COMPARISON OF CT BASED AND INTEGRATED F 18 FDG PET CT SCAN BASED GROSS TUMOUR VOLUME IN HEAD AND NECK CANCERS AND EVALUATION OF THE DIFFERENT SEGMENTATION METHOD FOR DELINEATION OF THE TARGET ON PET SCAN

DEPARTMENT OF RADIOTHERAPY

CHRISTIAN MEDICAL COLLEGE

VELLORE 632004

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF

MD BRANCH IX RADIOTHERAPY

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TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY

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CHRISTIAN MEDICAL COLLEGE, VELLORE

DEPARTMENT OF RADIOTHERAPY

CERTIFICATE

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I, Paul Gopu G, PG Registrar, Department of Radiation therapy, Christian Medical College Vellore hereby declare that the dissertation titled 'COMPARISON OF CT BASED AND INTEGRATED F 18 FDG PET CT SCAN BASED GROSS TUMOUR VOLUME IN HEAD AND NECK CANCERS AND EVALUATION OF THE DIFFERENT SEGMENTATION METHOD FOR DELINEATION OF THE TARGET ON PET SCAN' is a bonafide work done by me for partial fulfilment towards MD Radiotherapy (Branch IX) Degree examination of the Tamil Nadu Dr M G R Medical University to be held in April 2016.

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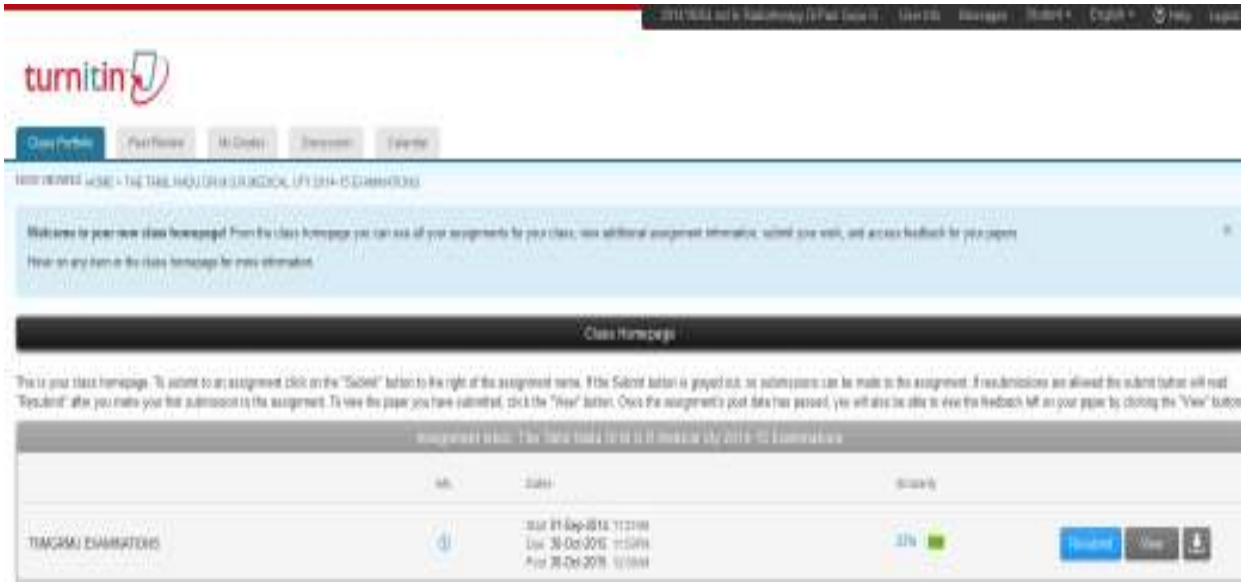
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Contents

ABSTRACT TITLE: COMPARISON OF CT BASED AND INTEGRATED F 18 FDG PET CT SCAN BASED GROSS TUMOUR VOLUME IN HEAD AND NECK CANCERS AND EVALUATION OF THE DIFFERENT SEGMENTATION METHOD FOR DELINEATION OF THE TARGET ON PET SCAN

DEPARTMENT: Department of Radiotherapy, Dr Ida B Scudder Cancer Centre

NAME OF THE CANDIDATE: Dr. Paul Gopu G

DEGREE& SUBJECT: MD Radiotherapy

NAME OF THE GUIDE: Dr Subhashini John

Objective:

To evaluate the differences in radiotherapy gross tumour volumes (Primary and lymph nodes) delineated on CT and PET for radiotherapy planning of Head and neck cancers.

Methods and materials:

Patients with biopsy proven malignancy of the oropharynx, laryngopharynx and nasopharynx, who had undergone treatment with Intensity Modulated Radiation Therapy (IMRT) technique where treatment planning was done using a planning PET/CT, from June 2012 to September 2015 were included. The GTV primary (GTVp) and GTV node (GTVn) for all the patients was drawn on the CT scan using the soft tissue window level. The GTV primary (GTVp) and GTV node (GTVn) for each node for all the patients was drawn on the PET images using the following methods and separate GTVp and GTVn volumes were obtained. SUV values for SBR

was calculated and the contours were done with the help of 3D slicer. The SUV-based delineation was obtained by applying an isocontour around the tumor with two thresholds which were based on fixed percentages of the maximum signal intensity in the primary tumor; 40% (GTV40%) and 50% (GTV50%). The absolute volumes of tumour (primary and lymph nodes) obtained using the CT scan and the PET data were documented. The CT volume was compared with PET volume that was got through the SBR technique. Volume was also segmented using fixed SUV technique with SUV 40% and SUV 50%, and these volumes were also compared with each other.

Results:

The study was done in 17 head and neck cancer patients. There were 7 patients with oropharyngeal cancer, 5 with hypopharyngeal cancer, 4 with nasopharyngeal cancer and 1 with laryngeal cancer. There were 7 patients with stage IV A, 4 with stage IVB and 2 each in stage I, II and III cancers. After obtaining the SUV max of the tumour, background SUV mean and volume from Otsu algorithm the SBR formula was run, thus deriving the tumour specific SUV percentage. The SUV percentage obtained with SBR technique varied from 26% to 71 % and this was different in the same patient between primary and node, and also was different between nodes in the same patient. There is significant difference between the volumes derived from fixed threshold methods with 40% and 50% and in the volumes between SBR technique and fixed threshold techniques using SUV 40% and SUV 50%. PET based volume using fixed threshold technique with 40% and 50% and the volume obtained using SBR technique was significantly less than the CT volume. But this difference in volume with SBR technique was less than that obtained with fixed threshold methods using 40% and

50%. i.e adaptive method was better than the fixed threshold methods. In some instances the nodal volumes derived using the SBR technique was grossly less than the CT volumes. The necrosis part of the node failed to pick up FDG and thus the contoured metabolic tumour volume was very different from the anatomical volume.

Conclusion:

The SBR technique was superior to the fixed threshold technique using SUV 40% and SUV 50% for target volume delineation and therefore should be the method for autocontouring on PET scan. Creating metabolic tumour volume from PET alone without considering the anatomical part from the CT scan can fail in most cases to give an accurate delineation of tumour. Integrating the metabolic tumour volume obtained with autocontouring using the SBR technique on the PET scan along with anatomical part on CT which does not show uptake on the PET scan and clinical findings probably will be the best method of target volume delineation.

Introduction

Head and neck malignancy are a major cause of morbidity and mortality throughout the world. The incidence of head and neck malignancies are very high in India and it ranks third commonest, after breast and cervical cancer.(1)(2)

A patient diagnosed with stage I or II head and neck cancer is offered single modality treatment in the form of surgery or radiotherapy. Multidisciplinary approach with surgery, radiation therapy and chemotherapy forms the mainstay of treatment of locally advanced HNSCC. Radiotherapy forms a major treatment modality in the form of radical radiotherapy, concurrent chemoirradiation as part of organ preservation protocol, post operative radiotherapy with or without chemotherapy and palliative radiotherapy.

Last century saw the technique of radiation therapy evolving from conventional 2 dimensional radiation therapy to 3 dimensional conformal radiation therapy (3D CRT) and Intensity Modulated Radiation Therapy (IMRT).(3) Intensity Modulated Radiation Therapy, is presently considered the standard of care in managing head and neck malignances.(4)

With the use of IMRT the dose to the primary tumor can be escalated while keeping the dose to the adjacent normal structures at the minimum. There is a sharp fall of in dose at the edges of the tumour volume which results in reducing the doses to normal structures. So appropriate imaging for precise delineation of target volume and organs at risk is required for planning in conformal radiotherapy, otherwise there is a chance of geographical miss.(5)

The imaging used in head and neck for staging and for target volume delineation are contrast enhanced CT scan, contrast MRI, PETCT scan or a combination of these imaging modalities. Most commonly CT scan is used by the radiation oncologist, to delineate tumours and MRI is done when required, for better visualization of extent of tumour. Anato-metabolic imaging using a combined 18F-fluoro-deoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) is used in the diagnosis, initial staging, and response assessment in various malignant tumors with high diagnostic accuracy. (6)The advantages of PET/CT in radiotherapy planning is that it improves tumour delineation, reducing intra-observer and inter-observer variability and making treatment volumes more standard across individuals and institutions.(7) Comparison of PET-GTVs with CT-GTVs was done in pathology series has shown that PET was superior to CT for detecting primary tumors.(8)

PET CT is not widely available and therefore not done in all head and neck cancer patients for planning conformal radiotherapy treatment. We need to know whether the addition of PET CT as an imaging in head and neck cancer patients will add any value in treatment of patient. A study was done to see whether GTV delineated with use of PET images are better than CT alone or do they give any additional information compared to CT. A comparison of target volumes, GTV delineated with CT and GTV using Source-to-Background Ratio (SBR) method of delineation, where done. Also the SUV-based delineation was obtained by applying a fixed threshold methods like fixed percentages of the maximum signal intensity in the primary tumor; 40% (GTV40%) and 50% (GTV50%).

Aim-

Primary objective:

To evaluate the differences in radiotherapy gross tumour volumes (Primary and lymph nodes) delineated on CT and PET for radiotherapy planning of Head and neck cancers

Secondary objective:

- To assess the impact of the addition of PET scan on staging and thus the change in management

1. Change in nodal tumour volume

2. Change in primary tumour volume (T staging) and identifying synchronous malignancy

Review of Literature

Head and Neck squamous cell cancers are a major cause of morbidity and mortality throughout the world. Although the trend of incidence and prevalence of head and neck malignancies had decreased throughout other parts of the world, the incidence and prevalence is still very high in India.(9)(10)

WHO GLOBOCAN report 2012 reported the most common malignancies seen in india are breast, cervix, lip and oral cavity cancers. When we consider cancers of the head and neck region, lip and oral cavity cancers had an incidence of 11.6%, laryngeal cancers 4.8%, nasopharynx 0.6% and other pharynx 6.6%. In India this constitute about 23.6% of new diagnosed cancers .(10)

The WHO GLOBOCAN Report 2012 also showed a very high 5 year prevalence rates for head and neck cancers in India. The 5 year prevalence rate of lip and oral cavity was 12.6%, while for Laryngeal cancers it was 6.8%, nasopharynx 1.1% and other pharynx 7%. This clearly points out the high burden of head and neck cancers in India with 5 year prevalence rates of nearly 27%.(10)

There is currently no National Cancer Registry which provides comprehensive information regarding the cancer incidence or mortality data in India. The Indian Council of Medical Research (ICMR) started National Cancer Registry Programme (NRCP) in 1981 (1) . It has got only 28 cancer registries and theses are located throughout the country. The cancer registries have been classified as hospital based cancer registries and

population based cancer registries and data from 7 hospital based cancer registries showed that the head and neck cancers accounted for around 30% of all cancers in males. In females ,the incidence of head and neck cancers ranged from 4.8% in Chandigarh to 15% in Guwahati for all head and neck regions with an average of about 11%.(11) The most common head and neck cancers seen In India are mouth and tongue cancers followed by pharyngeal cancers. A solid reason for this high incidence can be accounted to the tobacco chewing practices which are followed in various parts of the country.(2)

Anatomy

The anatomy of head and neck regions discussed in this paper consist of the oral cavity, the oropharynx, larynx, hypopharynx and the nasopharynx. The various subsites of oral cavity considered are the lip, buccal mucosa, alveolar ridge and retro molar trigone, the floor of mouth, hard palate and anterior one third of the tongue. The pharynx is divided into nasal part, oral part and the laryngeal part. The oropharynx is constituted by the soft palate, base of tongue, tonsillar pillars and tonsillar fossa. The hypopharyngeal subsites consists of the 2 pyriform sinuses, posterior pharyngeal wall and the post cricoid area. The supraglottis, Glottis and subglottis together forms the larynx.

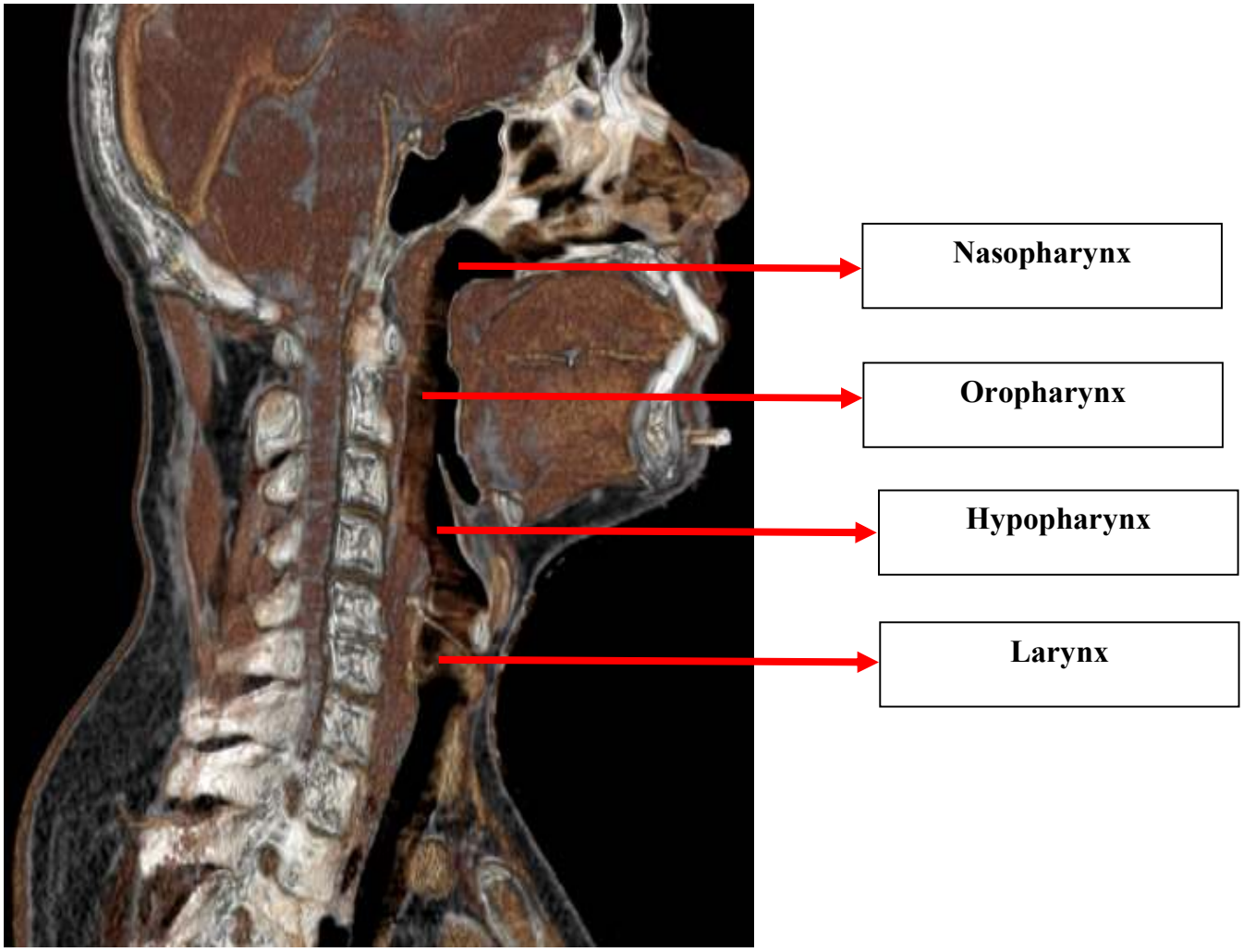


Diagram 1 showing anatomy of Head and Neck subsites.

Oral Cavity:

The oral cavity is divided into a number of areas namely:

The Lip

Buccal mucosa - Membrane lining inner surface of the lip and cheeks to the attachment of mucosa to alveolar ridges and pterygomandibular raphe

Lower alveolar ridge - Extends from lower buccal gutter to free mucosa of the floor of the mouth and goes to ascending ramus of the mandible posteriorly.

Upper alveolar ridge - Extends from upper buccal gutter to junction of hard palate and it posteriorly goes to upper end of pterygopalatine arch

Retro molar trigone – extends from the mucosa overlying ascending ramus of mandible from the posterior surface of last molar tooth to the apex, adjacent to tuberosity of maxilla

Floor of mouth – It is a semilunar space lying over the mylohyoid and hyoglossus muscle and it extends from inner surface of lower alveolar ridge to under surface of tongue, and posteriorly to base of anterior pillar of the tonsil. Contains ostia of submaxillary and sublingual salivary glands

Hard palate – It is a semilunar area between the upper alveolar ridge and mucous membrane which is covering the palatine process of maxillary palatine bones. It is the region from inner surface of superior alveolar ridge to posterior edge of the palatine bone

Oral tongue – Anatomically it extends anteriorly from circumvallate papillae to under surface of the tongue at the junction of the floor of mouth.

Oropharynx :

The oropharynx is bounded anteriorly by the anterior pillars of the pharyngeal fauces (the palatoglossus muscle), the circumvallate papillae (sulcus terminales) or the junction of the hard and soft palates. Posterior and lateral boundaries are formed by the muscular pharyngeal wall (superior and middle constrictors). The superior extent is the level of the soft palate. The inferior extent is the level of the base of tongue (level of the hyoid). The oropharynx is subdivided into five areas. These include lateral pharyngeal walls, tonsillar regions, posterior wall, base of tongue, and soft palate.

