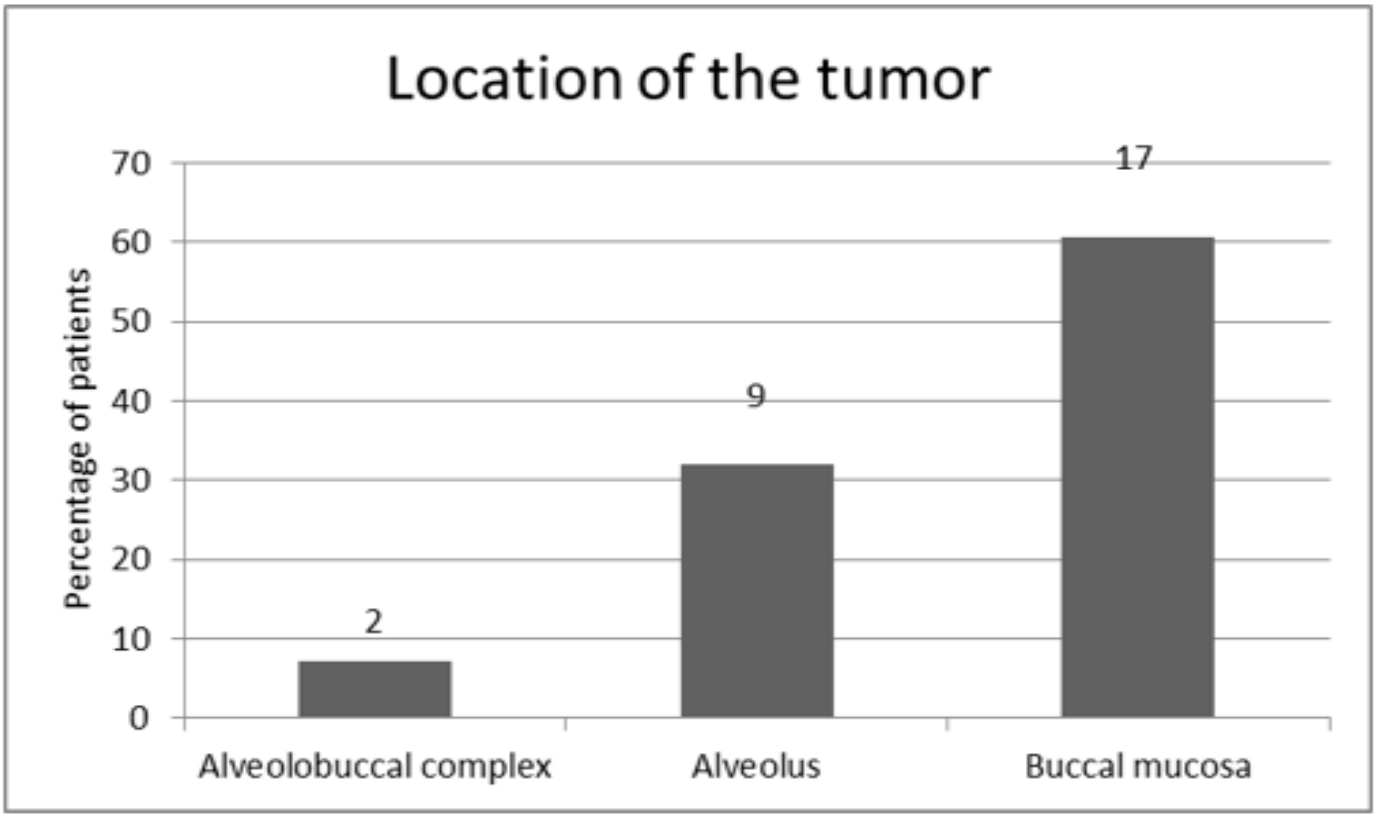

Fig 3 Shows the Different Sites of Tumor

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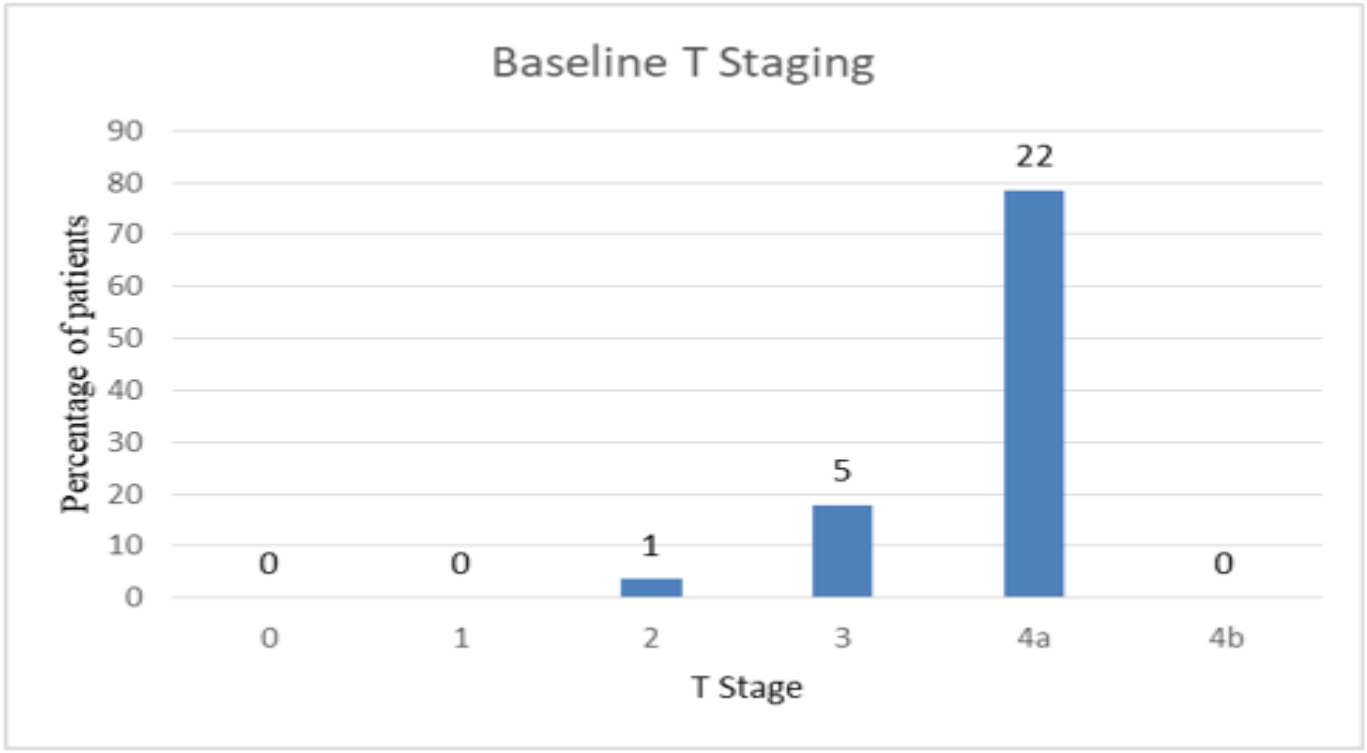

Fig 4 Shows the Baseline Tumor Staging

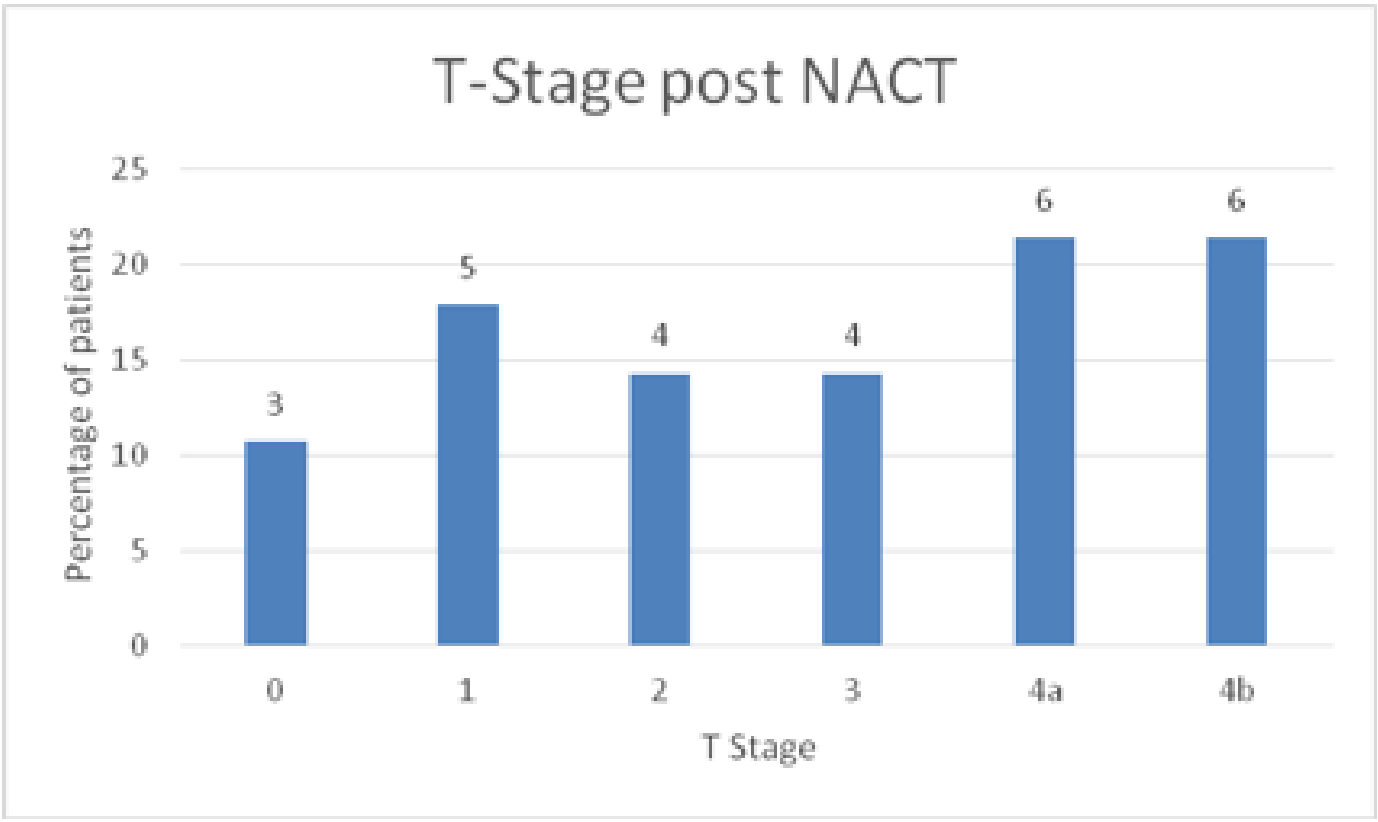

Fig 5 Tumor Staging post NACT

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- Percentage Response based on the Different Methods of Assessment Clinico-Pathological Assessment (Reference Standard)

