INTRODUCTION

Head and neck malignancy is the sixth most prevalent type of cancer worldwide. The treatment methods include surgery, chemotherapy, radiotherapy, either as a single modality or in combination. The choice of treatment depends on the size, location of the tumour, staging and patient condition.

Irradiation of head and neck tumours are increasingly being used and usually involves the region of temporal bone and Eustachian tube. The auditory apparatus which is sensitive to radiation, is often in the field of irradiation leading to numerous hearing complaints. Sequelae from this treatment and its clinical manifestations may occur during the treatment, just after finishing it or even months after finishing it.

The effects of radiation on hearing function have not received much attention unlike other sequelae like xerostomia, mucositis which have been extensively studied. Many patients are developing conductive hearing loss, but SNHL is more disabling to the patient because it has a chronic and often progressive history.

The experimental datas so far on hearing loss are sparse and mostly of historical interest, dating back to 1930’s. In most studies, experimental animals

(Often dogs or guinea pigs) have been exposed to large single doses of ionizing radiation and sacrificed shortly after treatment.

With modern conformal radiation techniques, the incidence of radiation induced side effects on hearing apparatus has reduced a lot, due to better visualisation of the organs at risk (OAR) on planning CT images and a better capability to spare inner ear.

Newer technologies like intensity modulated radiotherapy (IMRT) helps us in giving dose adjustments to organs at risk. Various published data clearly states that IMRT has significantly reduced the radiation dose received by cochlea, thereby reducing the incidence of SNHL.

But exposure of Eustachian tube in the field of radiation makes conductive pattern of hearing loss more prominent complaint in head and neck malignancy patients, which is unnoticed. So, majority of patients developed ear fullness, ear pain and tinnitus initially during radiotherapy which then subsides on its own after 4 to 6 weeks once radiotherapy has been stopped.

In addition to radiation, Cisplatin (cis-diammine- dichloro platinum) is commonly used as a radiosensitizer in radiotherapy department. It is also used as a main chemotherapeutic agent in some malignancies of head and neck like Nasopharyngeal carcinoma. Major known side effect of cisplatin is ototoxicity, particularly for higher frequencies with late onset.

Audiometry is a technique used by an audiologist or an otolaryngologist to measure hearing. There are two types of hearing loss, conductive hearing loss- which is due to exposure of radiation on the external and middle ear, sensorineural hearing loss – which is related to radiation effects on the cochlear apparatus.

Hence the present study has been taken up to determine incidence of hearing loss and other hearing complaints in head and neck malignancy patients undergoing radiotherapy.

PRINCIPLES OF RADIOTHERAPY

INTRODUTION

(i) Radiotherapy is a clinical branch of medicine which include use of ionizing radiation for the purpose of therapeutic gain in benign or malignant tumours. Used modalities are

a) External beam radiotherapy -EBRT (Teletherapy) - Radiation beam is directed from a machine placed outside the patient to a target volume inside.

b) Brachytherapy : Radioactive material introduced directly within the tumour.

(ii) The standard megavoltage treatment in use today is linear accelerator. In a linear accelerator, a stream of electrons produced from a filament in a electrically charged field is accelerated through a series of wave guides in conjunction with radiofrequency pulse to within a fraction of the speed of light.

(iii) The dose in therapeutic radiation is measured as absorbed dose with SI unit Gray (Gy) where 1 Gy is equal to 1 joule of energy absorbed per kg of material.

(iv) This electron beam can itself be used for treatment or can impact on a target to produce a photon beam of maximum energy between

4 and 20 MV according to the design and calibration of the machine. Beams of 10 MV or greater are mostly used in the treatment of abdominal and pelvic tumours, while beams of 4 to 6 MV are used in treatment of head and neck malignancy.

Fig 1- Linear Accelerator

EVOLUTION IN RADIATION DELIVERY

(i) The aim of radiotherapy planning is to deliver a homogenous dose to the primary tumour and potential areas of micro metastasis, while minimizing the dose to the organs at risk. Accurate tumour localization is central to radiotherapy planning.

(ii) For more than two decades conventional two-dimensional (2D) planning has utilized standard orthogonal x-ray films taken by a simulator, a diagnostic x-ray machine connected to a television

screen which is geometrically identical to the linear accelerator or cobalt-60 treatment unit. Cross wires mounted in the light beam from the simulator define the size of the area to be treated.

(iii) As diagnostic x-rays have poor soft tissue resolution, the radiotherapist defines the area to be treated on the simulator films using bony landmarks together with clinical and radiological knowledge of the position and extent of the tumour. Resultant volumes are therefore relatively crudely derived from 2D x-ray films with, at best, assumed knowledge of the position of critical soft tissue structures, tumour and organs at risk.

(iv) Fast computers introduced in the 1990s permitted the use of CT scanning and other axial slice imaging modalities to allow the radiotherapist to define the tumour and organ at risk using software which permits a three-dimensional (3D) reconstruction of these volumes- 3D conformal radiotherapy (3DCRT). The software also calculates the dose of radiation delivered to specific volumes of both the tumour bearing target and normal tissue 'organs at risk' and displays these by dose–volume histograms.

(v) The development of intensity modulated radiotherapy (IMRT) is a potential leap ahead. Multiple beams of varying intensities allow the creation of irregular shapes, if necessary, with concave

contours. The ability to reduce toxicity by avoidance of critical organs at risk, specifically the parotid glands, hearing apparatus without compromising tumour coverage and control has been clearly demonstrated.

(vi) There is a potential downside to IMRT. Since multiple beams are used, often seven or more as compared to two or three with 2D or 3D conformal radiotherapy, a larger volume of normal tissue receives low dose radiation with concerns being raised about the potential of an increased risk of second malignancies.

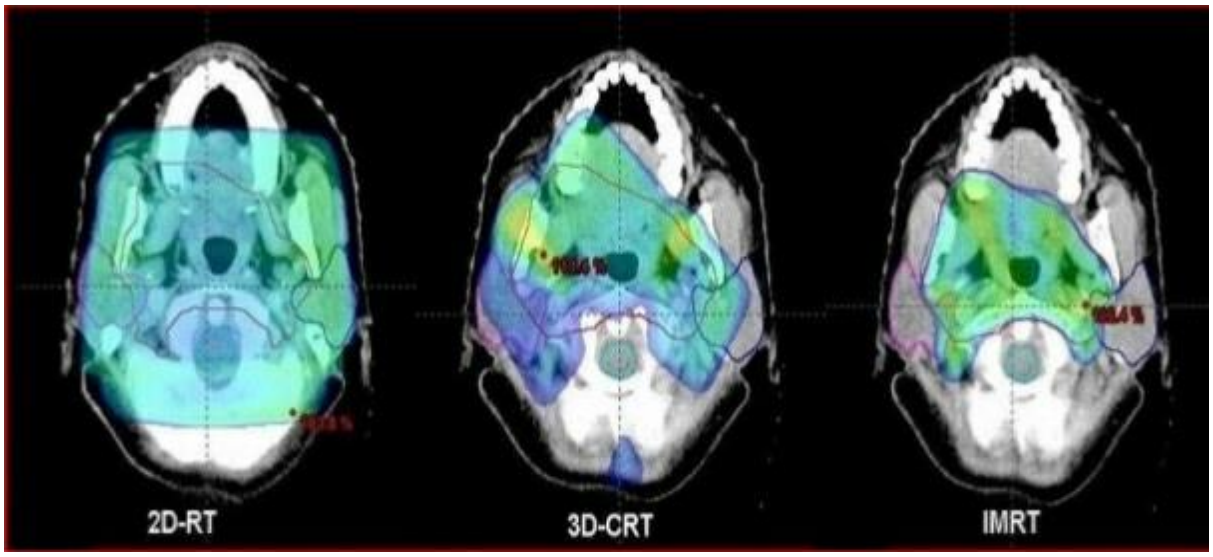


Fig 2- Showing comparison of RT techniques.

CHEMOTHERAPY DRUGS

(i) Chemo therapy plays a crucial role in multimodality management of locally advanced head and neck cancer in improving locoregional control and survival.

(ii) It is commonly used concurrently with radiation therapy or as induction 2 or 3 drug therapy before radiation therapy. Commonly used drugs are Cisplatin, Carboplatin, Fluorouracil, Bleomycin, Methotrexate.

- Cisplatin- used either weekly dose of 30 to 40 mg/m^2 or 75 to 100 mg/m^2 three weekly.
- Carboplatin- dose is AUC 5 every 3 weekly
- Fluorouracil- dose is 10 to 12mg/kg intravenous route for three days followed by 7 to 10 mg/kg intravenous weekly. Another regimen is 1000mg/m^2 infusion for 4 days.
- Bleomycin- dose is 15 units/m^2 intramuscular once or twice each week. As a continuous infusion, it is administered as 15 units/m^2 daily for seven days, 3weekly.
- Methotrexate- general oral dosage is 2.5 to 7.5 mg daily. Intravenous dosage is 40 to 50 mg each week.

TYPES OF TREATMENT

Radiation therapy can be either prescribed with curative or palliative intent. There are different types of delivering radiotherapy.

(i) DEFINITIVE RADIATION THERAPY

Is given upfront as the only treatment modality or concurrently with the chemotherapy. The dose is usually 60-70 Gy in 30 to 35 fractions (#) over 6 to 7 weeks. It is conventionally delivered 5 days a week.

(ii) SEQUENTIAL THERAPY

It is usually induction chemotherapy which is a two drug combination (Cisplatin or Fluorouracil) given for 2 to 3 cycles followed by definitive radiation therapy.

(iii) ADJUVANT RADIATION (CHEMO) THERAPY

This is offered after surgery in cases with poor prognostic factors and is usually 50 to 60 Gy in 25 to 30 fractions in 5 to 6 weeks. In highrisk patients with positive surgical margins or extracapsular spread of disease, adjuvant concurrent chemo radiation therapy is advised.

TARGET DEFINITION AND COVERAGE

(i) Nowadays radiotherapy planning is done using computed tomography (CT) images obtained within the immobilization shell. According to the clinical situation, the gross tumour volume (GTV) and/or clinical target volume (CTV) is outlined on screen. This allows for inclusion of areas at risk, such as nodal areas, or potential routes of spread. [1,2]

(ii) A number of radiotherapy treatment plans include two consecutive phases of treatment, the first covering areas of known involvement together with areas at risk and the second solely the areas of known involvement. In this case, a phase 1 CTV and a phase 2 CTV are outlined separately. These volumes are 'grown' three-dimensionally to derive the planning target volume (PTV) for each phase by adding an additional margin. This margin allows for patient movement and normal set-up variation.

(iii) In most cases, this margin is 1 cm although tighter margins may be used in circumstances where there is a need to minimize dose to adjacent normal tissues. Organs at risk, such as spinal cord, ear, parotid and submandibular glands are also outlined. Radiotherapy planning technicians and physicists then devise a treatment plan which defines the positioning and weighting of two or more photon beams to provide adequate coverage of the PTV

while not exceeding agreed maximum doses to adjacent normal tissues.

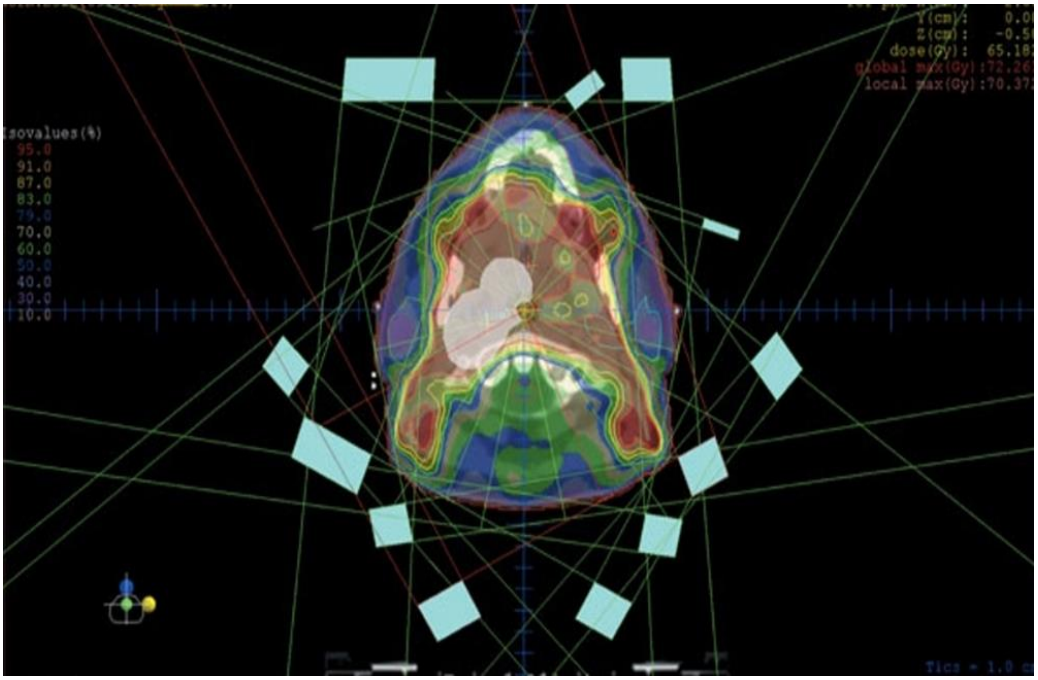


Fig 3- Radiotherapy plan demonstrating Intensity Modulated Radiotherapy (IMRT) to treat nasopharyngeal carcinoma.

RADIOTHERAPY FRACTIONATIONS

Optimum total dose is a balance between tumour cell kill and the impact of early and late side effects. Different fractionations available are conventional fractionation, hypofractionation, hyper fractionation and accelerated fractionation.

1. CONVENTIONAL FRACTIONATION

(i) The term conventional fractionation refers to the use of individual treatments (fractions) of 1.8–2Gy each given daily for 5 days per

week. Curative doses are generally in the range 66–70Gy delivered in 33–35 fractions over 6.5–7 weeks.

(ii) Postoperative doses have been 10 per cent lower, in the range of 60–64Gy delivered in 30–32 fractions over 6–6.5 weeks. This lower dose is on the basis of lower doses being sufficient to control microscopic (as opposed to bulk) disease and on the lower tolerance of patients to radiotherapy when given postoperatively.

2. HYPOFRACTIONATION

These are courses of treatment using larger fraction sizes than 2Gy, which means fewer fractions and larger doses per fraction.

3. HYPERFRACTIONATION

Hyper fractionation involves use of smaller fractions (less than 1.8Gy). The use of smaller fractions may reduce the risk of late damage for a given total dose, but the increase in the overall treatment time tends to reduce the effectiveness of treatment. [3]

4. ACCELERATED FRACTIONATION

(i) Accelerated regimes are those where the overall treatment time has been shortened. While this can be done by hypofractionation, a greater benefit can theoretically be obtained from combining acceleration with hyper fractionation and treating two or three times each day. This combines the reduced risk of normal tissue

damage with the benefits of completing treatment in a shorter overall time. Sufficient time between fractions must be allowed for repair of sublethal damage.

(ii) Some schemes in the past have used a 4-hour gap but it is now believed that a minimum 6-hour interval between fractions is preferable. A good example is the CHART regime (Continuous Hyper fractionated Accelerated Radiotherapy) in which radiotherapy at 1.5Gy per fraction is given three times daily and continuously for 12 days to a total dose of 54Gy (i.e. without a weekend break). [4]

GENERAL PRINCIPLES OF TREATMENT

(i) Patients with head and neck cancer should be seen in a multidisciplinary setting by a team comprising specialist surgeons, oncologists, pathologists, radiologists and palliative care doctors, together with dietitians, speech and language therapists and clinical nurse specialists.

(ii) At the initial visit, a full history and examination, including nasal endoscopy should be carried out. Further pre treatment assessment should include examination under anaesthesia (EUA) and tumour biopsy, imaging in the form of computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck, chest x-ray or CT thorax, full blood count, urea and electrolytes, liver

function tests, dietitian assessment, and assessment by a speech and language therapist. In particular, patients with poor dietary intake and a low body mass index should be identified and considered for elective percutaneous gastrostomy or nasogastric feeding. [5]

(iii) Dental assessment is also essential for any patient in whom the radiation field is likely to include either mandibular or maxillary alveolus, since dental extraction subsequent to a radical dose incurs a greater risk of chronic non-healing ulceration or osteoradionecrosis.[6]

(iv) Written informed consent, detailing both the acute and late toxicities of radiation, should be obtained prior to embarking on a course of radical treatment. Smoking cessation should be advised since smoking is known to both increase radiation-induced toxicity and reduce cure rates. Alcohol cessation should also be advised at least for the duration of the radiation since, again, toxicity is likely to be increased. [7,8]

(v) Most patients with early tumours will usually be treated in a single-phase radiation plan, although the field arrangements will vary for each site. However, tumour sites such as tongue base and hypopharynx, which are associated with a higher risk of occult

nodal micro metastasis, are more likely to receive their radiation in two phases.

(vi) Phase 1 is typically a larger volume encompassing the primary tumour, involved lymph nodes and potential areas of microscopic nodal spread while in phase 2, a smaller volume including the primary tumour and involved lymph nodes alone is treated. Elective irradiation of lymph nodes is indicated when the risk of microscopic lymphatic spread exceeds 15–20 per cent.

FIELD ARRANGEMENT AND BEAM MODIFICATION

(i) Lateral parallel opposed fields and a wedged pair field arrangement are the most commonly employed, although more complex beam arrangements are sometimes necessary.

(ii) The most common methods of beam modification used in radical radiotherapy are the use of wedges and shielding. A radiation beam may be modified by the introduction of a wedge which alters the dose distribution, due to greater absorption of radiation through the thicker end of the wedge.

(iii) In head and neck radiation, wedges are used primarily to improve dose homogeneity of unilateral wedged pair fields, although they may also be employed to compensate for the natural curvature of skin surfaces, or for a sloping target volume.[9]

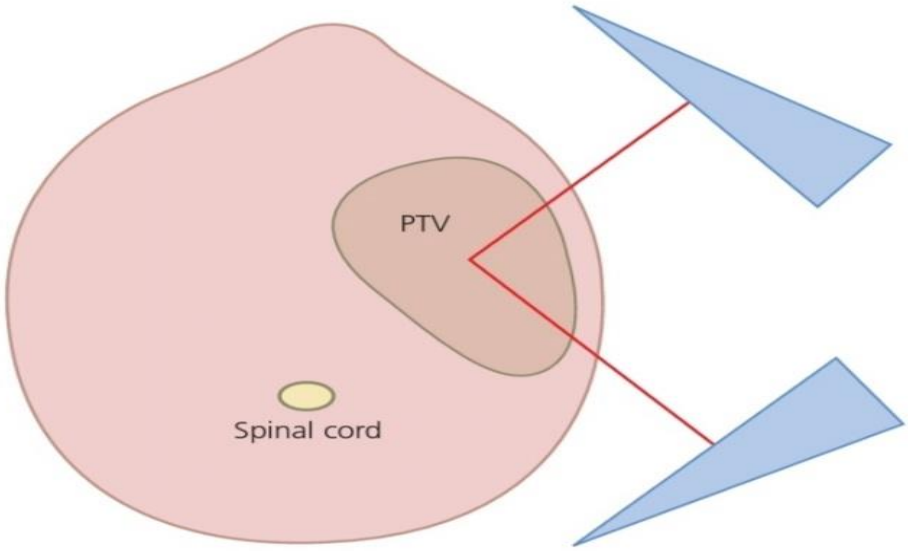


Fig 4- Unilateral wedge pair- dose homogeneity improved through the use of wedged radiation fields.