Hypopharynx:

The hypopharynx anatomically extends from the inferior extent of oropharynx at the tip of the epiglottis (or level of the hyoid bone) superiorly to the inferior border of the cricoid

cartilage. Hypopharynx can be divided into four subsites: the two pyriform sinus, the post cricoid area, and the posterior pharyngeal wall. The pyriform sinus is a funnel shaped structure that is bounded superiorly at the glossoepiglottic fold and extends inferiorly with its apex at the level of the cricopharyngeus. It is bounded posteriorly by the lateral wall of the hypopharynx and laterally by the thyroid lamina. Its medial boundary is the lateral surface of the arytenoid. The third area is the post cricoid area. This includes the posterior surface of the aryepiglottic fold and posterior surface of the arytenoid to the inferior border of the cricoid cartilage. The fourth region is the posterior pharyngeal wall, which extends from a plane drawn at the level of the tip of the epiglottis to a plane at the inferior border of the cricoid. The superior and inferior margins of the hypopharynx blend with the posterior wall of the oropharynx and esophagus, respectively.

Larynx:

The Larynx consists of 3 parts – The Supraglottic larynx, the Glottic larynx and the Sub Glottic larynx. The Supraglottic larynx consists of epiglottis, aryepiglottic folds, arytenoid cartilages and false cord.

The Glottic larynx is made up of true vocal cords and anterior & posterior commissures down to 5 mm below free margin of vocal cords.

Subglottic larynx extends from 5mm below the free margin of true vocal cords to level of inferior margin of cricoid cartilage.

Nasopharynx:

The Nasopharynx begins superiorly border is the cribriform plate and sphenoid sinus. Anteriorly it extends from the end of the nasal cavity, at the posterior choana. It extends along plane of the airway to the level of free border of the soft palate posteriorly. Lateral walls consist of the torus tubarius (opening of eustachian tube), pharyngeal recess (Fossa of Rosenmuller) posterior to torus tubarius, and behind these are the superior pharyngeal constrictor muscles, and behind this is the medial pterygoid plate. The posterior boundary of the nasopharynx consist of clivus which is part of the sphenoid bone (behind the sinus, the tail end of the sella turcica) and part of the occipital bon. Hard and soft palates (the inferior border) sits about at the level of C2.

Clinical examination of nasopharyngeal cancers includes cranial nerve examination because of the anatomical relationship of the nasopharynx to cranial nerves and commonly extend along them intracranially:

Cavernous sinus – Cranial nerves III, IV, V1 + V2, VI - (all pass through superior orbital fissure except V2 is through foramen rotundum)

Foramen rotundum – Cranial nerve V2

Foramen ovale – Cranial nerve V3 - anterolateral to clivus

Foramen lacerum - lateral to front part of clivus - plugged with cartilage in vivo

Jugular foramen – Cranial nerves IX, X, XI - lateral to foramen magnum

Hypoglossal canal – Cranial nerve XII - lateral to foramen magnum

Pharyngeal recess (Fossa of Rosenmuller) is postulated to be the most common site of origin of nasopharyngeal cancers. It is located posterior to torus tubaris (posterior lip of the medial end of the cartilaginous eustachian tube).

Lymphatics of head and Neck

Level Ia

Level Ia nodes are the submental group of nodes. Anotomically these are placed between the anterior belly of the digastric muscles. There is no actual medial boundary for level Ia and it is continuous with level Ia nodal region on the opposite. The region from which level Ia nodes drain are floor of the mouth (mainly the anterior part), tip of the anterior tongue, the middle third of the lower lip and skin of the chin. Submental nodes has the potential risk of developing metastases from cancer arising from or involving the anterior portion of floor of the mouth, the anterior oral tongue, the lower lip and the anterior mandibular alveolar ridge.(12)

Level Ib

Level Ib represent the submandibular nodes, which are located in the submandibular triangle. The submandibular triangle is anatomically bounded laterally by the inner side of the mandible laterally. The medial border is digastric muscle and anterio posteriorly it extends from the symphysis menti to the submandibular gland. The The lymphatic drainage of submandibular nodes is mainly from the level Ia, the hard and soft palate, the lower nasal cavity, the mandibular and maxillary alveolar ridges, the cheek, the upper and lower lips, and major part of the anterior tongue. Nodes in level Ib are at risk of harboring metastases from cancers of the submandibular gland and the oral cavity. This group of

node also receive efferent from anterior nasal cavity and soft tissue structures of the mid-face.(12)

Level II

Level II group are the upper jugular nodes located around the upper 1/3rd of the IJV (internal jugular vein) and the upper spinal accessory nerve. The nodal region is bounded by medial margin of sternocleidomastoid muscle laterally. The medial edge of the internal carotid artery and the scalenius muscle is the boundary in the medial side. The antero posterior extend is from the posterior border of the submandibular gland to the posterior margin of the sternocleidomastoid muscle posteriorly. Cranio caudally it extend from the level of first cranial vertebra's lateral process to the region upto level of caudal edge of the hyoid bone. The nodal region of level II can be further subdivided into two by the posterior edge of the internal jugular vein into level IIa and IIb. The nodal region of level II receives efferent lymphatics from the parotid gland, and the submandibular, the face, submental and retropharyngeal nodes. Level II also directly receives the collecting lymphatics from the external auditory canal, the middle ear, the nasal cavity, the pharynx, the larynx, and the sublingual and submandibular glands. The nodes in level II are therefore at greatest risk of harboring metastases from cancers of the nasopharynx, oropharynx, hypopharynx, larynx, nasal cavity, oral cavity and the major salivary glands. Level IIb is more likely associated with primary tumors of the nasopharynx or

oropharynx, and less frequent of cancer sites of efferents are the oral cavity, larynx, hypopharynx or oral cavity.(12)

Level III

Level III forms the middle jugular nodes located around the mid third of the the IJV. Cranio – caudally it extends from the caudal edge of the body of the hyoid bone to the caudal edge of the cricoid cartilage. The anterior boundary is the anterior edge of the sternocleidomastoid muscle or the posterior third of the thyro-hyoid muscle, and the posterior margin is the posterior edge of the sternocleidomastoid muscle. Medially, level III is limited by medial edge of the common carotid artery and the scalenius muscles and laterally by the deep surface of the sternocleidomastoid muscle. Level III receives efferent lymphatics from levels II and V, and some efferent lymphatics from the pretracheal, recurrent laryngeal and retropharyngeal nodes. It collects the lymphatics from the larynx, hypopharynx, base of the tongue, tonsils and thyroid gland.(12)

Level IV

Level IVa is the lower jugular lymph nodes located around the inferior third of the internal jugular vein from the inferior limit of level III to a limit set arbitrarily 2 cm cranial to the sternoclavicular joint, caudally. The anterior margin is the anterior edge of the sternocleidomastoid muscle cranially and the body of the sternocleidomastoid muscle

caudally; the posterior margin is the posterior edge of the sternocleidomastoid muscle cranially and the scalenius muscles caudally. Laterally the level IVa is limited by the medial surface of the sternocleidomastoid muscle cranially and the lateral edge of that muscle caudally; the medial margin of level IVa is the medial border of the common carotid artery, the medial edge of the thyroid gland and the scalenius muscle in the upper part, and the medial edge of the sternocleidomastoid muscle in the lower part. Level IVa receives efferent lymphatics primarily from levels III and V, some efferent lymphatics from the recurrent laryngeal, pretracheal and retropharyngeal, and collecting lymphatics from the larynx , hypopharynx, and thyroid gland.(12)

Level IVb group are the medial supraclavicular lymph nodes located in the continuation of level IVa down to the cranial edge of the sternal manubrium. The anterior margin is the deep surface of the sternocleidomastoid muscle; the posterior margin is the anterior border of the scalenius muscle cranially, and the apex of the lung, the brachiocephalic vein, the brachiocephalic artery on right side and the common carotid artery and subclavian artery on the left side, in the lower section the lateral limit is the lateral edge of the scalenius muscle, while the medial limit abut level VI and the medial edge of the common carotid artery. Level IVb receives efferent lymphatics mainly from levels IVa and Vc, some efferent lymphatics from the recurrent laryngeal nodes and pretracheal nodes, and collecting lymphatics from the esophagus, larynx, hypopharyn, trachea and thyroid gland. (12)

Level V (Va and Vb)

Level Va and Vb include the nodes of the posterior triangle group which are located posterior to the sternocleidomastoid muscle. It is found around the lower part of the spinal accessory nerve and the transverse cervical vessels. It extends from a plane at the level of the cranial edge of the body of the hyoid bone to a plane crossing the cervical transverse vessels caudally. Laterally the level V is limited by the platysma muscle and the skin, and medially by the levator scapulae (cranially) and the posterior scalenius (caudally) muscles. Posterior margin is the limit set at the anterior border of the trapezius muscles. Level V is subdivided into levels Va and Vb using the caudal edge of the cricoid cartilage as an anatomic landmark. Level V receives efferent lymphatics from the retroauricular and occipital nodes as well as those from the parietal and occipital scalp, the skin of the lateral and posterior neck and shoulder, the oropharynx, the nasopharynx, and the thyroid gland. Level V lymph nodes are at high risk for developing metastases from cancers of the nasopharynx, oropharynx and thyroid gland.(12)

Level Vc are the lateral supraclavicular nodes located in continuation with the posterior triangle nodes (level Va and Vb) from the cervical transverse vessels down to a limit set arbitrarily 2 cm cranial to the sternal manubrium. Level VI are the anterior compartment nodes including superficially, the anterior jugular nodes (level VIa), and in the deep

previsceral space, pre-tracheal, the pre-laryngeal, and para-tracheal (recurrent laryngeal nerve) nodes (level VIb)(12)

Level VIIa

Level VIIa are the retropharyngeal nodes, extending superiorly from the upper edge of the first cervical vertebrae and inferiorly upto the cranial edge of the body of the hyoid bone. Anteriorly the margin is the pharyngeal constrictor muscles, and posterior margin is the longus capitis and longus colli muscles. Lateral margin is the medial edge of the internal carotid artery. Retropharyngeal node receives efferent lymphatics from the Eustachian tube, the mucosa of the nasopharynx and the soft palate. These nodes are at risk of harboring metastases from cancers of the the oropharynx (mainly the tonsillar fossa and the soft palate)., nasopharynx and the posterior pharyngeal wall.

Other groups of node are VIIb which are the retro styloid nodes, level VIII are the parotid group, IX is the bucco-facial and malar nodes, Xa are retroauricular and Xb are the occipital nodes.(12)

Etiology

Some of the known causes of head and neck cancers are consumption of tobacco and tobacco products, alcohol consumption, exposure to chemicals , human papilloma virus infection, precancerous conditions, dietary factors, and some other factors like sharp tooth and consumption of spicy food(13) .Out of all these, the most important factor is consumption of tobacco and tobacco products. The various forms in which tobacco is smoked are in cigarettes, cigars, bides, hukkas and pipes. The other forms of smokeless tobacco are also having high consumption rates and form a major cause of head and neck malignancies. Some of the popular modes are chewing tobacco, gutkha, betel quid or pan and moist snuff. All these varieties of tobacco products have been found to have carcinogens and have been implicated to be the main causative agent in large number of malignancies including head and neck malignancies.(13)

One other important agent in causation of head and neck malignancies is consumption of alcohol. It has been linked to various vitamin deficiencies and that also may leads to the causation of head and neck malignancies. Consumption of alcohol along with tobacco smoking has got a synergistic effect and will increases the risk of head and neck malignancies by many folds.(13)

Head and neck malignancies may present as multiple primaries in the entire mucosal tracts of head and neck region and this is referred as field cancerization, that is synchronous primaries. (14) The people who smokes and drink are mainly at risk for

synchronous malignancies since the entire mucosal tract of had and neck region was under the exposure of various carcinogens.

Recently there are lot of studies which shows the association of Human papilloma virus 16 (HPV 16) for causation of oral cavity and oropharyngeal cancers in particular. (15,16) HPV are small DNA viruses and are widely distributed in vertebrates. However, in the past few years there is an increased incidence of head and neck cancers even though there is decreased usage of tobacco products. HPV has been seen to be associated with a variety of head and neck cancers, especially the oropharyngeal cancers (base of the tongue, soft palate, tonsils and tonsillar fossa). The reason for the increase in the incidence of HPV associated oral cancers is attributed to the sexual practice of genito-oral sex. Cigarette smoking adds an additive role in the causation of these cancers associated with HPV.

Nasopharyngeal cancers studies has shown that it is associated with Ebstein Barr viruses (EBV). (17,18) The incidence of nasopharyngeal cancers are high in areas which are endemic for the Ebstein Barr Virus. EBV titres are used for determining the tumor burden in these areas at the time of diagnosis and has high sensitivity and specificity in diagnosing nasopharyngeal cancer.(19,20) The post treatment EBV DNA titres shows prognostic role also and high titres are associated with a poorer prognosis . A high EBV DNA titres after treatment is correlated with higher risk of recurrence.(21–23)

There are many precancerous lesions which have been implicated in the causation of head and neck cancers. Oral cancers in particular can be linked to precancerous conditions.(24) Erythroplakia and leucoplakia are the two most common premalignant lesions seen which can transform into invasive carcinoma of the oral cavity.(25) The term Leucoplakia is defined by WHO as white plaques of questionable risk having excluded other known diseases or disorders that carry no increased risk for cancer.(26) The term Erythroplakia is defined as a red patch on the oral mucosa that cannot be accounted for by any specific disease entity; it exists on a continum both in appearance and behaviour with leukoplakia and mixed erythroleukoplakia (a lesion that is both white and red). The other types of lesions which have also been implicated are actinic keratosis, submucosal fibrosis and lichen planus. Erythroplakia has a 20 times more chance for transformation into invasive cancer when compared to leucoplakia.

Other factors which have been found to be associated in the causation of head and neck cancers are some dietary factors which includes spicy food, exposure to certain chemicals and sharp teeth.

Histology of head and neck cancers

The World Health Organisation (WHO) has given a classification for the different histological classification of

head and neck malignancies. (27)

According to this classifications, head and neck cancers are divided into:

1. Malignant epithelial tumours: Squamous cell carcinoma, Basaloid squamous cell carcinoma, Adenosquamous carcinoma, Verrucous carcinoma, Papillary squamous cell carcinoma, Acantholytic squamous cell carcinoma, Spindle cell carcinoma, Lymphoepithelial carcinoma, Giant cell carcinoma

2. Malignant salivary gland-type tumors: Mucoepidermoid carcinoma, Adenoid cystic carcinoma,

3. Neuroendocrine tumours: neuroendocrine type, Combined small cell carcinoma, neuroendocrine type, typical carcinoid, Atypical carcinoid, Small cell carcinoma,

4. Benign epithelial tumours: Papillomatosis , Papilloma

5. Salivary gland-type adenomas: Pleomorphic adenoma, Oncocytic papillary cystadenoma

6. Soft tissue tumours

a. Malignant tumours: Liposarcoma, Leiomyosarcoma, Fibrosarcoma, Malignant fibrous histiocytoma, Rhabdomyosarcoma, Angiosarcoma, Kaposi sarcoma, Malignant peripheral nerve sheath tumour, Synovial sarcoma

b. Borderline tumours / LMP: Inflammatory myofibroblastic tumour

7. Benign tumours: Lipoma, Leiomyoma, Rhabdomyoma, Schwannoma, Neurofibroma, Hemangioma, Lymphangioma, Granular cell tumour, Haematolymphoid tumours

8. Tumours of bone and cartilage: Chondroma, Giant cell tumour, Chondrosarcoma, Osteosarcoma

9. Haematolymphoid tumours: Diffuse large B-cell lymphoma, Extranodal NK/T cell lymphoma, Follicular dendritic cell sarcoma/tumour, Hodgkin lymphoma, Extramedullary plasmacytoma

10. Mucosal malignant melanoma

11. Secondary tumours

Amongst all these, the most common malignancies arise from the epithelium. Squamous cell carcinomas and its variants (lymphoepithelioma, verrucous carcinoma, spindle cell carcinoma, and undifferentiated carcinoma) are the most common epithelial malignancies seen in head and neck region.(13) (Other tumors which are also commonly seen are salivary gland tumors, sarcomas and lymphoma). However, the incidence of these tumors is very less as compared to squamous cell carcinomas.

Nasopharyngeal carcinomas have been classified by the WHO as the following three subtypes:(27)

1. Nonkeratinizing Carcinoma

2. Keratinizing Squamous cell Carcinoma

3. Basaloid Squamous cell Carcinoma

Of all these subtypes histology, non-keratinizing carcinomas of nasopharynx have been found to have the best prognosis.

Natural History(13)

Most common cancer of the head and neck region are malignant epithelial tumors. Squamous cell carcinoma is the most common histology which is seen in this region. These tumors usually start as surface lesions, but sometimes originate below the surface of the mucosa. Very early surface lesions may show only a superficial erythema and a slightly elevated mucosa.

The local spread is governed by the anatomical location of tumour, and thus varies by each site. Muscular invasion is common, and tumor spread along muscle or fascial planes. Tumor may abut the periosteum or perichondrium, but bone or cartilage invasion is usually a late event as bone and cartilage usually act as a barrier to spread. Tumors that encounter these structures are often diverted and spreads along a path of least resistance.

Tumor extension into the parapharyngeal space fascilitate superior or inferior spread from the skull base to the low neck.

Perineural invasion (PNI) is seen in Squamous cell carcinomas as well as salivary gland tumors, especially significant in adenoid cystic carcinomas. The presence of PNI predicts a poorer rate of local and distant control.(28) Tumors can track along a nerve to the skull base and central nervous system. Patients with PNI may develop neurologic symptoms due to entrapment of the nerve or secondary to nerve invasion.

Vascular space invasion is also attributed with an increased risk for regional and distant metastases.

Lymphatic spread

The risk of lymph nodal metastasis can be predicted by the size of the primary lesion, differentiation of the tumor, presence of vascular space invasion, perineural invasion and density of capillary lymphatics.(28) Recurrent cancers have an increased risk of lymph nodal involvement.

Lymphatic spread is also influenced by the the histology of the tumor. Sarcomas and low-grade minor salivary gland tumors have a lower risk of lymph node metastases than squamous cell carcinomas.

The probability of spread to a nodal region is is determined by the primary site and T stage of the tumor. Well-lateralized cancers spread more to ipsilateral neck nodes. Lesions near the midline like tongue base and nasopharyngeal lesions, may spread to both sides of the neck, although the risk is higher to the side occupied by the bulk of the lesion. If there is a positive ipsilateral neck nodes then there is high risk for contralateral disease, especially if the nodes are large or multiple.