Table 2 Clinico-Pathological Assessment

	Frequency	**Percentage**
Progressive disease	7	25
Stable disease	6	21.4
Partial response	12	42.9
Complete response	3	10.7
Total	28	100

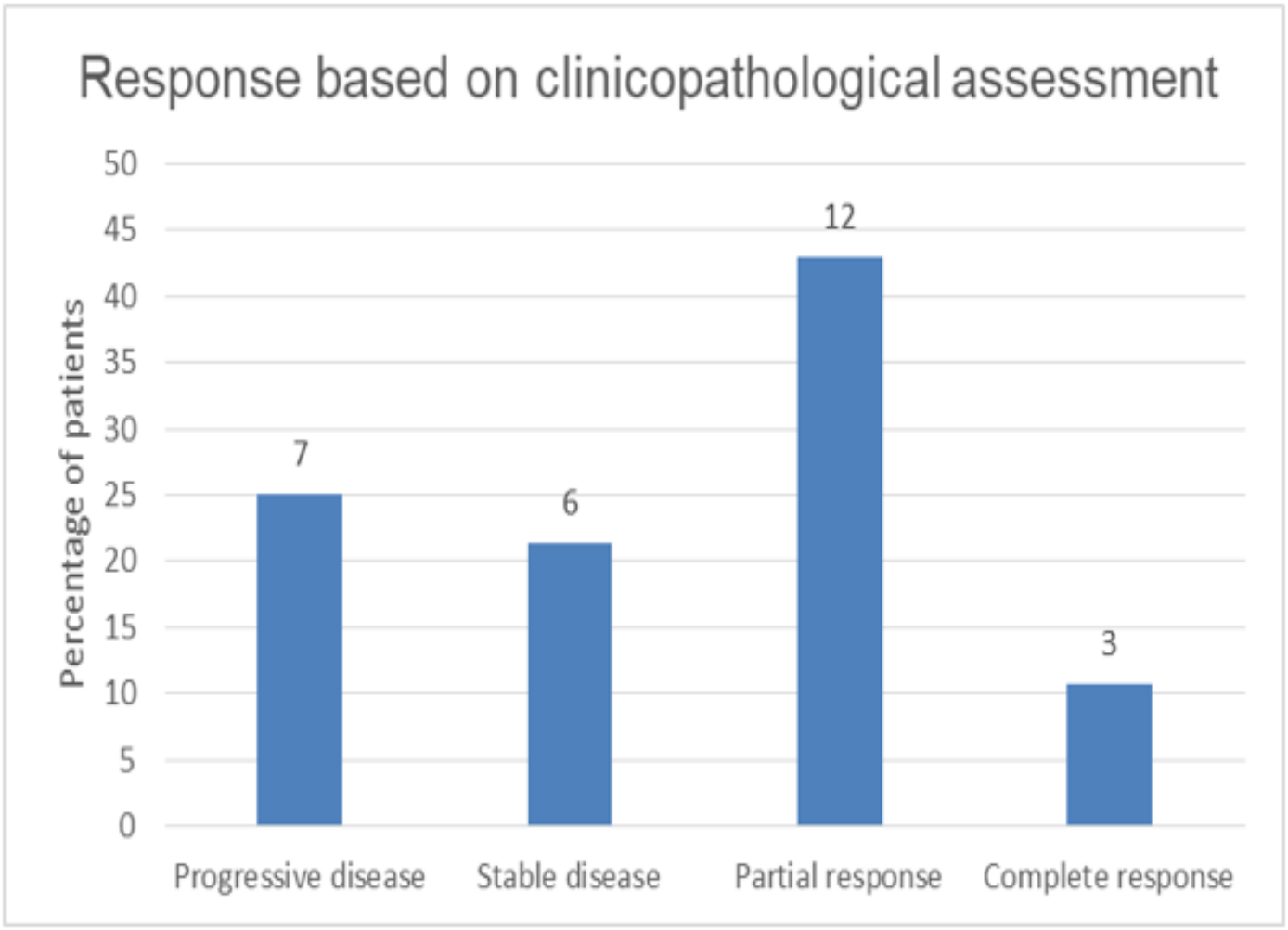

Fig 6 Bar Chart Showing Frequency of Progressive Disease, Stable Disease, partial Responders and Complete Responders Based on Clinicopathological Criteria in our sample

- *RECIST*

Table 3 RECIST

	Frequency	**Percentage**
Progressive disease	7	25
Stable disease	15	53.6
Partial response	4	14.3
Complete response	2	7.1
Total	28	100

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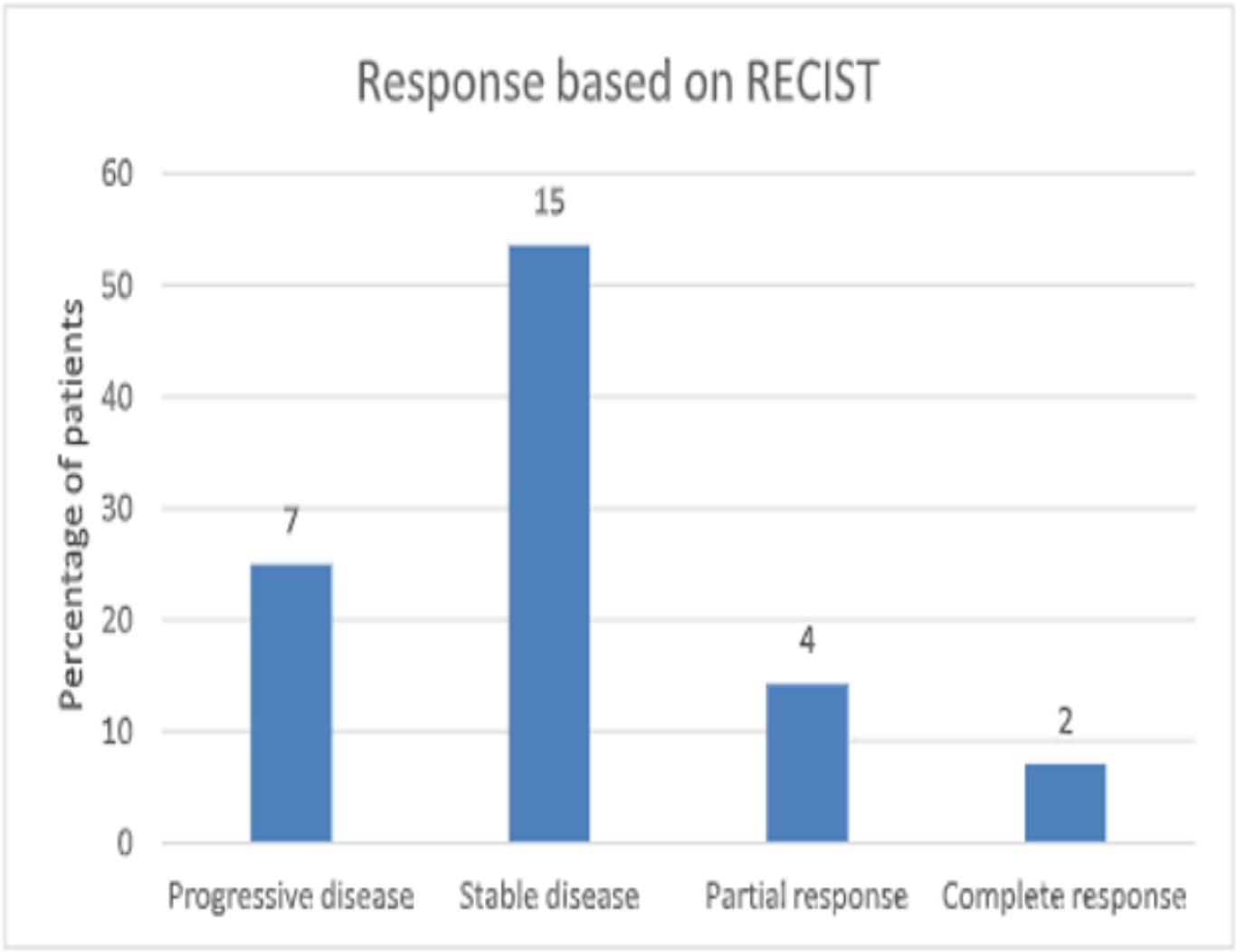

Fig 7 Bar Chart Showing Frequency of Progressive Disease, Stable Disease, PartialResponders and Complete Responders Based on RECIST Criteria in our Sample.

➢ *CT Volumetry*

Table 4 CT Volumetry

	Frequency	**Percentage**
Progressive disease	7	25
Stable disease	10	35.7
Partial response	9	32.1
Complete response	2	7.1
Total	28	100

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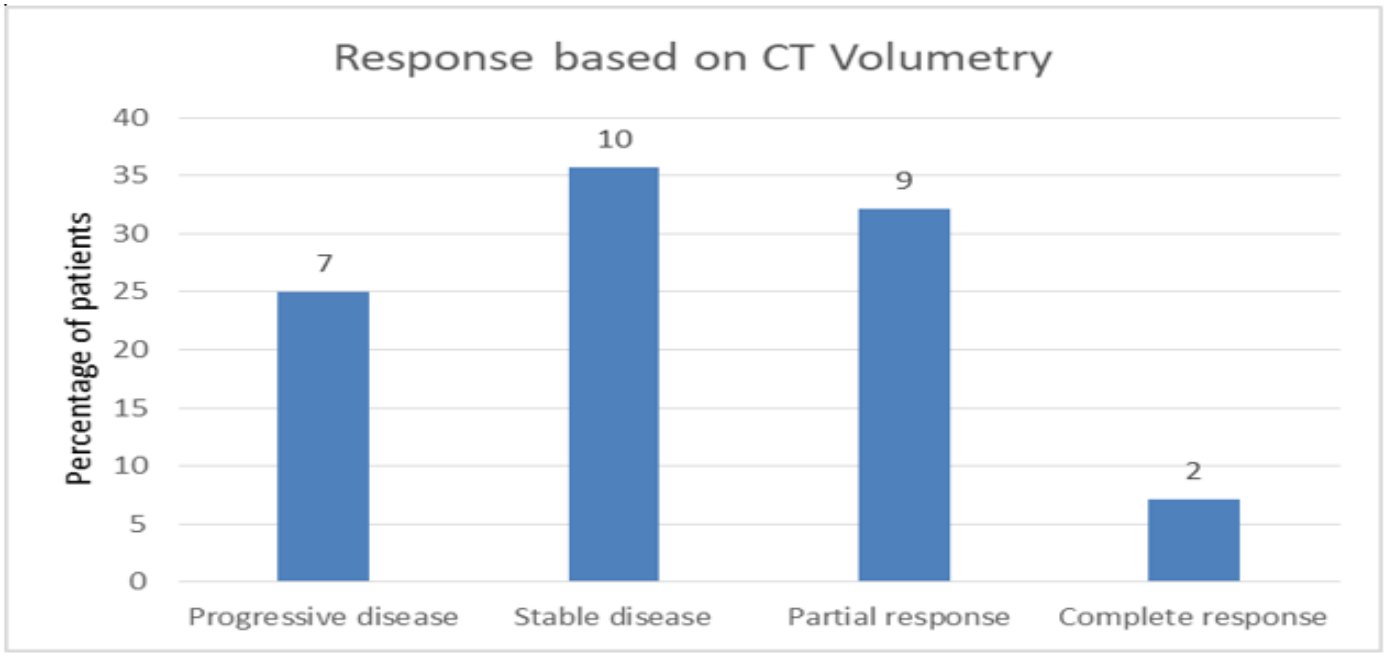