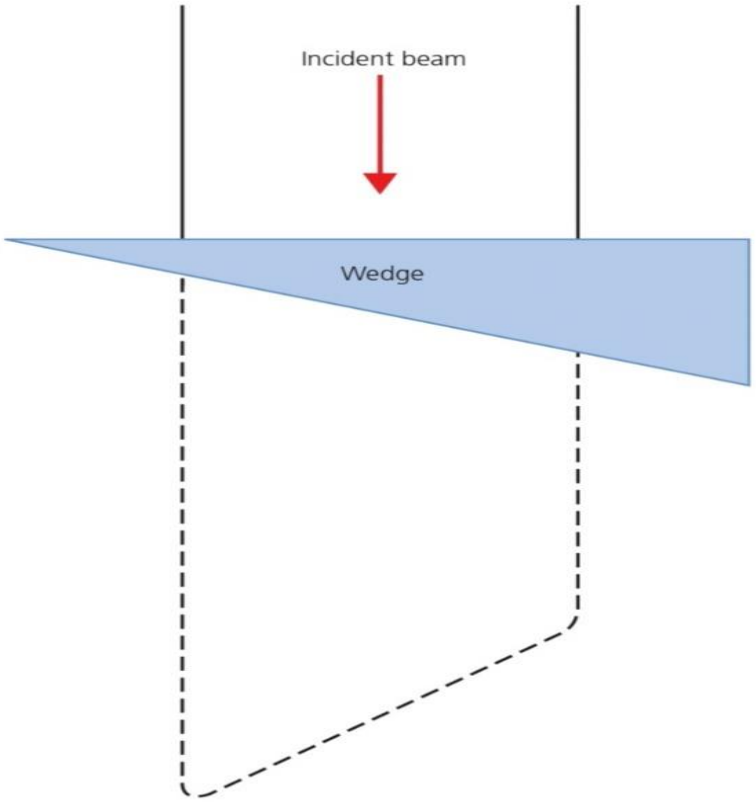


Fig 5-Radiation beam modified by introduction of wedge, showing greater attenuation of the beam through the thicker end of the wedge.

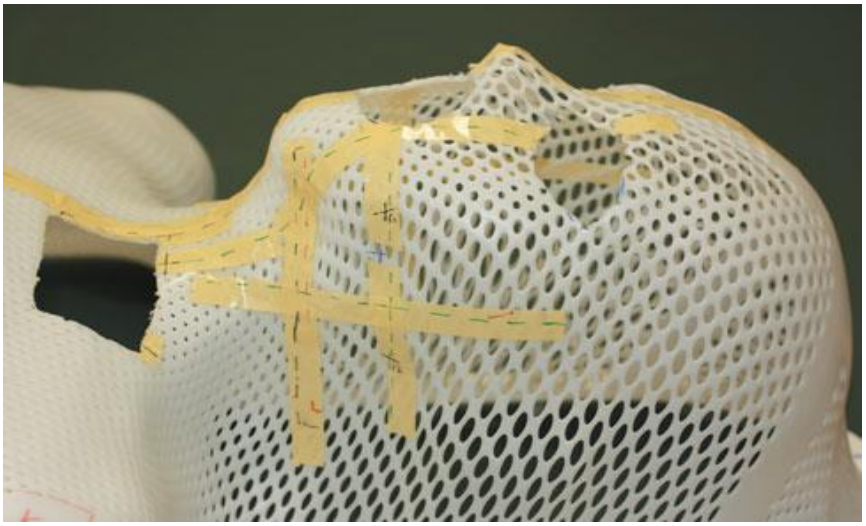


Fig 6- Individually moulded thermoplastic shell covering the head and neck area used for patient immobilization. Field centres and field borders are marked on the outside of the shell. The areas around the eyes and mouth are cut out for patient comfort and the part of the lower neck field to reduce the surface dose.

SITE SPECIFIC TREATMENT PLANNING

1. LARYNX

The larynx is divided into

(i) Supra glottis - laryngeal epiglottis, false vocal cords, ventricles, aryepiglottic folds and arytenoids.

(ii) Glottis - true vocal cords, anterior and posterior commissure.

(iii) Sub glottis - 10mm below the free edge of the vocal cords to the inferior border of the cricoid cartilage.

Each has its own natural history and pattern of spread, which dictates treatment recommendations. Immobilization for all larynx cancer patients should be in the supine position with the cervical spine straight.

GLOTTIS

(i) Most stage T1/T2, N0 glottic tumours are treated with radical radiotherapy, with surgery reserved for salvage after radiotherapy failure. A lateral parallel opposed field arrangement is used, with 5 cm (T1) or 6 cm (T2) square fields centred on the vocal cord (1 cm below thyroid promontory and anterior to the lower border of C5 cervical vertebra).

(ii) For T1 lesions, the radiotherapy portal extends from the lower border of the hyoid bone superiorly, to the lower border of the cricoid cartilage inferiorly. Anteriorly, the field border should be in air at the field centre, and posteriorly through the anterior part of the vertebral body.

(iii) For T2 tumours, the field size is extended based on the supraglottic and/or subglottic disease extension. In cases of extensive subglottic extension, it is recommended that the para oesophageal and paratracheal lymph nodes are included.[10]

(iv) The dose prescription, dependent on field size:

- < 36 cm2, 50Gy in 16 fractions treating daily, five fractions a week;
- 36–42 cm2, 55Gy in 20 fractions treating daily, five fractions a week;

- * > 442 cm2, 64–66Gy in 2Gy per fraction, treating daily, five fractions a week.

SUPRA GLOTTIS

(i) Radical radiation is indicated for most early (T1/T2, N0) supraglottic tumours. However, in contrast to glottic disease, the supraglottic region has richer lymphatics and, consequently, a higher incidence of occult lymph node metastases in levels II and III.

(ii) All patients, therefore, require elective nodal irradiation of these levels. This is achieved through the use of a two-phase technique. Phase I includes the primary tumour, the whole larynx, the pre-epiglottic space and the cervical lymph nodes bilaterally in levels IB, II and III anterior to the spinal cord. Phase II includes the primary tumour and larynx only. Parallel opposed wedged fields are used for both phases.

(iii) Dose prescription: The total dose is 66–70Gy in 2Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50Gy in 2Gy per fraction, treating daily, five fractions a week, to microscopic disease (phase I: 50 Gy/25#/5 weeks; phase II: 20 Gy/10#/2 weeks).

SUBGLOTTIC TUMOURS

(i) Subglottic tumours are rare, and usually present with locally advanced disease requiring surgery followed by adjuvant radiotherapy. However, for patients with early-stage disease, definitive radiation is a recognized larynx preservation approach.

(ii) Although the incidence of cervical lymph node metastases is rare, the involvement of paratracheal nodes is estimated at 50 per cent, and therefore these nodes should be treated electively.

(iii) The radiation portal should extend from the top of the thyroid cartilage superiorly to the mid-trachea inferiorly. This requires the use of either an anterior oblique beam arrangement or a coronal technique, in order that good coverage of the inferior-most area is achieved.

(iv) Dose prescription is 66–70Gy in 2Gy per fraction, treating daily, five fractions a week.

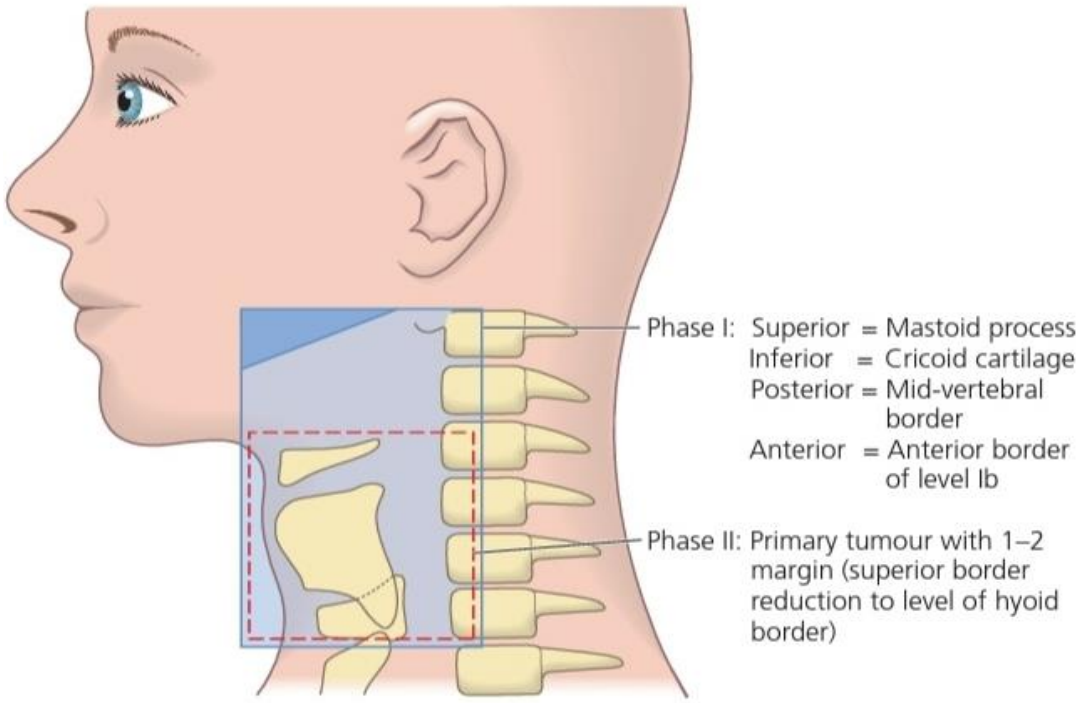


Fig 7- Radiation therapy technique for carcinoma larynx

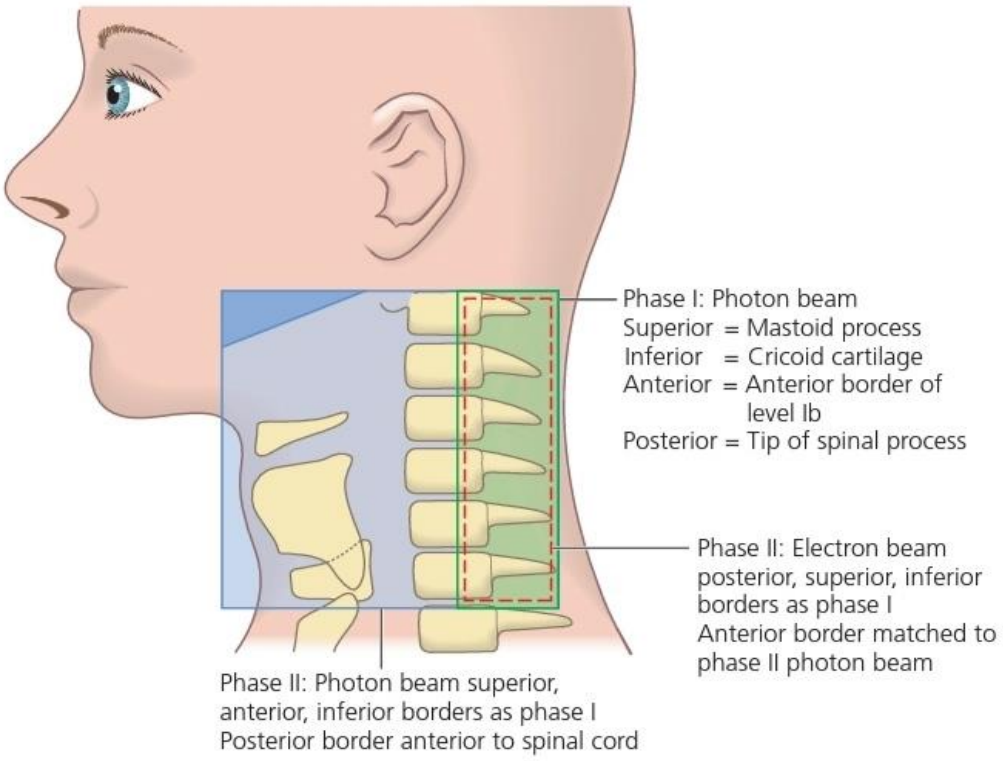


Fig 8- Field borders of phase I and phase II will be coincident for advanced cases.

2. OROPHARYNX

The oropharynx is divided into four main subsites- the tonsil, tongue base, soft palate, posterior pharyngeal wall.[11,12]

TONSIL

(i) Small (T1/T2, N0) well-lateralized tumours of the tonsil are amenable to treatment with irradiation alone. Immobilization is in the supine position with the cervical spine straight.

(ii) The target volume for the macroscopic dose includes the tonsillar fossa while the ipsilateral cervical lymph nodes, levels IB–IV, are treated to a microscopic dose.

(iii) This is achieved by using a wedged pair field technique to treat the tonsil, with anterior and posterior oblique radiation portals, extending from the hard palate superiorly to the lower border of the hyoid bone inferiorly. This field arrangement encompasses the upper cervical lymph nodes levels IB–II. At the level of the hyoid bone, a matched ipsilateral anterior neck radiation portal is used to treat the cervical lymph node levels II–IV.

(iv) Dose prescription: The total dose is 66–70Gy in 2Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50Gy in 2Gy per fraction, treating daily, five fractions a week,

to microscopic disease (phase I: 50Gy/25#/5 weeks; phase II: 20Gy/10#/2 weeks).

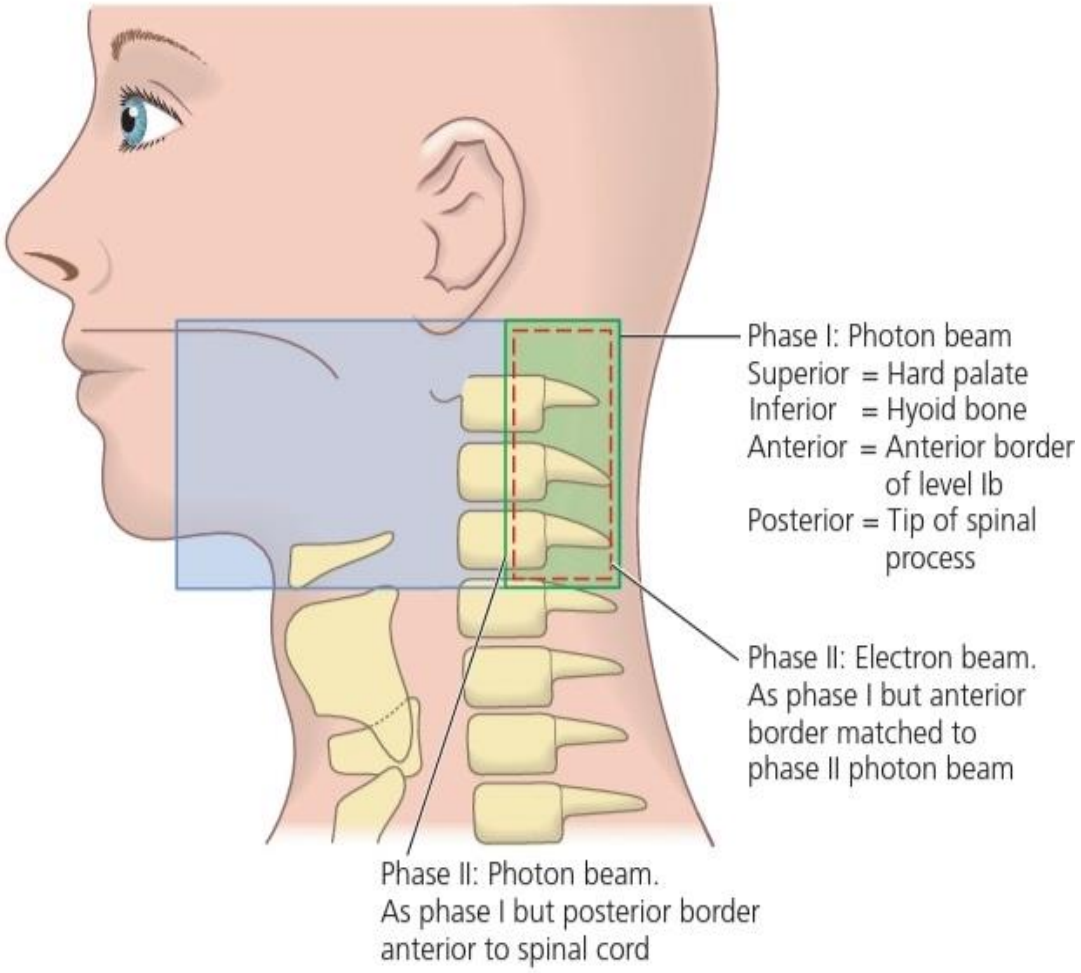


Fig 9 – radiotherapy technique for oropharyngeal tumours using parallel opposed fields.

TONGUE BASE

(i) Most tongue base tumours present with locally advanced and/or node positive disease, which are best treated with radical chemoradiation, since resection is usually associated with poor swallow and speech function. However, small tongue base tumours (T1/T2) presenting early (N0), particularly exophytic

tumours without fixity, may be offered radical radiotherapy, with locoregional control rates of approximately 70 per cent.

(ii) However, either side of the neck may harbour occult lymph node metastases, so bilateral neck irradiation to levels IB–V is mandatory. Immobilization is in the supine position with the cervical spine straight. The radiation technique employs the use of lateral parallel opposed fields to the primary tumour and upper echelon lymph nodes, with the field extending from the hard palate superiorly to the lower border of the hyoid bone inferiorly.

(iii) Anteriorly, the CTV extends to include the level IB lymph nodes or 1 cm anterior to the tumour, whichever is the more anterior. Posteriorly, the CTV includes the posterior level II and level V lymph nodes. After 40–44Gy, the posterior border is reduced to come off the spinal cord and the primary tumour continues to the radical dose. The posterior upper neck is treated with applied electron fields to complete the dose for microscopic disease. The lymph nodes below the level of the hyoid bone are treated with a bilateral anterior neck field with midline shielding as described above under Larynx, but with matching at the level of the hyoid bone.

(iv) Dose prescription: The total dose is 66–70Gy in 2Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50Gy in 2Gy per fraction, treating daily, five fractions a week,

to microscopic disease (phase I: 50Gy/25#/5 weeks; phase II : 20Gy/10#/2 weeks).

SOFT PALATE

(i) Immobilization is in the supine position with the cervical spine straight. For early (T1/T2) node-negative tumours, elective nodal irradiation is not necessary. The target volume is therefore the GTV with a 2 cm margin, and can be irradiated with small lateral opposed radiation portals to the radical dose.

(ii) Dose prescription: The total dose is 66–70Gy in 2Gy per fraction, treating daily, five fractions a week.

3. HYPOPHARYNX

Subsites of hypopharynx are-

Pyriform fossa, Posterior pharyngeal wall and Post cricoid. [13,14,15]

PYRIFORM FOSSA

(i) Immobilization is in the supine position with the cervical spine straight. The target volume includes the primary tumour and levels IB–V lymph nodes bilaterally.

(ii) The radiation technique usually involves the use of lateral opposed beams to treat the primary disease, involved nodes and upper cervical lymph nodes in phase I, with a small matched

lower anterior split neck field to treat the lower echelon lymph nodes. The lateral radiation portals extend superiorly from the skull base to the lower border of the cricoid cartilage inferiorly.

(iii) Dose prescription: The total dose is 66–70Gy in 2Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50Gy in 2Gy per fraction, treating daily, five fractions a week, to microscopic disease (phase I: 50Gy/25#/5 weeks; phase II: 20Gy/10#/2 weeks).

POSTERIOR PHARYNGEAL WALL AND POSTCRICOID REGION

(i) Immobilization is in the supine position with the cervical spine and upper thoracic spine as straight as possible. For both posterior pharyngeal wall and post cricoid tumours, an inherent radiation planning difficulty is the ability to adequately cover the inferior-most extent of disease once a margin has been added for CTV and PTV. The CTV includes the primary tumour with a 2 cm (posterior pharyngeal wall) or 5 cm (post-cricoid) margin craniocaudally and levels IB–V lymph nodes bilaterally.