The probability of retropharyngeal nodal spread is related to the presence of clinically involved lymph nodes and primary site, and is particularly high for nasopharyngeal carcinomas. (13)

Distant Spread:

The risk of distant metastasis is directly related to the nodal stage of the disease. There is less than 10% chance for distant metastases for node negative disease and rises to approximately 30% for node positive disease. It presence of nodes below the level of the thyroid notch has higher chance of distant metastases. The lung accounts for most common site for distant metastases in head and neck cancers.(13)

Evaluation and Diagnosis

All patient presenting with diagnosis of head and neck malignancy should undergo a thorough general clinical evaluation, including a thorough head and neck examination endoscopy. The site and extent of the primary tumor with its dimensions (T staging) and all clinically positive lymph nodes should be documented. Physical examination is not complete without examination of cranial nerve, percussion and auscultation of the chest, palpation of the abdomen for possible liver involvement, and percussion of the spine and bones for possible bone metastasis.(29)

Head and neck cancer patient is evaluated by multidisciplinary team and hence patient is also needs dental evaluation, nutritional assessment, swallowing and speech therapy, counseling, audiology, addiction services, etc. (30) These work up will help patient in maintaining a good quality of life.

Visualisation of tumour with a nasopharyngolaryngoscopy (NPLscopy) should be performed in all cases of head and neck malignancies. This helps in better defining the extent of the tumor, aids by direct visualisation of the mucosa and also assessment of airway. Direct visual assessment is better than any imaging in lesion confined to mucosal surface. Synchronous second primaries can also be diagnosed with the scopy. Lesions amenable to transoral biopsy may be done with the same during the scopy itself. If scopy fails to properly visualise the tumor or biopsy the tumor, a direct laryngoscopy under

anaesthesia should be performed to determine the extent of the tumor and to obtain a tissue diagnosis. (29,31)

Those patients who present with a metastatic node from a primary of unknown site can undergo fine-needle aspiration (FNA) of the enlarged node to obtain a tissue diagnosis. FNA Biopsy of node is only done in cases were the primary lesion can only be biopsied under general anaesthesia and patient is unfit for anaesthesia. Incisional biopsies are avoided in head and neck cancer to prevent tumor spread along the biopsy tracks. Excisional biopsy is performed usually in cases suspecting lymphoma or if the FNA results are inconclusive. (31)

A contrast enhanced computed tomography (CECT) and/or magnetic resonance imaging (MRI) is performed to further define the extent of locoregional disease. The widely used imaging is contrast enhanced CT which clearly defines the primary and the metastatic nodes. The advantage of CT scan is that it is better tolerated, cost is less and that it is better in assessing cortical bone involvement.(31) MRI is reserved mostly in cases of very early disease and it defines the soft tissue extent of the disease. MRI scan is more useful in staging oral, oropharyngeal and nasopharyngeal tumours as they give a better delineation of the soft tissues and the extent of the tumor into adjacent structures, muscles, fascia, vessels and nerves. The other added advantage of MR is better characterization of laryngeal cartilage invasion, tumour involvement of the skull base, orbit, cervical spine and neurovascular bundle structures. Sensitivity of MRI was

compored with CT scan and it was seen that sensitivity of MRI was higher in conditions like skull base involvement (60% vs. 40%), intracranial involvement (57% vs. 36%), retropharyngeal node (58% vs. 21%), and tumor infiltration of prevertebral muscles (51% vs. 22%) compared to CT. MR studies also changed the T-staging in 27% of patients, with 22% being upstaged and 4% being downstaged.(32)

MRI scan is the imaging of choice in Parotid gland malignancies where the incidence of peri neural invasion/spread is very high. MRI scan with contrast help in visualising the spread of the tumor along the nerves. As a general rule MRI is imaging of choice in suprahyoid neck tumours (nasopharynx, oropharynx , base of tongue, anterior tongue and hard palate) and CT with contrast for infrahyoid lesion. MRI scans(both non contrast and post gadolinium) from base of skull to root of neck is advised.(33)

USG of neck for assessment of node is done in cases where the primary cannot be biopsied and we use ultrasound guided nodal FNA as a method of histological diagnosis. USG neck is not used as a staging imaging of a neck in HNSCC.

A chest radiograph should be obtained in all head and neck cancer cases to rule out lung metastasis and also to rule out a synchronous lung cancer. CT scan of the thorax is indicated if there is any suspicious lesions on the chest radiograph and it helps in proper characterization of the lung parenchyma. (31) Bone scan is done as a metastatic work up

in patients with high alkaline phosphatase or bony tenderness. This is offered to patients who are not willing for whole body PET CT.

Role of PET CT

^{18}F-fluorodeoxy-D-glucose positron emission tomography- computed tomography (^{18}F-FDG PET-CT) has gained lot of importance as a diagnostic tool for evaluation of head and neck squamous cell carcinomas (HNSCCs). Its application ranges from pre-treatment staging to radiotherapy planning, treatment response assessment and post-therapy on follow-up.(34) The ^{18}F-FDG PET-CT plays an important role in patients with cervical lymph node metastasis from a carcinoma of unknown origin and it is a useful diagnostic tool to detect the primary tumour, with a detection rate of 25-38.5%. (35–37) It is well documented in many studies that there is a superiority of PET-CT over anatomical imaging in detecting lymph node involvement.(34,38) Synchronous primaries are can be diagnosed with the help of PET CT scan. It is important to screen for distant metastases in patients with advanced disease, especially in nasopharyngeal carcinomas and with nodal involvement. (34) Major limitation of PET CT is that it shows false positive results in inflammatory or infective condition.(34)

Treatment of head and neck cancer is through a multidisciplinary approach and before initiation of treatment, the patient should be evaluated by head and neck surgeons, radiation oncologists, medical oncologists, diagnostic radiologists, plastic surgeons,

pathologists, dentists, speech and swallowing therapists, and social workers. The treatment options with pros and cons are discussed and recommendations are presented to the patient who makes the final decision.

Prognostic factors

Progostic factors varies in head and neck cancers according to the subsites. In general the T stage of the disease and the presence or absence of nodal metastasis which are the 2 most important prognostic factors related to survival. Histology of the tumor and occasionally the sex predilection of tumor have also been seen as important prognosic indicators.

Nasopharyngeal Carcinoma

The important prognostic factors are:

Extent of local invasion(T stage)

Regional lymphatic spread(N stage), and

Distant metastasis (M)

Advanced T stage is associated with poor local control and decreased overall survival. In advanced N stage there is a increased risk of distant metastasis and worse survival.

Presence of distant metastasis (M1) at the time of presentation is an indicator of poor prognosis. The presence of lower nodal level, bone erosion or a cranial nerve palsy are all poor prognostic factors.

Histology wise - Undifferentiated carcinomas and Nonkeratinizing are more radiosensitive and shows better prognosis after treatment than keratinizing squamous cell carcinoma

Oral cavity and Oropharynx(28)

In oral cavity carcinoma the most important prognostic factor is the presence of cervical nodal metastases. When there is positive cervical metastases the 5-year survival is reduced by nearly 50% as compared to those without cervical metastases. When there is multiple levels of nodal involvement or extra capsular extension of the tumor the prognosis is much worse.

Histopathologic factors in the primary lesion that have shown prognostic significance are-

 Thickness and depth of invasion in the primary lesion – more thickness and depth of invasion is shown to have a higher risk of regional metastases.

 Perineural invasion – is associated with higher chance of cervical lymph node metastases and extracapsular extension all of which then leads to decreased survival.

 Microvascular invasion has also been correlated significantly with higher cervical lymph node metastases

Hypopharynx

In hypopharyngeal tumors, age and sex have been associated as a progostic factors for survival. Age, particularly more than 70 years, has been seen as an unfavorable predictor of outcome. Women have been found to have relatively better outcomes compared to men. Tumor location has also shown an important impact on outcome. Cancers of the pyriform sinus generally respond better than cancers arising in the postcricoid or posterior pharyngeal wall regions.

Larynx

The major determinants of prognosis in laryngeal cancers are the extent of the primary lesion and the presence of nodal disease. The likelihood of local control is determined primarily by T stage. The T stage and N stage are the major determinants of survival. The patients with positive nodes in the low neck below the level of the thyroid notch tend to

have a lower survival rate than those with nodal disease confined to the upper neck. Women tend to have a better prognosis compared to men.

Management of Locally advanced head and neck cancers

The treatment options for a patient with squamous cell carcinoma of the head and neck depends on the site and stage of the disease and on the overall performance status of the patient. In most cases of stage I or II cancers, the single modality treatment in the form of surgery or radiotherapy is the initial treatment offered. (39)

Before 1980, the initial treatment of patients with locally advanced stage III or IV (M0) carcinoma of the head and neck was surgery and/or radiation therapy. The choice depended on the site of the disease, the resectability of the cancers and the performance status patient. The results obtained with "traditional" therapy in this group, especially those with stage IV disease or unresectable cancers were poor. Hence systemic chemotherapy was tried in the mid 1970s as part of combined modality treatment to improve the treatment efficacy. Later, chemotherapy was introduced in patients with earlier disease stages and with resectable disease for organ preservation and better cure rates. The use of systemic chemotherapy alone is usually with palliative intent to patients with advanced stage IV disease, metastatic cancers, or recurrent disease beyond local salvage treatment.(40)

The treatment of locally advanced head and neck cancer patients has evolved after the introduction of combined modality treatment. Initially a single agent chemotherapy such as methotrexate or cisplatin was given before local definitive treatment. Then the

combination of Cisplatin and Bleomycin was introduced, which was administered as a single course before local therapy. Later two or three cycles of cisplatin plus bleomycin were given as part of combined modality treatment. Methotrexate alone and/or vinca alkaloids (vincristine or vinblastine) were then added in combination with cisplatin plus bleomycin. In 1980, the combination of cisplatin and continuous infusion of 5-fluorouracil (5FU) over 96-120 hours was introduced, which has become a widely used combination chemotherapy in patients with HNSCC. In 1980s the concept of concurrent chemotherapy with radiation therapy was revisited and cisplatin was given concurrently with radiotherapy as the primary treatment for inoperable and/or unresectable head and neck cancers.(39,40)

In the last quarter of a century, clinical trials for squamous cell carcinoma of the head and neck have shown improvement in treatment outcomes, including local control, lower incidence of systemic recurrences, better disease-free survival and, improved overall survival. The quality of life has improved for head and neck patients, especially when the larynx and voice function is preserved in cancers of the larynx or hypopharynx. (39)

Stage I or II squamous cell carcinoma of the head and neck, the treatment of choice is single-modality treatment with either surgery or radiation achieves and it has excellent outcomes. Metastases to nodes are considered the single most important prognostic factor in head and neck cancer. (41)The “standard” treatment for patients with locally advanced tumor stages (stage III and IV) has been surgery followed by radiation therapy. The

radiation was given as an adjuvant to reduce the incidence of local failure, but this approach has not been investigated in prospective, randomized studies to show improvement in overall survival. Despite adequate surgical resection with negative margins and the addition of adjuvant radiation therapy, the 5-year survival rate for these patients is usually less than 30%. Induction chemotherapy has not gained scientific support, since any reduction of the tumor bulk would not change tumor resection margins. Induction chemotherapy has been investigated in patients with resectable cancers where planned surgery was performed on all patients, and the results were negative. This resulted in a sense that induction chemotherapy is ineffective in patients with locally advanced disease regardless of their resectability or operability.

PRINCIPLES OF SURGERY: (30)

Surgery is the mainstay of management of early head and neck cancers. It also forms the part in the multimodality management of locally advanced head and neck malignancies. The aim of surgical resection is the total removal of the lesion with an adequate margin so as to prevent local recurrences. The surgeon attempt an en block removal of the tumor whenever possible and in-continuity neck dissection is carried on when there is direct extension of the tumor into the neck. As the thickness/depth of the lesion increases, there is a high risk of nodal metastasis and elective nodal dissection is carried out. In cases of suspected gross peri neural invasion, the nerve is dissected both proximally and distally as possible to obtain disease clearance. Margin status are of uttermost importance in an oncologic surgery. A clear margin is defined as a distance from the invasive tumor which is 5 mm or more from the resected margin. If the margin is less than 5 mm from the resection margin it is termed as close margin and a positive margin is defined as presence of in situ carcinoma or invasive carcinoma at the resection margin. Margin status is considered with great significance in planning treatment for a patient with head and neck malignancies. Positive margins following surgery form a major risk factor and imply the addition of radiation therapy with chemotherapy for the proper sterilization of the area and to make the area tumor free.Whereas for close margin radiation therapy without chemotherapy is the treatment of choice. The extent of mandibular resection(a partial or segmental resection) depends on the degree of

involvement of the mandible and the proximity to the primary tumor, to get adequate tumor free margins.

Surgery in laryngeal tumors may either be total laryngectomy or conservative surgeries like trans oral resection, hemi laryngectomy or supraglottic laryngectomy. These subsites of tumours can also be taken up for the organ preservation protocol in which these can be treated with radiation therapy and concurrent chemotherapy with surgery reserved as a salvage. The organ preservation protocols in this sub group of head and neck tumors has shown similar overall survival benefits with improved quality of life and larynx preservation. The role of surgery is limited only for a biopsy proof of malignancy in nasopharyngeal canceersn and occasionally as a salvage option in cases of recurrence. Radical radiation therapy with or without the use of chemotherapy forms the mainstay of management of nasopharyngeal carcinomas.

All tumours are not resectable and there is criteria which aids surgeon to help to define the resectibility of the tumors.

Criteria of Unresectability : (30)

1. Gross extension of tumor into the base of skull.

2. Involvement of the pterygoid muscles especially when associated with severe trismus and pterygopalatine fossa involvement with cranial neuropathy .

3. Direct extension of the tumor into superior nasopharynx or lateral nasopharyngeal walls and deep extension into Eustachian tubes.

4. Invasion or encasement of common or internal carotid artery. Encasement of artery is assessed radiologically and is defined as tumor encasing the carotid artery by 270 degrees or greater.

5. Direct extension to mediastinal structures, prevertebral fascia or cervical vertebrae

6. Presence of subdermal metastasis

Based on the anatomic extent of the tumor which is assessed both clinically and radiologically, surgery is planned which best suit the patient and give an adequate resection margin.

Chemotherapy in head and neck cancers

The different settings were we add chemotherapy in the management of head and neck cancer are neoadjuvant, concurrent, adjuvant or definitive (palliative). Meta-analysis of chemotherapy in head and neck cancer for 4 subsites(oral cavity, oropharynx, larynx and hypopharynx) showed survival benefit in all subsite with addition of chemotherapy

concurrently to radiotherapy. The addition of chemotherapy concurrently to radiotherapy results in a reduction of the risk of death of 13%, which was consistent in all 4 sites. The 5-year absolute benefits associated with concomitant chemotherapy added to radiotherapy was around 8% for oral cavity and oropharynx cancers, and around 5% for larynx and hypopharyngeal cancers.(42)

In meta-analysis of chemotherapy in Nasopharynx Carcinoma analyzed the benefit of chemotherapy in concurrent and adjuvant setting. The meta-analysis of data of individual nasopharyngeal carcinoma patients showed significant and clinically relevant improvements in overall survival and progression-free survival, reductions in locoregional failure, distant failure, and nasopharyngeal carcinoma-related mortality. Even though this study was very large, it did not completely answer the question whether there is a benefit of the adjuvant chemotherapy in the concomitant setting.(43)

There are some studies showing benefit of addition of neoadjuvant chemotherapy in locally advanced head and neck cancers showed benefits in a subset of patient but the study compared two induction chemotherapy regimen.(44) A multicentre PARADIGM study compared the use of docetaxel, cisplatin, and fluorouracil (TPF) induction chemotherapy followed by concurrent chemoradiotherapy with cisplatin-based concurrent chemoradiotherapy alone in patients with locally advanced head and neck

cancer.The results of this study showed no difference in survival between the 2 groups.(45)

Radiotherapy

During the second half of the twentieth century, key technological innovations in diagnostic imaging, computer science and radiotherapy technology greatly changed the routine practice of radiotherapy, leading to substantial improvements in treatment delivery and outcome.(46) During the 1970s and 1980s, the treatment planning was based on the use of planar diagnostic x rays. The “simulator,” a specialized imaging unit for radiotherapy employing an x-ray imaging system and having the same geometry and degrees of freedom as a rotational 60Co unit or LINAC, was used as a tool for planning the treatment delivery. The planar x rays showed only bony anatomy, but the location of soft tissues including tumors was difficult to ascertain and was deduced from correlating with bony landmarks, air cavities and sometimes contrast enhanced images. With the advent of use of x-ray computed tomography (CT) in the 1980s and magnetic resonance imaging (MRI) in the 1990s enabled much more accurate three-dimensional (3D) characterization of the location and extent of the disease. With these imaging improvements when applied with advances in treatment-planning techniques it became practical to design treatment fields that conformed more closely to the regions of disease. Conventional radiotherapy is administered using multiple number of coplanar beams and

the intensity will be relatively uniform or smoothly varying across the field. They also employed low-melting-point heavy cast-metal alloys which allowed the treatment fields to be more easily custom shaped than with lead blocks. With the advent of Multileaf collimators (MLCs), the heavy metal blocks were replaced and this made it easier to use multiple complex-shaped fields even in the same treatment session.(47)

Linacs were equipped with electronic portal-imaging systems which helped in verifing patient position and thus improving conformity between the planned and delivered doses. Digitally reconstructed radiographs (DRRs) were build from the CT scan data set by digitally simulating the passage of x rays through the patient's CT representation in the same geometry as the treatment. (48) The Digitally reconstructed radiographs were comparable with x-ray images acquired at the time of treatment to verify the treatment position. All these technical innovations made sure more accurate treatment were delivered to tumors, potentially allowed higher absorbed doses to tumor and thus lead to increased local tumor control and reduced absorbed doses to the normal tissues around. The techniques of 3D planning and special delivery systems to shape the field are made use to reduce normal tissue damage close to the target volume, the technique is usually referred to as conformal radiotherapy (CRT) or three-dimensional conformal therapy (3D-CRT). (47)

The concept of intensity-modulated radiation therapy (IMRT) arose because radiotherapy treatment-planning optimization algorithms predicted that the optimal radiation pattern from any single direction was typically non-uniform.(49) A set of intensity modulated beams from different directions could be designed such that it can result in dose

homogeneity inside the tumor similar to that from conventional radiotherapy but with better conformality. It holds good more in cases of concave or other complex-shaped target volumes and there will be better sparing nearby normal tissues (50). IMRT also makes it easier to produce non-uniform absorbed-dose distributions if required for treatment of a volume within another defined volume (also known as simultaneous integrated boost techniques) . IMRT tries to achieve the best possible optimal absorbed-dose distributions by varying the beam intensity (fluence) within each incident beam, by subdividing the beam into a number of smaller segments and modulating each beam to achieve its selected fluence contribution. Modulation of the beam is mostly achieved by the use of MLCs or of binary collimators.(49–51)

Calculation of the fluence required from each beam segment is made possible with the use of high-performance computers which uses algorithms taking an iterative approach to dose calculation and referred to as "inverse treatment planning"(47). In Inverse treatment planning system the planner starts by describing a goal, which is a series of descriptors characterizing the desired absorbed-dose distribution within the tumor, with additional descriptors designed to spare normal tissues. The process of inverse-planning works iteratively to determine beam shapes and fluence patterns to attain an acceptable or optimal absorbed-dose distribution. The descriptors include the dose–volume specifications for both tumor and organs at risk (OAR), minimum absorbed dose to the target volume and the maximum absorbed dose to an organ at risk. (47)

There are several ways for delivering IMRT, which are Segmental MLC (step and shoot), Dynamic MLC (sliding window), Intensity-modulated arc therapy (IMAT) , Serial tomotherapy , Helical tomotherapy and Robotic radiotherapy.(52)(53)(54)(55) In head and neck malignancies, IMRT is the technique that is routinely opted. Tumors close to the base of the skull, such as nasopharyngeal and sinonasal cancers, showed higher rate of local control and a lower incidence of complications with IMRT in comparison with standard two-dimensional (2D) techniques in retrospective comparisons.(56) There was a substantially lower rate of late radiation-induced toxicity, such as xerostomia, which has been documented following the use of IMRT for pharyngolaryngeal squamous cell carcinomas (SCCs)(57). Some retrospective studies has reported that, despite the high conformality in dose distribution, geographical miss is rather an uncommon event in IMRT for pharyngolaryngeal tumors, provided that an adequate selection of target volumes is made(58,59).