Fig 8 Bar Chart Showing Frequency of Progressive Disease, Stable Disease, PartialResponders and Complete Responders Based on CT Volumetry in our Sample

- *Dimensional Assessment*

Table 5 Dimensional Assessment

	Frequency	**Percentage**
Progressive disease	8	28.6
Stable disease	11	39.3
Partial response	7	25
Complete response	2	7.1
Total	28	100

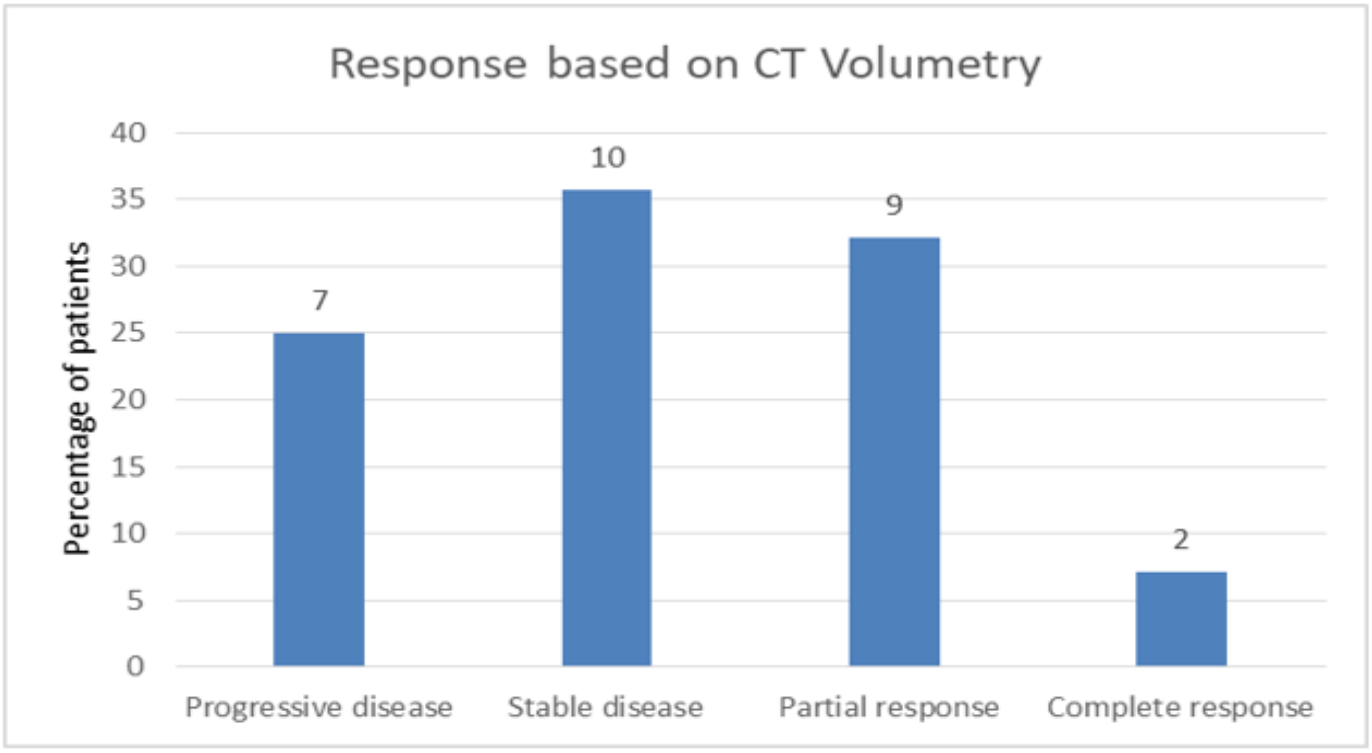

Fig 9 Bar Chart Showing Frequency of Progressive Disease, Stable Disease, Partial Responders and Complete Responders based on 3 Dimensional Assessment in our Sample

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➢ *Categorising the Response into Responders and Non-Responders*

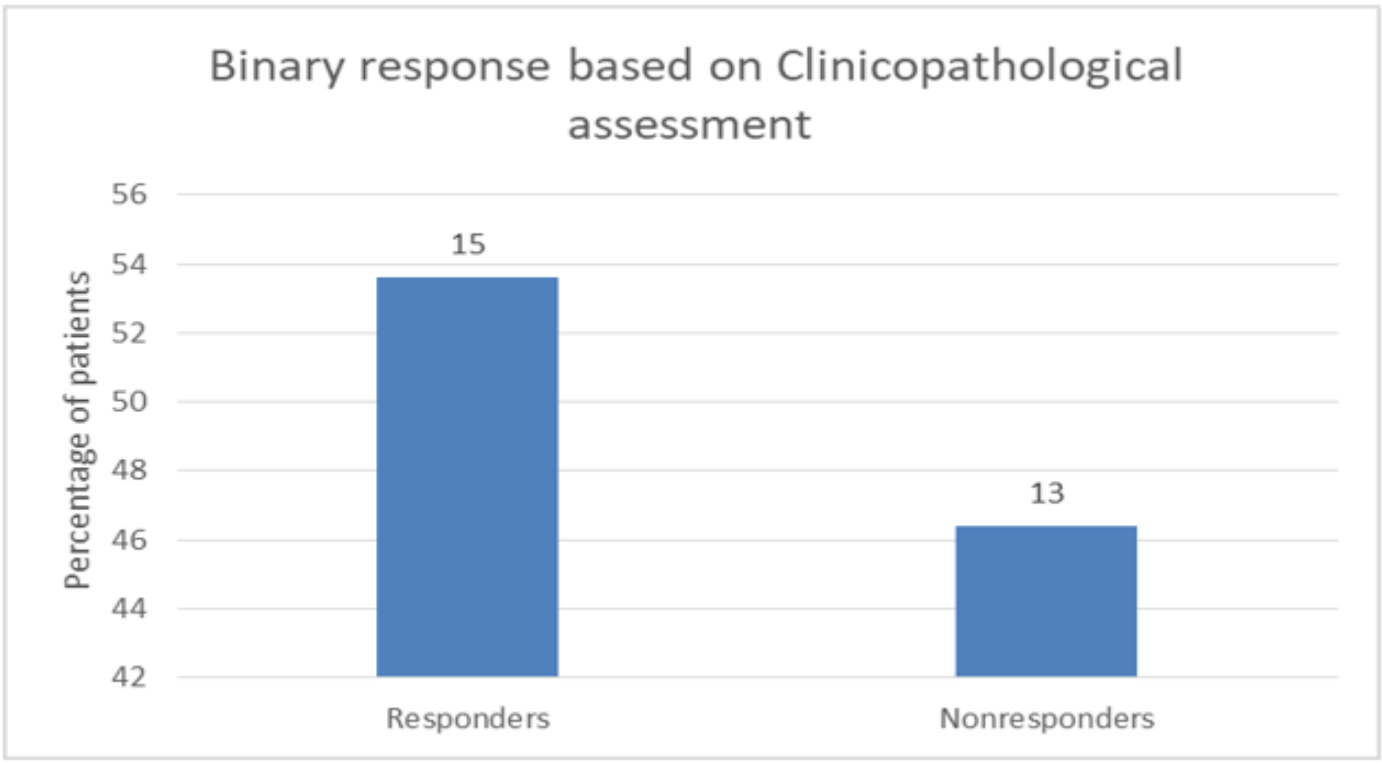

Fig 10 Bar Chart Showing Percentage of Responders and NonrespondersBased on Clinico-Pathological Assessment

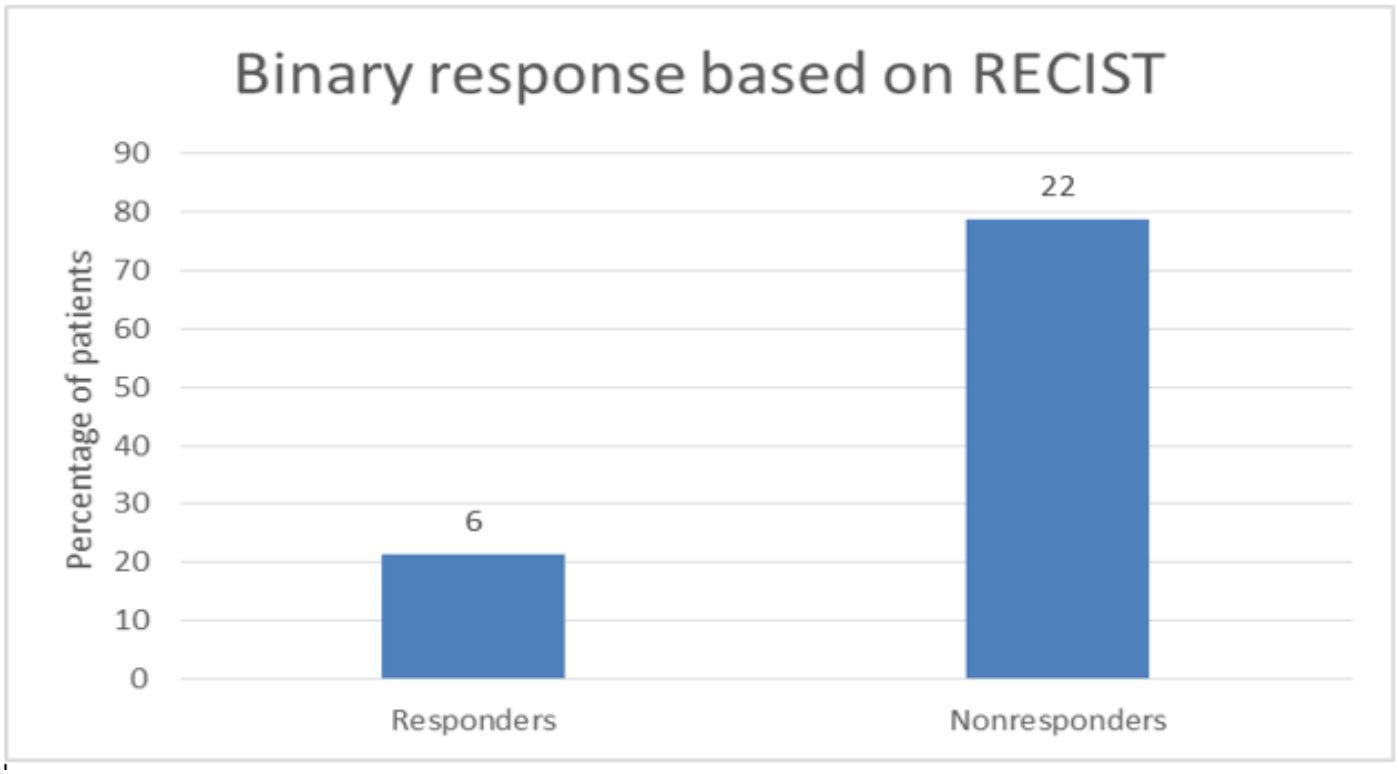

Fig 11 Bar Chart Showing Percentage of Responders and NonrespondersBased on RECIST Criteria