(ii) It is therefore usually necessary to use the coronal technique, although even this may not achieve an adequate dose distribution in the superior mediastinum. In this instance, a low-weighted anterior field with a superior to inferior wedge may increase the

dose in this region, although often at the expense of spinal cord dose.

(iii) Dose prescription: The total dose is 66–70Gy in 2Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50Gy in 2Gy per fraction, treating daily, five fractions a week, to potential microscopic disease.

4. NASAL CAVITY AND PARANASAL SINUSES

PARANASAL SINUS [75,76]

(i) Immobilization is in the supine position with the cervical spine straight and a mouth bite in place to exclude the tongue and lower part of the oral cavity from the radiation field. CT planning is recommended due to the close proximity of many critical OAR.

(ii) The CTV is therefore the maxillary sinus, the ethmoid sinus, the nasal cavity, pterygoid fossa and the lateral pharyngeal node. It may be necessary to consider IMRT to boost to this area (‘field within a field’) to improve PTV coverage and dose homogeneity, although care must be taken with the dose to the optic chiasm and brainstem.

(iii) Dose prescription: The total dose is 66–70Gy in 2Gy per fraction, treating daily, five fractions a week.

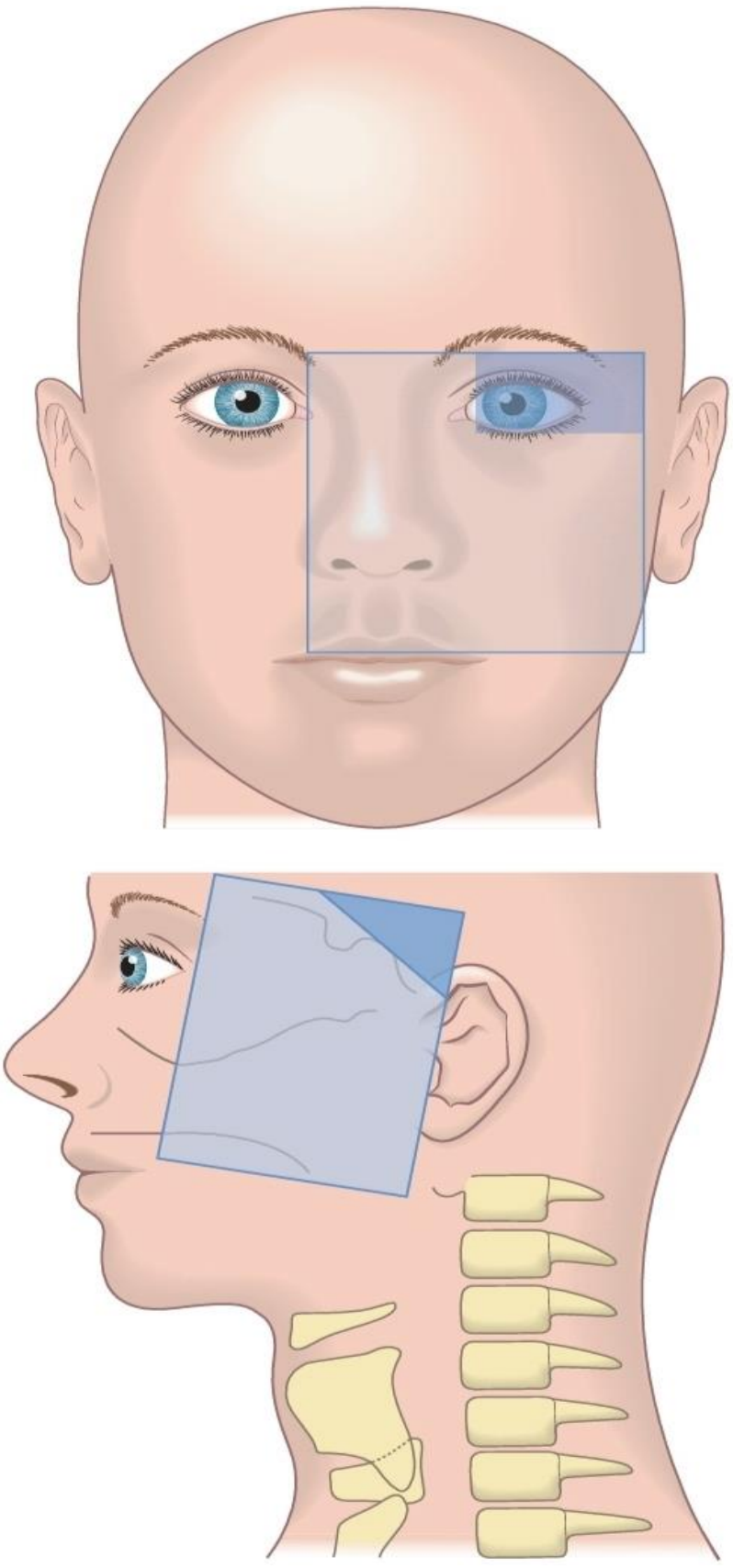


Fig 10– Anterior and lateral field for maxillary antrum tumour.

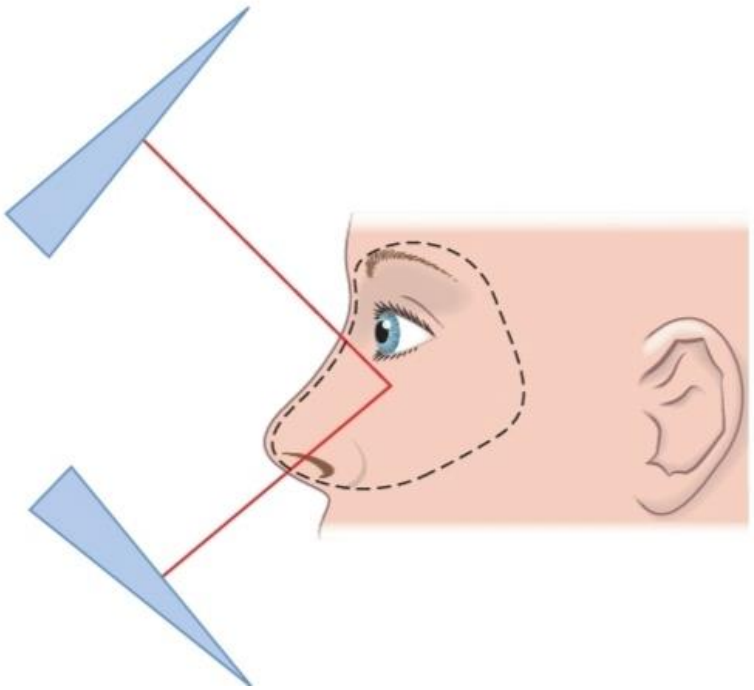


Fig 11 – Ethmoid tumour- using superior and inferior anterior oblique techniques

NASAL CAVITY

(i) As nasal cavity tumours are being treated with radical radiation, rather than surgery, immobilization and CT planning are recommended. The probability of lymph node metastases is very low, such that the CTV includes the primary lesion and a 1 cm margin.

(ii) The field arrangement may be either an anterior wedged pair of photon fields, or in more advanced disease, a three-field technique similar to maxilla/ethmoid sinus plans, where the entire nasal cavity is included in the CTV.

(iii) Dose prescription: The total dose is 66–70Gy in 2Gy per fraction, treating daily, five fractions a week.

NASOPHARYNX

(i) The primary treatment modality for locoregionally confined nasopharyngeal carcinoma is radiotherapy as the tumour is radiosensitive.

(ii) Nasopharyngeal carcinoma has a tendency of early spread to para nasopharyngeal and cervical lymphatics, hence prophylactic nodal treatment is mandatory and radiotherapy can cover these areas adequately.

(iii) For effective treatment of nasopharyngeal carcinoma, the radiation target volume includes the nasopharynx and also the para nasopharyngeal space, oropharynx, base of skull, sphenoid sinus, posterior ethmoid sinus and posterior half of maxillary antrum. Cervical nodal irradiation is mandatory even in clinically node-negative patients due to the high incidence of neck relapse in the absence of prophylactic nodal irradiation. Employing high megavoltage radiation, a dose of 65–70Gy is normally given to the primary tumour, 65–70Gy to the involved neck nodes, and 50–60Gy to the node negative neck.

(iv) Conventional two-dimensional treatment planning and radiotherapy use two or three large fields to cover the primary upper neck and one or two fields to cover the lower neck.

5. ORAL CAVITY

Oral cavity is divided into several subsites- the oral tongue, floor of mouth, buccal mucosa, alveolus and hard palate. [18,19,20]

TONGUE

(i) Immobilization is in the supine position with the cervical spine straight, and a mouth bite may be considered. The CTV includes the primary tumour with a 2 cm margin, which if well lateralized, may be achieved with a wedged pair field arrangement.

(ii) Tumours that are more deeply infiltrating or approaching the midline, lateral parallel opposed beams are required, since the CTV is then expanded to include irradiation of the neck.

(iii) The dose prescription for interstitial brachytherapy is 60Gy over 6 days with iridium-192 LDR. For EBRT, the total dose is 66–70Gy in 2Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50Gy in 2Gy per fraction, treating daily, five fractions a week, to microscopic disease.

FLOOR OF MOUTH

(i) The mouth should be held open during immobilization with a mouth bite, to limit the dose to the upper oral cavity, in particular the hard palate. Tumours of the floor of mouth are frequently in the midline, such that EBRT requires the use of lateral parallel opposed radiation portals to cover the target volume, which includes the primary tumour and locoregional lymph nodes.

(ii) The dose prescription for interstitial brachytherapy is 60Gy over 6 days with iridium-192 LDR. For EBRT the total dose is 66–70Gy in 2Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50Gy in 2Gy per fraction, treating daily, five fractions a week, to microscopic disease.

6. INTRACRANIAL TUMOURS

(i) The most commonly employed radiotherapy techniques in the management of CNS tumours are partial-brain irradiation, whole-brain radiotherapy (WBRT), craniospinal irradiation (CSI), stereotactic radiosurgery (SRS), fractionated stereotactic radiotherapy (FSRT), less commonly brachytherapy, and, recently, emerging utilization of proton therapy.

(ii) The values for whole-brain fractionated radiotherapy at 2 Gy/fraction are 60 and 70 Gy, respectively. With partial-brain

irradiation, the corresponding values are 70 and 80 Gy, respectively. In the setting of fractionated radiotherapy with a fraction size <2.5 Gy, quantitative analyses of normal tissues effect in the clinic (QUANTEC) have estimated 5% and 10% rates of symptomatic necrosis at 72 and 90 Gy maximum equivalent doses in 2- Gy fractions, respectively

EAR TOXICITY IN RADIOTHERAPY

The acute ear complications of radiation therapy are classified as external, middle, and inner ear injuries.

(i) The acute external ear complications - otitis externa or skin reactions involving the preauricular region, the auricle, and the external auditory canal that occur in about 28% of head and neck cancer patients treated with radiation therapy.[21]

(ii) The acute middle ear complications - mastoiditis, Eustachian tube dysfunction, consequential otitis media, and transient conductive hearing loss occur in 40–45% of head and neck cancer patients during or after radiation therapy.

(iii) The acute inner ear complications - sensorineural hearing loss (SNHL) and tinnitus. SNHL may occur early after treatment in up to 50% of patients with head and neck tumours treated with radiation therapy.[22,23,24]

SCORING SYSTEM FOR EAR TOXICITY

Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) have defined the ear toxicity grading system, which considers all three parts as an organ.[25]

Table 1- Scoring system for ear toxicity after radiotherapy

Grade	RTOG/ EORTC ear toxicity scoring
Grade 1	Mild external otitis with erythema, pruritis, secondary to desquamation not requiring medication. Audiogram unchanged from baseline.
Grade 2	Moderate external otitis requiring topical medication/serous otitis media/hypoacusis on testing only
Grade 3	Severe external otitis with discharge or moist desquamation/symptomatic hypoacusis/ tinnitus not drug related
Grade 4	Deafness

RISK FACTORS

(i) Background skin disease such as lupus erythematous and other autoimmune disease may cause more toxicity for the external ear.

(ii) Previous middle ear disease such as otitis media or mastoiditis may also increase middle ear radiation-induced toxicities. Concomitant administration of chemotherapy may also increase the risk and severity of otitis in external ear.

(iii) Platinum-based regimens are used as induction or concurrent chemotherapy in locally advanced head and neck cancers and can potentially affect inner ear toxicity so the risk of SNHL may increase.

MECHANISM

THE EXTERNAL EAR

(i) It is a tube covered by skin that conducts sound waves to the middle ear. Radiation effects on the external ear mimics the skin effects of radiation. A prompt skin reaction may appear after exposure that is related to the inflammatory response, release of histamine-like substances, permeability and dilation of capillaries, and subsequent dermal edema.

(ii) It presents with early transient skin erythema that can be seen within a few hours after radiation and subsides after 24–48 hrs. After subsidence of initial erythema, the later phase includes additional edema, an increased dilation in capillaries, and erythrocyte extravasation, which resulted in an erythematous reaction.

(iii) This phase is followed by thinning of the epidermis, damage to epithelial cells, degeneration of glands, reduced secretion of sebum, and sweat and clumps of exfoliated corneocytes (scales), which manifests as dry desquamation.

(iv) If damage to the basal cells and glands is more severe, epidermal necrosis, fibrinous exudates, and moist desquamation occur. The manifestation of moist desquamation results from the formation of small blisters in and around the basal layer of the epidermis that may also extend into the more superficial layers. The epidermis sloughs when these blisters rupture and coalesce, denuding the dermis and causing permanent epilation. Finally, skin necrosis or ulceration of the full-thickness dermis may develop as the most severe damage of higher radiation doses.

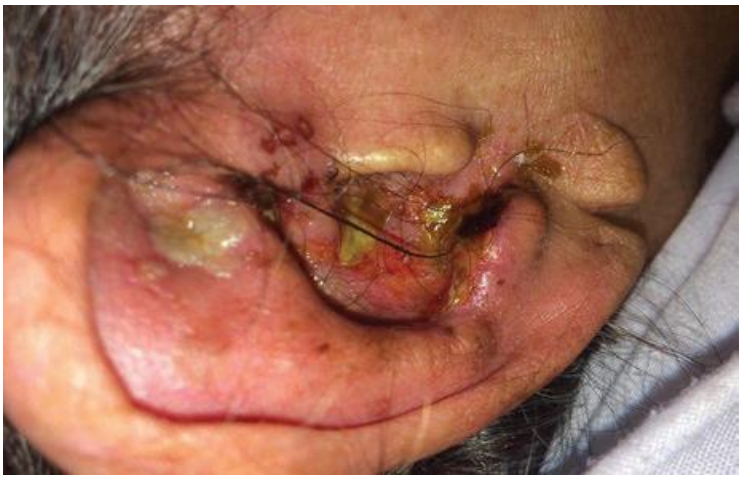


Fig 12- Radiation induced Otitis externa

THE MIDDLE EAR

(i) The mechanism of radiation-induced otitis media is due to swelling of the mucosa following the radiation and subsequent obstruction of the Eustachian tube. The Eustachian tube obstruction results in resorption of the air oxygen and nitrogen

from the middle ear, which results in negative pressure and tympanic retraction leading to conductive hearing loss. [26,27]

(ii) With further reduction of the negative pressure in the middle ear cavity, fluid transudation takes place resulting in serous otitis media.

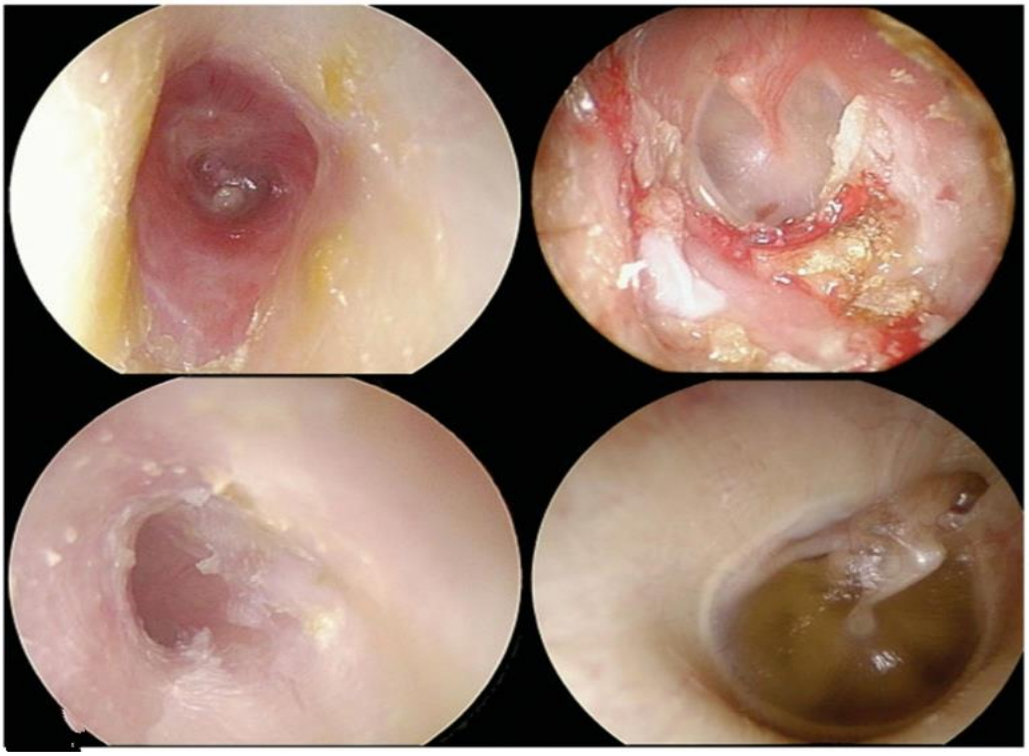


Fig 13- Effects of radiation on Ear canal, TM, Middle ear.

THE INNER EAR

(i) Stria vascularis in the inner ear is responsible for endolymph production and absorption. Stria vascularis injury after radiation exposure leads to endolymphatic hydrops and temporarily increased intra labyrinthine pressure, which could lead to ear fullness, hearing loss, tinnitus, dizziness, and vertigo.[28]

(ii) Hearing loss may be conductive, sensorineural, or mixed type. Early hearing loss during radiation therapy is usually conductive due to Eustachian tube dysfunction and radiation-induced otitis media.

(iii) The incidence of SNHL increases with time, and sensorineural or mixed-type hearing loss occurs either near the end of or shortly after the completion of radiation therapy. The sensory component of early hearing loss is usually related to stria vascularis degeneration and disturbances in normal perilymph and endolymph physiology.

TIMING FOR APPERANCE OF TOXICITY

(i) Acute otitis media usually occurs within a few weeks of radiation therapy. It is usually transient and resolves within a few weeks after completion of the treatment.[27]

(ii) SNHL may occur near the end of treatment or after the completion of radiation therapy and increase with time. SNHL may be transient or permanent. Transient SNHL could recover within 6–12 months; however, it may last over 12 months in a few cases.[22]

(iii) Patients with no severe SNHL (less than 30 dB drop from baseline) and no post irradiation serous otitis media have a good chance for recovery of sensorineural hearing within 6 months to 1

year. On the other hand, if severe SNHL develops or the SNHL persists beyond 1 year, it is likely permanent.[22]

SYMPTOMS AND DIAGNOSIS

(i) Symptoms of otitis media are conductive hearing loss, ear pain, fullness, and tinnitus in the affected ear. As a result of radiation therapy, the tympanic membrane may become dull, retracted, bulged, and congested or may remain normal. An inner ear injury can manifest with tinnitus, dizziness, vertigo, and high-frequency SNHL.[22]

(ii) Diagnosis of these complications is based on patient symptoms and ear examination including otoscopic assessment. Hearing loss may be diagnosed by simple tests like general assessment of each ear with words spoken at various volumes or a tuning fork or by more thorough audiometry testing.