Therapeutic Index or Therapeutic Ratio(60) is a concept which compares the tumor control probability (TCP) with the normal tissue complication probability (NTCP), this is an important and integral part of any radiation therapy plan.

Therapeutic Ratio (Therapeutic Index): “The ratio of tumor response to the normal tissue damage is termed as therapeutic ratio/index”. The tumor response is quantified by a parameter known as Tumor Control Probability (TCP) while the normal tissue

complications are measured by another parameter called as Normal Tissue Complication Probability (NTCP).

It is never possible to avoid the whole normal tissue during a course of radiation therapy.(61) This is because the normal tissue always lies in surrounding areas to the tumor cells and radiation dose given to the tumor cells for eradication of the tumor will always cause some damage to the normal tissues in close proximity.

The newer techniques allows radiation therapy plan to take into consideration the normal tissue complications with respect to the tumor dose. It tends to give us a higher the therapeutic index, i.e. high tumor control probability with less normal tissue complication probability.

The major hurdle in head and neck malignancies radiation therapy is that there are several critical organs at risk which are found to be in very close proximity to the target volume. The tissue inhomogeneity is also a major factor in the head and neck region which can affect the dose and delivery of radiation. The tumor wraps around the normal tissues and it it becomes nearly impossible by conventional radiation therapy to deliver high doses to the tumor tissue without giving unacceptable doses to the adjacent normal structures. Sometimes because critical organs are in close range sometimes we may end up in compromising doses to the tumour. Conformal techniques like IMRT, it is practically possible to decrease the normal tissue dose below the acceptable level while delivering

adequate dose to the tumor. The documented advantages of IMRT in head and neck cancers is parotid sparing and prevention of late dysphagia with dose escalation to the tumor.(3,62) Intensity Modulated Radiation Therapy (IMRT), thus, is presently the radiation therapy technique which is considered as the standard of care in managing head and neck malignancies.(63)

Radical Radiotherapy

Radical radiotherapy is considered as treatment of choice in early stage cancers in sites like nasopharynx, oropharynx, hypopharynx and larynx.(33,64) There is good local control and better quality of life for patients who are treated with RT alone.

Radiotherapy with concurrent chemotherapy

The loco-regional control and overall survival are improved by concurrent chemoirradiation in locally advanced nasopharyngeal cancers.(43) In oropharynx the locally advanced tumour is treated with concurrent chemoradiotherapy followed by neck dissection, if residual node is present.(42) In patients with laryngeal and hypopharyngeal tumours we can consider organ preservation protocol. Patients with preserved laryngeal function, no thyroid cartilage infiltration, not extending more than 1 cm into the base of tongue and has a good creatinine clearance can be offered concurrent chemoirradiation.(45,65)

Radiotherapy with concurrent Biological therapy

Cetuximab is a humanized monoclonal mouse antibody that gets attached to the extracellular ligand binding domain of the EGFR. It prevent the activation and dimerization of the receptor and this blockade disrupts EGFR signal transduction. This inhibits the tumor growth and metastasis Majority of HNSCC expresses high level of EGFR. This activation of EGFR results in phosphorylation of its intracytoplasmic tyrosine kinase domain, leads the cell to a cascade of signal transduction and result in synthesis of DNA, proliferation of cells, anti-apoptosis and transcription of various growth factors. Cetuximab causes blockade of the EGFR pathway and forms an effective anti-neoplastic strategy.(66)

In locally advanced cancers of oropharynx, hypopharynx and larynx can be offered concurrent biological agent with Cetuximab if patient is having poor creatinine clearance. Studies have shown concurrent cetuximab with radiotherapy was better than radiotherapy alone in locally advanced oropharynx, hypopharynx and larynx.(67)

Radiotherapy in post operative HNSCC

Adjuvant radiotherapy in head and neck cancer is indicated in advanced T stage, advanced nodal disease (N2–N3), close margin , bone, perineural or lymphovascular invasion ,high likelihood of occult disease in an undissected neck. Concurrent

chemotherapy is added to adjuvant RT when the post op HPE shows extracapsular extension or positive margins.(68–70)

Target Volume Delineation

The target volumes of the radiation therapy field were defined by International Commission on Radiation Unit (ICRU) reports. ICRU in reports 50 and 62 gave the concept of Gross Tumor Volume (GTV), Clinical Target Volume (CTV) and Planning Target Volume (PTV). ICRU 50 (71) defined 5 target volumes which were the GTV, CTV, PTV, Treated Volume (TV) and the Irradiated Volume (IrV). Normal tissue was considered as Organs at Risk (OAR). ICRU report 62 (72)was a supplementary article to the earlier published report 50 and introduced the concept of Internal target motion(ITV) for the CTV with respect to anatomic variations with time (eg: movement with respiration, bladder filling, rectal emptying, etc.). It defined a new concept which was known as the Internal Margin (IM) for Internal Target Motion Volume (ITV).

According to ICRU report 50 (71) Gross Tumor Volume (GTV): is the gross palpable or visible/demonstrable extent and location of malignant growth. It is determined by history given by the patient, clinical examination and by the radiological extent of the tumor seen on imaging. In post-operative setting where the complete tumour is removed, there is no GTV which can be identified.

The GTV can be categorized into a primary tumor (primary tumor G TV or GTV-T), metastatic regional node(s) (nodal GTV or GTV-N), or distant metastasis (metastatic GTV, or GTV-M). Ideally different GTVs are defined for the primary tumor and the regional node(s). In clinical practice we come across situations were the metastatic node cannot be distinguished from the primary tumor, e.g., a nasopharyngeal undifferentiated carcinoma infiltrating into the retropharyngeal space, including possible infiltrated nodes. In these kind of situations, a single GTV encompassing both the primary tumor and the node(s) may be delineated. (73)

The GTV should be delineated and reported in a complete and accurate way. It is required for staging, e.g., according to the TNM system (prognostic significance). We must ensure that adequate absorbed dose must be delivered to the whole GTV to obtain a good local tumor control. The evaluation of the regression of the GTV might be needed for redefining the CTV and the PTV during the course of treatment. And changes of the GTV during treatment might be predictive of treatment outcome.(73)

ICRU 83 recommends to report which modality of imaging is used for delineating GTV. Until recently, anatomic imaging with CT or magnetic resonance (MR) scans was the most commonly used technique to define the extent of the GTV. The use of functional imaging with positron emission tomography (PET) using various tracers such as 18F-fluoro-2-deoxy-D-glucosea (18F-FDG) , 18F-fluoro-ethyl-tyrosinea (18F-FET) , 18F-30-deoxy-30-fluoro-thymidine (18F-FLT) ,18F-fluoro-methyl-D-tyrosine (18F-FMT) 11C-

methioninea (11C-MET) 11C-acetate, 18F-fluoro-misonidazole (18F-FMISO) give information regarding glucose metabolism, protein synthesis, cell proliferation and hypoxia. Functional MRI can also reveal some biological factors like metabolic status, hypoxia, cellular proliferation that are likely to impact on the treatment outcome.(73) Some studies have recommended the use of functional information to define sub-GTVs that are to receive some additional absorbed dose.(74)

Clinical target Volume (CTV): It is the tissue target volume that contains the GTV and/or subclinical microscopic malignant disease, which has a certain probability of occurrence considered relevant for therapy. In the absence of any general consensus on what probability is considered relevant for therapy, a likelihood of occult disease higher than from 5 % to 10 % is assumed to require treatment. The ambiguities in GTV delineation generally propagate to CTV delineation and therefore this volume has to be treated adequately in order to achieve the aim of therapy: cure or palliation. The CTV is an anatomical-clinical concept and therefore it depends upon the clinical judgment were we consider the type of malignancy, the consequence of failure, and the expected feasibility of salvage treatment.(73)

In head and neck squamous cell carcinoma, the probability of pathologic lymph-node involvement has been well studied, and the distribution follows a predictable pattern allowing clinicians to tailor the CTV (75–78) . At the primary tumor site, the selection of the CTV is guided by the general principle that the microscopic spread of tumor cells

follows anatomical compartments (para-laryngeal, para-pharyngeal, pre-epiglottic spaces in the head-and-neck area) bounded by anatomical barriers (bone cortex, muscular fascia, ligaments). (73,76)

Planning Target Volume (PTV): It is a geometrical concept which was brought for planning and evaluation. PTV helps to select appropriate beam sizes and beam arrangements, taking into consideration the net effect of all the possible geometrical variations such as organ motion and setup errors in order to ensure that the prescribed dose is actually absorbed in the CTV. Its size and shape is given by CTV but it also consider the treatment technique used, to compensate for the effects of organ and patient movement, and inaccuracies in beam and patient setup.(73)

Internal Margin (IM): This is a margin provided to the CTV to account for the anatomical changes with respect to physiological functions (eg. movements with respiration, bladder filling and rectal emptying)

Setup margin (SM): This was another margin which was given to the CTV to account for the various setup errors which may have occurred from the time of planning the patient till the delivery of radiation therapy.

Planning Target Volume (PTV): PTV which was defined as per ICRU report 62 comprises of

PTV = CTV + IM + SM

Aa absorbed dose variation of +7% and -5% within the PTV was considered to be acceptable. (72)

Treated Volume: This is the volume enclosed by an isodose surface (e.g. 95% isodose), selected and specified by radiation oncology team as being appropriate to achieve the purpose of treatment. In an ideal condition Treated Volume would be identical to PTV.(73)

Organs at Risk (OAR):(73) These comprise the normal tissues which can cause significant morbidity and are within the radiation therapy field and thus may significantly influence treatment planning and/or prescribed dose.

Planning Organ at Risk Volume (PRV):(73) This was defined as the planning organ at risk volume which was analogous to the PTV for tumor and accounted for the organ motion and setup errors for OAR during treatment.

The organs at risk can be classified accordingly either serial organs, parallel organs or mixed serial and parallel organs. The concept of serial and parallel organs evolved with the concept Functional Subunits (FSU) in the organs and its arrangement(79). Functional subunit is the structural arrangement of tissue in an organ, which has a relationship between organ functioning and failure. In serial organs, the FSU's are arranged serially like the links of a chain and the disruption of one of these FSU's leads

to dysfunction of organ below that level(eg. Spinal cord, nerves, gastrointestinal organs etc). However, in parallel organs, the functional units are stacked in parallel and the disruption of a single or a small group of FSU does not lead to organ dysfunction. But when a considerable number of FSU's are damaged, that leads to organ dysfunction. (73)

The response to radiation therapy in different types of organs is different. In serial organs, as discussed the FSU's are arranged in a series, there is a binary all or none response to radiation therapy. Doses below the threshold level of that organ do not cause any significant effect, but once that threshold dose is reached, the link is broken and the entire organ becomes dysfunctional below that level. On the other hand, the response of radiation therapy is entirely different in parallel organs. Small areas within the organs can receive very high doses of radiation and still the organ may be functioning well. Dysfunction of few FSU's does not lead to complete organ dysfunction as other FSU's can compensate. Organ dysfunction occurs only when a specific number of FSU's are inactivated by the action of radiation therapy following which organ dysfunction becomes clinically quantified. This is a graded response in which as the radiation therapy mean dose is increased or the volume that receives an absorbed dose is in excess of some defined value and this predicts the loss of function.(80,81)

Head and neck region encomposes of number of organs at risk which may can be categorized under serial or a parallel organs. The close proximity of these OARs to the

treatment volumes warrants the use of modern techniques in head and neck cancers and thus it is important to know about the spatial organization of these organs.

The serial organs found in the head and neck region are:

1. Brainstem

2. Optic Nerves and Optic Chiasm

3. Spinal cord etc.

The important parallel organs of the head and neck region is:

1. Parotid glands

The knowledge of tolerance of normal tissue tissue is very important and the dose constraints to organs at risk was first given by Emami et al(81) In the paper published in 1991, they collected data from literature and came up with dose constraints to the various organs at risk based on the amount of tissue irradiated and the time taken to develop radiation induced complications. They formulated the probability of developing radiation induced toxicity in an organ at 5 years in 5% and 50% of the population based on the volume of organ/normal tissue which was irradiated. The knowledge about the normal

tissue tolerance is always evolving and the current guideline which defined the dose volume relationship of toxicity to various organs at risk was published in 2010. The QUANTEC(82)study (Quantitative Analysis of Normal Tissue Effects in the Clinic). This paper has tried to give a quantitative measure of radiation toxicity to various organs at risk on the dose volume relationship. In this 3 dimensional era it mentioned the probability of developing a radiation induced toxicity depending on the dose-volume relationships of normal tissue irradiated or on the maximum dose received by the organ at risk.

IMRT Planning and execution:

1. Pre radiotherapy work up

- Patient history
- Diagnosis
- 3D Imaging and Staging
- Multi disciplinary tumour board decision

2. Radiotherapy preparation –

- Positioning and Immobilisation of the patient
- Imaging in the position planned with the immobilisation device Target volume delineation (GTV,CTV,PTV,PRV)

3. Planning

- Defining dose constraints to the target volumes and the organs at risk
- Inverse Planning of IMRT

4.Treatment

- Data transfer to treatment machine
- Dosimetry prior to starting treatment
- Setup verification followed by treatment execution

Patient is decided for radiotherapy after clinical workup and decision in multidisciplinary tumour board. The patient positioning and immobilization forms and important step in IMRT planning. Proper immobilization devices are used which help in reproducing the same position over the entire course of the treatment and care should be taken to see that patient is comfortable in the immobilized position. The immobilization devices which is used in head and neck region is ray casts. The main aim of an immobilization device is to help reproduce the same position throughout the course of the treatment so that the chances of missing the target is minimal. After the immobilization device has been custom made for the patient, the patient undergoes a planning CT scan or a planning PET CT scan with the immobilization device. The CT scan is then used to contour the

structures which are the target and also the organs at risk, based on the anatomical details on the CT scan. Proper discussion with the Radiologist, head and neck surgeon(especially in post op patients) and ENT surgeons helps to ensure no areas are being missed and all information regarding the disease condition has been obtained. Initially the Gross tumor volume (GTV) is contoured. Then depending on the pattern of spread of the disease and clinical judgement of the clinician, the clinical target volume (CTV) is contoured which comprises of the GTV, microscopical disease region and all potential areas of risk. The Planning target volume (PTV), is then created based on institutional protocols. It consider the site of cancer and the amount of variation which is expected with the immobilization device. The organs at risk (OAR) are also contoured and a PRV is given to it.

Dose is prescribed to target volumes and we prescribe the tumoricidal dose to PTV . Dose to OAR's needs to be minimised and proper dose constraints are given based on the guidelines which have been provided.

The QUANTEC (83) in 2010 published dose constraint guidelines for the organs at risk in case of conformal radiotherapy planning and provides us with a benchmark guide to give the dose constraints to the organs at risk.

Once all the dose constraints to the defined volumes is provided, the IMRT plan optimization can be started. Beam selection and selection of the beam energy is the initial step. Equiangular 7 or 9 beams is selected. Opposing beams are avoided and for that only odd number of beams are selected. Planning is done by the "Inverse Planning" technique.

Adequate weightage are given to the target organs and organs at risk, the planner also takes into consideration of hot spots and target volume coverage. The plan is computed in an iterative process by generating fluence maps for the various selected beam angles and Dose Volume Histogram (DVH) graphs are produced. Once the desired DVH is attained, the iterative process is stopped and leaf motion calculation is done which defines the movement and positioning of the multileaf collimators (MLC). Now the plan is evaluated by the Medical Physicist and the Radiation Oncologist.

The plan evaluation is done with the help of tools like the dose volume histograms and the slice by slice dosimetric analysis. The evaluation of a IMRT plan can be done by both subjective and objective methods. Subjective evaluation is done by visualisation tools like DVH graphs and slice by slice dosimetric analysis. Objective evaluation can be carried out by checking other parameters of the plan like the conformity and homogeneity indices. After the plan has been thoroughly evaluated, once all the achievable goals are met, it is finalised for delivery to the patient. Once the plan is finalized, the other very important process is the Quality Assurance (QA). The accepted plan is initially run on a dummy in the linear accelerator to check whether the plan which has been approved, is having the same dosimetric profile on the machine as on the computer. Phantoms are used for the dosimetric purposes can be either a point dosimetry or a fluence map verification. An error between the generated plan and the phantom dosimetry of +/- 3% will be considered acceptable. Once the QA check is in acceptable range, the plan is ready to be executed on the patient.