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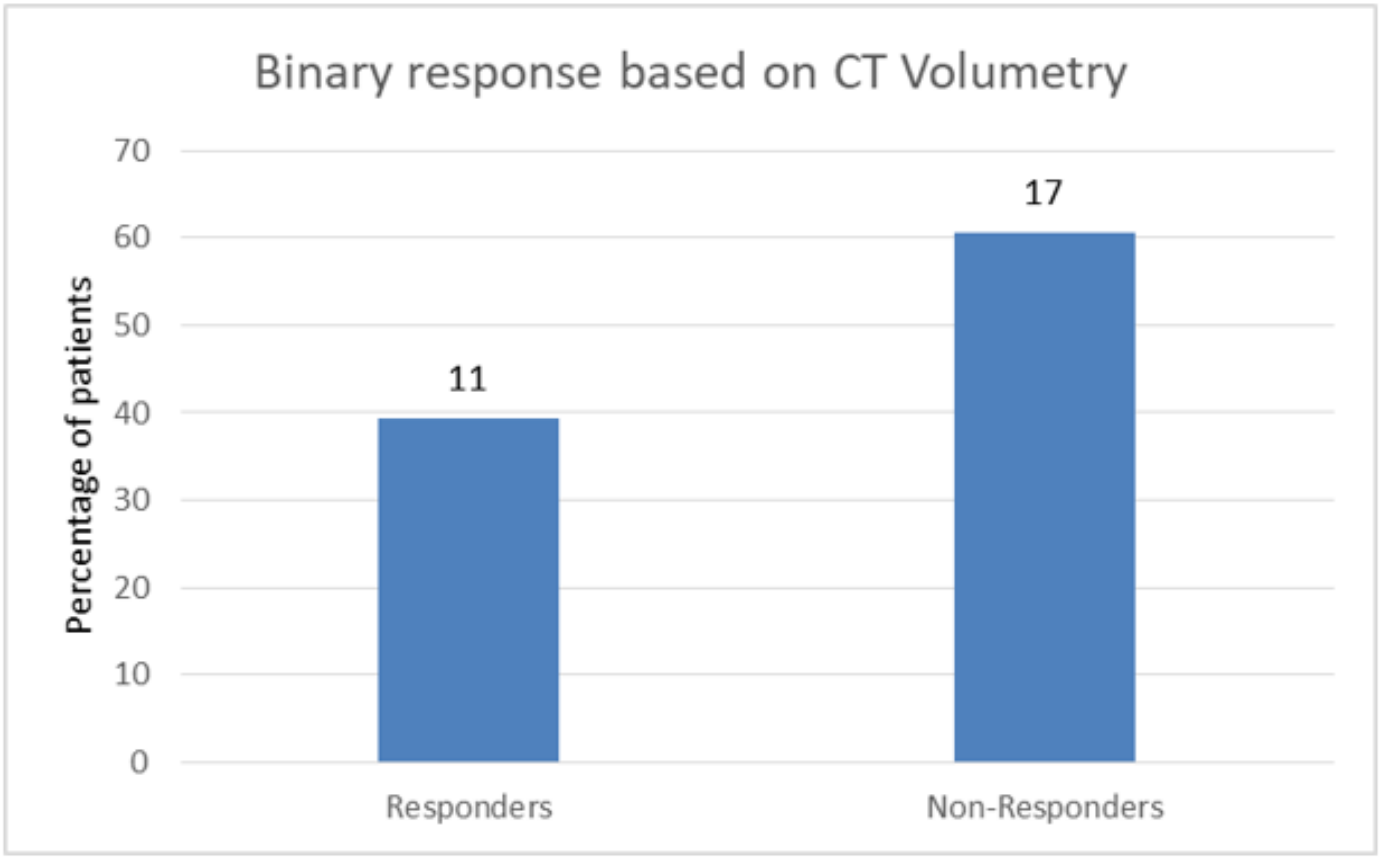

Fig 12 Bar Chart Showing Percentage of Responders and NonrespondersBased on CT Volumetry

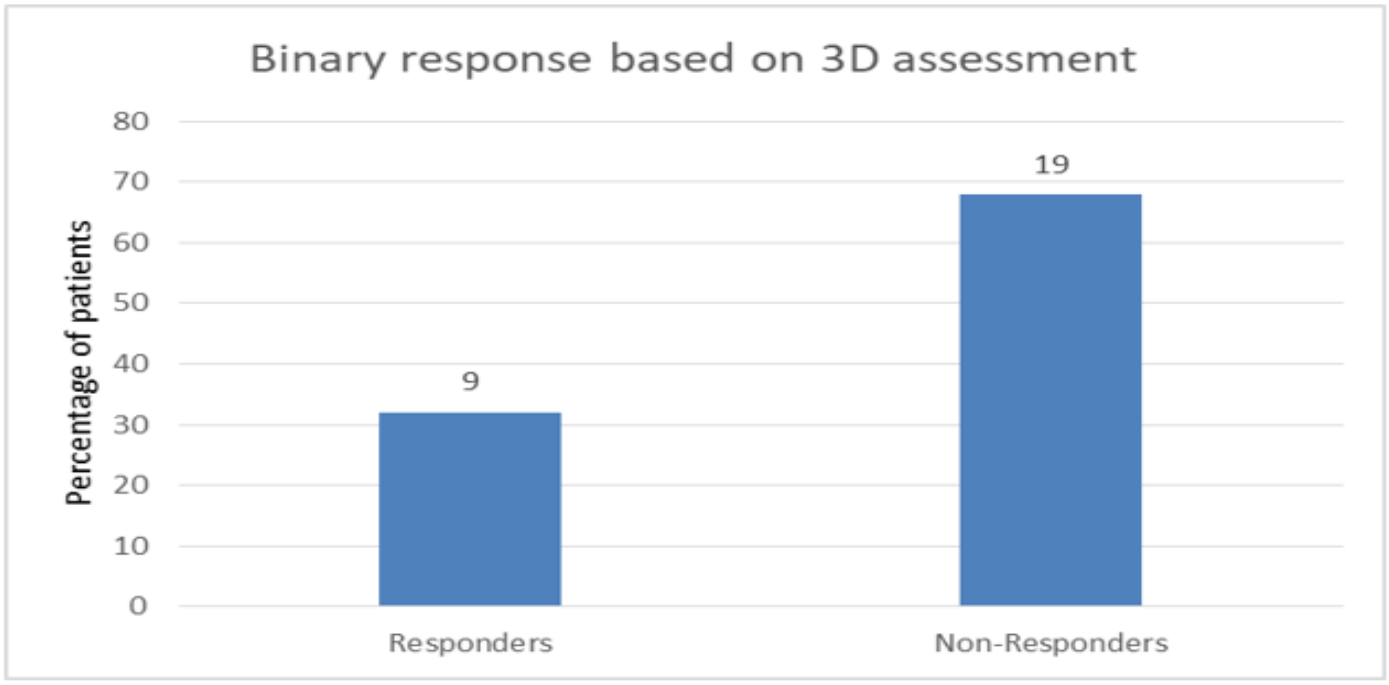

Fig 13 Bar Chart Showing Percentage of Responders and NonrespondersBased on 3D Assessment

- *Comparison of RECIST, CT Volumetry, 3 Dimensional Assessment and Clinico- Pathological Assessment.*

- *Response To Neoadjuvant Chemotherapy Was Assessed Using Recist,Ct Volumetry, 3 Dimensional Assessment And Clinicopathological Assessment In The Same Group Of Patients.*

- *Response Based On Recist As Compared To Clinicopathological Response*

Table 6 Response Based on Recist as Compared to Clinicopathological Response

Response based onRECIST	**Clinicopathological response**	
	Responders	**Non-Responders**
Responders	6	0
Non-Responders	9	13

- *Response Based on CT Volumetry as Compared to Clinicopathological Response*

Table 7 Response Based on CT Volumetry as Compared to Clinicopathological Response

Response based on CT volumetry	**Clinicopathological response**	
	Responders	**Non-Responders**
Responders	11	0
Non-Responders	4	13

- *Response Based on 3D Assessment as Compared to Clinicopathological Response*

Table 8 Response Based on 3D Assessment as Compared to Clinicopathological Response

Response based on 3Dassessment	**Clinicopathological response**	
	Responders	**Non-Responders**
Responders	9	0
Non-Responders	6	13

➢ *Comparison of Binary Response Outcome by RECIST, CT Volumetry and 3D Assessment with Respect to the Reference Standard of ClinicopathologicalResponse.*

Table 9 Comparison of Binary Response Outcome by RECIST, CT Volumetry and 3D Assessment with Respect to the Reference Standard of ClinicopathologicalResponse.

	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
RECIST	40%	100%	100%	59.1%	67.9%
CT Volumetry	73.3%	100%	100%	76.5%	85.7%
3D Assessment	60%	100%	100%	68.4%	78.6%

➢ *Agreement Between RECIST, CT Volumetry and 3 Dimensional Assessment for Categorisation of Treatment Response with Respect to the Reference Standard of Clinicopathological Assessment*

- *Weighted Kappa with Linear Weighting was Calculated to Find Agreement between RECIST, CT Volumetry, 3Dimensional Assessment and Clinicopathological Assessment.*

Table 10 Weighted Kappa with Linear Weighting was Calculated to Find Agreement between RECIST, CT Volumetry, 3Dimensional Assessment and Clinicopathological Assessment.

	Clinicopathologicalassessment (Weighted kappa)	**Std. Error**	**95% CI**
RECIST	0.66	0.101	0.46-0.86
CT Volumetry	0.83	0.07	0.69-0.97
3Dimensional assessment	0.73	0.09	0.56-0.90

➢ *Correlation between Percentage Change in Size Calculated By RECIST, CTVolumetry and 3 Dimensional Assessment.*

- *Spearman Correlation was used as the Data were Nonparametric and ShowingMonotonous Relationship. the Same Data Was used to Estimate the Bland Altman Plot.*

Table 11Spearman Correlation was used as the Data were Nonparametric and ShowingMonotonous Relationship. the Same Data Was used to Estimate the Bland Altman Plot.

	Spearman's rho	**Significance**
	CT Volumetry	
RECIST	0.829	< 0.001
3D Assessment	0.926	< 0.001

➢ *This Data Was Represented In Scatter Plot As Shown*

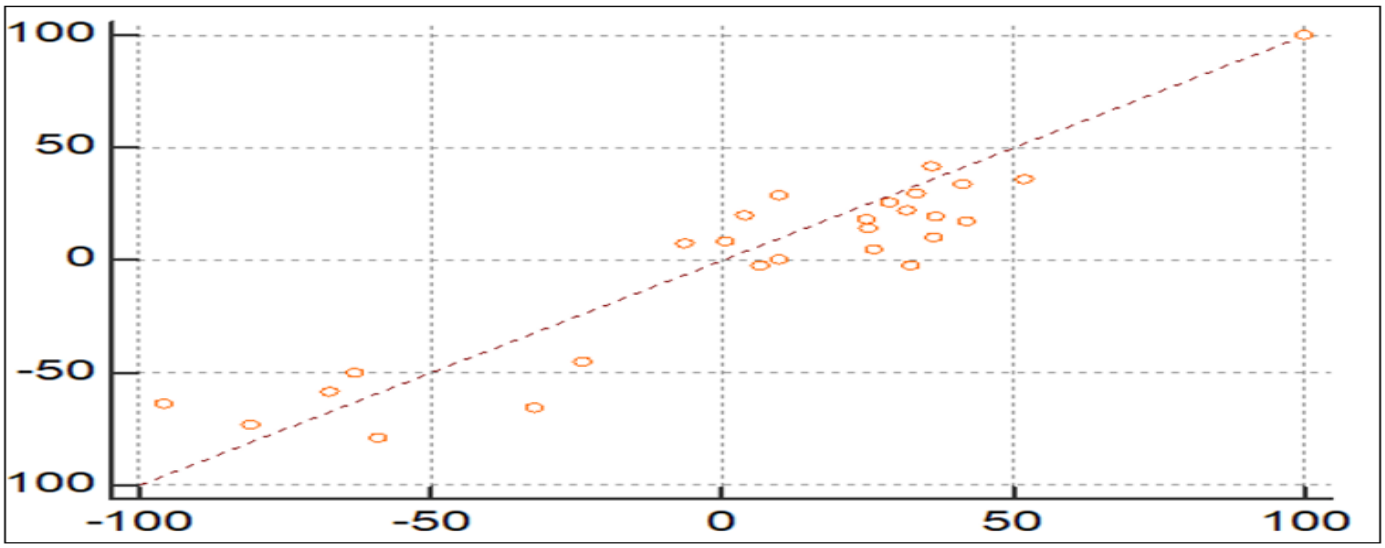

Fig 14 Scatter Plot Showing Correlation Between CT Volumetry and RECIST. Response by CT Volumetry is Plotted Along the x axis and Response by RECIST is Plotted Along Y axis

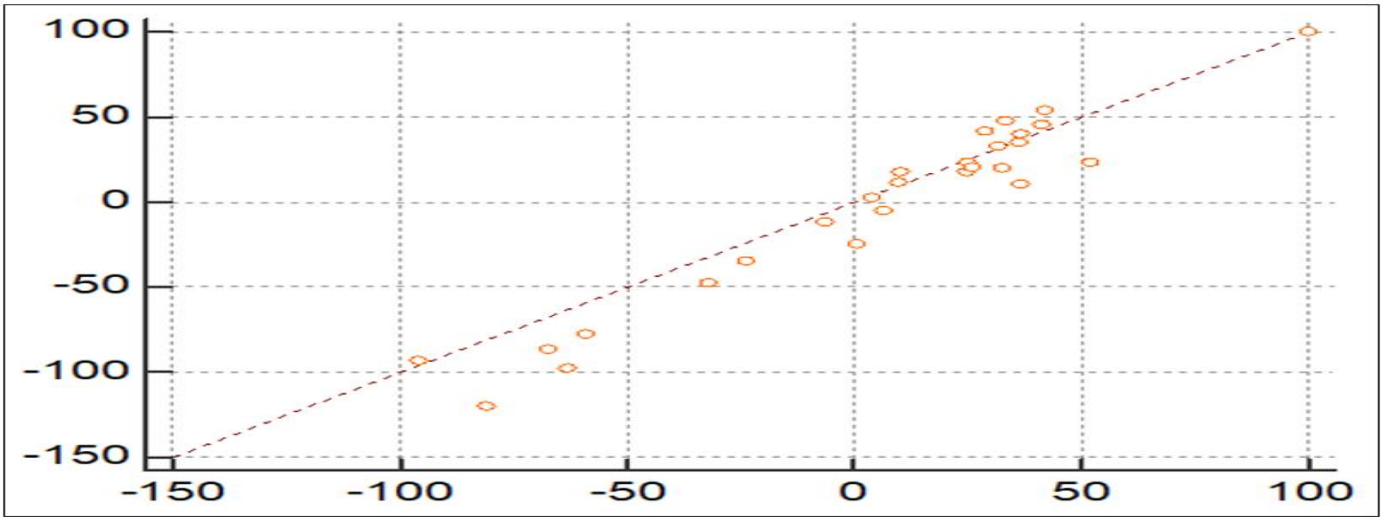

Fig 15 Scatter Plot Showing Correlation Between CT Volumetry and 3Dimensional Assessment. Response by CT Volumetry is Plotted Along the x axis and Response by 3 Dimensional Assessment is Plotted Along Y axis

➢ *Comparison of CT Volumetry, RECIST and 3 Dimensional Measurement.*[41-46]

Bland Altman plot analaysis was done to evaluate the differences between the three methods of response assessment. Cube root of measurements pre and post NACTwere taken in case of CT volumetry and three dimensional assessment to make it comparable to RECIST. CT volumetry was taken as the reference method as it gives the exact measurement of tumor volume. The differences were calculated as *reference – measurement.* So a positive difference is underestimation and negative difference is overestimation. The difference scores were plotted against the reference test, which was CT volumetry. The difference scores were assessed for normality by Kolmogorov Smirnov test. P values were > 0.1 in the case of RECIST and 3 Dimensional assessment. Further limits of agreement were calculated. The constant difference between the two methods across the intervals were plotted as line ofequality. This was useful in detecting a systematic difference or bias. Limit ofagreement is a range within which 95% of the difference between the two measurements are included. Thus in case of a better agreement between the two tests, the limit of agreement should be smaller. The percentage error was indicative of a proportional bias, which is proportional to the magnitude of measurement. The variance was calculated as

$$Var = \frac{SD^2}{n}$$

SD is the standard deviation and n is the sample size.

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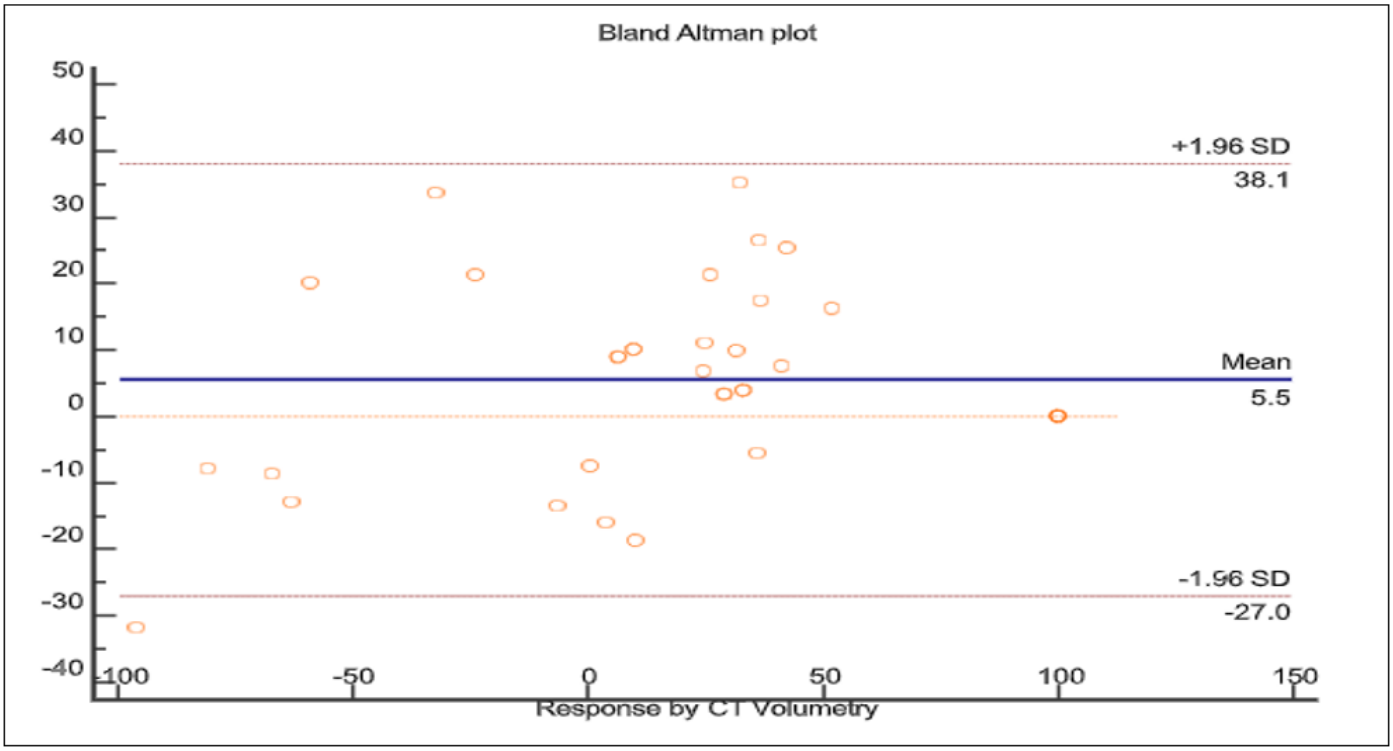

Fig 15 Plot of Differences Between CT Volumetry and RECIST with CT Volumetry Taken as the Standard of Measurement. The bias is Represented by the Gap Between the X axis Corresponding to a zero Difference (dotted line) and the Parallel line to the X axis at 5.5 units.

The systematic bias of using RECIST criteria when compared to CT volumetry was 5.5%. RECIST underestimated the percentage response by a mean of 5.5%. The standard deviation of the difference score was 16.61. The upper limit of agreement was 38.1% and lower limit of agreement was -28.0%. The variance of the difference between the two methods was 9.85. The absolute percentage error was 39.04%.

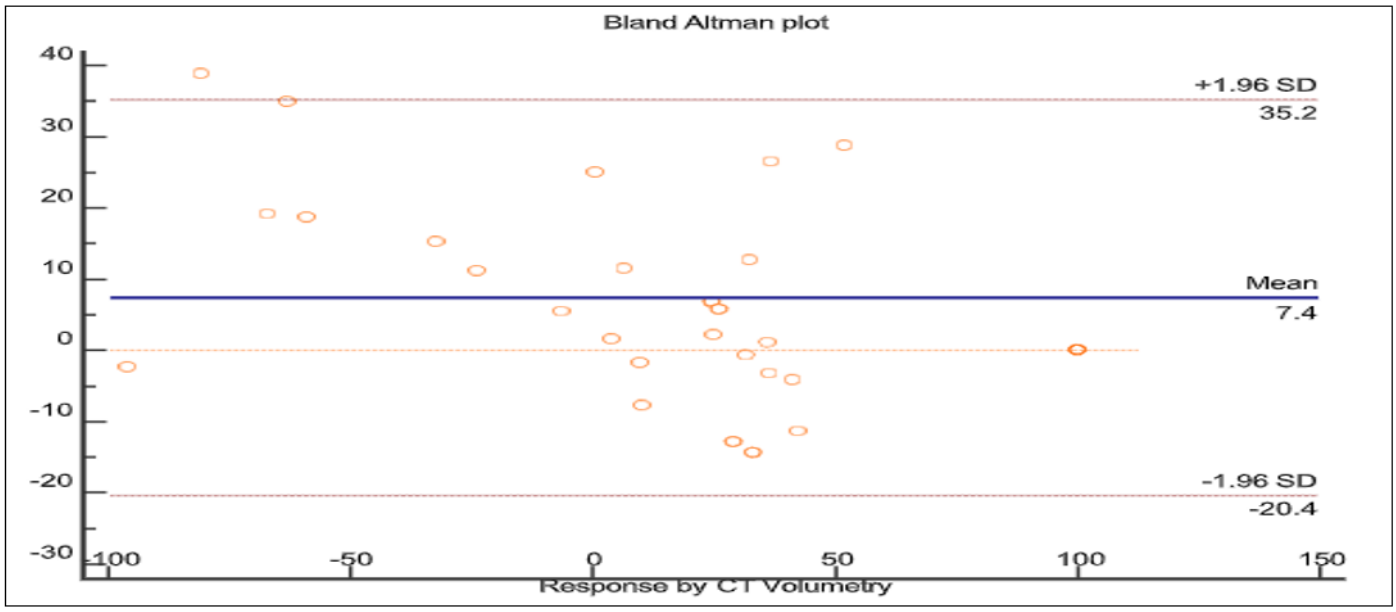

Fig 16 Plot of differences between CT Volumetry and 3 Dimensional assessment with CT Volumetry taken as the standard of measurement. The bias is represented by the gap between the X axis corresponding to a zero difference (dotted line) and the parallel line to the axis at 7.4 units.

The systematic bias of using 3 Dimensional assessment when compared to CT Volumetry was 7.38%. CT Volumetry underestimated the percentage response by a mean of 7.38%. The standard deviation of the difference score was 14.19. The upper limit of agreement was 35.2 % and lower limit of agreement was -20.4%. Thevariance of the difference between the two methods was 7.19. The absolute percentage error was 35.38%.

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CHAPTER SEVEN
DISCUSSION

The standard approach used to assess the response of solid tumors to neoadjuvant chemotherapy by imaging is RECIST (Response evaluation criteria in solid tumors).[6,7] However RECIST which uses unidimensional imaging may not be accurate in response evaluation in oral cavity cancers owing to its complex anatomy. Hence we conducted this cross sectional study to find out whether Volumetry was a better method of assessing response to NACT compared to RECIST criteria which takes into account only the single largest dimension of the tumor in axial plane.28 patients with cancer of oral cavity who underwent neoadjuvant chemotherapy having pre and post NACT CT scans were included. Of these 28 patients, pathologicaldata was available for 17 patients who underwent surgery. The tumor measurementsin three dimension and the pathological stage of the tumor in resected specimen was mentioned in pathological data. The percentage response was calculated using RECIST criteria, CT Volumetry and 3 Dimensional assessment. Response was then assessed by comparing the pre and post NACT measurements using RECIST, CT Voumetry and 3 D assessment. The patients were categorised into progressive disease, stable disease, partial response and complete response based on the percentage response. Progressive disease and stable disease were grouped as nonresponders and partial response and complete response as responders . The sensitivity, specificity, positive predictive value and negative predictive value of RECIST, Volumetry and 3 Dimensional assessment was then calculated using Clinico-pathological assessment asthe reference standard. Results showed that in assessing the number of responders CT Volumetry had a significantly higher sensitivity(73.3%) compared to RECIST (40%) and 3 Dimensional assessment(60%). A low sensitivity (40%) of RECIST implies thatsignificant number of patients who were actually responders would have been missed by RECIST, thereby leading to change in management and jeopardising their survival benefit. The reason for this could be that the tumor is undergoing asymmetric shrinkage in dimensions other than the longest dimension in axial plane. The study by Hou et al in head and neck cancers had similarly reported that change in RECIST diameters, post treatment is much smaller than change in volume and that RECIST measurements did not correlate with clinical outcome.[8] The study by V. Patil et al hadalso reported that head and neck cancers have a complex shape and hence unidimensional measurements was not accurate in assessing response.[9] The results obtained in our study was consistent with the results obtained in these studies. However our study showed a different result when compared to the study conducted by Lubneret al.[15] Lubner et al who had conducted a study comparing one dimensional and volumetric measurements for response assessment in metastatic colorectal carcinoma however reported that both the measurements were similar in predicting response and categorising it into responders and nonresponders. This discrepancy could probably be due to the different anatomic location of tumor in their study. And this further justifies the need to evaluate performance of RECIST, particularly in headand neck tumors CT Volumetry in spite of showing better sensitivity over RECIST, had wrongly predicted 4 out of 15 responders as nonresponders. 4 cases of partial response were predicted as stable disease by CT Volumetry. One case of complete response was considered as partial response. This could probably be due to the inherent limitationof CT scan in differentiating residual tumor from post treatment changes. Similar result was also reported by V Patil et al. The study by V. Patil et al had reported that radiological decrease in size could not accurately predict post operative pathological response.[9] The relatively low contrast resolution of CT scan for soft tissue tumors could probably explain this limitation.[47,48] The specificity of all the three tests in calculating the responders were similar (100%).

The linear weighted Kappa was calculated for assessing the agreement between the different categories of response by RECIST, CT Volumetry, 3 Dimensional assessment and clinicopathological correlation. It was shown that there was good agreement between RECIST and clinicopathological assessment (kappa = 0.66) whereas there was very good agreement between CT Volumetry and clinicopathological assessment (kappa = 0.83). There was good agreement between clinicopathological and 3 Dimensional assessment (kappa = 0.73). The discordance between the methods were primarily in categorising tumors into stable disease and partial responders. Using RECIST criteria, about 8 patients with partial response and 1 patient with complete response were categorised as stable disease. Using Volumetry criteria, only 4 patients with partial response were categorised as stable disease. Using 3 Dimensional assessment, 6 patients with partial response were categorised as stable disease. This was in comparison to the composite clinico-pathological assessment being taken as the reference standard. The study by Zhao et al in lung cancer reported that more patients were identified as partial responders and progressive disease by volumetry compared to one dimensional and 2 Dimensional methods. The study by Lubner et al also reported a discordance betweenstable disease and partial responders. Thus the results in our study was similar to their results.

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RECIST is based on unidimensional measurement. A unidimensional measurement basically assumes a tumor to be spherical. Hence by calculating the difference in radius, change in volume could be assessed. The results presented by the kappa statistic supports the hypothesis that oral cavity tumor shrinkage in response to treatment is asymmetric. Owing to the tumor location and anatomical shape of oral cavity, these tumors especially those arising from the buccal mucosa probably shrink more rapidly in thickness rather than length (Antroposterior) or height (craniocaudal) along the wall. A further study to separately assess percentage change in tumor size in 3 orthogonal planes in response to treatment would be required to evaluate thishypothesis. Hence the unidimensional measurement model of RECIST shows lesser agreement as compared to volumetry. The correlation between the percentage response calculated by RECIST, Volumetry and 3 Dimensional assessment were calculated. There was a higher correlation between 3 Dimensional assessment and CT Volumetry (Spearman's rho 0.926) when compared to RECIST and CT Volumetry (Spearman's rho 0.829). Bland Altman analysis was further used to accurately assess the agreement and differences between RECIST, 3 Dimensional assessment and CT Volumetry. The systematic bias, limits ofagreement, variance and absolute percentage error were calculated. The systematic bias of using RECIST criteria when compared to CT volumetry was 5.5%. RECIST underestimated the percentage response by a mean of 5.5%. The standard deviation ofthe difference score was 16.61. The upper limit of agreement was 38.1% and lower limit of agreement was -28.0%. The variance of the difference between the two methods was 9.85. The absolute percentage error was 39.04%. The systematic bias of using 3 Dimensional assessment when compared to CT Volumetry was 7.38%. CT Volumetry underestimated the percentage response by a mean of 7.38%. The standard deviation of the difference score was 14.19. The upper limit of agreement was 35.2 % and lower limit of agreement was -20.4%. The variance of the difference between the two methods was 7.19. The absolute percentage error was 35.38%.

The variance between the two methods when compared to CT Volumetry is more relevant in our study. A tumor has irregular shape and undergoes shrinkage irregularly. This volume is exactly assessed by volumetry. However volumetry is a tedious procedure which requires manual mapping of tumor extent in serial thin axial sections. So, it was to be assessed if the ellipsoidal model using 3 Dimensional assessment was as good as volumetry in predicting response. Though the 3 Dimensional measurements showed slightly better agreement than RECIST with CT Volumetry, the difference was not significant. The study by Shah et al on patients with high grade glioma however reported that 3D assessment showed a poor correlation with progression free survival compared to 1 Dimensional and Volumetric methods.[23] This difference could have been due to the difference in biological behaviour of the tumors. Another important finding as stated in a current update of radiologic evaluation of oncologic treatment response by Prasad et al was that in considering progressive disease more than 20 % increase in unidimensional measurement corresponds to 25 %increase in the cross product and 73 % increase in volume.[22] In considering partial response, more than 30 % decrease in diameter corresponds to more than 50 % decrease in cross product and 65 % reduction in volume. In our study cube root of volume pre and post NACT was calculated and then percentage response was assessed in order to categorise the response. This was done in order to compare the values with RECIST which was unidimensional. However if volumetry is accepted as standard, its better to use the cut off of 73% and 65% for progressive disease and partial response respectively. The percentage response was calculated directly in our study too with the above mentioned cut offs. Similar categories were obtained as when cube root was taken and made into one dimensional data. It is suggested that further studies need to be done in this regard. With improvements in software, automated volumetry could become more accessible and thus couldeventually replace unidimensional measurements. Automated segmentation modelfor volume calculation using 3 D sequences in MRI which has an inherently better contrast resolution could further improve the diagnostic accuracy in response assessment of oral cavity tumors.

- *Limitations of the Study:*

Pathological data was not available for all the patients in the study. This was inevitable as patients with progressive disease had advanced stage and hence concurrent chemoradiation or palliative chemoradiotherapy was offered. Sample size calculated was 52. It could not be achieved within the period of study. Hence the study is likely to be underpowered. Interobserver variability for CT Volumetry was not done as all volume measurements were done by a single observer. Hence the reproducibility of CT Volumetry could not be assessed. Pathological response was assessed by comparing 3 Dimensional measurement of tumor in resected specimen with comparison to 3 Dimensional measurement in baseline CT, which could have resulted in inaccuracies. However there was no alternative method of measuring entire tumor size at baseline.

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CHAPTER EIGHT
SUMMARY

- This study was conducted in the Department of Radiodiagnosis, JIPMER, Puducherry. A total of 28 patients were studied.
- The study was carried out to assess if volumetry was a better method of assessing treatment response compared to RECIST, by CT scan in oral cavity cancers.
- Outline of the tumor was plotted manually and volume was calculated in Advantage Workstation 3.2. Largest dimension in axial plane and largestdimensions in three orthogonal plane was calculated.
- Post surgery pathological data was obtained. Clinical evaluation was used to assess the stage in patients for whom pathological data was not available.
- Using RECIST, Volumetry, three dimensional assessment and clinico- pathological assessment, each of the patients were grouped into progressive disease, stable disease, partial responders and complete responders.
- Clinicopathological assessment was taken as the composite reference standard
- The statistical analyses were performed using SPSS 19 Software. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for all three methods using clinico-pathological assessment as reference standard.
- Sensitivity of RECIST to detect responders was significantly low as comparedto CT Volumetry.
- There was more agreement between CT Volumetry and clinicopathological assessment compared to RECIST, in categorisation of response assessment.
- Hence, CT volumetry may definitely be a better method than RECIST in assessing response to NACT in oral cavity tumors.
- Bland Altman plot analysis showed that there was slightly better agreement between 3 Dimensional assessment and volumetry as compared to RECIST. However the difference was not significant and hence 3 Dimensional measurement cannot be used as a substitute for volumetry in response assessment.

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CHAPTER NINE
CONCLUSION

- In conclusion, our evaluation of 28 patients with oral cavity carcinoma undergoing NACT showed that CT Volumetry had better sensitivity for identifying response to NACT when compared to RECIST.
- There was more agreement in categorising patients as progressive disease, stable disease, partial response and complete response between CT Volumetry and clinicopathological assessment compared to RECIST.
- Hence, CT Volumetry may be a better method to assess response to NACT.
- Though 3 Dimensional assessment had a better sensitivity and a slightly better agreement with volumetry as compared to RECIST yet it may not be useful as a substitute for volumetry.

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ANNEXURE

A. Pgrmc Certificate

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PG Research Monitoring Committee (PGRMC)

Dr. S. C. Parija	Dr. B. Vishnu Bhat	Dr. D. M. Thappa
Director	Dean (Research)	Faculty Research

CERTIFICATE

This is to certify that the PG dissertation proposal with the following details has been approved by the PG Research Monitoring Committee, in the 9th meeting of PGRMC held on 21th October 2016, subject to clearance of Institute Ethics Committee.

Reg. No. of the Proposal: **PGRMC- 21.10.2016/25**

Title of the proposal: **Comparison of treatment response assessment in CT scan by RECISTand volumetric assessment in patients with cancers of oral cavity**

Name of the postgraduate: Dr. Nrithi S Prasad

Guide: Dr. Ramkumar. G, Assistant Professor, Department of Radio-Diagnosis, JIPMER,

Co-guides: Dr. Prasanth Penumadu, Assistant Professor, Department of Surgical oncology, JIPMER,

Dr. Biswajit Dubashi, Associate Professor, Department of Medical oncology, JIPMER,

Date: 10th November 2016

Dr. Vikram Kate
Member-Secretary
PGRMC

Copy to by mail: Dr. Ramkumar. G, Assistant Professor, Department of Radio-Diagnosis, JIPMER,– Guide

B. Ethics Committee Certificate

जवाहरलाल स्नातकोत्तर आयुर्विज्ञान शिक्षा एवं अनुसंधान संस्थान
JAWAHARLAL INSTITUTE OF POSTGRADUATE MEDICAL EDUCATION & RESEARCH
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INSTITUTIONAL ETHICS COMMITTEE (HUMAN STUDIES)

CERTIFICATE

Date: 30/01/2017

To,

Dr. Nrithi S Prasad, Junior Resident,
Department of Radio diagnosis

Ref: Your project no. **JIP/IEC/2016/1084** entitled, "Comparison of treatment response assessment in CT scan by RECIST and volumetric assessment in patients with cancers of oral cavity".

Dear Dr. Nrithi S Prasad,

The following documents of the above mentioned project were reviewed and approved through a full board review process.

1. Research Protocol
2. Patient Information Sheet in English and Tamil Language.
3. Consent Form in English and Tamil Language.
4. Data Collection Performa

It is understood that the study will be conducted under your direction, **in a total of 52 research** participants, at as per the submitted protocol.

The IEC approves the above mentioned study.

This approval is valid for three years, the entire duration of the project or a shorter period based on the risk whichever is less.

It is the policy of IEC that, it be informed about any onsite serious adverse event or any unexpected adverse event report within 24 hours as per the formats specified in SOP 09 to IEC or by email if there is holiday. The report of SAE or death after due analysis shall be forwarded by the Investigator to the chairman of IEC and the head of the institution where the trial is been conducted within 10 calendar days of SAE or death.

In case of injury or death of participant(s) occurring during the trial, the sponsor (whether a pharmaceutical company or an institution) or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial shall make payments

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for medical management of the subject and also provide financial compensation for the clinical trial related injury or death.

No deviations from, or changes of the protocol and Informed Consent Document should be initiated without prior written approval by the IEC of an appropriate amendment. The IEC expects that the investigator should promptly report to the IEC any deviations from, or changes of, the protocol to eliminate immediate hazards to the research participants and about any new information that may affect adversely the safety of the research participants or the conduct of the trial.

For studies which will continue for more than a year, a continuing review report needs to be submitted (within 1 month of the due date i.e. 11 months from the date of approval) on or before 30/12/2017.

A copy of the final report should be submitted to IEC for review.

Sincerely yours

Dr. D. Kadambari
Member Secretary
Date of approval of the study: 30-01-2017

MEMBER SECRETARY
INSTITUTE ETHICS COMMITTEE
(HUMAN STUDIES) JIPMER, PUDUCHERRY

C. Data Collection Proforma

Name:

Age:

Gender:

Hospital number:

Telephone/Mobile number

Address:

Tumour site :

Clinical diagnosis:

Tumour stage :

Pathological Diagnosis:

	Baseline	Post NACT
Tumour dimension by clinical measurement. (two dimensional)		
Tumour diameter by RECIST (onedimensional)		
Tumour volume by CT Volumetricassessment		
Tumour diameter in CT (by threedimensional measurement)		
Tumour dimensions in pathologicalspecimen	NA	

	CompleteResponse	Partial Response	Progressivedisease	Stable disease
RECIST				
CT volumetricassessment				
CT three dimensionalassessment				
Clinical				
Pathological				

Remarks:

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INFORMED CONSENT DOCUMENT (ICD)

Patient / Participant information sheet

INFORMATION FOR PARTICIPANTS OF THE STUDY

1. **Title of the project: Comparison of treatment response assessment in CT scan by RECIST criteria and volumetric assessment in patients with cancers of oral cavity.**

2. **Name of the investigator** : Dr. Nrithi S Prasad
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Co guide: : Dr. Biswajit Dubashi Additional Professor and Head
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3. **Purpose of this project/study:** To compare the response to chemotherapy in CTscan by two different methods in patients with cancers of oral cavity.

4. **Procedure/methods of the study**: You have been selected to participate in the study as you have been advised to receive chemotherapy for your oral cavity tumor. ACT scan will be acquired at the end of chemotherapy and images will be compared with the pretreatment scan for response assessment by two different methods. No additional imaging or intervention will be done for the sake of the study.

5. **Expected duration of the subject participation**: Two visits, one before treatmentand another at the end of chemotherapy.

6. **The benefits to be expected from the research to the participant or to others and the post trial responsibilities of the investigator**: The study may help in more accurate assessment of response to chemotherapy and thereby guide in appropriate management.

7. **Any risks expected from the study to the participant**:

Minimal risk due to contrast enhanced CT which is however required as part of the treatment. While you are undergoing CT scan you will be exposed to radiation. Care will be taken to perform the imaging as per ALARA (As Low As Reasonably Achievable). There is a rare possibility that you might experience allergic reactions to injection of contrast media in the form of fever, rashes, body ache, breathing difficultyetc which will be promptly treated with appropriate medications. We will perform a mandatory check up of your renal function prior to contrast injection to avoid contrastinduced kidney injury.

8. **Maintenance of confidentiality of records:** Confidentiality of your participation and data will be maintained during data collection, analysis, publication, sharing of data and after completion of study. Records will be preserved for a period of three years.

9. **Provision of free treatment for research related injury**: All the necessary treatment for research related injury will be provided for free as per JIPMER guidelines.

10. **Compensation for participating in the study**: Compensation will not be provided for participating in the study

11. **Compensation to the participants for foreseeable risks and unforeseeable risks related to research study leading to disability or death**: No major risks involved with the study and you will be compensated as per institutional protocol, in case of any unforeseen events leading to death or disability.

12. **Freedom to withdraw from the study at any time during the study period without the loss of benefits that the participant would otherwise be entitled:** You are given the full freedom to withdraw from the study at anytime without assigning any reasons and without losing medical care.

13. **Possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used forsecondary purposes or would be shared with others, this should be mentioned** : The data generated will be used for publication purpose only. Your personal identity will be kept confidential.

14. **Address and mobile number of the Principal investigator (PI) and Co- PI, ifany** :

15. **Name of the investigator** **:** Dr. Nrithi S Prasad
Junior Resident
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Email ID- gramk80@gmail.com

Signature of the investigator:

Signature / Thumb impression of the participant:

Place:Date :

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CONSENT FORM

Title of the project: Comparison of treatment response assessment in CT scan by RECIST and volumetric assessment in patients with cancers of oral cavity
Participant's name:

Address:

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected.I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).The risks and benefits of the study has beenexplained to me. I have been given an information sheet giving details of the study. I fully consent to participate in the above study.
Signature/ Thumb Impression of the participant: _____Date: _____

Signature of the witness:_____Date: _____

Name and address of the witness:

Signature of the investigator:_____Date: _____

Dr. Nrithi S Prasad

Department of Radiodiagnosis, JIPMER

D. Abbreviations :

RECIST	Response evaluation criteria in solid tumors
RMT	Retromolar trigone
FOM	Floor of mouth
GBS	Gingivobuccal sulcus
ENE	Extranodal extension
DOI	Depth of invasion
FDG	Fluorodeoxyglucose
IMRT	Intensity modulated radiotherapy
RT	Radiotherapy
NACT	Neoadjuvant Chemotherapy
PD	Progressive disease
SD	Stable disease
PR	Partial response
CR	Complete response

E. Key To Master Chart

PD	Progressive disease
SD	Stable disease
PR	Partial response
CR	Complete response
R	Responders
NR	Nonresponders

F. Master Chart

Serial number	Age	Gender	Tumor site	Tumor stage	Pre NACT clinical T stage	Baseline tumor dimension by clinical measurement	Baseline tumor dimension by RECIST	Baseline tumor volume by CT volumetry	Baseline tumor volume by 3D measurement	Tumor dimension post NACT by clinical measurement	Tumor dimension post NACT by RECIST	Tumor dimension post NACT by CT Volumetry	Tumor volume post NACT by 3D assesment	Tumor volume in pathological specimen	Pathological stage	Clinical stage post NACT	T staging post NACT by clinicopathological assessment	Percentage response by RECIST criteria	Percentage response by CT volumetry	Percentage response by 3D assesment	Percentage response by pathological assessment		Cube root of response by CT Volumetry	Cube root of response by 3D assesment	Cube root of response by pathological assessment	Response evaluation based on Clinicopathological assesment	Response evaluation based on RECIST	Response evaluation based on CT Volumetry	Response evaluation by 3D assesment	Binary response outcome based on clinicopathological assessment	Binary response outcome based on RECIST	Binary response outcome based on CT volumetry	Binary response outcome based on 3D assesment
1	50	Male	Right upper alveolus	T4aN1m0	T4a	12	7.3	51.46	82.31	12	5.2	37.48	45.84	25	T4aN0M0		T4a	29	27	44	51		10	18	21	SD	SD	SD	SD	NR	NR	NR	NR
2	75	Male	Mid lower alveolus	T4aN2cM0	T4a	20	5.6	27.6	26.6	20	5.2	33.29	37.31	_		T4aN2cM0	T4a	7	21	40	_		6	12	_	SD	SD	SD	SD	NR	NR	NR	NR
3	40	Female	Right buccal mucosa	T4aN1M0	T4a	30	3.6	6.71	5.625	64	5.9	50.38	40.72	_		T4bN2cM0	T4b	64	651	624	_		96	93	_	PD	PD	PD	PD	NR	NR	NR	NR
4	49	Male	Right Buccal mucosa	T3N2aM0	T3	20	3.69	12.07	16.226	20	2.6	3.58	2.22	2	T2N1M0		T2	50	70	86	83		33	48	45	PR	PR	PR	PR	R	R	R	R
5	35	Female	Right alveolobuccal complex	T4aN1M0	T4a	35	5.8	24.01	19.285	0	0	0	0	0	T0N0M0		T0	100	100	100	100		100	100	100	CR	CR	CR	CR	R	R	R	R
6	41	Female	Right buccal mucosa	T4aN1M0	T4a	12	5	22.92	24.975	9	4.3	9.66	11.438	4.725	T2N0M0		T2	14	58	54	79		25	23	41	PR	SD	SD	SD	R	NR	NR	NR
7	50	Male	Right lower alveolus	T2N2bM0	T2	8	3.1	3.4	3.1	6	2.5	0.858	2.24	_		T1N2bM0	T1	19	75	28	_		37	10	_	PR	SD	PR	SD	R	NR	R	NR
8	50	Male	Left lower alveolus	T3N2bM0	T3	12	4.2	9.4	13.86	6	2.7	1.04	6.2775	_		T2N2bM0	T2	36	89	55	_		52	23	_	PR	PR	PR	SD	R	R	R	NR
9	45	Male	Left buccal mucosa	T3N1M0	T3	16	4.1	10.57	8.364	25	6.5	49.37	54.11	_		T4bN1M0	T4b	59	367	547	_		67	86	_	PD	PD	PD	PD	NR	NR	NR	NR
10	50	Male	Right buccal mucosa	T4aN1M0	T4a	24	4.3	8.9	6.99	30	7.7	35.77	39.2	_		T4bN1M0	T4b	79	502	461	_		59	78	_	PD	PD	PD	PD	NR	NR	NR	NR
11	56	Male	Right upper alveolus	T4aN2bM0	T4a	20	4.1	11.63	12.3	16	6.8	26.88	39.368	_		T4bN1M0	T4b	66	131	220	_		32	47	_	PD	PD	PD	PD	NR	NR	NR	NR
12	49	Male	Lower alveolus	T4aN0M0	T4a	24	5.5	31.58	36.848	24	4.4	28	34.276	27	T4aN0McX		T4a	20	11	7	15		4	2	5	SD	SD	SD	SD	NR	NR	NR	NR
13	50	Male	Right lower alveolus	T3N2bM0	T3	35	2.6	5.22	4.95	30	4.5	30.92	52.54	19	T4aN0McX		T4a	73	492	961	-264		81	120	54	PD	PD	PD	PD	NR	NR	NR	NR
14	46	Male	Left buccal mucosa	T3N2bM0	T3	20	5.6	19.08	20.21	6	4.6	8.15	11.22	_	T3N2bMcX		T3	18	57	44	_		25	18	_	SD	SD	SD	SD	NR	NR	NR	NR
15	46	Male	Left alveolobuccal complex	T4aN2bM0	T4a	35	6.5	40.56	35.36	12	4.3	8.15	5.676	_	T1N1McX		T1	34	80	84	_		41	46	_	PR	PR	PR	PR	R	R	R	R
16	62	Female	Left lower alveolus	T4aN2bM0	T4a	30	5.3	36.79	45.315	2	4.4	7.1	4.54	0	T0N0M0		T0	17	81	90	100		42	54	100	CR	SD	PR	PR	R	NR	R	R
17	60	Male	Left upper alveolus	T4aN2cM0	T4a	20	4.2	17.43	18.816	15	4.3	14.26	21.758	_		T4aN2cM0	T4a	2	18	16	_		6	5	_	SD	SD	SD	SD	NR	NR	NR	NR
18	35	Male	Left buccal mucosa	T4aN2bM0	T4a	42	6	40.95	37.49	12	5.5	10.69	10.29	21	T2N0McX		T2	42	74	73	49		36	35	20	PR	PR	PR	PR	R	R	R	R
19	48	Male	Left buccal mucosa	T4aN1M0	T4a	30	5.9	35.61	27.5	20	4.6	11.3	8.44	_	T1N0McX		T1	22	68	69	_		32	33	_	PR	SD	PR	PR	R	NR	R	R
20	63	Male	Right buccal mucosa	T4aN2bM0	T4a	42	3.9	11.72	17.745	2	2.9	4.21	3.5	_	T3N0McX		T3	26	64	80	_		29	42	_	PR	SD	SD	PR	R	NR	NR	R
21	55	Female	Right buccal mucosa	T4aN1M0	T4a	12	4.1	14.6	7.75	6	3.9	5.9	3.93	_	T1N0McX		T1	5	60	49	_		26	20	_	PR	SD	SD	SD	R	NR	NR	NR
22	55	Male	Right buccal mucosa	T4aN1M0	T4a	50	6.2	57.93	37.789	16	5.7	57.07	72.96	60	T4aN0McX		4a	8	1	93	-4		0	25	1	SD	SD	SD	PD	NR	NR	NR	NR
23	55	Female	Right buccal mucosa	T4aN1M0	T4a	20	5	18.75	15.725	6	4.5	4.8	3.44	_	T1N0McX		T1	10	74	78	_		37	40	_	PR	SD	PR	PR	R	NR	R	R
24	55	Female	Left buccal mucosa	T4aN2bM0	T4a	24	5.1	18.574	16.83	28	7.4	35.31	41.393	_		T4bN2bMcX	T4b	45	90	146	_		24	35	_	PD	PD	PD	PD	NR	NR	NR	NR
25	44	Male	Right buccal mucosa	T4aN1M0	T4a	20	3.7	15.56	15.096	12	3.7	11.36	10.4	3	T3N2bMcX		T3	0	27	31	81		10	12	42	PR	SD	SD	SD	R	NR	NR	NR
26	48	Male	Left buccal mucosa	T4aN1M0	T4a	15	4	12.05	7.54	20	4.1	3.7	3.888	1.5	T3N1McX		T3	2	69	48	88		33	20	50	PR	SD	PR	SD	R	NR	R	NR
27	62	Male	Left buccal mucosa	T4aN2bM0	T4a	16	9	10.3	9.36	0	0	0	0	0		T0N0M0	T0	100	100	100	100		100	100	100	CR	CR	CR	CR	R	R	R	R
28	40	Male	Right buccal mucosa	T4aN2bM0	T4a	20	5.2	23.77	15.314	30	7.8	103	118.63	_		T4bN2bM0	T4b	50	333	675	_		63	98	_	PD	PD	PD	PD	NR	NR	NR	NR