(iii) A pure tone audiometer test offers an audiogram based on a person's ability to hear sounds with different loudness and pitches and characterizes the type and degree of hearing loss.

REVIEW OF LITERATURE

Though hearing apparatus are not intentionally included in the radiation field for many head and neck malignancies, they do get clinically measurable doses from primary beam entrance, exit and as via scatter radiation. Since this is an epidemiologic study, the primary factors of interest were the exposure to the hearing apparatus and its sequalae.

In 1982, **Black et al.** [29] studied on 16 adult head and neck malignancy patients receiving cisplatin dosages between 100-800 mg/$m^{2,}$ 31.2 % had abnormal rotational tests after completing chemotherapy, 12.5 % had transient reduction of vestibular function tests.

In 1985, **Schaefer et al.** [30,31] studied on 24 adult head and neck malignancy patients receiving cisplatin 100-800 mg/$m^{2,}$ vestibular function tests showed 4.2 % had bilateral decreased caloric response before chemotherapy then absent response after the treatment. 3% had dizziness along with concurrent sensorineural hearing loss.

In 1993, **Myers et al.** [32] studied on 34 adult head and neck malignancy patients receiving cisplatin 100-600 mg/m^2, 2.9% had abnormal caloric test results after the treatment. 20.6% abnormal results after rotational tests. 58.3 % had hearing loss and 66.7 % had tinnitus.

In 1998, **Low and Fong** [33] prospectively evaluated 33 patients (66 ears) with nasopharyngeal malignancy who received Radiation therapy. Otoscopy and pure-tone audiometry were performed before and after RT. If OME was suspected after otoscopy or pure-tone audiometry, the diagnosis was confirmed by tympanometry. Eleven out of 66 ears (17%) developed OME and 9/66 ears (14%) developed conductive hearing loss after RT. All patients with abnormal hearing developed hearing loss secondary to OME. No one had abnormal hearing as a result of sensorineural hearing loss before or after RT.

The incidence of post RT sensorineural deficit has been reported to range from 0% to 50%, In 1999, **Kwong et al.** [34] reported a 24% incidence of sensorineural hearing loss particularly for higher frequencies.

In 1999, **Wai-kuen Ho** [34] in a prospective study reported a 31% incidence of deterioration of bone conduction thresholds at 4 kHz.

In 2000, **Kew et al.** [35] studied 32 (64 ears) nasopharyngeal malignancy patients and studied pre- and post-RT middle ear effusion by evaluation of magnetic resonance imaging (MRI) before after RT. After RT, 17/64 ears (27%) developed radiologic verified OME after RT.

In 2003, **Wang et al.** [36,37] reviewed 150 (261 ears) nasopharyngeal malignancy patients treated with RT. Pure-tone audiometry and tympanometry were conducted 3months after completion of RT and at

yearly intervals thereafter. Before RT, there were 51/261 ears (20%) with OME. Twenty-nine of them resolved after RT treatment, but additionally 17/210 normal ears (8%) before RT developed OME.

In 2004, **Merchant et al.** [38] found the rate of permanent hearing loss ranged from 24.2% to 36% for doses approaching 60 Gy.

In 2006, **Lakhai et al.** [39] reported that hearing loss after cisplatin therapy occurs mainly at high frequencies and at cisplatin dosages more than 60 mg/sqm. Only 13% patients developed grade 2 and more when cumulative doses ranged from 100 to 300 mg/sqm. Risk increases almost 3fold when cumulative dose exceeds 700 to 1300 mg /m^2.

In 2008, **Zuur** [40] in prospective analysis of hearing loss due to concurrent daily low dose cisplatin chemo-radiation for locally advanced head and neck malignancy reported a total incidence of ototoxicity in CTCAEV 3.0 as 31% in audiograms up to 8 kHz. Low dose cisplatin chemoradiation (CRT) caused less acute hearing loss (31%) compared to high dose cisplatin CRT (78%).

In 2011, **Wakisaka et al.** [41] retrospectively studied 24 nasopharyngeal cancer patients (48 ears) and studied long-term ipsilateral and contralateral ototoxicity following radiotherapy. Otoscopy and pure-tone audiometry were conducted at intervals of 2–3 months for at least 12 months. OME and CSOM were diagnosed by otoscopy and hearing loss by audiometry.

The investigators found that 7/24 patients (29%) developed OME and 2/24 of these patients (8%) developed CSOM 1, 3 and 4 years after RT.

In 2011, **Jereczek-Fossa et al.** [42] prospectively studied 17 (34 ears) post parotidectomy patients who received 3D-conformal radiotherapy as post-surgery treatment. Pure-tone audiometry and tympanometry were performed at 3, 6 and 24 months after RT. Three months post-RT, 3/17 patients (18%) showed transient symptoms of middle ear negative pressure or effusion that resolved completely at the following evaluations at 6 and 12 months. The mean irradiation dosage to the ET and middle ear was 33.0 and 30.9 Gy, respectively

In 2011, **Upadhya et al.** [43] prospectively included 58 patients with different head and neck cancer locations: laryngopharynx, oropharynx, oral cavity, neck (nodes with unknown primary cancer), maxillary sinus, parotids and thyroid. Patients with hearing loss or abnormal impedance audiometry before RT were excluded. Therefore, the study comprised of total 70 ears. All patients were treated with external beam RT. The patients were exposed to pure-tone audiometry and tympanometry immediately after, 3 months after and 6 months after RT. Immediately after RT, 18/70 ears (26%) developed OME, which fell to 11/70 ears (16%) and 4/70 ears (6%) 3 and 6 months after RT, respectively. However, 6 months after RT, the incidence of ET dysfunction was still

high, 22/70 ears (31%), and conductive hearing loss was found in 14/70 ears (20%).

In 2013, **Hsin et al.** [44] retrospectively studied 105 patients (210 ears) of nasopharyngeal malignancy patients treated with intensity-modulated RT (IMRT). After Radiotherapy treatment, the incidence of OME for ears that were normal before RT (132 ears), was 24/132 ears (18%) and additionally 9/132 ears (7%) developed CSOM. Thus, in total 33/132 new ears (25%) developed OM after RT.

In 2015, **Kaul et al.** [45] prospectively studied 120 patients with head and neck malignancies treated with RT. Different cancer locations were included: 17% hypopharyngeal carcinoma, 20% laryngeal, oral cavity and oropharyngeal carcinoma, 13% with salivary gland carcinoma and 10% had paranasal sinus and nasopharyngeal carcinoma. Oesophageal, thyroid and occult primary carcinoma were present in 10% of patients. All patients underwent radical RT. Pure-tone audiometry was done during mid-treatment, at the end of treatment and once a month for 3 months afterwards. Tympanometry was done at follow-up if required.

OME developed in 23% of the patients undergoing RT with four patients (3.3%) developing OME during the early phases of treatment while 24 additional patients (20%) developed OME during the middle part of the treatment. None of the patients had OME at follow-up after three months.

MATERIALS AND METHOD

STUDY DESIGN

A prospective study with 25 patients of histologically proven head and neck malignancy receiving radiation therapy is undertaken to study occurrence of hearing loss and other hearing complaint among these population.

SOURCE OF DATA

All patients with histologically proven head and neck malignancy visiting the Radiotherapy department at Madras Medical College from June 2020 to September 2021 were taken up for study.

METHOD OF COLLECTION OF DATA

SAMPLE SIZE:

The sample size chosen is 25. This was estimated based on number of cases being treated in the previous years from our hospital records.

INCLUSION CRITERIA:

1. All patients with histologically proven head and neck malignancy
2. Patient with no significant comorbid condition.
3. Understand the protocol and is able to give informed consent.

EXCLUSION CRITERIA:

1. History of hearing or other vestibular disturbance prior to the diagnosis of head and neck malignancy.

2. External or middle ear pathologies on clinical examination.

3. Patients receiving drugs known to cause ototoxicity other than cisplatin.

METHOD:

(i) Estimated sample size was 30 to 50. A total of 25 patients were enrolled into the study. Informed consent was taken from all patients for the participation in the study.

(ii) Standard of care according to the institution has been delivered. History taken, thorough clinical examination done, Necessary investigations like diagnostic nasal examination (DNE), fine needle aspiration cytology (FNAC), Biopsy, CT of specific area was done. Before enrolling into the radiotherapy audiological evaluation done in our department (OTOSCOPIC EXAMINATION, TUNING FORK TESTS, PTA, IMPEDANCE).

(iii) Tuning fork test- tests are performed using tuning fork of 512Hz frequency, which is ideal for routine clinical practice. A tuning fork is activated by striking it gently against the examiner’s elbow, heel of hand or the rubber heel of the shoe.

To test air conduction (AC), a vibrating fork is placed vertically in line with the meatus, about 2 cm away from the opening of external auditory canal. The sound waves are transmitted through the tympanic membrane, middle ear and ossicles to the inner ear. Thus, by the air conduction test, the function of both the conducting mechanism and the cochlea are tested.

To test bone conduction (BC), the footplate of vibrating tuning fork is placed firmly on the mastoid bone. Cochlea is stimulated directly by vibrations conducted through the skull bones. Thus, BC is a measure of the cochlear function only. The three clinically useful tests done are Rinne Weber and Air bone conduction done.

(iv) Pure tone audiometry was performed for both air conduction and bone conduction for 250, 500, 1000, 2000, 4000, 8000Hz. Because bone conduction hearing testing is limited to 4000 Hz, measurements ≥ 4000 Hz were performed using air conduction testing alone. It is charted in the form of graph called audiogram. The threshold of bone conduction is a measure of cochlear function. The difference in thresholds of air and bone conduction (A-B gap) is a measure of the degree of conductive deafness.

(v) Impedance audiometry- equipment consists of a probe which snugly fits into external auditory canal and has three channels, namely

(a) To deliver a tone of 220Hz

(b) To pick up the reflected sound through a microphone and

(c) To bring about changes in air pressure in the ear canal from positive to normal and then negative. By charting the compliance of tympano-ossicular system against various pressure changes, different types of graphs called tympanogram are obtained which are diagnostic.

Type A- Normal tympanogram.

Type As- Compliance is lower at or near ambient air pressure. Seen in fixation of ossicles, e.g. Otosclerosis or malleus fixation.

Type Ad- High compliance at or near ambient pressure. Seen in ossicular discontinuity or thin and lax tympanic membrane.

Type B- A flat or dome-shaped graph. No change in compliance with pressure changes. Seen in middle ear fluid or thick tympanic membrane.

Type C- Maximum compliance occurs with negative pressure in excess of 100 mm H2O. Seen in retracted tympanic membrane and may show some fluid in middle ear.

(vi) All patients were treated in our radiotherapy department. 23 patients received either weekly cisplatin (35 to 40 mg/m^2) or three

weekly cisplatin (100 mg/m^2) according to the individual situation.

(vii) All the patients were treated with Ct based RT treatment planning. Volumes of interest and OARs were delineated on CT images. Inner ear was contoured according to the guidelines so that inner ear radiation dosage does not exceed 40 Gy. Planned treatment was done using 6 Mv linear accelerator- conformal technique (3DCRT/ IMRT).

(viii) All audiological investigations repeated just before starting RT, immediately 1 month after completing the RT and 6 months after completing RT (follow up).

STATISTICAL ANALYSIS

The collected data were entered in the excel spread sheet and variables were coded accordingly. The statistical analyses were performed using graph and bar charts.

Data are presented as percentage and the number of cases. Continuous variables were compared using paired sample ‘t’ test. Categorical data’s were analysed with Pearson chi- square test. Significance was defined by p value less than 0.05 using a two tailed test.

Data analysis was performed using software IBM-SPSS version 21.0 (IBM- SPSS Science Inc., Chicago, IL).

Table 2: Showing age distribution in the study population.

AGE GROUP	NO OF PATIENTS	PERCENT
<40	5	20.0
41-50	4	16.0
51-60	11	44.0
>61	5	20.0
Total	25	100.0

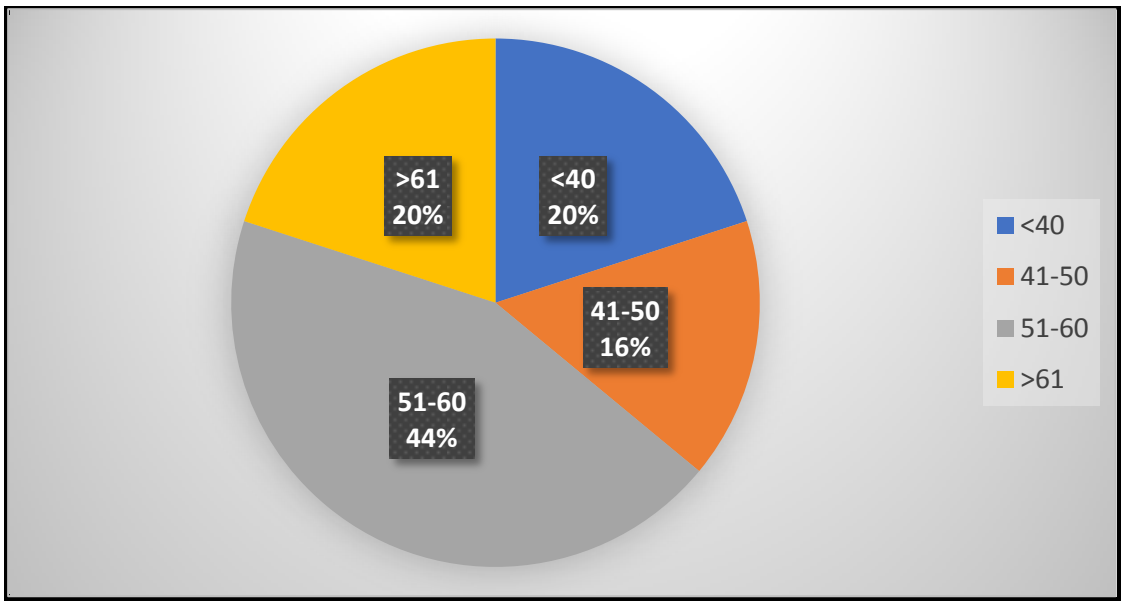


Fig 14: Age distribution in study population

In this proposed study, 5 (20%) patients are between age less than 40, 4 (16%) patients are between 41-50 years of age, 11 (44%) patients are between 51- 60 years of age, 5 (20 %) patients are above 61 years of age.

Table 3: Showing gender distribution in the study population.

SEX	NO OF PATIENTS	PERCENT
FEMALE	6	24.0
MALE	19	76.0
Total	25	100.0

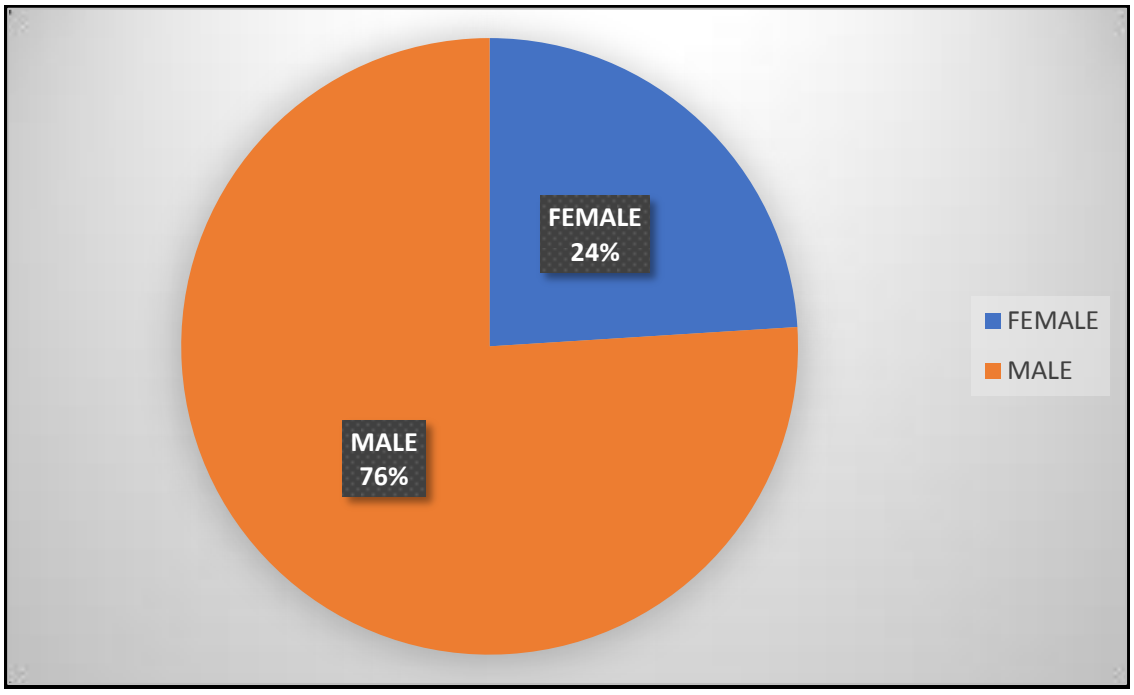


Fig 15: Gender distribution in the study population.

In this proposed study, 19 (76%) patients are male and 6 (24%) are female patients.

Table 4: Showing malignancy distribution in the study population.

DIAGNOSIS	NO OF PATIENTS	PERCENT
MALIGNANT GROWTH BRAIN	1	4.0
MALIGNANT GROWTH HYPOPHARYNX	3	12.0
MALIGNANT GROWTH LARYNX	8	32.0
MALIGNANT GROWTH NASOPHARYNX	2	8.0
MALIGNANT GROWTH ORAL CAVITY	10	40.0
MALIGNANT GROWTH OROPHARYNX	1	4.0
TOTAL	25	100.0

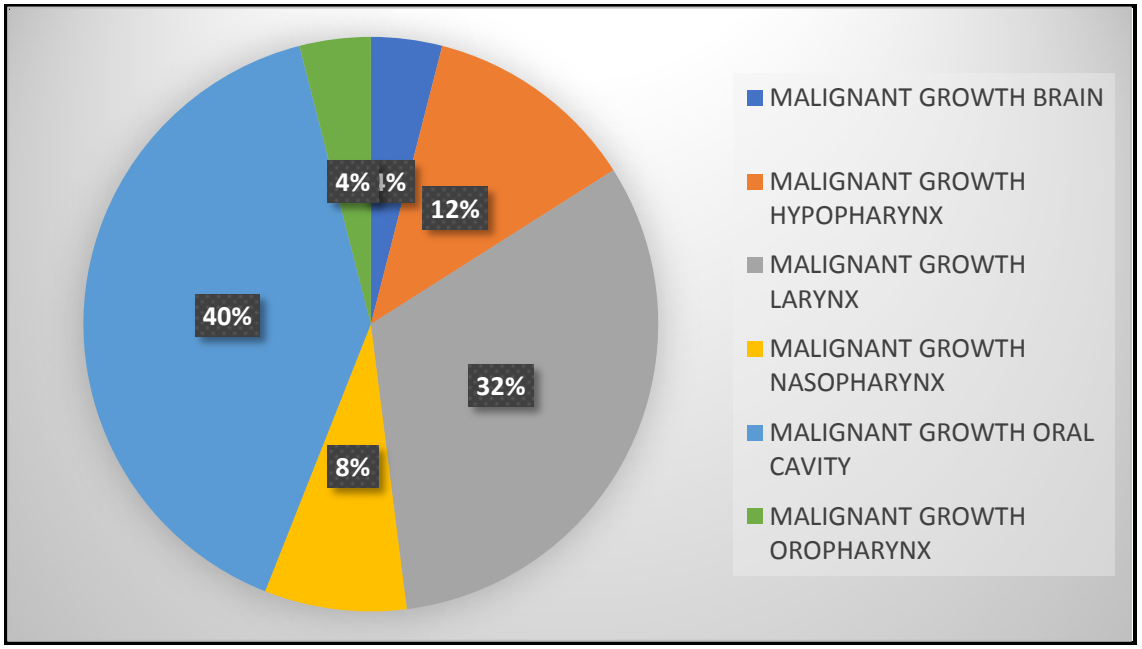


Fig 16: Malignancy distribution in the study population.