The patient is positioned on the couch of the Liner accelerator with the same immobilization and in the same position in which he was during the process of planning. A final check is made by taking an on board image which can either be by 2 dimensional verification method (X Rays) or by 3 dimensional volumetric verification method (Cone beam CT scans - CBCT) of the patient in treatment position and this verify that there are no setup errors. As IMRT gives very sharp dose gradients along the target areas, there are high chances of a geographical miss to the tumor and excessive radiation dose being delivered to the in proximity organ at risk if the patient positioning is not correct.

Unacceptable ranges of error leads to the abandoning of current treatment plan and recheck/replanning are carried out so that the patient can be treated more accurately.

Usually on the first 3 days of treatment on board imaging will be done for verifying proper target volume coverage and if the target coverage is found to be adequate during the first 3 days of verification, then weekly verification checks are made. However, if there is gross random error requiring shift before treatment seen during the first 3 days of verification, then the verification process is carried out daily to ensure proper delivery of radiation therapy.

Thus, the entire planning, optimization and execution process of IMRT goes through various check points and every detail is very important for the proper delivery of radiation by an IMRT technique. In 2014 American College of Radiologists (ACR) and

the American Society of Therapeutic Radiation Oncology (ASTRO published an amendment to the practice parameters in Intensity Modulated Radiation Therapy which gives guidelines for the personnels involved in IMRT planning and execution, Quality Assurance of an IMRT planning system, IMRT treatment plan implementation, Quality Assurance of IMRT delivery system, patient specific quality assurance, documentation and quality control.

PET CT in Head and Neck cancers

Positron emission tomography (PET) using the radiotracer 18-fluorodeoxyglucose (FDG) is a widely applied mode of imaging for the better evaluation of head and neck squamous cell carcinomas (HNSCC*).* Cancer cells demonstrate an increased glucose metabolism as compared to normal tissues. [18F]- fluoro-2-deoxy-D-glucose is a glucose analogue that is delivered intravenously and preferentially transported into cancer cells by glucose transporters. Neoplastic cells make use of anaerobic glycolysis more than surrounding normal tissues, due to intracellular signaling abnormalities, high metabolic rate, and poor vascular supply. [18F]- fluoro-2-deoxy-D-glucose is converted within these cells to 2-deoxyglucose-6-phosphate after undergoing phosphorylation by hexokinase, which cannot be utilized by the glycolytic pathway and becomes trapped within the cells. This trapping of FDG inside the cell allows tissue with preferential uptake to be imaged by PET, which detects positrons emitted by the 18F incorporated into the glucose analogue. However, FDG is also incorporated in some of the normal tissue like the brain, active muscle, lymphoid tissue, and salivary glands. Some of the benign tumors that show accumulation of FDG are the salivary oncocytomas, salivary Warthin's tumors, and thyroid Hurtle cell adenomas. The major hurdle in PET CT scan is that areas of inflammation, infection, and trauma may also lead to increased FDG uptake. (84,85)

Application of FDG-PET scanning ranges from pre-treatment staging to radiotherapy planning, treatment response assessment and post-therapy on follow-up. The ^{18}F-FDG

PET-CT plays an important role in patients with cervical lymph node metastasis from a carcinoma of unknown origin and it is a useful diagnostic tool to detect the primary tumour, with a detection rate of 25-38.5%. It is well documented in many studies that there is a superiority of PET-CT over anatomical imaging in detecting lymph node involvement(74.7% vs 52.6%)(86). It is important to screen for distant metastases in patients with advanced disease, especially in nasopharyngeal carcinomas and with nodal involvement. (34–37)

Role of PET CT in radiotherapy contouring

Radiation oncologists use anatomical CT and MR images to delineate the gross tumour volumes (GTVs) for radiotherapy treatment planning. This allows precise target volume and organs at risk identification and delineation. CT and MRI give very good details on lesion location size, morphology and structural changes compared to adjacent tissue. There is no information about the tumor physiology and in this era of molecular therapy, we should give importance to tumor's biological functions and its surrounding microenvironment.(87) Now with advent of newer imaging modalities which gives us metabolic information about the cancer, we have to consider how to use this information in treatment. With the capability of modern radiation therapy units and the availability of combined PET/CT scanners stimulated the development of biological PET imaging-guided radiation therapy treatment planning with the aim to produce highly conformal radiation dose distribution to the tumour. The first hurdle in front of a treatment planner

who utilise PET information for contouring the lesion is the typical blurred and noisy functional images.(88)

The increased diagnostic accuracy of ^{18}F-FDG PET-CT is made use in RT planning, reducing interobserver variability in target delineation, and modifying the extension of gross tumor volume (GTV), clinical tumor volume (CTV) and planning target volume (PTV) for both primary tumor and regional lymph nodes. With the dual -modality integrated PET/CT scanning systems we have an opportunity of improving target localization and facilitating treatment planning for radiation therapy. (6) One advantage of FDG-PET for HNSCC appears to be in identifying metastatic nodal disease that is equivocal on CT scans for inclusion in the IMRT planning.(89) The decision to designate a node as involved or not with disease translates into the difference between delivering tumoricidal doses applicable for gross versus delivering prophylactic dose for elective at-risk nodes. Several studies that have examined the role of PET/CT in the context of radiotherapy planning have concluded that that there are significant quantitative and qualitative differences between PET-derived and CT-derived tumor volumes in a large proportion of these patients.(89,90)

With high degree of conformal radiotherapy, we face an issue - what exactly needs to be included in the treatment volume? Because IMRT has a very sharp dose fall-off gradient between the gross tumor target and surrounding normal tissue, adequate target volume delineation is absolutely essential. Inadequate coverage in the treatment volume can result in tumor recurrence. The treatment planning system will not treat areas which are

not drawn on the CT slices, and the algorithm will try to spare regions that are not contoured. Significant inter-physician variability exists in producing target volumes and radiation treatment plans for conformal radiotherapy. One study comparing target volumes delineated by three diagnostic radiologists and eight radiation oncologists showed up to a three-fold variation in volumes outlined by the different clinicians.(91) To minimize such variability, it is strongly encouraged that GTV delineation be done in a multidisciplinary fashion, including a team consisting of a radiation oncologist, a radiologist, and, whenever necessary, a head and neck surgeon, particularly in the postoperative setting. When such a team is not available, fusion of the diagnostic MRI, CT, and/or positron emisssion tomography (PET)/CT scans with the treatment planning CT should be implemented to further assist the radiation oncologist in GTV delineation. (4) Inter observer variability when PET CT is used for radiotherapy planning is much less compared to CT based plan.(7)

There are valid criticisms that have hindered the widespread application of FDG-PET/CT in the radiation therapy clinic. One of the main difficulties is the delineation of the treatment volume from noisy PET data. Identification of lesion edges in general is not a trivial problem in PET imaging. Changing the PET window level can lead to a considerable overestimation or underestimation of the target volume. However, several techniques including threshold-based methods and gradient-based methods have been suggested and used, but still consensus needs to be met.(92) Several investigators have compared different segmentation methods in an attempt to solve this issue. Various

methods used are visual method, SUV 2.5 isocontour, 40% and 50% threshold of maximum tumor SUV (SUVmax), and an adaptive threshold based on the signal-to-background (S/B) ratio that was specific for each case. Adaptive threshold algorithms appears promising with regard to segmentation, and may reduce variability among radiation oncologists.(93) Comparison of PET-GTVs with CT-GTVs has limited value unless it is in the context of pathology and true disease. The investigators reported that PET was superior to CT for detecting primary tumors with a sensitivity of 94% and 82%, respectively, and superior for staging of the neck with a sensitivity of 90% and 67%, respectively.(94) To better understand the optimal segmentation for GTV delineation using PET data, investigators have correlated GTVs with pathologic specimens. No single SUV threshold gives a metabolic tumor volume that adequately captures pathologic tumor volume but the gradient-based volume performed relatively better than other volumes.(8)

The major problems encountered in functional volume quantitation are image segmentation and imperfect system response function. The difficulty in image segmentation is compounded by the low spatial resolution and high noise characteristics of PET images. Despite the difficulties and known limitations, several image segmentation approaches have been proposed. Manual delineation of target volumes using different window level settings and look up tables is the most common and widely used technique in the clinic. However, the method is highly operator dependent with wide

inter-observer variability. Semiautomated or fully-automated delineation techniques offer an advantage over manual techniques by improving reproducibility.(6,93)

Methods and Materials

Patients with biopsy proven malignancy of the oropharynx, laryngopharynx and nasopharynx, who had undergone treatment with Intensity Modulated Radiation Therapy (IMRT) technique where treatment planning was done using a planning PET/CT, from June 2012 to December 2014were retrospectively included and patients with biopsy proven malignancy of the nasopharynx, oropharynx, larynx and hypopharynx, scheduled for undergoing treatment with IMRT using a planning PET/CT, from January 2015 to September 2015 were prospectively included.

Inclusion Criteria:

Patients of age more than 18 years

Patients diagnosed to have biopsy proven Head and Neck cancers of the nasopharynx, oropharynx and laryngopharynx

Patients undergoing radiation therapy with Intensity Modulated Radiation Therapy (IMRT) with planning PET/CT

Patients consenting to be a part of the study

Exclusion Criteria:

Patients of age less than 18 years

Patients diagnosed to have any head and neck malignancy other than the primary sites mentioned in the inclusion criteria

Patients not consenting to be a part of the study

The study included 17 patients from June 2012 to September 2015. Among them, the 9 patients who were included retrospectively were treated with IMRT for head and neck cancers using planning PET/CT during June 2012 to December 2014 and had signed a consent form prior to starting radiation therapy, stating that their data may be used in future for scientific purposes.

There remaining 8 patients were prospectively recruited during January 2015 till September 2015 after an informed consent and these patients also had a planning PET/CT scan done. 4 sets of target volume delineation (GTV) and organs at risk (OAR) volumes was carried out, one on the CT scan and the other on the integrated PET scan.

<u>PET CT procedure:</u>

The patient's blood glucose is checked prior to the scan and if the blood glucose level is below 150, the F-18-FDG is administered intravenously (dosage range from 259 to 370 MBq), followed by oral & IV contrast. At 60 minutes post-injection of F-18-FDG,

imaging is initiated with Siemens BIOGRAPH -6 (LSO-crystal /6-slice) PET-CT scanner. CT images are obtained from the vertex to mid thigh in whole body scan and vertex to diaphragm level in regional scans. PET images are obtained from the same region. Using CT scans for attenuation correction and localization, images are reconstructed. Transaxial, coronal and sagittal PET images were reviewed concurrently with fused PET/contrast CT images and standardized uptake values (SUV) is calculated wherever applicable.

PET and CT images are loaded into the 3D slicer software. CT window levels adjusted to window/level : 350/40. PET images are set to a colour scale of warm shade2 or cold to hot rainbow.

Contouring of the target and OARs were done on the CT and PET images and assessment on whether there was any upstaging or down staging of the cancer with PET CT compared to the CT alone was also done.

Contouring of the primary and nodal target volumes

Target Volume contouring

The GTV primary (GTVp) and GTV node (GTVn) for all the patients was drawn on the CT scan using the soft tissue window level (level - 40; window - 350)

The GTV primary (GTVp) and GTV node (GTVn) for each node for all the patients was drawn on the PET images using the following methods and separate GTVp and GTVn volumes were obtained.

Volume contouring usingAdaptive threshold method

Step 1 – Otsu segmentation is applied to get initial contour of the tumour. Otsu is an algorithm where it compute the between class-variance.(95)

Step 2 – The SUV max inside that tumour is calculated and the PET minimum to maximum intensity value to 0/SUV max is set.

Step 3 – The otsu contour 4 pixel is dilated in all directions.

Step 4 – The otsu contour 20 pixel is dilated in all directions.

Step 5 – A new contour is made, whose shape is a 3D shell by subtracting step 3 contour from step 4 contour.

Step 6 – From the Otsu contour document the SUV maximum value inside the tumour, SUV minimum value inside tumour and volume of the contour are obtained.

Step 7 – From the step 5 contour the mean value of SUV in background region is obtained and document

Step 8 – The adaptive threshold value for that tumour is obtained by applying the formula - 94.933 – [73.938 x {1-(mean background /SUV max)}]+ [2.739 x (1/volume)]. (96)

Step 9 – The SUV value got from the formula is applied and auto-contouring is done with the help of 3D slicer software.

Step 10 – All the steps, from 1 to 9 is repeated in cases were the patient has nodes or a second primary.

Volume contouring using fixed threshold method

SUV values for the 40% and 50% are calculated and the contours were done with the help of 3D slicer.

The SUV-based delineation was obtained by applying an isocontour around the tumor with two thresholds which were based on fixed percentages of the maximum signal intensity in the primary tumor; 40% (GTV40%) and 50% (GTV50%).

Volumes got from SBR technique and CT volume was compared with each other. The volumes of nodes and primary were evaluated separately. We also did a volume comparison between the fixed threshold methods with CT volumes. Metabolic tumour volumes segmented with different techniques on PET CT were compared with each other.

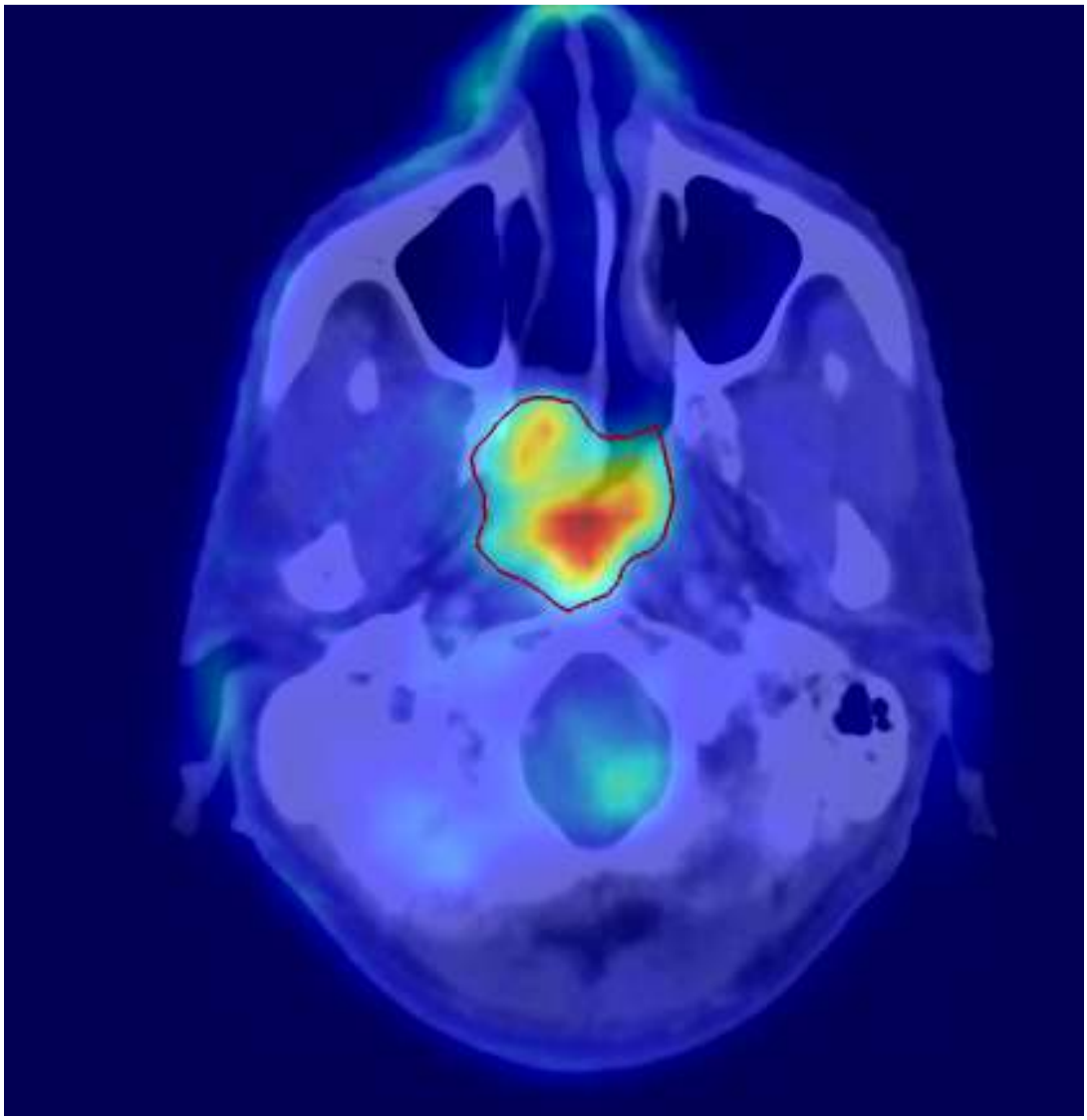


Diagram 2 showing the step 1 – the Otsu volume

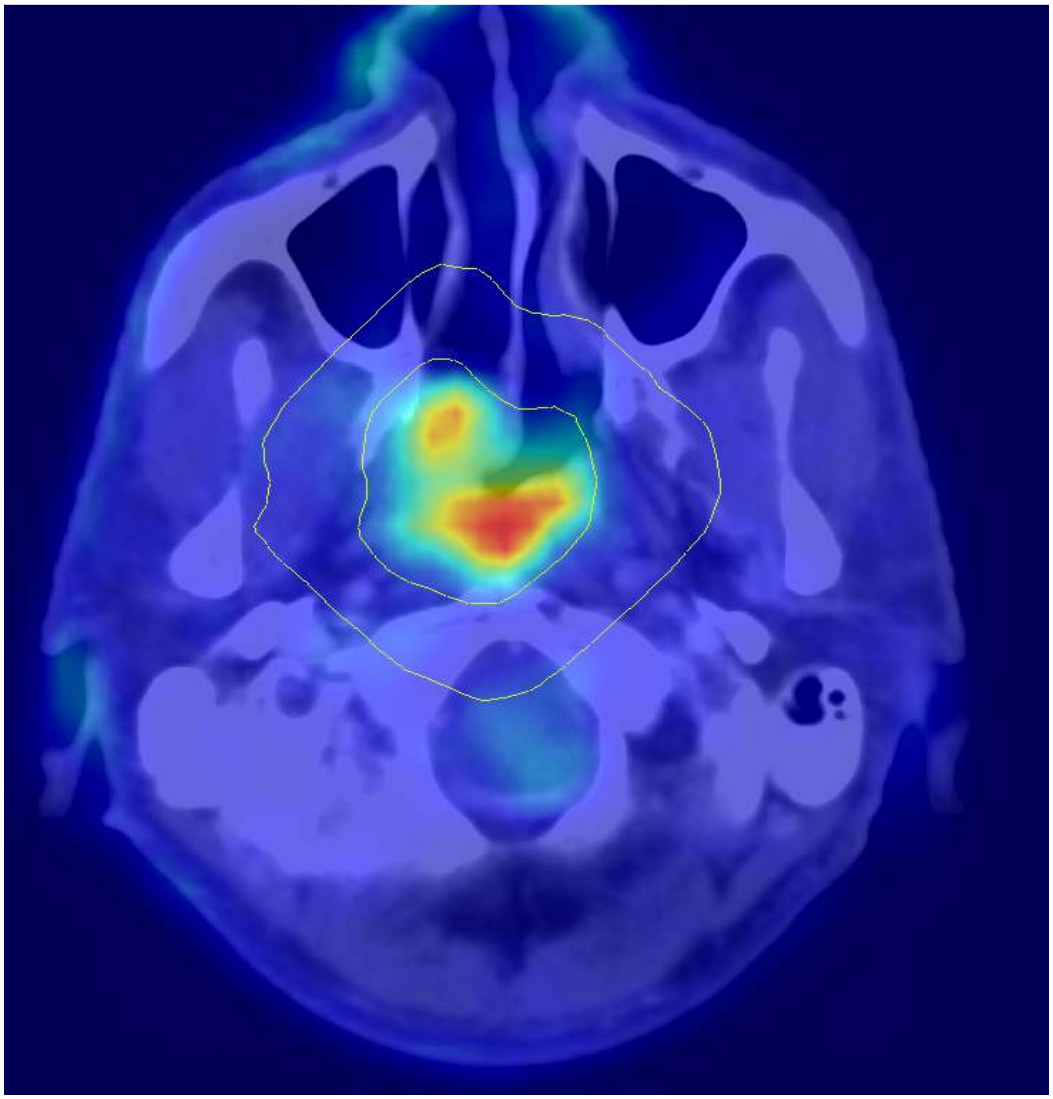


Diagram 3 showing the step 5 – volume made to check the background SUV mean.

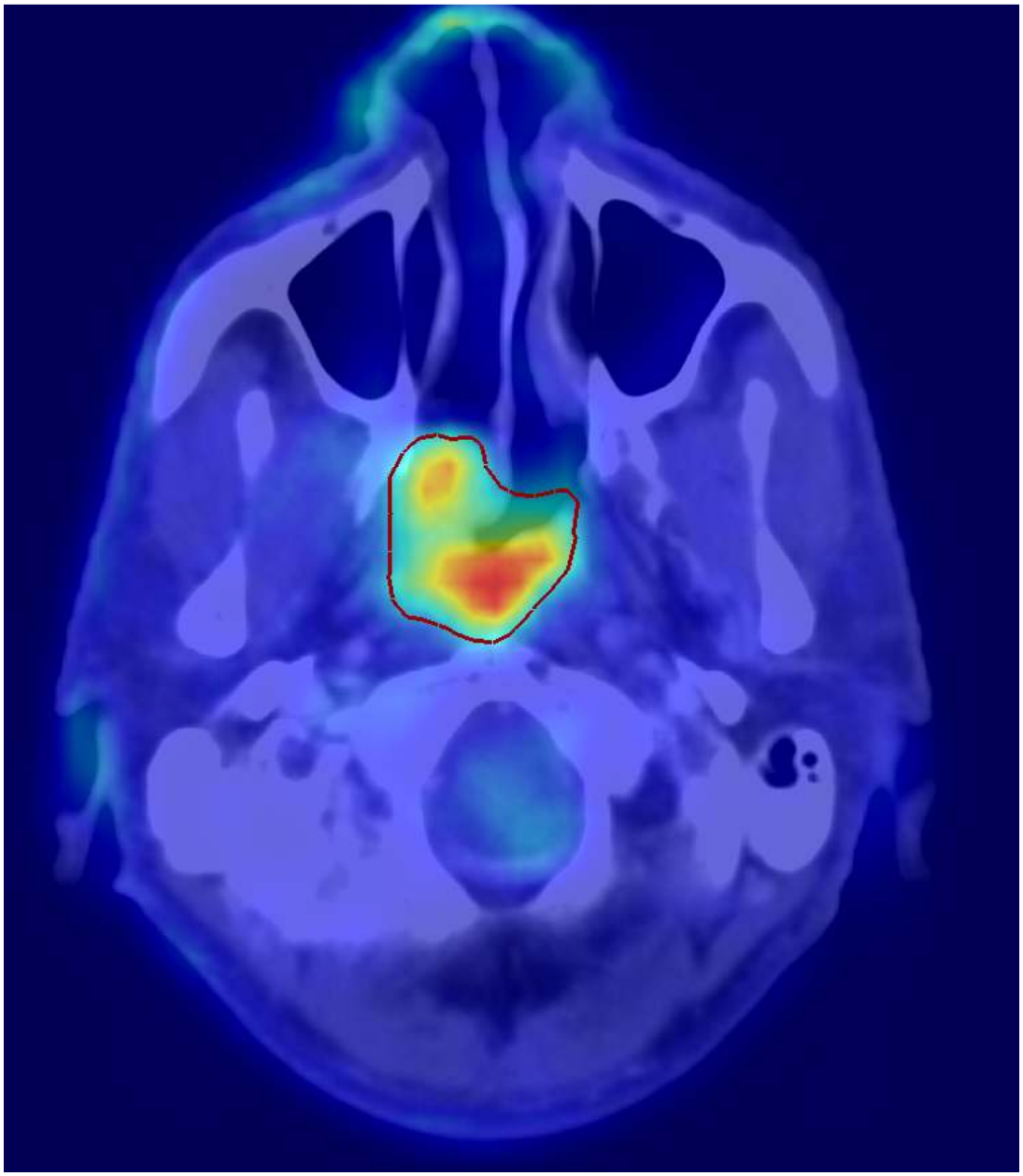


Diagram 4 showing the step 9 – Auto contoured adaptive threshold volume.

Results

The study was done in 17 head and neck cancer patients. Out of the 17 patients, 12 were males and 5 were females. Median age of the patients was 55.5. There were 7 patients with oropharyngeal cancer, 5 with hypopharyngeal cancer, 4 with nasopharyngeal cancer and 1 with laryngeal cancer. There were 7 patients with stage IV A, 4 with stage IVB and 2 each in stage I, II and III cancers. All the patients were planned for treatment with IMRT technique using PET CT in treatment position with immobilization for treatment planning and dose delivered was 66 – 70 Gy. The table 1 shows the patient characteristics.

The absolute volumes of tumour (primary and lymph nodes) obtained using the CT scan and the PET data were documented. The CT volume was compared with PET volume that was got through the SBR technique. Volume was also segmented using fixed SUV technique with SUV 40% and SUV 50%, and these volumes were also compared with each other.

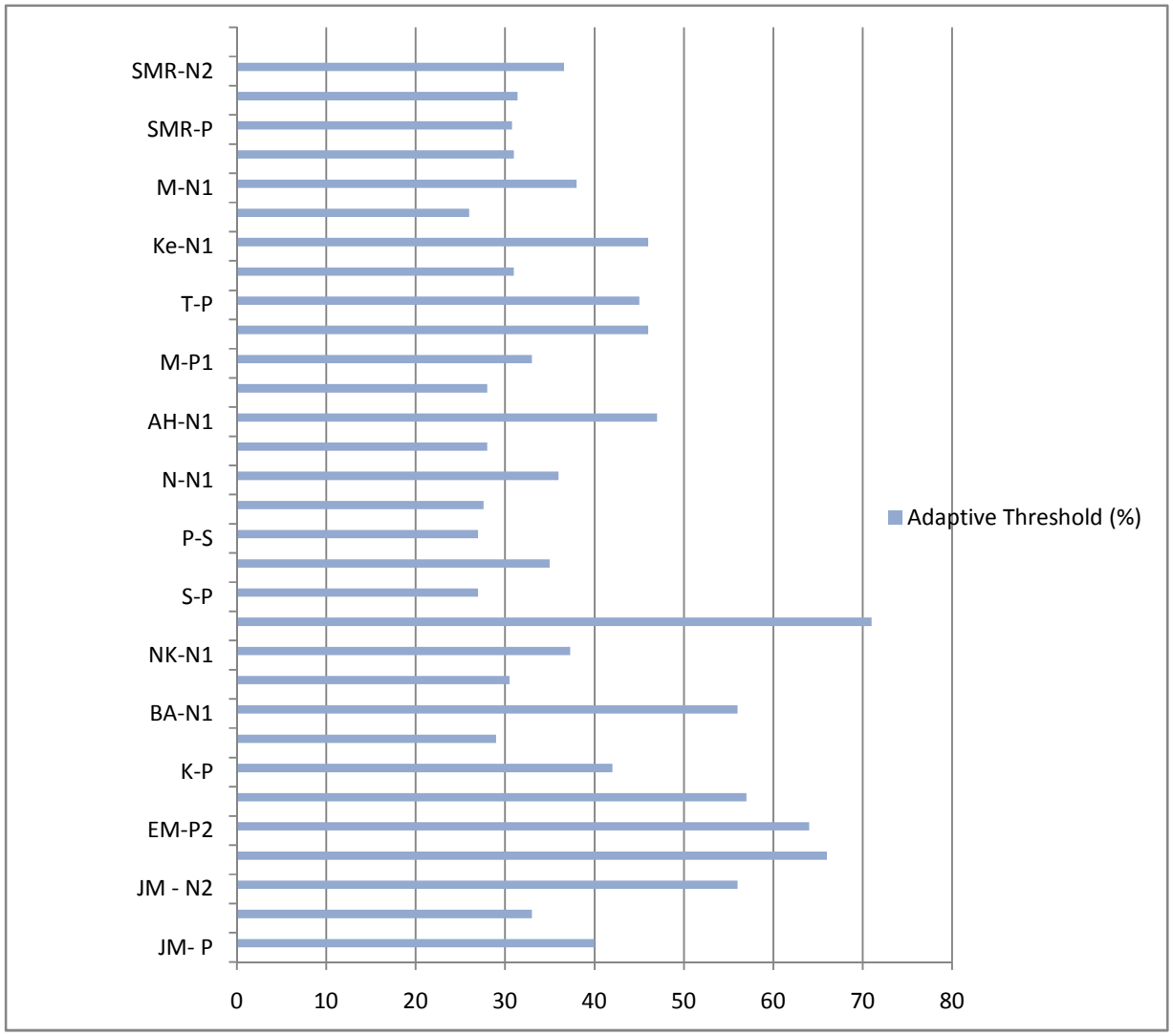
Table 1. Patient characteristics.

Patient Characteristic		
Number Of Patients		
	Total	17
	Male	12
	Females	5
Age		
	Median Age	55.5 (range 24 – 68)
Primary Tumour Site		
	Nasopharyngeal Cancer	4
	Oropharyngeal Cancer	7
	Hypopharyngeal cancer	5
	Laryngeal Cancer	1
Stages		
	I	2
	II	2
	III	2
	IVA	7
	IV B	4
Technique Of Treatment		
	IMRT	
Dose		
	66-70Gy	

SUV% obtained with SBR Technique

After obtaining the SUV max of the tumour, background SUV mean and volume from Otsu algorithm the SBR formula was run, thus deriving the tumour specific SUV percentage. Figure 1 is showing the different SUV percentages obtained with SBR technique. The SUV percentage obtained with SBR technique varied from 26% to 71 %. The SUV percentage varied in the same patient between primary and node, and also the SUV percentage was different between nodes in the same patient.

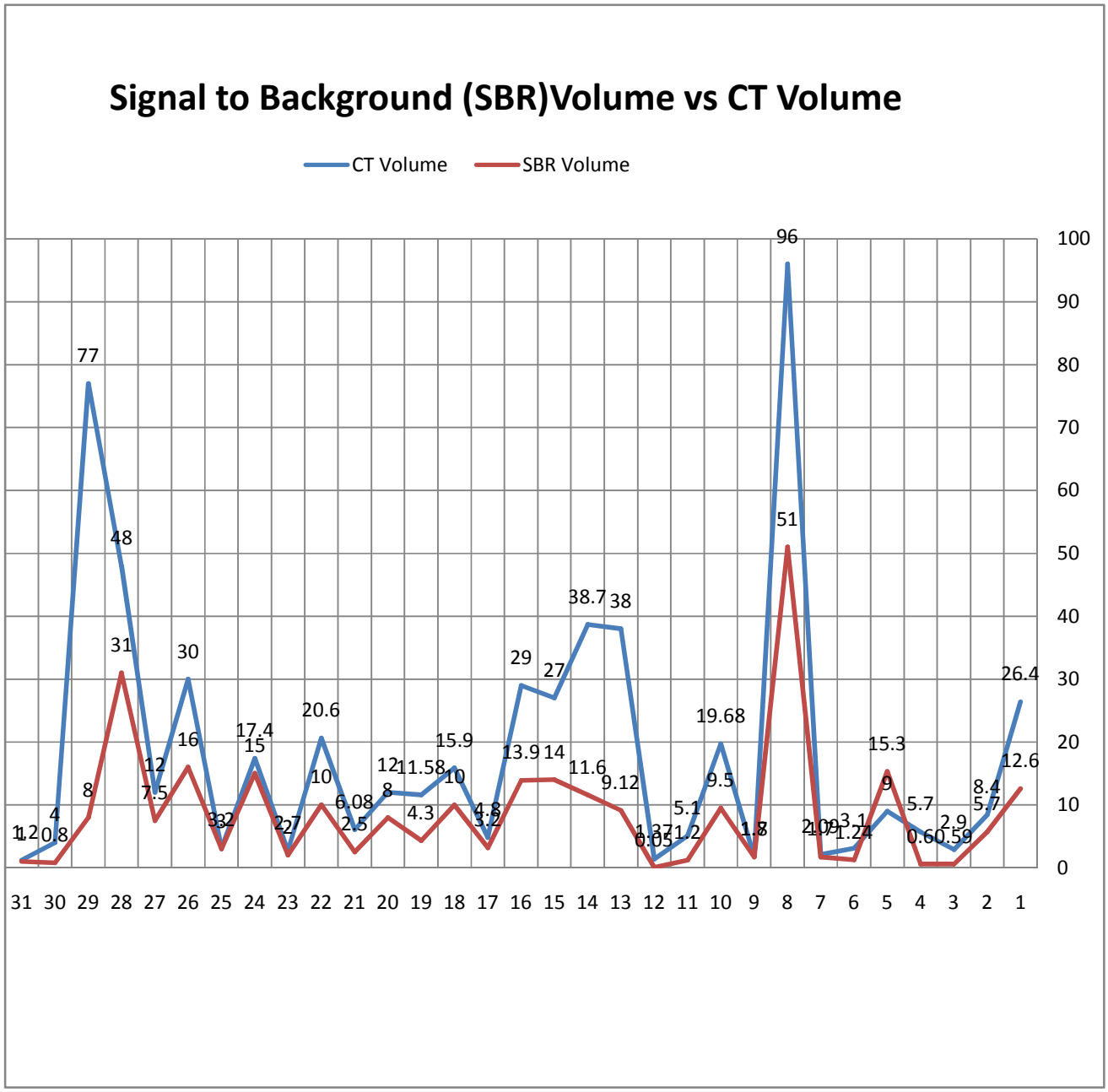
Figure 1 The different SUV% obtained with SBR Technique



Comparison of CT volume and SBR volume

The volumes of the tumour GTVp and GTVn got from SBR technique (adaptive method) and CT were compared with each other. Figure 2 shows that there was a difference between the volumes obtained with CT and using the SBR technique. The volume obtained using SBR technique was less than the CT volume.

Figure 2. Comparison between CT Volume and SBR Volume.

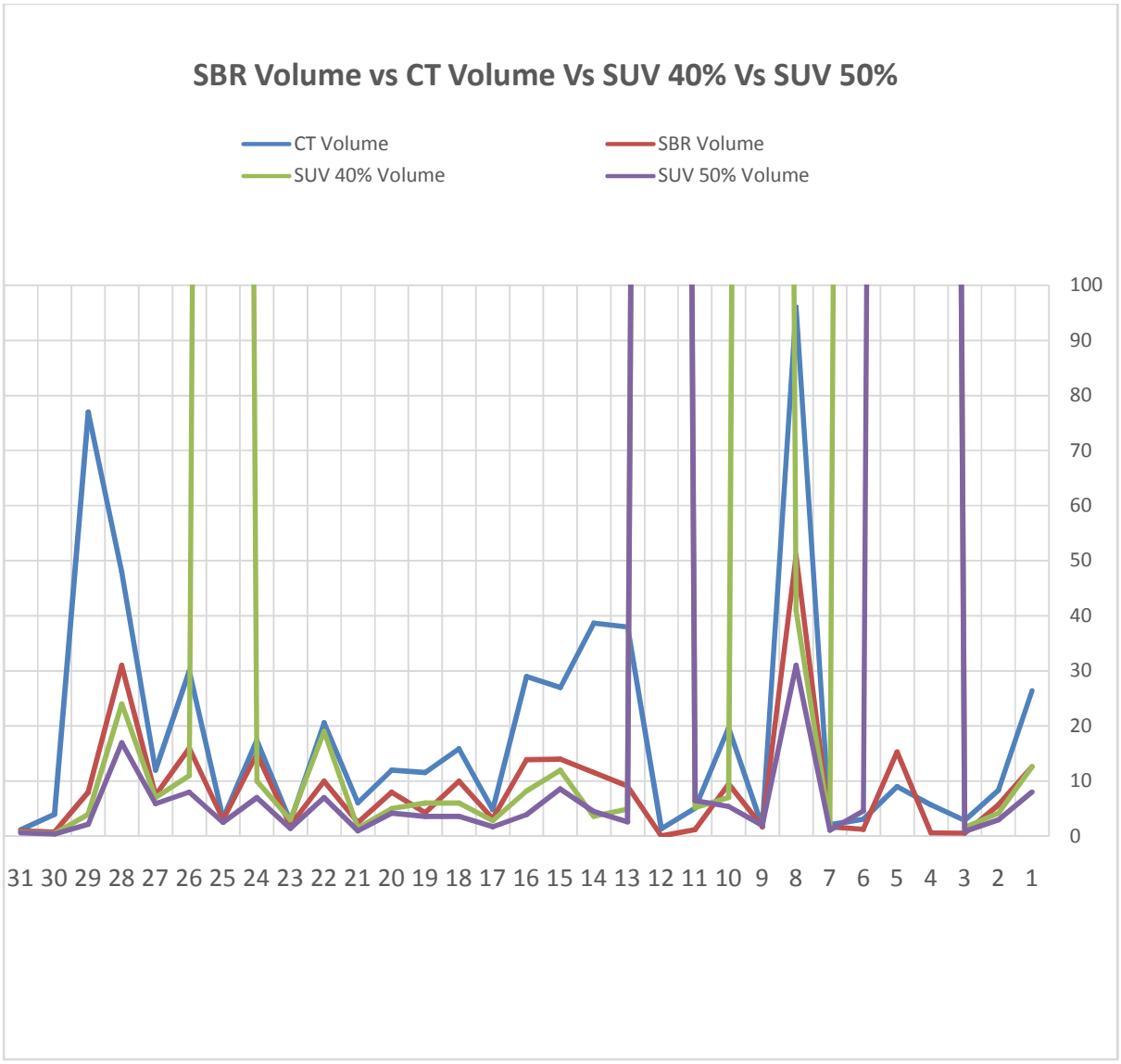


Comparison between CT volume, SBR and fixed threshold technique volume (Fig 3)

PET based volume using fixed threshold technique with 40% and 50% were less than CT volumes and failed to contour GTV in some instances.