The various tumours included in the study are head and neck cancers (Intracranial, Oral cavity, Oropharynx, Nasopharynx, Hypopharynx, Larynx).

Table 5: Showing type of treatment given in the study population.

TREATMENT PLAN	FREQUENCY	PERCENT
CCRT	23	92.0
RT	2	8.0
TOTAL	25	100.0

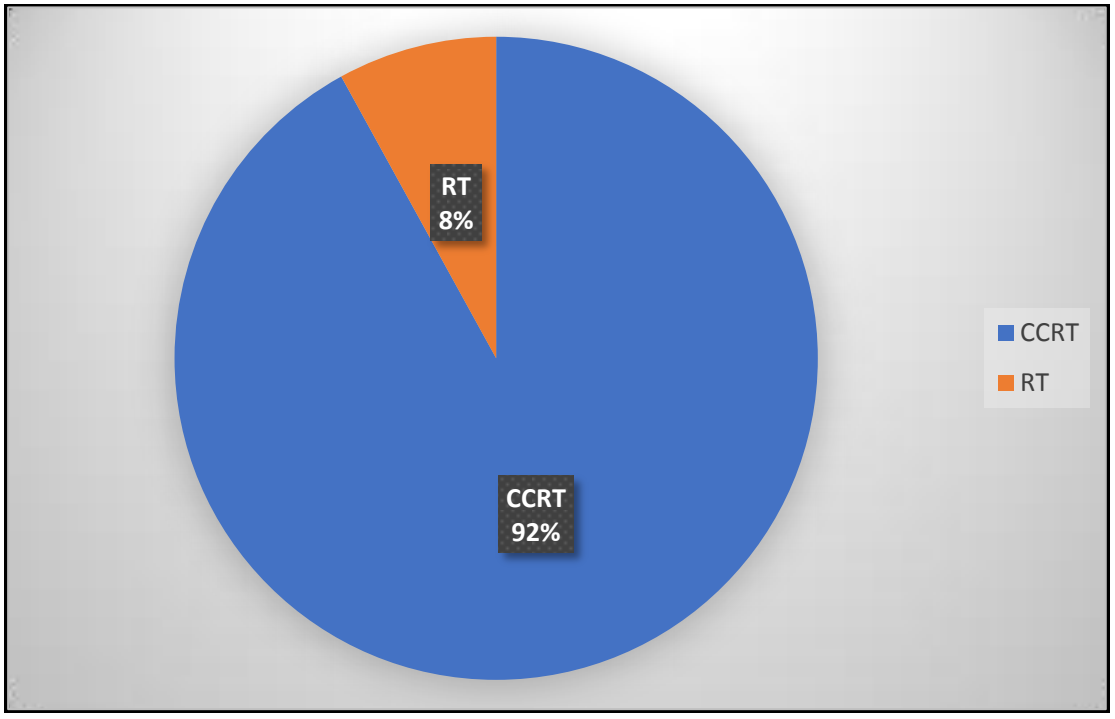


Fig 17: Type of treatment given in the study population.

Among the 25 patients, concurrent cisplatin chemotherapy is received by 23 patients and 2 patients received radiotherapy only. Cumulative dose of cisplatin varied from 200 mg- 400 mg.

Table 6: Showing technique of treatment used in the study population

TECHNIQUE OF RT	FREQUENCY	PERCENT
3D CRT	17	68.0
IMRT	8	32.0
TOTAL	25	100.0

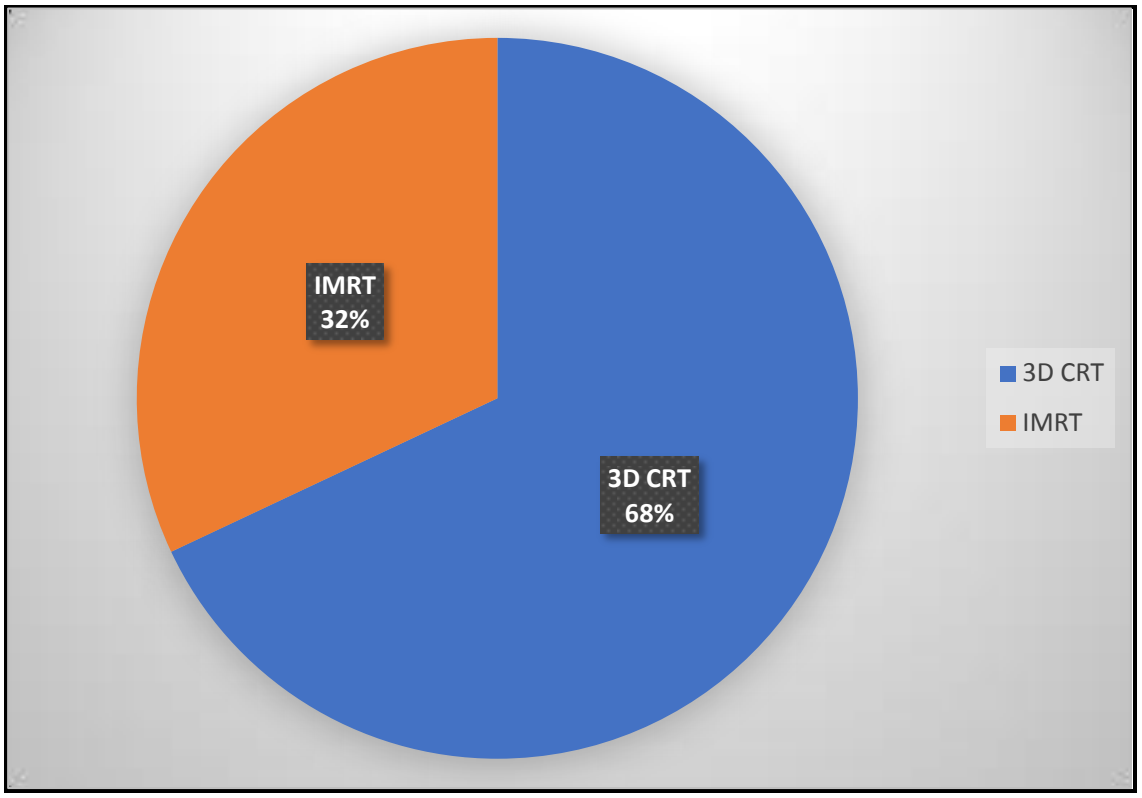


Fig 18: Distribution of treatment technique in the study population.

Among the study population, 3DCRT and IMRT are executed using 6 MV linear accelerator. 17 (68%) patients were treated with 3DCRT technique and 8 (32%) were treated with IMRT technique.

Table 7- Comparison of Ear fullness symptom in both ears - Before radiotherapy and after 1 month of completing radiotherapy.

			EAR FULLNESS 1 MONTH		TOTAL	P VALUE
			No	Yes		
EAR FULLNESS PRE RT	No	Count	22	26	48	0.201
		%	45.8%	54.2%	100.0%	
	Yes	Count	0	2	2	
		%	0.0%	100.0%	100.0%	
TOTAL		Count	22	28	50	
		%	44.0%	56.0%	100.0%	

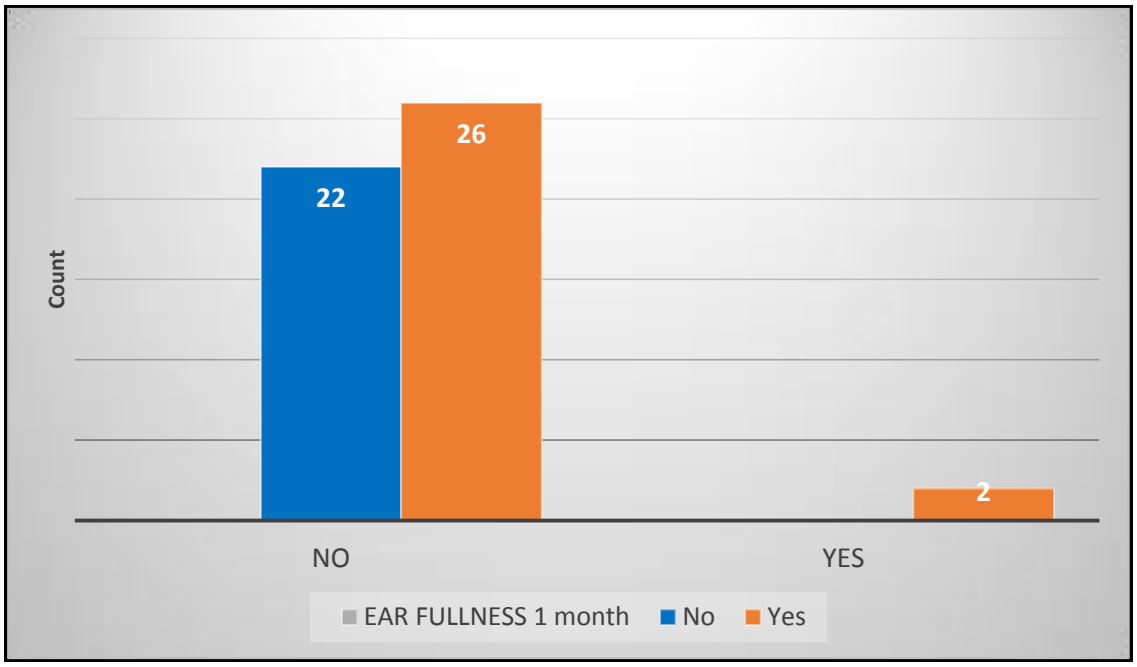


Fig 19- Showing ear fullness symptom in both ears prior to radiotherapy and 1 month after radiotherapy.

Following table shows no statistical significance of ear fullness between pre radiotherapy and 1 month after radiotherapy (p value – 0.201). Even though p value is insignificant, 26 ears (54.2% population) developed ear fullness after 1 month of completing radiotherapy. Hence it should be considered.

Table 8- Comparison of ear fullness symptom in both ears – before radiotherapy and 6 months after completing radiotherapy.

			EAR FULLNESS 6 MONTHS	TOTAL
			No	
EAR FULLNESS PRE RT	No	Count	39	39
		%	97.5%	97.5%
	Yes	Count	1	1
		%	2.5%	2.5%
TOTAL		Count	40	40
		%	100.0%	100.0%

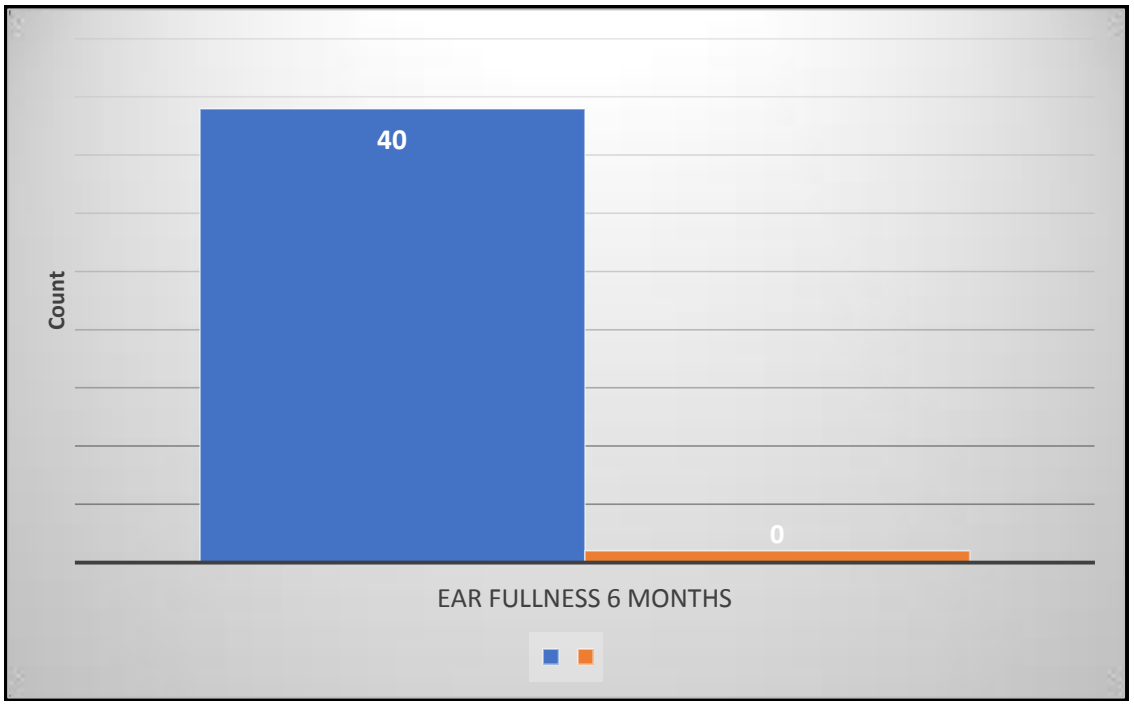


Fig 20- Comparing ear fullness symptom in both ears -before Radiotherapy and 6 months after completing radiotherapy.

Since no patients had ear fullness post 6 months after radiation treatment, p value could not be obtained.

Table 9- Comparison of Ear pain symptom in both ears – before radiotherapy and 1 month after completing radiotherapy.

			EAR PAIN 1 MONTH		TOTAL	P VALUE
			No	Yes		
EAR PAIN PRE RT	No	Count	22	27	49	0.371
		%	44.9%	55.1%	100.0%	
	Yes	Count	0	1	1	
		%	0.0%	100.0%	100.0%	
TOTAL		COUNT	22	28	50	
		%	44.0%	56.0%	100.0%	

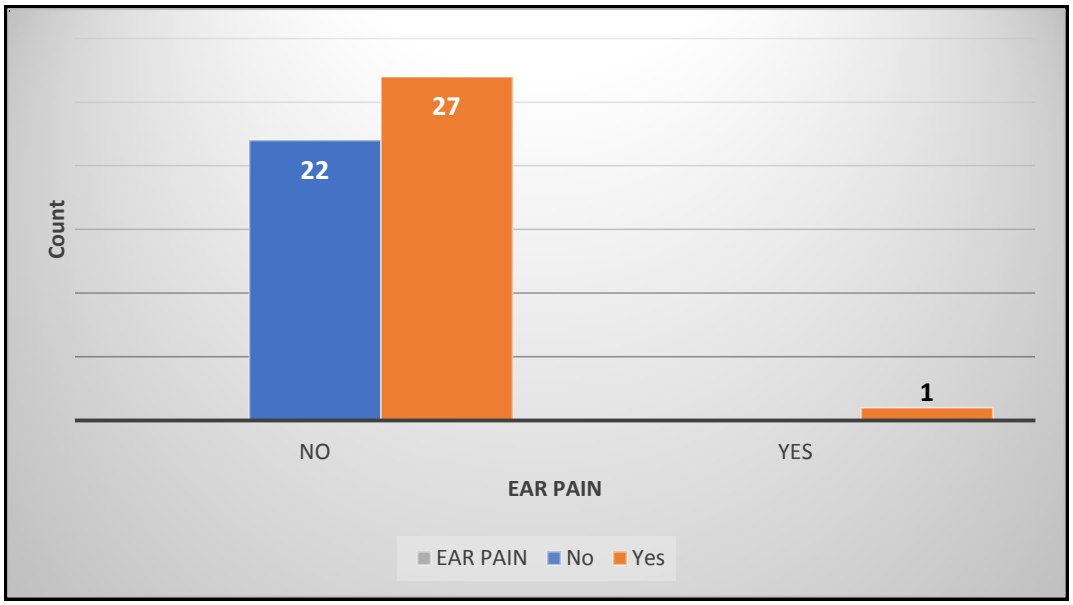


Fig 21- Comparison of ear pain symptom in both ears before radiation therapy and 1 month after completing radiation therapy.

From the following table, even though p value is insignificant (0.371), 27 ears (55.1% population) developed ear pain after 1 month of completing radiotherapy. Hence it should be considered.

Table 10- Comparison of ear pain symptom in both ears – before radiotherapy and 6 months after completing radiotherapy.

			EAR PAIN 6 MONTHS	TOTAL
			No	
EAR PAIN PRE RT	No	Count	39	39
		%	97.5%	97.5%
	Yes	Count	1	1
		%	2.5%	2.5%
TOTAL		Count	40	40%
		%	100.0%	100%

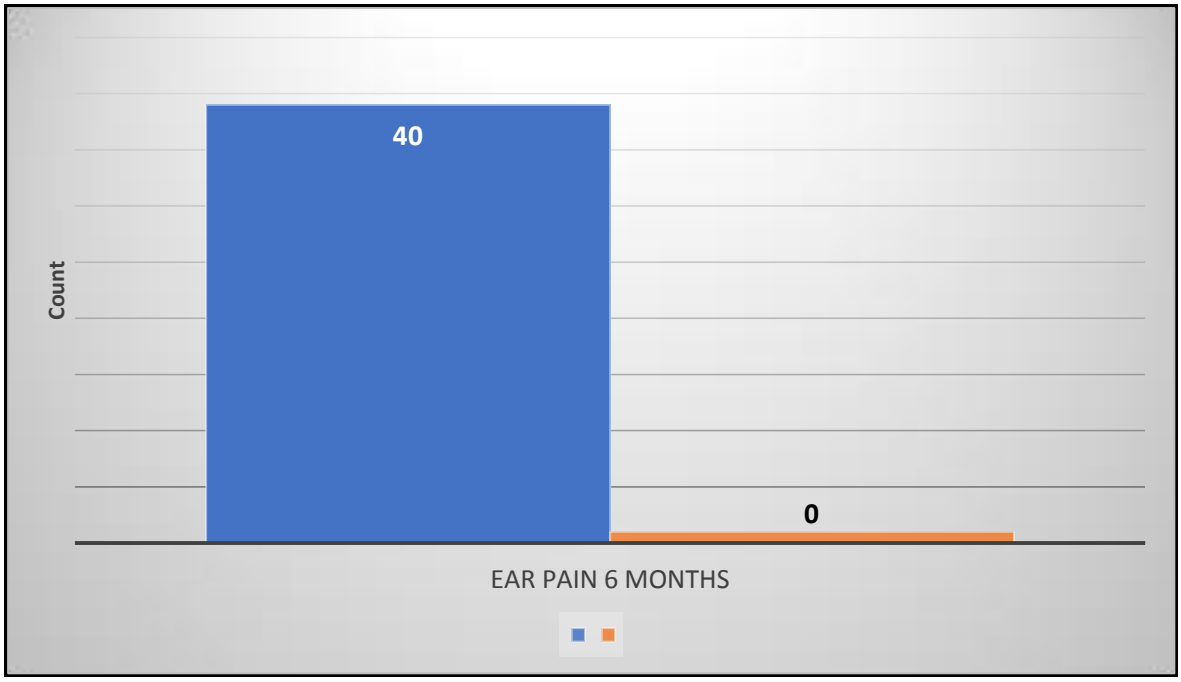


Fig 22- Comparing ear pain symptom in both ears before radiotherapy and 6 months after completing radiotherapy.

Since no patients had ear pain post 6 months after radiation treatment, p value could not be obtained.

Table 11- Comparison of Tinnitus symptom in both ears – before radiotherapy and 1 month after completing radiotherapy.

			TINNITUS 1 MONTH		TOTAL
			No	Yes	
TINNITUS PRE RT	No	Count	22	28	50
		%	44.0%	56.0%	100.0%
TOTAL		Count	22	28	50
		%	44.0%	56.0%	100.0%

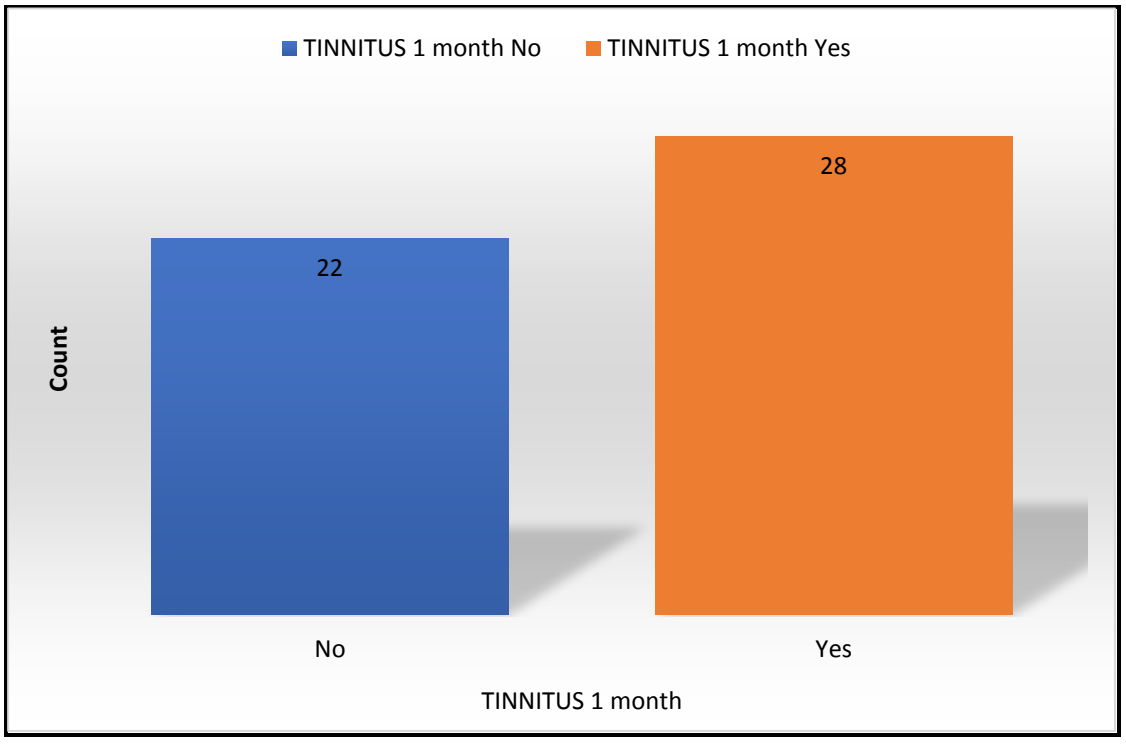


Fig 23- Showing comparison of Tinnitus symptom in both ears before radiotherapy and 1 month after radiotherapy.

In this study, 28 ears (56%) developed tinnitus complaint after 1 month of completing radiotherapy. Hence it should be considered significant.

Table 12- Comparison of Tinnitus symptom in both ears – before radiotherapy and 6 months after completing radiotherapy.

			TINNITUS 6 MONTHS		TOTAL
			No	Yes	
TINNITUS PRE RT	No	Count	16	24	40
		%	40.0%	60.0%	100.0%
TOTAL		Count	16	24	40
		%	40.0%	60.0%	100.0%

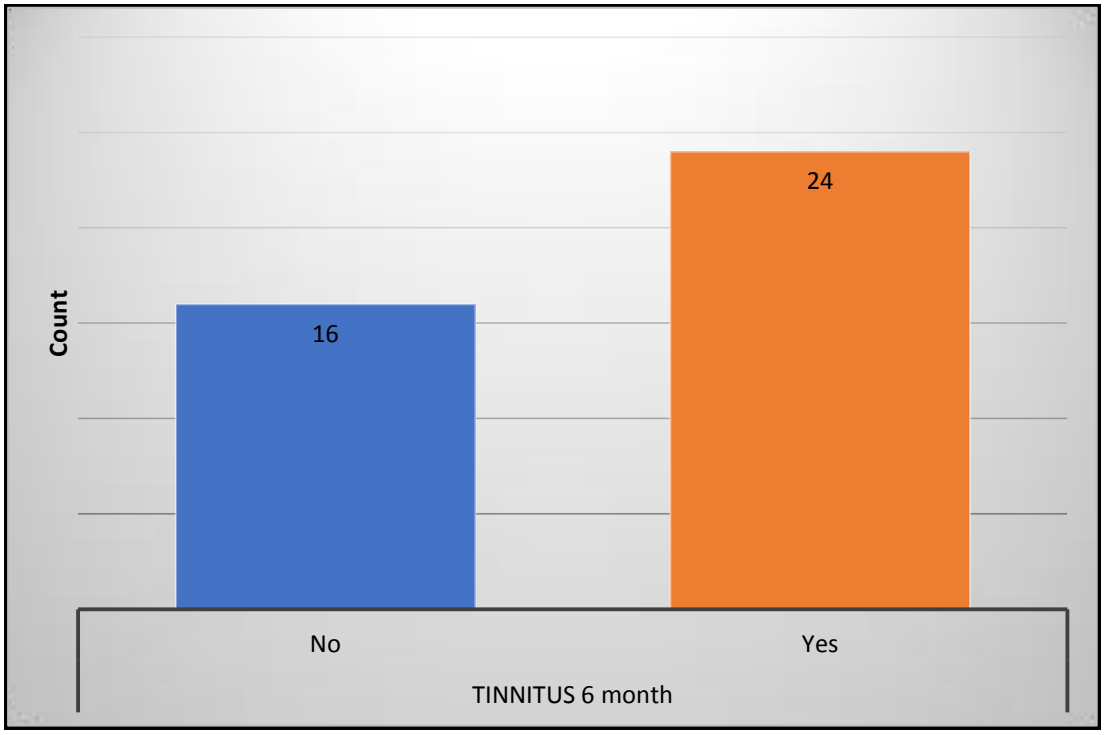


Fig 24- Showing comparison of tinnitus symptom in both ears before radiotherapy and 6 months after radiotherapy.

In this study,24 ears (60%) had tinnitus complaint after 6 months of completing radiotherapy. Hence it should be considered significant.

Table 13- Comparison of vertigo symptom – before radiotherapy and 1 month after completing radiotherapy.

			VERTIGO 1 MONTH		TOTAL
			No	Yes	
VERTIGO PRE RT	No	Count	42	8	50
		%	84.0%	16.0%	100.0%
TOTAL		Count	42	8	50
		%	84.0%	16.0%	100.0%

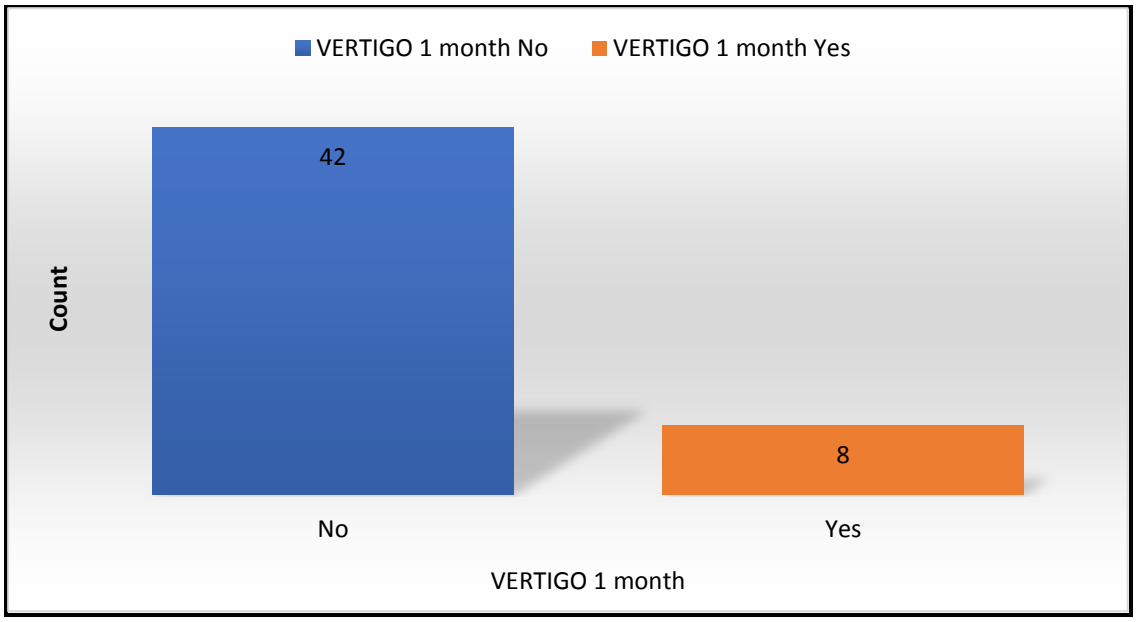


Fig 25- Showing comparison of vertigo symptom before radiotherapy and 1 month after radiotherapy.

In this study, 16% developed vertigo complaint after 1 month of completing radiotherapy.

Table 14- Comparison of vertigo symptom – before radiotherapy and 6 month after completing radiotherapy.

			VERTIGO 6 MONTHS		TOTAL
			No	Yes	
VERTIGO PRE RT	No	Count	16	24	40
		%	40.0%	60.0%	100.0%
TOTAL		Count	16	24	40
		%	40.0%	60.0%	125.0%

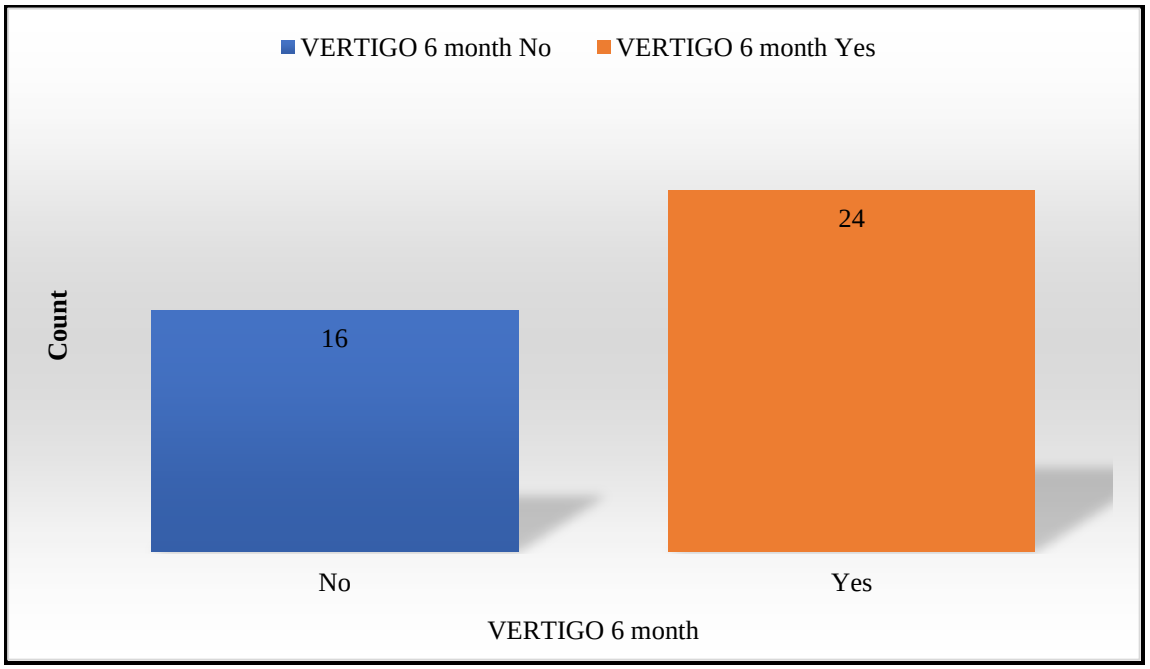


Fig 26- Showing comparison of vertigo symptom before radiotherapy and 6 months after radiotherapy.

In this study, 60% had vertigo complaint, increase in incidence after 6 months of completing radiotherapy. Hence should be considered significant.

Table 15- Comparison of Otoscopic examination of both ears – before radiotherapy and 1 month after completing radiotherapy.

			Otoscopic Examination 1 Month			Total	P value
			Normal	Bulged	Retracted		
Otoscopic Examination Pre RT	Normal	Count	28	11	10	49	0.164
		%	57.1%	22.4%	20.4%	100.0%	
	Abnormal	Count	0	0	1	1	
		%	0.0%	0.0%	100.0%	100.0%	
TOTAL		Count	28	11	11	50	
		%	56.0%	22.0%	22.0%	100.0%	

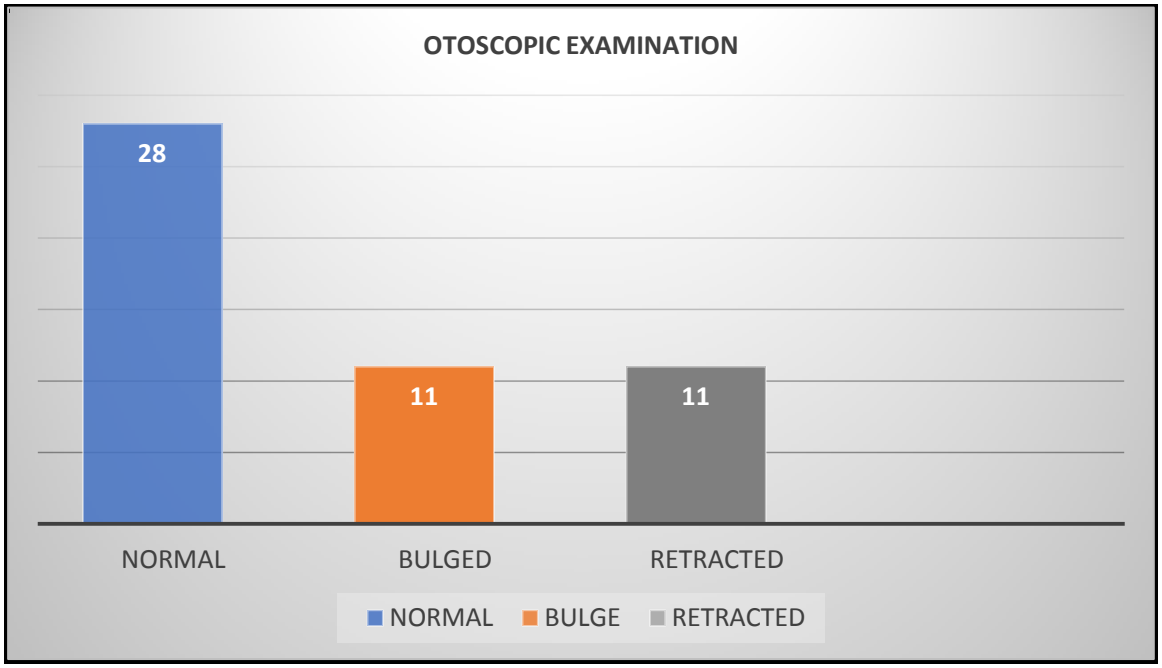


Fig 27- Showing otoscopic examination of both ears prior to radiotherapy and 1 month after radiotherapy.

From the following table, even though p value is insignificant (0.164), 22 ears (44% population) developed abnormal tympanic membrane after 1 month of completing radiotherapy. Hence it should be considered significant.

Table 16- Comparison of Otoscopic examination of both ears – before radiotherapy and 6 months after completing radiotherapy.

			OTOSCOPIC EXAMINATION 6 MONTHS	TOTAL
			Normal	
OTOSCOPIC EXAMINATION PRE RT	Normal	Count	39	39
		%	97.5%	97.5%
	Abnormal	Count	1	1
		%	2.5%	2.5%
TOTAL		Count	40	40
		%	100.0%	100.0%

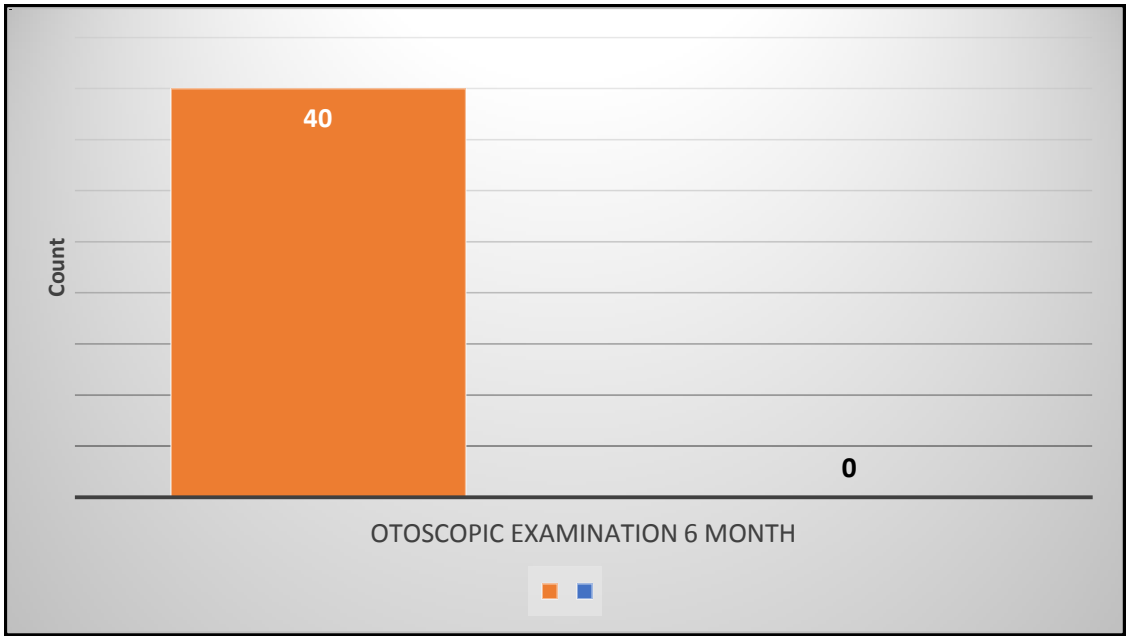


Fig 38- Showing otoscopic examination of both ears prior to radiotherapy and 6 months after radiotherapy.

In this study, no patient had retracted at 6 months follow up after completing radiotherapy.

Table 17- Comparison of Tuning fork test of both ears – before radiotherapy and 1 month after completing radiotherapy.

			TUNING FORK TEST 1 MONTH		TOTAL	P VALUE
			Abnormal (Rinne negative)	Normal		
TUNING FORK TEST PRE RT	Abnormal (Rinne negative)	Count	1	0	1	0.274
		%	100.0%	0.0%	100.0%	
	Normal	Count	22	27	49	
		%	44.9%	55.1%	100.0%	
TOTAL		Count	23	27	50	
		%	46.0%	54.0%	100.0%	

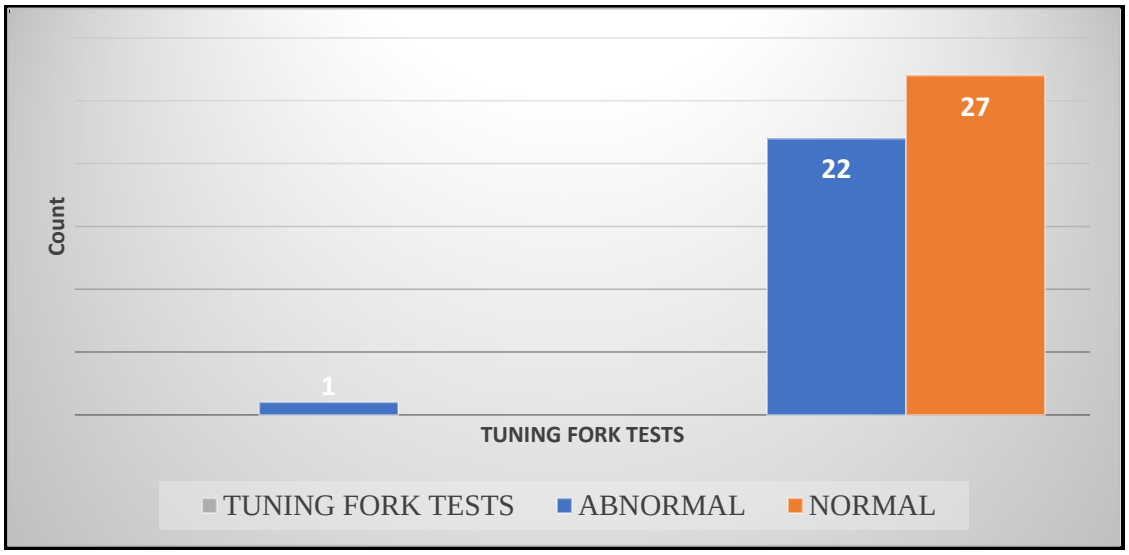


Fig 29- Showing tuning fork test of both ears- before and 1 month after radiotherapy.

From the following table, even though p value is insignificant (0.274), 23 ears (46% population) developed abnormal tuning fork tests (Rinne negative) after 1 month of completing radiotherapy. Hence it should be considered significant.

Table 18- Comparison of Tuning fork test of both ears – before radiotherapy and 6 months after completing radiotherapy.

			TUNING FORK TEST 6 MONTHS	TOTAL
			Normal	
TUNING FORK TEST PRE RT	Normal	Count	39	39
		%	97.5%	97.5%
	Abnormal	Count	1	1
		%	2.5%	2.5%
TOTAL		Count	40	40
		%	100.0%	100.0%

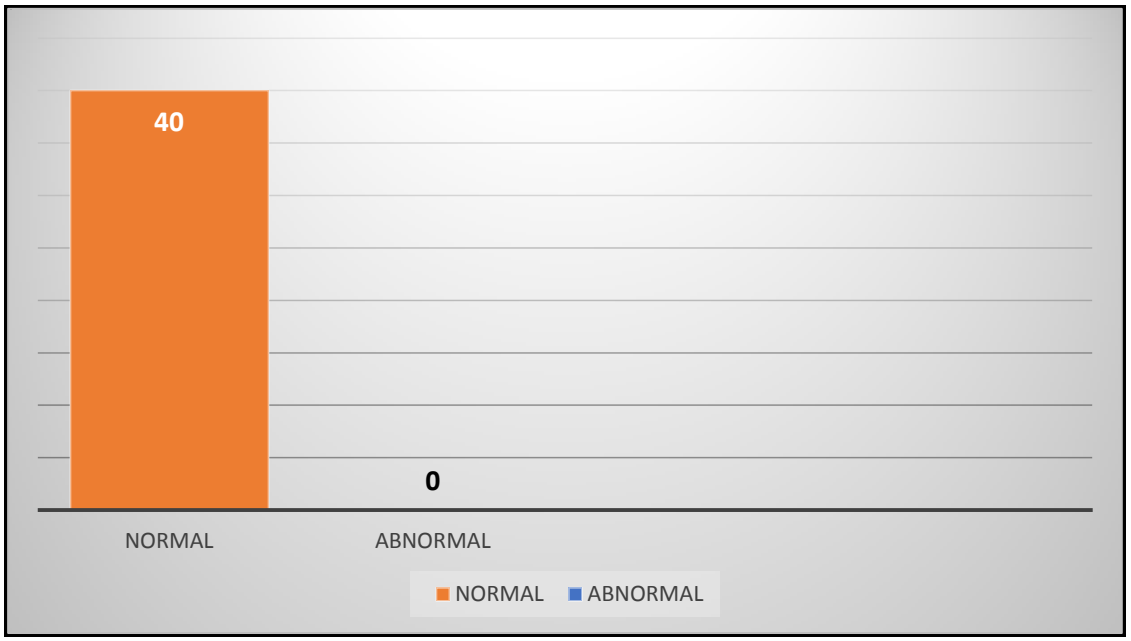


Fig 30- Showing tuning fork test of both ears prior to radiotherapy and 6 months after radiotherapy

Since no patients had abnormal tuning fork test results, p value could not be obtained.

Table 19- Comparison of Hearing loss complaint in both ears – before radiotherapy and 1 month after completing radiotherapy.

			HEARING LOSS 1 MONTH		TOTAL	P VALUE
			No	Yes		
HEARING LOSS PRE RT	No	Count	23	17	40	0.001
		%	57.5%	42.5%	100.0%	
	Yes	Count	0	10	10	
		%	0.0%	100.0%	100.0%	
TOTAL		Count	23	27	50	
		%	46.0%	54.0%	100.0%	

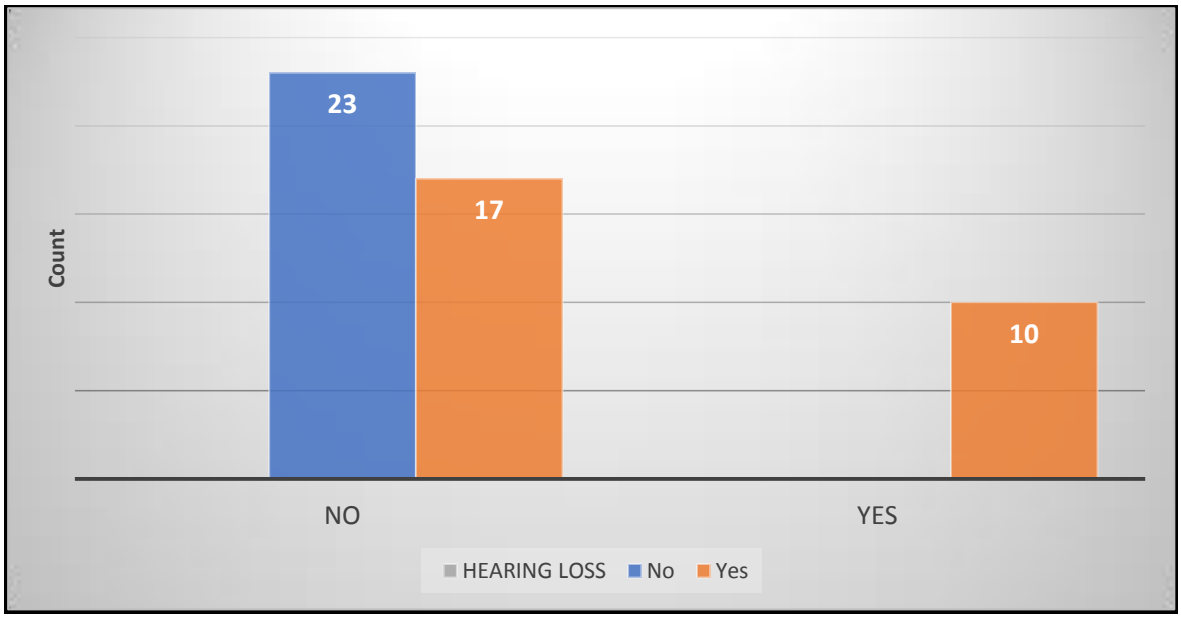


Fig 31 - Showing hearing loss in both ears prior to radiotherapy and 1 month after radiotherapy.

In the study population 27 ears (54 %) developed hearing loss on doing audiological evaluation 1 month after completing radiation therapy. P value is < 0.0001 showing statistical significance.

Table 20- Comparison of Hearing loss complaint in both ears – before radiotherapy and 6 months after completing radiotherapy

			HEARING LOSS 6 MONTHS		TOTAL	P VALUE
			No	Yes		
HEARING LOSS	No	Count	32	0	32	n/a
		%	100.0%	0.0%	100.0%	
	Yes	Count	0	8	8	
		%	0.0%	100.0%	100.0%	
TOTAL		Count	32	8	40	
		%	80.0%	20.0%	100.0%	

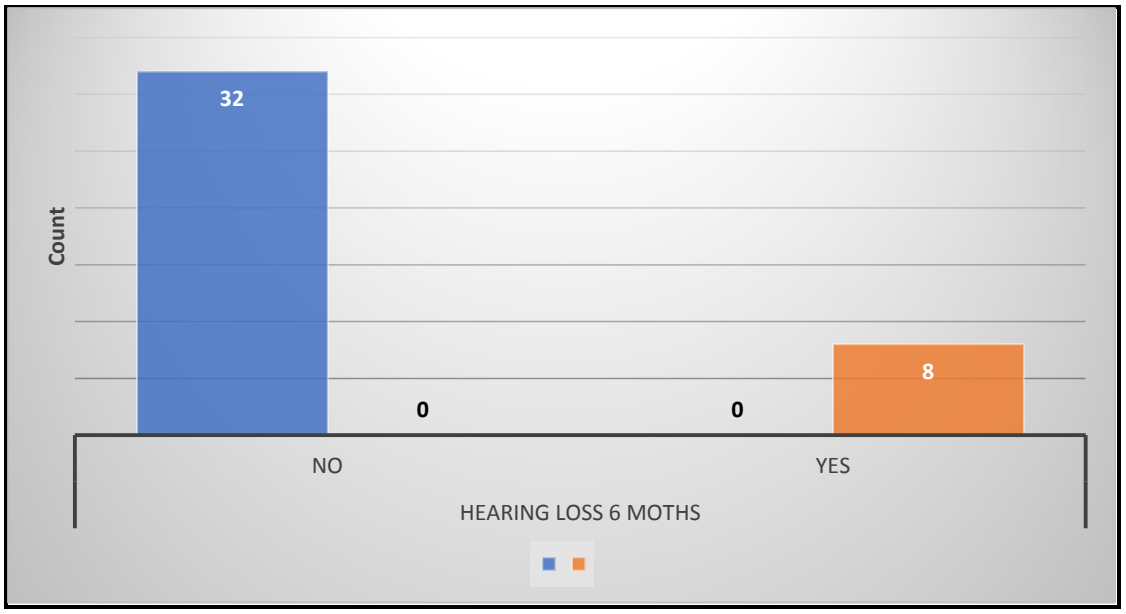


Fig 32- Comparing Hearing loss in both ears before Radiotherapy and 6 months after completing radiotherapy.

In this study, 20% population had hearing loss after 6 months completing radiotherapy.

Table 21- Showing paired samples statistical analysis of pure tone audiometry- tested 3 times.

PTA	MEAN	STD. DEVIATION	MEAN DIFFERENCE	P VALUE
PRE	30.20	10.31	-8.65	<0.0001
1 MONTH	38.85	10.40		
PRE	29.66	10.56	-5.75	<0.0001
6 MONTHS	35.42	10.18		

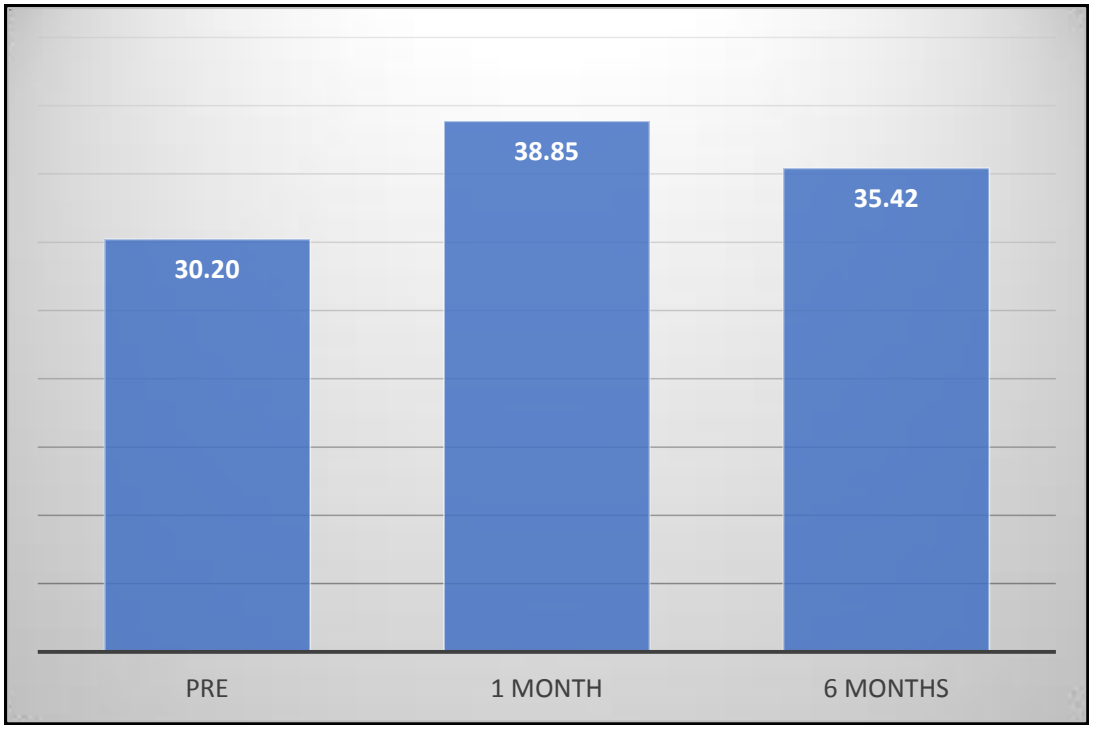


Fig 33- Showing comparison of Pure tone audiometry results during pre radiotherapy and follow up 1 and 6 months after completing radiotherapy.

Table 22- Comparison of impedance test of both ears – before radiotherapy and 1 month after completing radiotherapy.

			IMPEDANCE 1 MONTH			TOTAL	P Value
			Type-A	Type-B	Type-C		
IMPEDANCE PRE RT	TYPE A	Count	28	11	10	49	0.164
		%	57.1%	22.4%	20.4%	100.0%	
	TYPE C	Count	0	0	1	1	
		%	0.0%	0.0%	100.0%	100.0%	
TOTAL		Count	28	11	11	50	
		%	56.0%	22.0%	22.0%	100.0%	

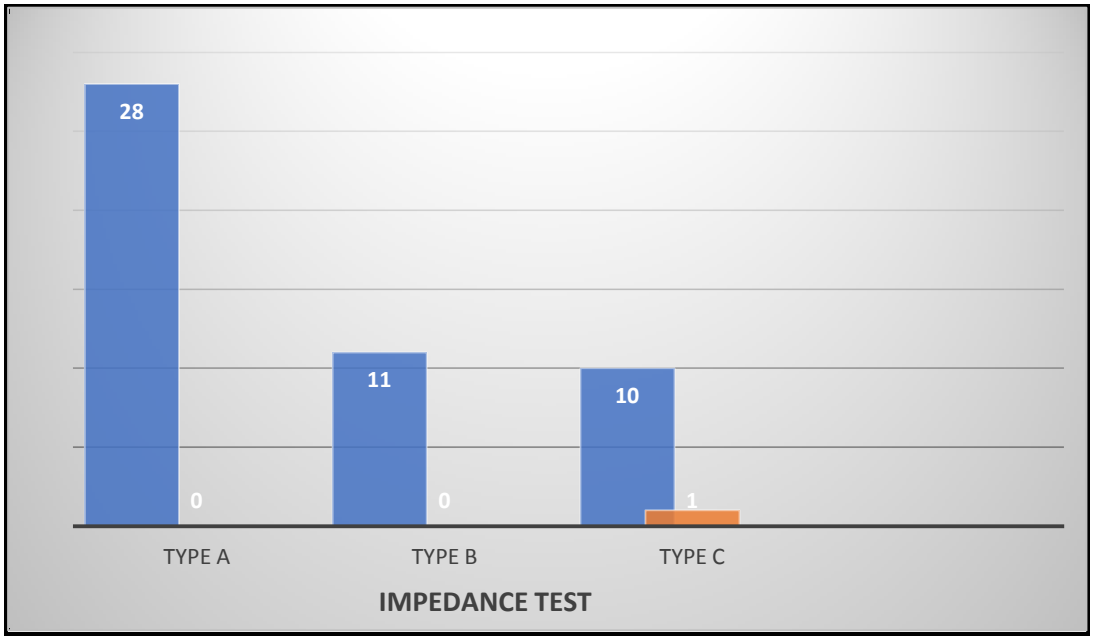


Fig 34- Showing impedance test of both ears prior to radiotherapy and 1 month after radiotherapy.

Following table shows out of 50 ears, 11 ears (22.0%) developed Type B curve and 11 ears (22.0%) developed Type C curve after 1 month completing radiotherapy.

Table 23- Comparison of Impedance test of both ears – before radiotherapy and 6 months after completing radiotherapy.

			IMPEDANCE 6 MONTHS	TOTAL
			TYPE A	
IMPEDANCE PRE RT	TYPE A	Count	39	39
		%	97.5%	97.5%
	TYPE C	Count	1	0
		%	2.5%	2.5%
TOTAL		Count	40	40
		%	100.0%	100.0%

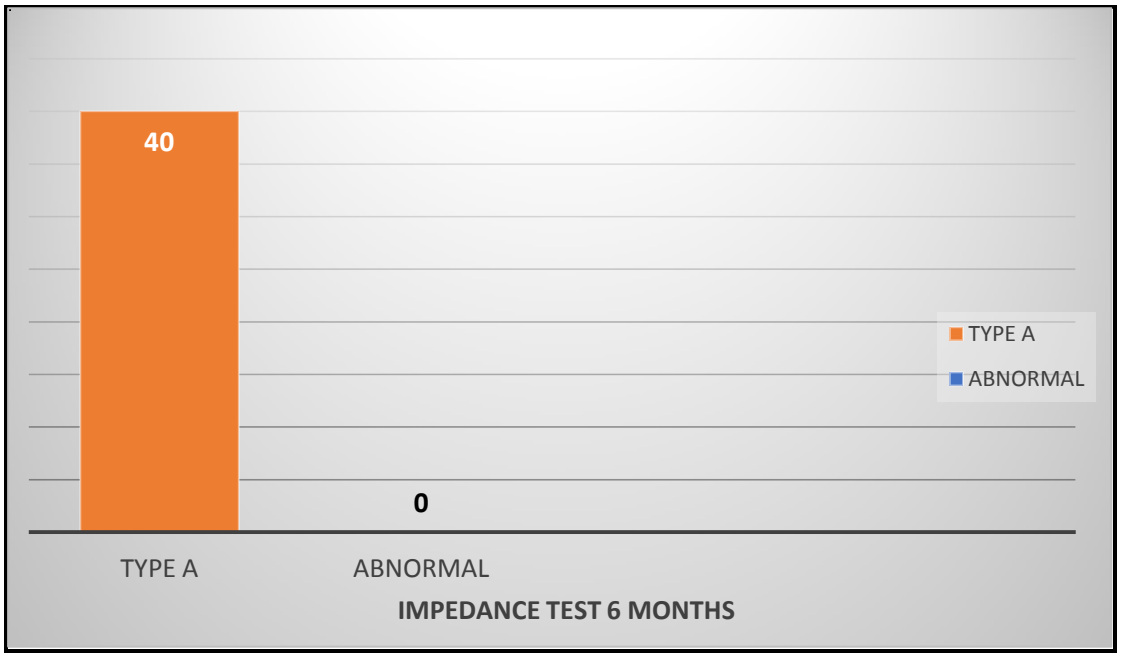
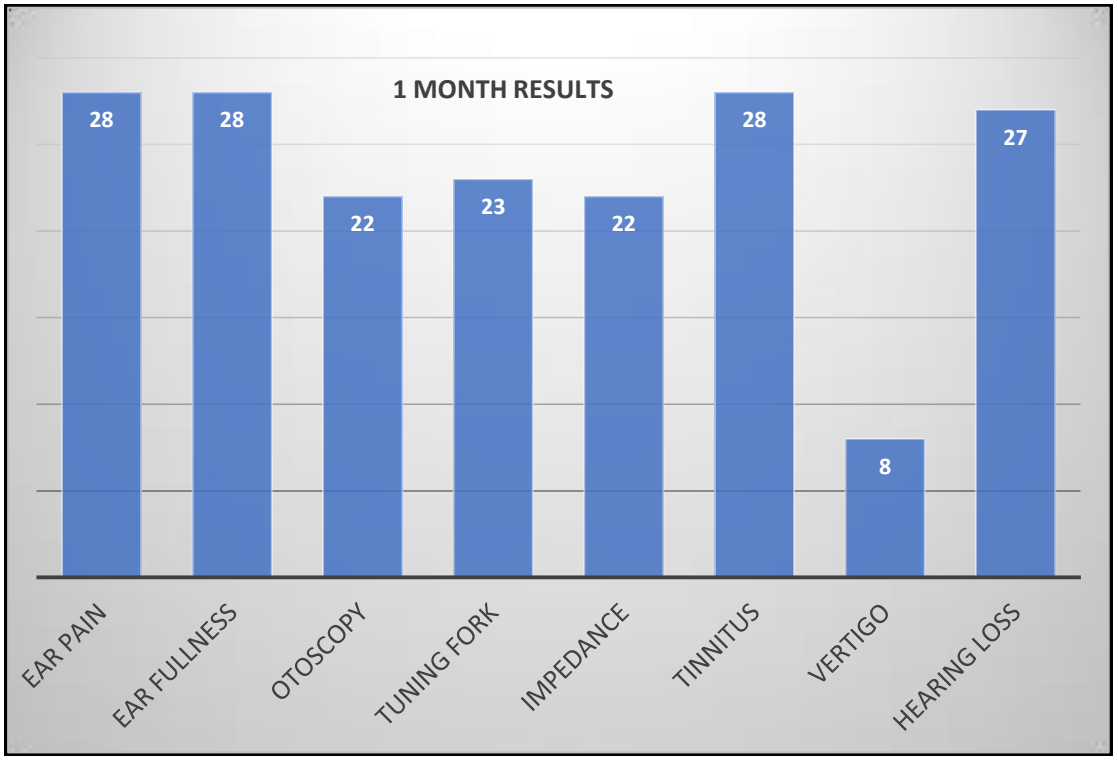


Fig 35- showing impedance test results before radiotherapy and 6 months after completing radiotherapy.

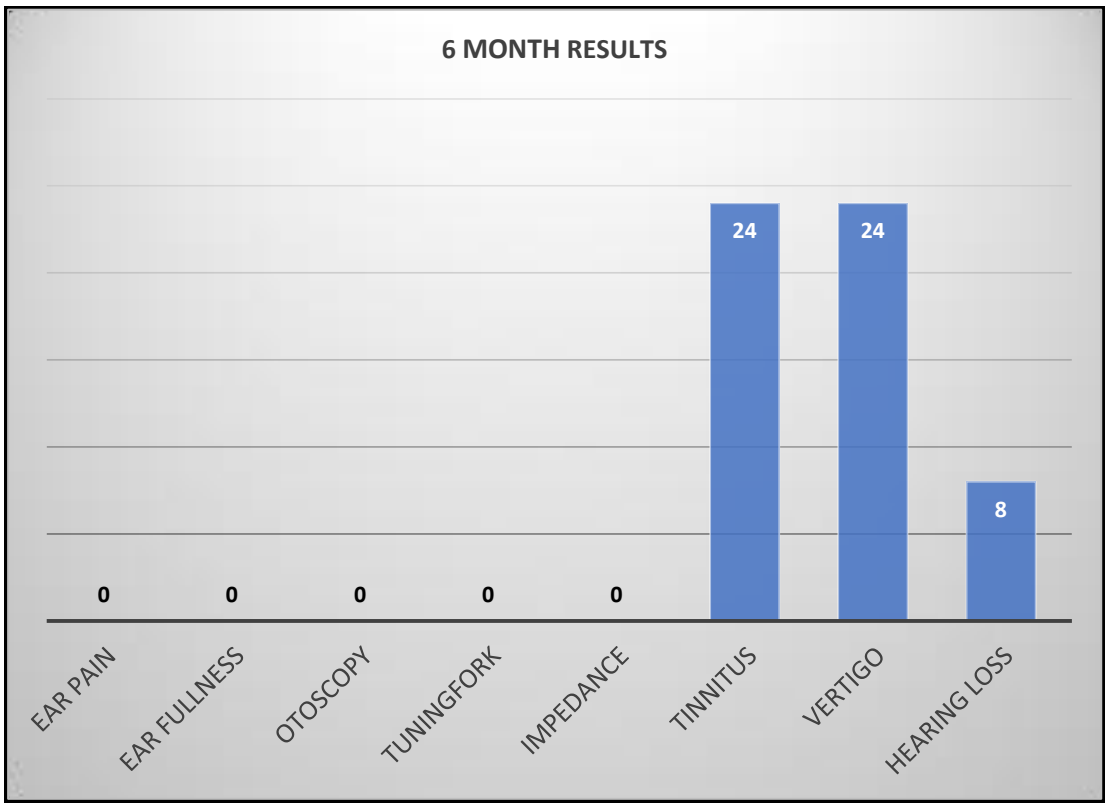
In this study, no patient had abnormal impedance results at 6 month follow up, so p value could not be obtained.

Fig 36- Showing results of all symptom analysis and audiological evaluation done at 1 month after completing radiotherapy.



In this study, When those 28 ears with ear fullness compared with other components, 27 ears had hearing loss complaint, 22 ears from those 26 ears had abnormal tympanic membrane (11 ears had bulged TM and 12 ears had retracted TM) , 23 ears from those 26 ears showed abnormal tuning fork results (Rinne negative) suggesting conductive pattern of hearing loss, 22 ears from those 26 ears showed abnormal impedance results (11 ears with type B and 11 ears with type C) suggestive of Eustachian tube dysfunction.

Fig 37- Showing results of all symptom analysis and audiological evaluation done at 6 months after completing radiotherapy.



All these ears when followed up after 6 months completing radiation therapy, incidence of ear fullness, abnormal appearance of tympanic membrane, Rinne negative tuning fork test and conductive pattern hearing loss in PTA has reduced by 99%. Hence eustachian tube dysfunction because of radiation exposure is transient and resolves over the time after completing radiotherapy.

At 6 month follow up, there is increased incidence of tinnitus vertigo and hearing loss at high frequencies suggesting use of concurrent chemotherapy playing a major role.

DISCUSSION

The present study has been done to analyse incidence of hearing loss and other hearing complaints after radiotherapy in head and neck malignancy patients. In the view of limited time period, study was done only for 1 year period, so only 6 months follow up after completing radiotherapy was considered.

Though hearing apparatus are not intentionally included in the radiation field for many head and neck malignancies, they do get clinically measurable doses from primary beam entrance, exit and as via scatter radiation. Since this is an epidemiologic study, the primary factors of interest were the exposure to the hearing apparatus and its sequalae.

In majority of the studies after effect of radiotherapy on hearing apparatus are published for nasopharyngeal carcinoma. The present study includes various head and neck malignancies (nasopharynx 8%, oral cavity 40%, oropharynx 4%, hypopharynx 12%, larynx 32%, brain 4%) where either Eustachian tube or middle ear or inner ear in the field of radiation.

The median age group of present study is 51-60 years. The present study is designed for head and neck malignancy which is more common in older age group. The median age is similar to studies published by **Herrmann et al.** [46] (57.9 & 54 years respectively).

Newer techniques like IMRT have shown an advantage in sparing non-target organs, yet dosage to the eustachian tube and middle ear is still high for head and neck malignancy, especially malignancy of nasopharynx and oral cavity. At present study 17 patients (68%) underwent 3DCRT and 8 patients (32%) underwent IMRT technique of radiotherapy.

Radiation therapy with or without chemotherapy is one of the first line of treatments in head and neck malignancy. Eustachian tube dysfunction and otitis media are known after effect of radiation therapy and it is characterised by ear pain, ear fullness, purulent secretion from the ear, tinnitus, hearing loss among the patients.

Techniques applied for establishing the diagnosis of otitis media have an influence on the outcome. Tympanometry gives accurate clinical results, results are presented in a type A curve suggesting a normal middle ear function, type B suggesting middle ear effusion, type C suggesting dysfunction of eustachian tube.

Otoscopy is also used to diagnose otitis media, showing either retracted TM or entrapment of air bubbles behind the TM (bulged TM). Pure tone audiometry also helps in the diagnosis of otitis media, when conductive hearing loss is present is suggestive of middle ear effusion.

Hsin et al [44] retrospectively studied 105 patients (210) ears of nasopharyngeal malignancy patients treated with IMRT, 25 % developed

otitis media after RT. Kaul et al. [3] prospectively studied 120 patients with head and neck malignancies treated with RT, Otitis media developed in 23% of patients undergoing RT during early phases which transiently reduced at follow up after 3 months.

Upadhya et al. [43] prospectively studied 58 patients with different head and neck malignancies, 26% developed Otitis media effusion, however after 3 months of radiotherapy symptoms subsided.

Low and Fong [33] retrospectively reviewed 33 (66 ears) patients with nasopharyngeal cancer, 17% developed Otitis media and 14% developed conductive hearing loss after radiotherapy. All patients with abnormal hearing developed hearing loss secondary to OME.

At the present study, regarding ear pain, 28 ears (56%) patients developed ear pain during and at 1 month follow up visit after radiotherapy. Complaint has fallen down to 2.5 % at 6 month follow up.

At the present study, regarding ear fullness 28 ears (56%) patients developed ear fullness complaint at follow up 1 month after radiotherapy. Majority of this patients fall under category of malignancy in nasopharynx oral cavity and oropharynx. Complaint has fallen to 2.5% at 6 months follow up.

Otoscopic examinations were done regularly on patient follow up. At present study 22 ears (44%) showed abnormal tympanic membrane.

11 ears (22%) showed bulged tympanic membrane and 11 ears (22%) showed retracted tympanic membrane. When tested again at 6 months follow up all patients had normal tympanic membrane. These when compared with impedance audiometry as said earlier 11 ears (22%) with bulged tympanic membrane had Type B curve suggestive of middle ear effusion and 11 ears (22%) with retracted tympanic membrane had Type C curve suggestive of eustachian tube dysfunction.

Regarding tuning fork examination, all the ears were tested with tuning forks of frequency 512 Hz. At follow up 1 month after radiotherapy, 23 ears (46%) patients had abnormal results – showing bone conduction better than air conduction (Rinne negative) suggestive of conductive hearing impairment. When tested again at 6 month follow up, no patients had Rinne negative result.

In this study**,** when those 28 ears with ear fullness compared with other components, 22 ears from those 26 ears had abnormal tympanic membrane on otoscopy examination (11 ears had bulged TM and 11 ears had retracted TM), 23 ears from those 26 ears showed abnormal tuning fork results (Rinne negative) suggesting conductive pattern of hearing loss, 22 ears from those 26 ears showed abnormal impedance results (11 ears with type B and 11 ears with type C) suggestive of Eustachian tube dysfunction, when done pure tone audiometry 17 ears had conductive pattern hearing loss and some with mixed pattern. All these ears when followed up after 6 months completing radiation therapy, incidence of

ear fullness, abnormal appearance of tympanic membrane, Rinne negative tuning fork test results and conductive pattern hearing loss in PTA has reduced by 99%.

Hence findings are suggestive of eustachian tube dysfunction because of radiation exposure causing otitis media and conductive pattern hearing loss, and is found to be transient and resolves over the time after completion of radiation therapy.

The dosage dependency was demonstrated by **Wang et al. and Yao et al.,** [36,37] who found that the incidence of otitis media effusion was reduced when dosage to eustachian tube and middle ear was below 52 Gy and 46 Gy respectively.

Jereczek- Fossa et al. [42] found a similar relationship when mean dosage to the eustachian tube and middle ear was 33.0 Gy and 30.9 Gy, only 18% of the patients developed ET tube dysfunction and OME at follow up. At the present study no comparison with eustachian tube dosage was done, hence should be studied further to document that titrating radiation dosage to eustachian tube reduces incidence of otitis media.

Since the age of study population falls between 51-60, majority had mild hearing loss of sensorineural pattern prior to radiotherapy. Hearing loss associated with aging is a highly prevalent phenomenon among elderly individual and it also leads to difficulty in

communication. Pure tone audiometry done at 1 month follow up showed 17 ears (42.5 %) with hearing impairment more of mixed component suggestive of middle ear effusion along with previous sensorineural hearing loss.

Even though Otitis media after radiotherapy of upper head and neck malignancy is well known between clinicians, it is not well documented. The reason may be during follow up visits focus is primarily towards relapse detection and not on side effects. Particularly, dry mouth and swallowing problems are very much common after radiotherapy of head and neck malignancy, less common side effects of middle ear are not noticed and detected at follow up.

Sensorineural hearing loss occurs after a latent period ranging from 6 months to 5 years after radiotherapy. Such hearing loss is due to loss of ciliated cells in cochlea (basal turn) or due to damage of spiral ganglion.

The incidence of post RT sensorineural deficit has been reported to range from 0% to 50%. **Kwong et al.** [34] reported a 24% incidence of sensorineural hearing loss particularly for higher frequencies.

Wai-kuen Ho [34] in a prospective study reported a 31% incidence of deterioration of bone conduction thresholds at 4 kHz. **Merchant et al.**[38] found the rate of permanent hearing loss ranged from 24.2% to 36% for doses approaching 60 Gy.

The dose received by cochlea is the most important determinant factor for the development of SNHL. In the present study SNHL (>10 dB) is observed in higher frequencies (4 kHz and 8kHz) during 6 months follow up after completing radiotherapy. Since 4kHz and 8kHz doesn't fall under speech frequency no patient complained about decrease in hearing on follow up. Since the study period was limited to 1 year further follow up could not be done. So further hearing loss progression could not be commented.

In cochlea, apical turn is responsible for lower frequencies and basal turn is responsible for higher frequencies. Chemotherapy related damage in the outer hair cells where sounds of higher frequencies are perceived. So, use of platinum based chemotherapy drugs like cisplatin causes outer hair cell damage leading to sensorineural hearing loss at higher frequencies.

Concurrent chemoradiation has become standard care in majority of head and neck malignancy patients since cisplatin is the most commonly used radiosensitizer. There are various published data suggestive of ototoxicity when radiation and chemotherapy given concurrently.

Zuur [40] in prospective analysis of hearing loss due to concurrent daily low dose cisplatin chemo-radiation for locally advanced head and neck malignancy reported a total incidence of ototoxicity in CTCAEV

3.0 as 31% in audiograms up to 8 kHz. Low dose cisplatin chemoradiation (CRT) caused less acute hearing loss (31%) compared to high dose cisplatin CRT (78%).

In the present study concurrent use of cisplatin has increased incidence of sensorineural hearing loss for higher frequencies. Cumulative dose of cisplatin plays an important factor for hearing loss.

Lakhai et al. [39] reported that hearing loss after cisplatin therapy occurs mainly at high frequencies and at cisplatin dosages more than 60 mg/sqm. Only 13% patients developed grade 2 and more when cumulative doses ranged from 100 to 300 mg/sqm. Risk increases almost 3fold when cumulative dose exceeds 700 to 1300 mg /sqm. In our study, total cumulative dose received by our patients ranged from 200 to 400 mg/sqm. Hence no attempt has been made to analyse the results with various doses of cisplatin.

Majority of patients in our study population received only low dose which is only safe treatment protocol with respect to ototoxicity as reported by Zuur et al.[40] A sudden SNHL is occasionally observed following higher cumulative doses and there are reports of spontaneous recovery following this pattern of hearing loss.

There is a strong potential for vestibular toxicity to be accompanied by cochlear toxicity in patients receiving Platinum based chemotherapy. A recent multi-centre study of 952 cancer patients

receiving cisplatin -based chemotherapy suggested 9.3% overall new cases of dizziness and vertigo.

Myers et al. [32] studied on 34 adult head and neck malignancy patients receiving cisplatin 100-600 mg/m^2, 2.9% had abnormal caloric test results after the treatment. 20.6% abnormal results after rotational tests. 58.3 % had hearing loss and 66.7 % had tinnitus.

In the present study, during 1 month follow up 8 ears (16%) complained of vertigo. But during 6 month follow up there was an increased incidence of vertigo complaint, which raised to 60 % involving 24 ears. Hence it signifies chemotherapy induced vestibular toxicity causing dizziness. Further research needed to find out dose relationship of chemotherapy and vertigo complaint.

In the present study, during 1 month follow up 28 ears (56%) complained of tinnitus. During 6 month follow up there was an increased incidence of tinnitus complaint, which raised to 60% involving 24 ears. Initially tinnitus was thought to be due to middle ear effusion, but the incidence didn't decrease even after months, hence it signifies chemotherapy induced vestibular toxicity causing tinnitus. The relationship between chemotherapy dose and incidence of tinnitus is well recognized but poorly quantified.

The rate of abnormal vestibular function test findings associated with Platinum based chemotherapy in the existing literature varied from

0 to 50% after chemotherapy treatment and 4.3% -36.5% during chemotherapy treatment. Therefore, the incidence and prevalence of vestibular abnormality after cisplatin drugs warrants further research.

SNHL is a late complication following radiotherapy. In the present study hearing loss was noted at 6 months follow up. Since the study has only 6 months follow up, it may require longer follow up to detect further progression of hearing loss.

As could be seen from the present study, patients exposed to radiotherapy presented with hearing loss and with other complaints as explained earlier. This is extremely important because behavioural patterns that are more depressive or that present greater tendencies for social isolation can sometimes be attributed to the malignancy or to the functional sequalae of the treatment.

CONCLUSION

The present study is taken up to determine the incidence of occurrence of hearing loss and other hearing complaints in head and neck malignancy patients undergoing radiotherapy.

Twenty five patients (50 ears) with histologically proven head and neck malignancy where hearing apparatus included in the field of irradiation were the subjects of the study. Standard of care according to the primary has been delivered. All patients had thorough history, clinical examination and audiological evaluation before starting radiotherapy. All the tests were repeated at completion of treatment and at 6 months follow up.

OME is seemingly most common adverse effect after radiotherapy to head and neck malignancy patients. There seems to be a link between the irradiation dosage to the eustachian tube and development of OME. Hence dose titration to eustachian tube should be done to reduce the complication.

Regarding vertigo and tinnitus, during 6 month follow up there was an increased incidence of complaint, hence it signifies chemotherapy induced vestibular toxicity causing dizziness and ringing sound in the ears. Hence dose limitation and rehabilitation plays crucial role.

Hearing loss is still given little recognition and little value. It is one of the chronic problem faced among elderly patients and from this study, population with cancer are even more affected by this.

Concern for the quality of life of patients undergoing cancer treatment is necessarily growing and determination of hearing loss should also form part of such investigation to enable better rehabilitation.