This graph shows the volume difference between the metabolic tumour volumes obtained by the SBR, SUV40%, SUV 50% technique and the CT volumes.

Figure 3. Comparison between volumes obtained with CT and different PET derived volumes using Adaptive Threshold, SUV 40% and SUV 50% techniques.



Primary tumour Volume (Table 2)

The primary tumour volume was contoured using CT scan and using the PET , volumes were contoured with signal to background ratio (diagram 5). The PET was also used to contour the primary tumour using the fixed threshold methods using SUV 40% and SUV 50%. (diagram 6 and diagram 7)

Comparison of volumes was done between the CT and SBR, CT and SUV 40%, CT and SUV 50%, SUV 40% and SUV 50%, SBR and SUV 40%, and SBR and SUV 50%.

In fixed threshold techniques SUV 40% failed to give results in 4 case (4 primary) and SUV 50% did not give for 2 cases (2 primary).

CT Vs SBR technique (Table 2 – comparison 1 n=21)

The volumes obtained with CT scan and the SBR technique were compared and it was seen that the mean volume with CT scan was 25.1cc (+/- 24.4) and that with adaptive was 11.7cc (+/- 11.4). The mean standard error of CT volume was 5.3 and adaptive was 2.5.Analysis of the primary tumour volumes obtained with the CT scan and the volume got from adaptive threshold showed that there is a significant difference between the volumes.

CT Vs SUV 40% (Table 2 – comparison 2) and CT Vs SUV 50% (Table 2 – comparison 3)

The volumes obtained with CT scan and the fixed threshold technique SUV 40% were compared, it was seen that the mean volume with CT scan was 29.8cc (+/-25) and that with SUV 40% was 10.3cc (+/- 10. The mean standard error of CT volume was 6 and SUV 40 was 2.4. SUV 40% failed to give results in 4 cases and therefore the number of cases used for comparison was only17.

The volumes obtained with CT scan and the fixed threshold technique SUV 50% technique were compared, it was seen that the mean volume with CT scan was 27cc (+/- 25) and that with SUV 50% was 6.5cc (+/- 7). The mean standard error of CT volume was 5.7 and SUV 50 was 1.6. SUV 50% did not give for 2 cases (2 primary) and hence the number of cases compared is 19.

The result showed that there is significant difference between the volumes of CT and both fixed threshold methods, SUV 40% and SUV 50%.

The difference in volumes with fixed threshold methods was more compared with that obtained with adaptive threshold method.

SUV 40% Vs SUV 50% (Table 2 – comparison 4)

The volumes obtained with the fixed threshold technique SUV 40% and SUV 50% technique were compared. The mean volume with SUV 40% was 10.2cc (+/- 10) and that

with SUV 50 was 6.8cc (+/- 7.3). The mean standard error of SUV 40 was 2.4 and SUV 50 was 1.8. There is significant difference between the volumes derived from fixed threshold methods with 40% and 50%.

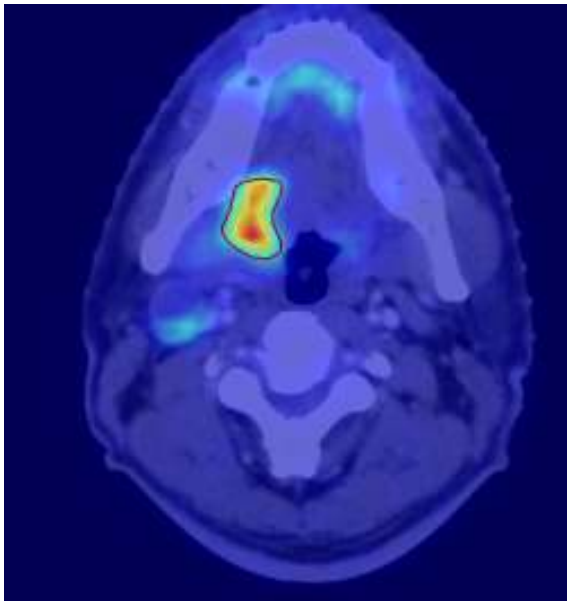


Diagram 5 Tumour delineated using SBR technique (primary)

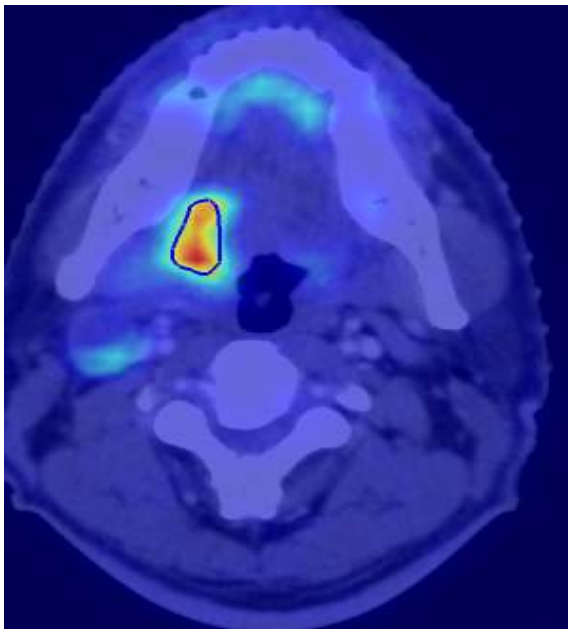


Diagram 6

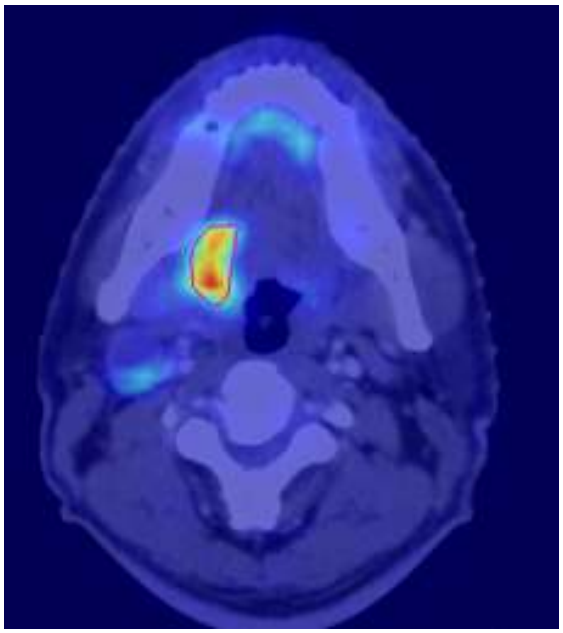


Diagram 7

Diagram showing tumour contoured using SUV 40% (Diag. 6) and SUV 50% (Diag. 7) in the same patient.

SBR Vs SUV 40% (Table 2 – comparison 5) and SBR Vs SUV 50%. (Table 2 – comparison 6)

The volumes obtained with the SBR and the fixed threshold technique SUV 40% were compared. The mean volume with SBR was 13.3cc (+/- 11.8) and that with SUV 40% was 10.3cc (+/- 10). The mean standard error of SBR was 2.9 and SUV 40 was 2.4. The volumes obtained with the SBR technique and the fixed threshold technique SUV 50% technique were compared. The mean volume with SBR was 12cc (+/- 11.7)and that with SUV 50% was 6.5cc (+/- 7). The mean standard error of SBR volume was 2.7 and SUV 50 was 1.6

There was significant difference in volumes between SBR technique and fixed threshold techniques, SUV 40% and SUV 50%.

Table 2. Comparison between CT Vs different PET derived volume in Primary.

Comparison		Mean	N	Std. Deviation	Std. Error Mean	P Value
1	**CT**	25.1	21	24.5	5.3	<0.05
	SBR	11.7		11.4	2.5	
2	**CT**	29.8	17	25.0	6.1	0.004
	SUV40	10.3		10.0	2.4	
3	**CT**	27.0	19	25.0	5.7	0.001
	SUV50	6.5		7.0	1.6	
4	**SUV40**	10.3	17	10.0	2.4	<0.05
	SUV50	6.9		7.3	1.8	
5	**SBR**	13.3	17	11.8	2.9	<0.05
	SUV40	10.3		10.0	2.4	
6	**SBR**	12.1	19	11.7	2.7	<0.05
	SUV50	6.5		7.0	1.6	

Nodal tumour Volume(Table 3)

The nodal tumour volume was contoured using CT scan and using the PET images, The nodal volumes on the PET were contoured with signal to background ratio (diagram 8) and using the fixed threshold methods using SUV 40% and SUV 50%. (diagram 9 and diagram 10)

Comparison of volumes was done between the CT and SBR, CT and SUV 40%, CT and SUV 50%, SUV 40% and SUV 50%, SBR and SUV 40%, and SBR and SUV 50%.(table 3) When the fixed threshold techniques were used, the SUV 40% failed to give results in 2 case and SUV 50% could not give for 1 case.

CT Vs SBR technique(Table 3 – comparison 1)

On comparison of volumes of CT scan and the SBR technique the mean volume with CT scan was 5.3cc (+/- 4) and that with adaptive was 2.6cc (+/-2.4). The mean standard error of CT volume was 1.3 and adaptive was 0.8. Analysis of Nodal volumes showed that there is significant difference between the CT volumes and adaptive threshold volumes.

CT Vs SUV 40% (Table 3 – comparison 2)and CT Vs SUV 50%(Table 3 – comparison 3)

The volumes obtained with theCT scan and the fixed threshold technique SUV 40% were compared. The mean volume with CT scan was 6.2cc (+/- 3.9) and that with SUV 40 was 3.5cc (+/- 2.4). The mean standard error of CT volume was 1.4 and SUV 40 was 0.9.

The SUV 40% failed to give results in 2 case and hence the number of cases taken for comparison is 8. The volumes obtained with the CT scan and the fixed threshold technique SUV 50% technique were compared. The mean volume with CT scan was 5.7 cc (+/- 4) and that with SUV 50 was 2.7cc (+/- 2.2). The mean standard error of CT volume was 1.3 and SUV 50 was 0.7. SUV 50% failed to give results in 1 case and hence the number of cases taken for comparison is 9.

There is significant difference between the volumes of CT scan and the two fixed threshold methods SUV 40% and SUV 50%.

SUV 40% Vs SUV 50%(Table 3 – comparison 4)

The volumes obtained with thefixed threshold technique SUV 40% and SUV 50% technique were compared. The mean volume with SUV 40% was 3.5cc (+/- 2.4) and that with SUV 50 was 2.8cc (+/- 2.3). The mean standard error of SUV 40 was 0.9 and SUV 50 was 0.8. The volume difference between the two fixed threshold was not significant.

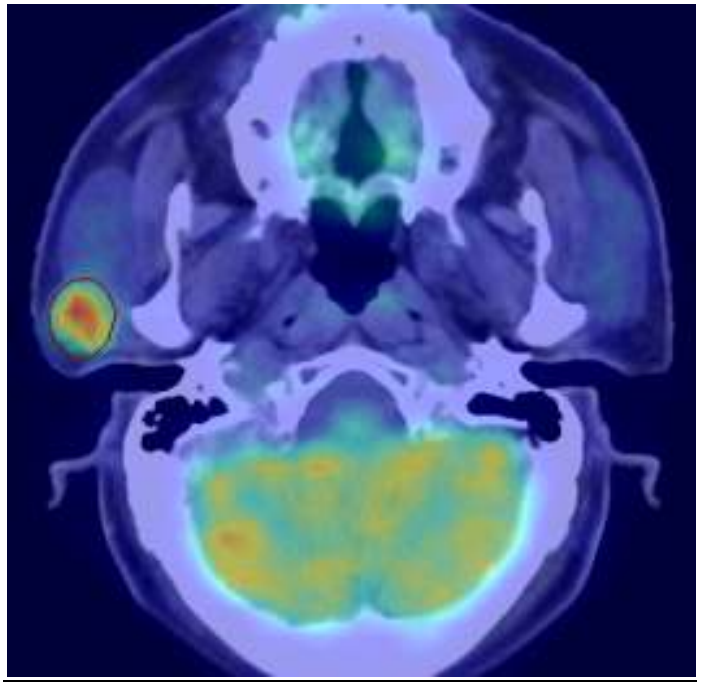


Diagram 8. Showing node delineated using SBR technique

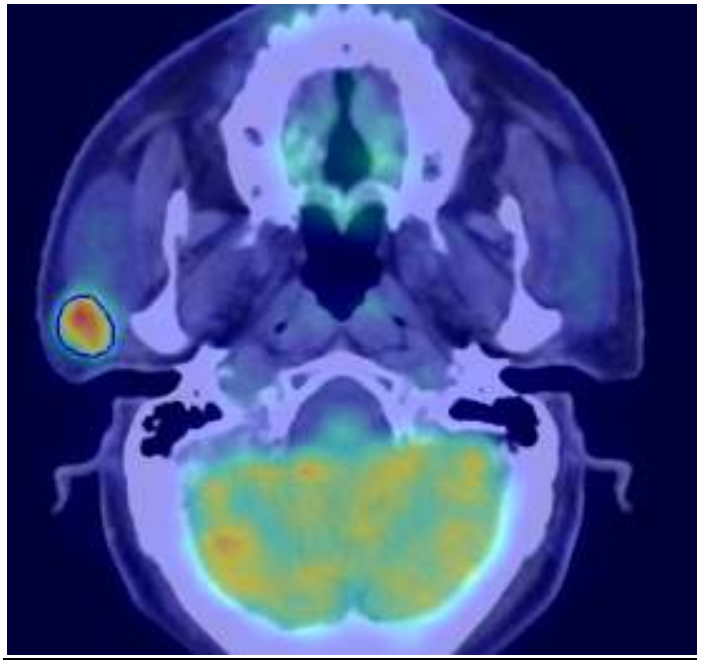


Diagram 9. Showing node delineated using SUV 40%

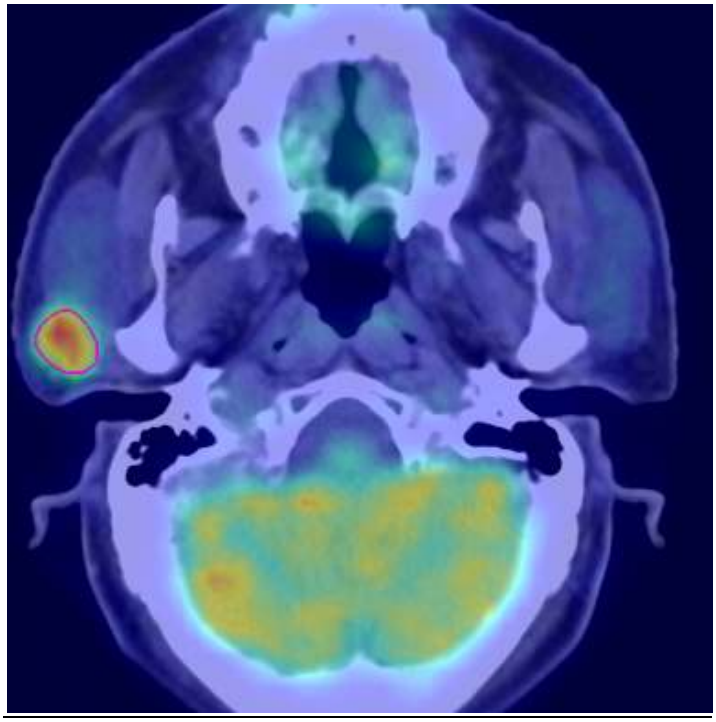


Diagram 10. Showing node delineated using SUV 50%

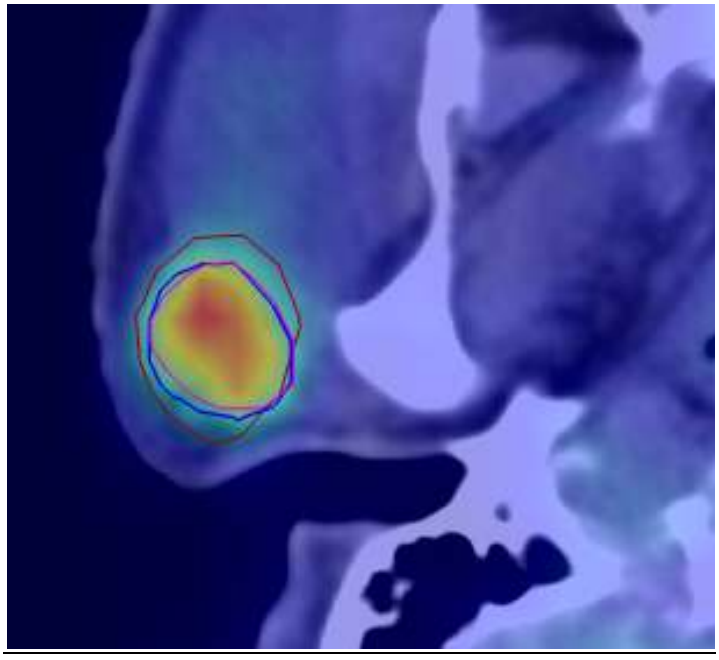


Diagram 11. Showing comparison of nodal volume by different PET based autocontouring technique- SBR,

SBR Vs SUV 40%(Table 3 – comparison 5) and SBR Vs SUV 50%(Table 3 – comparison 6)

The volumes obtained with the SBR and the fixed threshold technique SUV 40% were compared. The mean volume with SBR was 2.8cc (+/- 2.4) and that with SUV 40 was 3.5cc (+/- 2.4). The mean standard error of SBR was 0 .8 and SUV 40 was 0.9. The volumes obtained with theSBR technique and the fixed threshold technique SUV 50% technique were compared. The mean volume with SBR was 2.8cc (+/- 2.4) and that with SUV 50 was 2.7cc (+/- 2.2). The mean standard error of SBR volume was 0.8 and SUV 50 was 0.7.

Comparison of volumes obtained using adaptive method, SUV 40% and SUV 50% did not show any significant difference in the volumes.

Table 3 . Comparison between CT Vs different PET derived volume in Nodes

	Mean	N	Std Deviation	Std Error Mean	P value
CT Adaptive	5.3 2.6	10	4.0 2.4	1.3 0.8	0.003
CT SUV40	6.2 3.5	8	3.9 2.4	1.4 0.9	0.008
CT SUV50	5.7 2.7	9	4.0 2.2	1.3 0.7	0.019
SUV40 SUV50	3.5 2.8	8	2.4 2.3	0.9 0.8	0.117
Adaptive SUV40	3.0 3.5	8	2.6 2.4	0.9 0.9	0.467
Adaptive SUV50	2.8 2.7	9	2.4 2.2	0.8 0.7	0.843

Comparison of CT and PET auto contoured volumes by 3 techniques (Table 4)

Type 1 was when the PET delineated volume using the 3 different techniques was completely inside the CT derived volume.

This was seen in 85.65% volumes with adaptive threshold, 67.6% with SUV 40% and 83.9% with SUV 50%.

Type 2 was when the PET volume is more than the CT volume and this was seen only in SUV 50% (3.2%)

Type 3 was when the PET volume and the CT volumes were correctly matching. This was seen in 16.1 % with adaptive threshold method, while it was only in 6.5% in SUV 40% and there was none with SUV 50% technique.

Type 4 is when the PET volume was partly inside and partly outside the CT volume. This was seen in 3.2% in adaptive method, 6.5% with SUV 40% and 3.2 % with SUV 50% technique.

Type 5 was when the PET technique could not delineate tumour volume. SUV 40% could not delineate in 19.4% and SUV 50% could not delineate in 9.7% cases.

Table 4 Comparison of CT and PET auto contoured volumes by 3 techniques

			Adaptive Volume	40%	50%
1	PET CT volume in side CT volume		80.65	67.6	83.9
2	PET CT volume outside CT volume		nil	nil	3.2
3	PET CT volume = CT volume		16.1	6.5	nil
4	PET and CT volumes not matching		3.25	6.5	3.2
5	PET volume cannot be generated		Nil	19.4	9.7

Discussion

Along with the advances in imaging technology there has been a major advancement in radiation treatment planning and delivery techniques. Higher precision of treatment comes with a higher probability of geographical miss and one of the important factors contributing to this is inaccurate target volume delineation. CT provides a good anatomic detail for defining target volumes and the electron density data will help in dose calculation in radiotherapy and is what is generally used for target volume delineation. Manual delineation of tumour using CT is very subjective and any method which applies an objective technique will reduce the inter observer variability in contouring.(34) Anato-metabolic imaging using 18F-fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is currently used in the diagnosis, initial staging, and response assessment in head and neck cancers with high diagnostic accuracy. It is proven that there is a superiority of PET-CT over anatomical imaging in detecting lymph node involvement. Synchronous primaries also can be diagnosed with the help of PET CT scan. FDG-PET for HNSCC appears to be superior in identifying metastatic nodal disease that is equivocal on CT scans for inclusion in the IMRT planning. The decision to designate a node as involved or not with disease translates into the difference between delivering tumoricidal doses applicable for gross versus delivering prophylactic dose for elective at-risk nodes. Several studies that have examined the role of PET/CT in the context of radiotherapy planning have concluded that that there are

significant quantitative and qualitative differences between PET-derived and CT-derived tumor volumes in a large proportion of these patients.(34,89,90)

This was also seen in this study where 12% of patients were detected to have synchronous primary on PET scan and few patients had lymph nodes that was not detected on the CT scan, with significant uptake on the PET scan.

The availability of dual-modality integrated PET/CT systems gives us the opportunity of improving target localization and facilitating treatment planning for radiation therapy. The advantages of using a PET CT for target delineation in radiotherapy are, it can reduce the inter observer variations in GTV delineation, may reduce the GTV(and thus CTV), identify the tumour/lymph node missed by CT and identifying parts of GTV that may require higher dose. But the limitation of this biological tumour volume is that it has limited spatial resolution, lack of standardized methods for signalsegmentation and false positive and false negative PET readings. (7,97–99)

The major disadvantage on the TPS while using PET scan information for contouring the lesion is, the typical blurred and noisy functional images that is seen in the treatment planning machine. Identification of lesion edges in general is not a trivial problem on PET imaging used on the TPS. Changing the PETwindow level can lead to a considerable overestimation or underestimation of the target volume.(90) Several investigators have compared different segmentation methods in an attempt to solve this issue on the PET scanner. Various methods used are visual method, SUV 2.5 isocontour,

40% and 50% threshold of maximum tumor SUV (SUVmax), and an adaptive threshold based on the signal-to-background (S/B) ratio that was specific for each case. Adaptive threshold algorithms appears promising with regard to segmentation, and may reduce variability among radiation oncologists.(91)

Comparison of PET-GTVs with CT-GTVs was done in pathology and the investigators reported that PET was superior to CT for detecting primary tumors with a sensitivity of 94% and 82%, respectively, and superior for staging of the neck with a sensitivity of 90% and 67%, respectively. No single SUV threshold gives a metabolic tumor volume that adequately captures pathologic tumor volume but the gradient-based volume performed relatively better than other volumes.(91–93)

In this study metabolic tumour volume was created from PET CT which will be an objective method of delineating tumour in Head and Neck cancer. The metabolic tumour volume was created using the SBR method and it was compared with CT volume. Metabolic tumour volume was also created using the fixed threshold methods SUV 40% and SUV 50%.

The SUV percentage obtained with SBR technique varied from 26% to 71 % and this was different in the same patient between primary and node, and also was different between nodes in the same patient.

There is significant difference between the volumes derived from fixed threshold methods with 40% and 50% and in the volumes between SBR technique and fixed threshold techniques using SUV 40% and SUV 50%. PET based volume using fixed

threshold technique with 40% and 50% and the volume obtained using SBR technique was significantly less than the CT volume. But this difference in volume with SBR technique was less than that obtained with fixed threshold methods using 40% and 50%. i.e adaptive method was better than the fixed threshold methods.

When contouring was done with the help of SBR in 3D slicer this could contour tumour in all cases. In fixed threshold techniques SUV 40% failed to delineate the volume in 4 case (4 primary) and SUV 50% failed to do so in 2 cases (2 primary).

Analysis of nodal volumes showed that there is significant difference between the CT volumes and SBR volumes. There is also significant difference between the volumes of CT scan and the two fixed threshold methods, SUV 40% and SUV 50%.

Comparison of volumes obtained using adaptive method, SUV 40% and SUV 50% did not show any significant difference in the volumes. This showed that the SUV percentage value got when we applied the SBR technique was around 40-50%. When contouring was done with the help of adaptive threshold 3D slicer this was possible in all nodal cases with SBR technique. When the fixed threshold techniques were used, the SUV 40% failed to give results in 2 case (2 nodes) and SUV 50% could not give for 1 case (1 node).

In some instances the nodal volumes derived using the SBR technique was grossly less than the CT volumes. One such volume is shown in the diagram 12 and 13. The necrosis part of the node failed to pick up FDG and thus the contoured metabolic tumour volume was very different from the anatomical volume. It is a known fact that cystic and necrotic

nodes are missed in PET scan and need contrast enhanced CT for better characterization.(100)

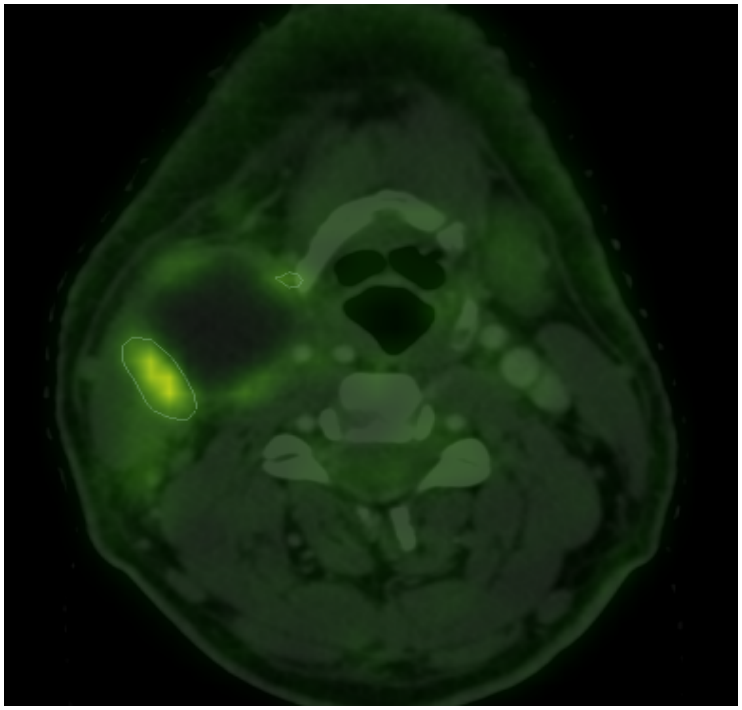


Diagram 12

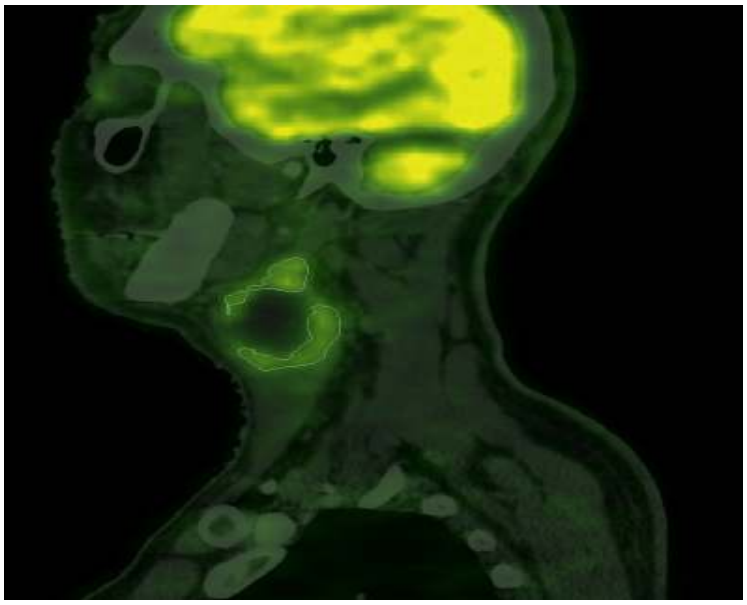


Diagram 13

Diagram 12 and 13 showing axial and sagittal section of PET CT respectively. This shows central necrosis in a node and the autocontouring could pick-up the volume which has uptake, this was like a shell around a tumour .

When comparison of the volumes between the adaptive derived volume and the CT volume, 80.65% subjects showed that PET volume is inside the CT volume. In 16.1% tumours volumes were exactly matching with the CT volumes. That is a total of 96.75% was within or same as the CT volume and in 3.25 % tumours PET derived and CT derived volumes were different.

In fixed threshold methods, comparison of volumes derived from SUV 40% showed 67.7% cases were inside CT volumes. In 6.5 % cases the volume was matching with the CT volume. The SUV 40% volume was not matching in 6.5% cases and this method failed to generate GTV in 19.4% cases. So total 64.2% cases the SUV 40% had concordant volume with CT and 35.8% volumes were discordant.

Comparison of volumes derived from SUV 50% showed 83.2% cases were inside CT volumes. There was no case where the volume was matching with the CT volume. The SUV 50% volume was not matching in 3.2% cases, 3.2% cases volume over estimated the CT volume and this method failed to generate GTV in 9.7% cases. SUV 50% generated 83.2 % volumes which were concordant and 16.8% volumes which were discordant to CT volumes or unable to be contoured.

Only in a small percentage of patients (3.2%), the PET and CT volumes were not matching using the SBR technique and no instances where volume could not be generated.

Since difference in volumes on CT as compared to that obtained with PET scan was least with the SBR technique and with this technique only in a small percentage of patients, the PET and CT volumes were not matching and no instances where volume could not be generated, this technique probably should be used for autocontouring on the PET scan and not the SUV 40% and SUV 50%.

Conclusion

The SBR technique was superior to the fixed threshold technique using SUV 40% and SUV 50% for target volume delineation and therefore should be the method for autocontouring on PET scan.

Creating metabolic tumour volume from PET alone without considering the anatomical part from the CT scan can fail in most cases to give an accurate delineation of tumour.

Integrating the metabolic tumour volume obtained with autocontouring using the SBR technique on the PET scan along with anatomical part on CT which does not show uptake on the PET scan and clinical findings probably will be the best method of target volume delineation.

The PET uptake of primary tumour and node is not clearly seen on the TPS, so the target volumes obtained with autocontouring using the SBR technique on the PET scanner may be superior to that obtained on the TPS.

Since only in a small percentage of patients, the PET and CT volumes were not matching and the difference in volume was not significant, CT alone could be used for target volume delineation.

PET scan gave additional information on synchronous primary in 12% of patients and significant uptake in nodes also, which influenced the management.

Defining an accurate biological tumour volume on PET scan, for target delineation for radiation therapy would assist in dose escalation.

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Appendix

Informed Consent Form

Christian Medical College, Vellore
Department of Radiation therapy

To see the difference in target volume when we use combined ^{18}F-FDG-PET/CT for RT target delineation of head-and-neck cancer compared with CT alone.

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.

[ ]

(ii) 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 my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) 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). [ ]

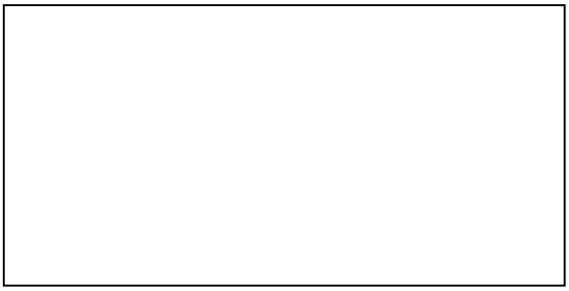
(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject.

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or



Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness:

_____

INFORMATION SHEET AND CONSENT FORM

Christian Medical College, Vellore
Department of Radiation therapy

To see the difference in target volume when we use combined ^{18}F-FDG-PET/CT for RT target delineation of head-and-neck cancer compared with CT alone.

Patient's Information sheet

You are being requested to participate in a study which aims to compare difference in target volumes of radiation therapy in head and neck cancers when PET CT is used for simulation.

What does this study do?

This is an observational study to compare the volume differences seen between CT and PET/CT wise volume delineation in Intensity Modulated Radiation therapy (IMRT) in head and neck cancers**.** In this study, the volume delineation for radiation therapy will be done by two different modalities of imaging ie CT and PET/CT. We will compare the volume difference when we use these two different methods. This study may also give us an insight into which areas of head and neck malignancies should be planned and treated with higher dose based on the dosimetric analysis.

Does this study have any side effects?

This is an observational study with no particular side effects. You will undergo a planning PET/CT scan following which target volume delineation will be done with CT and PET/CT. For your treatment GTV is delineated on CT will be performed according to current clinical protocols and treatment will be carried out on current standard clinical guidelines.

If you take part what will you have to do?

If you agree to participate in this study, you will only have to sign the consent form. The volume delineation, planning and dosimetric analysis will be done by the Radiation Oncologist with the help of Medical Physicist. There will be no change in your treatment and will be as per the standard.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

Since this is an observational study, no particular study related side effects are expected.

Will you have to pay for the study?

This is an observational study and there is no change in the standard treatment of care. You need not pay anything more than the regular treatment charges as applicable for the radiation therapy and the chemotherapy.

What happens after the study is over?

You will be advised to have regular checkups at the specified intervals as advised which will be every 3 months in the first one year, every six months for the next two years and yearly thereafter.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission.

If you have any further questions, please ask ----------, Ph No: ----------, email: ----------

PATIENT PROFORMA SHEET

Name: Case No:

Hospital Number: RT No:

Age: Sex:

Address:

Occupation:

Phone number:

Presenting complaints:

History of presenting illness:

Symptom	Yes/No	Duration
1. Throat pain		
2. Cough		
3. Hoarseness of voice		
4. Dyspnoea		
5. Stridor		
6. Headache		
7. Neck swelling		
8. Ulcer		
9. Dysphagia		
10. Others		

Past history:

Associated diseases: Premalignant conditions
DM/HTN/Pull TB/Others
Allergies

Prior malignancy

Prior surgery
Prior major illness

Addictions: Smoking
Other tobacco products
Alcohol

Drug history:

Treatment history:

	Yes/No	Outside/CMCH
Surgery		
Chemotherapy		
Radiation therapy		

Family history:

GENERAL PHYSICAL EXAMINATION

Performance Status: ECOG 0 / 1 / 2 / 3 / 4

	Yes/No
Pallor	
Icterus	
Cyanosis	
Clubbing	
Lymphedema	

Tracheostomy Yes/No
Ryle's tube Yes/No

Height: _____ cms Weight: _____ kgs
BSA : _____ m2

SYSTEMIC EXAMINATION

Respiratory system:

Cardiovascular system:

Per abdomen:

LOCAL EXAMINATION

Oral cavity:

Mouth opening:
Tongue movements:
Teeth:
Oral hygiene:
Lips:
Buccal mucosa:
Alveolus:
GB sulcus:
Retro molar trigone:
Tonsillar fossae:
Others:

NPL Scopy / IDL scopy:

Neck:

Thyroid:
Nodes:

Side	Level	Number	Size	Mobile/Fixed	Discrete/Matted	Skin – Free/Tethered/Ulcerated
Right	1 a					
	1 b					
	2					
	3					
	4					
	5					
Left	1 a					
	1 b					
	2					

	3					
	4					
	5					

CLINICAL DIAGNOSIS:

T N M

Stage:

Biopsy :

Number:

Squamous Cell Carcinoma / Adenosquamous carcinoma

Well differentiated / Moderately differentiated / Poorly differentiated

CT scan: