# EFFECTS OF RADIOTHERAPY ON OLFACTION AND NASAL FUNCTION IN HEAD AND NECK CANCER PATIENTS

*A dissertation submitted in partial fulfillment of MS Branch IV, ENT examination of the Tamil Nadu Dr.MGR Medical University, to be held in May 2018*

# EFFECTS OF RADIOTHERAPY ON OLFACTION AND NASAL FUNCTION IN HEAD AND NECK CANCER PATIENTS


*A dissertation submitted in partial fulfillment of MS Branch IV, ENT examination of the Tamil Nadu Dr.MGR Medical University, to be held in May 2018*

**DEPARTMENT OF OTORHINOLARYNGOLOGY**

**CHRISTIAN MEDICAL COLLEGE**

**VELLORE**

# CERTIFICATE

This is to certify that the dissertation **"EFFECTS OF RADIOTHERAPY ON OLFACTION AND NASAL FUNCTION IN HEAD AND NECK CANCER PATIENTS"** is the bonafide original work of **Dr. Preethi Rose Gurushekar**, carried out under my guidance, submitted in partial fulfillment of the rules and regulations for the **MS Branch IV**, **ENT** examination of the Tamil Nadu Dr.MGR Medical University, to be held in May 2018.

**Dr. Lalee Varghese**

Associate Professor

Dept of Otorhinolaryngology

Christian Medical College

Vellore- 632004.

# DEPARTMENT OF OTORHINOLARYNGOLOGY

# CHRISTIAN MEDICAL COLLEGE

# VELLORE

## CERTIFICATE

This is to certify that the dissertation entitled **"EFFECTS OF RADIOTHERAPY ON OLFACTION AND NASAL FUNCTION IN HEAD AND NECK CANCER PATIENTS"** is the bonafide original work of **Dr.Preethi Rose Gurushekar** submitted in partial fulfillment of the rules and regulations for the **MS Branch IV, ENT** examination of the Tamil Nadu Dr.MGR Medical University, to be held in May 2018.


**Dr. Anna B. Pulimood**
Principal
Christian Medical College
Vellore, Tamilnadu
India- 632002

**Dr. Rita Ruby Anbuselvi Albert**
Professor and Head
Dept of Otorhinolaryngology
Christian Medical College
Vellore - 632004.

# DEPARTMENT OF OTORHINOLARYNGOLOGY

# CHRISTIAN MEDICAL COLLEGE

# VELLORE

## DECLARATION

I, Preethi Rose Gurushekar , do hereby declare that the dissertation titled "**EFFECTS OF RADIOTHERAPY ON OLFACTION AND NASAL FUNCTION IN HEAD AND NECK CANCER PATIENTS** " submitted towards partial fulfilment of the requirements of the Tamil Nadu Dr. M.G.R.Medical University for the MS Branch IV, Otorhinolaryngology examination to be conducted in May 2018, is the bonafide work done by me, and due acknowledgements have been made in text to all materials.

Preethi Rose Gurushekar

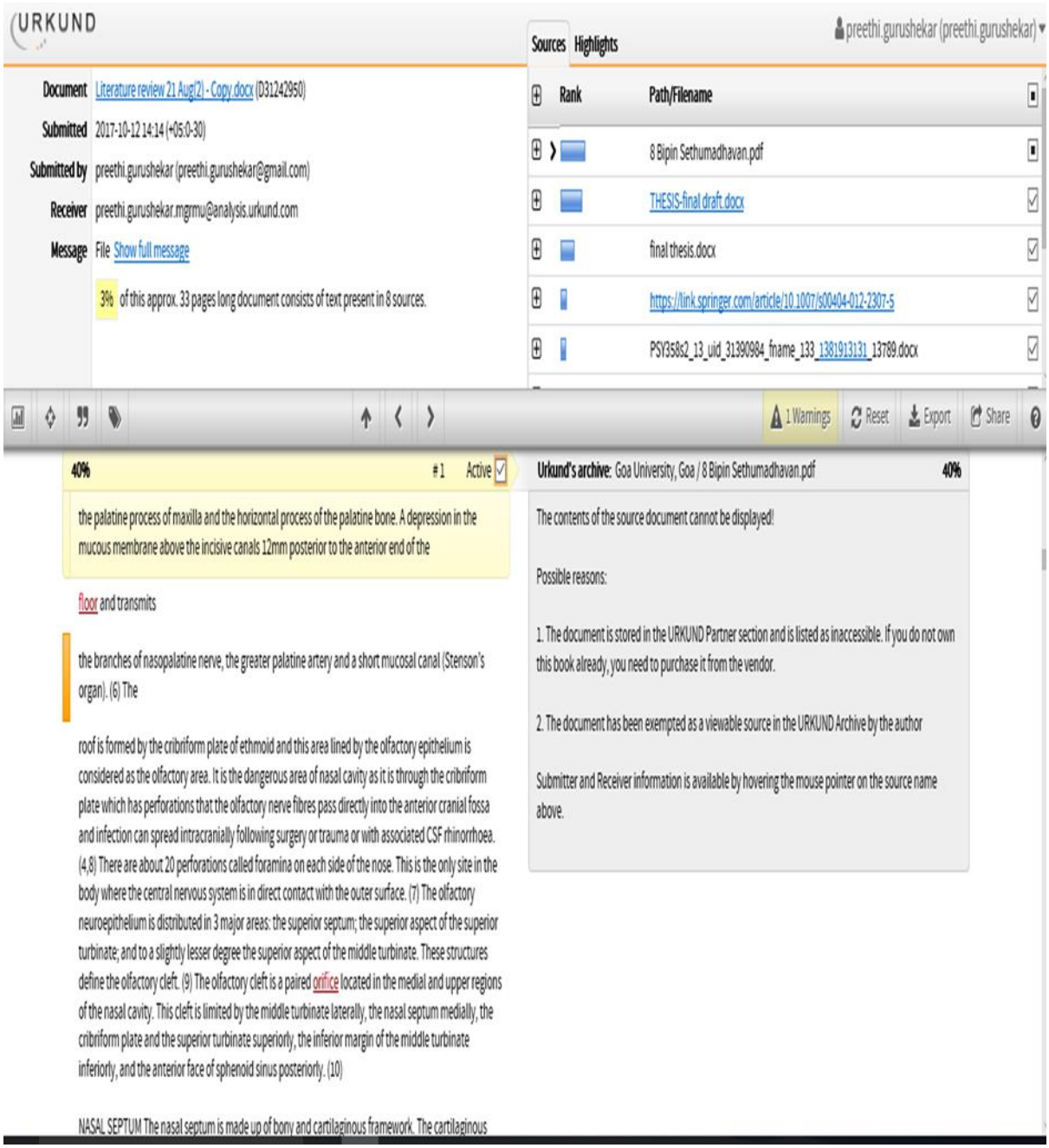
PG Registrar, MS ENT

Registration No. – 221614353

Dept of Otorhinolaryngology

Christian Medical College

Vellore - 632004.


URKUND
preethi.gurushekar (preethi.gurushekar)
Sources
Highlights
Document Literature review 21 Aug(2) - Copy.docx (D31242950)
Submitted 2017-10-12 14:14 (+05:0-30)
Submitted by preethi.gurushekar (preethi.gurushekar@gmail.com)
Receiver preethi.gurushekar.mgrmu@analysis.urkund.com
Message File Show full message
3% of this approx. 33 pages long document consists of text present in 8 sources.
Rank
Path/Filename
8 Bipin Sethumadhavan.pdf
THESIS-final draft.docx
final thesis.docx
https://link.springer.com/article/10.1007/s00404-012-2307-5
PSY3582_13_uid_31390984_fname_133_1381913131_13789.docx
1 Warnings
Reset
Export
Share
40%
#1
Active
the palatine process of maxilla and the horizontal process of the palatine bone. A depression in the mucous membrane above the incisive canals 12mm posterior to the anterior end of the
floor and transmits
the branches of nasopalatine nerve, the greater palatine artery and a short mucosal canal (Stenson's organ). (6) The
roof is formed by the cribriform plate of ethmoid and this area lined by the olfactory epithelium is considered as the olfactory area. It is the dangerous area of nasal cavity as it is through the cribriform plate which has perforations that the olfactory nerve fibres pass directly into the anterior cranial fossa and infection can spread intracranially following surgery or trauma or with associated CSF rhinorrhoea. (4,8) There are about 20 perforations called foramina on each side of the nose. This is the only site in the body where the central nervous system is in direct contact with the outer surface. (7) The olfactory neuroepithelium is distributed in 3 major areas: the superior septum; the superior aspect of the superior turbinate; and to a slightly lesser degree the superior aspect of the middle turbinate. These structures define the olfactory cleft. (9) The olfactory cleft is a paired orifice located in the medial and upper regions of the nasal cavity. This cleft is limited by the middle turbinate laterally, the nasal septum medially, the cribriform plate and the superior turbinate superiorly, the inferior margin of the middle turbinate inferiorly, and the anterior face of sphenoid sinus posteriorly. (10)
NASAL SEPTUM The nasal septum is made up of bony and cartilaginous framework. The cartilaginous
Urkund's archive: Goa University, Goa / 8 Bipin Sethumadhavan.pdf
40%
The contents of the source document cannot be displayed!
Possible reasons:
1. The document is stored in the URKUND Partner section and is listed as inaccessible. If you do not own this book already, you need to purchase it from the vendor.
2. The document has been exempted as a viewable source in the URKUND Archive by the author
Submitter and Receiver information is available by hovering the mouse pointer on the source name above.

## ACKNOWLEDGEMENTS

*I would like to thank God Almighty for giving me this opportunity, being with me through every step and helping me to complete this dissertation.*

*I wish to express my sincere gratitude to my guide Dr. Lalee Varghese, Associate Professor, Department of Otorhinolaryngology, Christian Medical College and Hospital, Vellore, for her constant support, hard work, motivation, meticulous guidance and encouragement from the very first step, without which this dissertation would not have been possible.*

*I would like to thank Dr. V. Rupa, Professor and Head of Unit 3, Department of Otorhinolaryngology, Christian Medical College and Hospital, Vellore, for her invaluable advice and support throughout the study.*

*I am grateful to Dr. Rita Ruby Anbuselvi A., Professor and Head of Otorhinolaryngology, Christian Medical College and Hospital, Vellore for her constant support and words of encouragement in carrying out this study.*

*I am extremely grateful to Dr. Rajesh I, Department of Radiotherapy for his valuable help, advice and guidance in this study.*

*I express my gratitude to Dr Subhashini John, Department of Radiotherapy for all her input and guidance during the study.*

*I am very thankful to all the treatment room nurses and the receptionist, Mrs. Hepsy without whose help the study could not have been completed.*

*I would like to thank Mrs. Tunny Sebastian, Department of Biostatistics for her patiently understanding and helping me with the analysis of the data.*

*I am thankful to our PG coordinator, Dr. Lalee Varghese for conducting timely interim thesis update presentations which helped me to complete the project on time.*
*I am grateful to all my friends and colleagues from the Department of ENT for helping me in collecting the cases and making the study a reality.*

*I would like to thank all the patients who agreed to be a part of this study.*

*I would also like to thank the Fluid Research Committee, CMC Hospital for granting me permission for conducting this study.*

*A special thanks to my parents and my husband Dr. Daspin for their love, concern and support throughout the work on this study.*

# OFFICE OF RESEARCH
# INSTITUTIONAL REVIEW BOARD (IRB)
# CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

**Dr. B.J. Prashantham,** M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

**Dr. Anna Benjamin Pulimood,** M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

**Dr. Biju George,** M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

October 05, 2016

Dr. Preethi Rose Gurushekar,
PG Registrar,
Department of ENT,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Funding: New Proposal**
Effect of radiotherapy on olfaction and nasal function in head and neck cancer patients. Dr. Preethi Rose Gurushekar (Emp. No. 33886), PG Registrar, ENT, Dr. Lalee Varghese (emp. No. 20258), ENT, Dr. Subhashini John (Emp. No. 01426), Radiotherapy, Dr. Rajesh I (Emp. No. 20297), Radiotherapy , Ms. Tunny Sesbastian (emp. No. 32291), Biostatistics.

Ref: IRB Min No: 10209 [OBSERVE] dated 08.08.2016

Dear Dr. Preethi Rose Gurushekar,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Lalee Varghese, Dept. of ENT, CMC, Vellore

**OFFICE OF RESEARCH**
**INSTITUTIONAL REVIEW BOARD (IRB)**
**CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA**

**Dr. B.J. Prashantham,** M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

**Dr. Anna Benjamin Pulimood,** M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

**Dr. Biju George,** M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

October 05, 2016

Dr. Preethi Rose Gurushekar,
PG Registrar,
Department of ENT,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Funding: New Proposal**
Effect of radiotherapy on olfaction and nasal function in head and neck cancer patients. Dr. Preethi Rose Gurushekar (Emp. No. 33886), PG Registrar, ENT, Dr. Lalee Varghese (emp. No. 20258), ENT, Dr. Subhashini John (Emp. No. 01426), Radiotherapy, Dr. Rajesh I (Emp. No. 20297), Radiotherapy , Ms. Tunny Sesbastian (emp. No. 32291), Biostatistics.

Ref: IRB Min No: 10209 [OBSERVE] dated 08.08.2016

Dear Dr. Preethi Rose Gurushekar,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Effect of radiotherapy on olfaction and nasal function in head and neck cancer patients" on August 08th 2016.

The Committee reviewed the following documents:

1. IRB Application format
2. Cv's of Drs. Tunny S, Preethi, Rajesh, Subhashini and Lalee Varghese,
3. Consent forms and Patient Information Sheets,
4. Proforma
5. Questionnaire
6. No. of documents 1 - 5

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on August 08th 2016 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.



Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

**Dr. B.J. Prashantham,** M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

**Dr. Anna Benjamin Pulimood,** M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

**Dr. Biju George,** M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)


| Name | Qualification | Designation | Affiliation |
|---|---|---|---|
| Dr. Biju George | MBBS, MD, DM | Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC,Vellore | Internal, Clinician |
| Dr. B. J. Prashantham | MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling) | Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore | External, Social Scientist |
| Dr. Anuradha Rose | MBBS, MD, MHSC (Bioethics) | Associate Professor, Community Health, CMC, Vellore | Internal, Clinician |
| Dr. Jayaprakash Muliyil | BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC | Retired Professor, Vellore | External, Scientist &Epidemiologist |
| Rev. Joseph Devaraj | BSc, BD | Chaplaincy Department, CMC, Vellore | Internal, Social Scientist |
| Mr. C. Sampath | BSc, BL | Advocate, Vellore | External, Legal Expert |
| Dr. Visalakshi. J | MPH, PhD | Lecturer, Biostatistics, CMC, Vellore | Internal, Statistician |
| Mrs. Sheela Durai | MSc Nursing | Professor, Medical Surgical Nursing, CMC, Vellore | Internal, Nurse |
| Ms. Grace Rebekha | M.Sc., (Biostatistics) | Lecturer, Biostatistics, CMC, Vellore | Internal, Statistician |
| Mrs. Pattabiraman | BSc, DSSA | Social Worker, Vellore | External, Lay Person |
| Dr. Rajesh Kannangai | MD, PhD. | Professor, Clinical Virology, CMC, Vellore | Internal, Clinician |
| Dr. Balamugesh | MBBS, MD(Int Med), DM, FCCP (USA) | Professor, Pulmonary Medicine, CMC, Vellore | Internal, Clinician |




Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

**Dr. B.J. Prashantham,** M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

**Dr. Anna Benjamin Pulimood,** M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

**Dr. Biju George,** M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

| | | | |
|---|---|---|---|
| Dr. Sneha Varkki | MBBS, DCH, DNB | Professor, Paediatrics, CMC, Vellore | Internal, Clinician |
| Mrs. Emily Daniel | MSc Nursing | Professor, Medical Surgical Nursing, CMC, Vellore | Internal, Nurse |
| Dr. Sathish | MBBS, MD, DCH | Professor, Child Health, CMC, Vellore | Internal, Clinician |
| Dr. Inian Samarasam | MS, FRCS, FRACS | Professor, Surgery, CMC, Vellore | Internal, Clinician |
| Dr. Mathew Joseph | MBBS, MCH | Professor, Neurosurgery, CMC, Vellore | Internal, Clinician |
| Dr. Ranjith K Moorthy | MBBS, MCh | Professor, Neurological Sciences, CMC, Vellore | Internal, Clinician |

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Effect of radiotherapy on olfaction and nasal function in head and neck cancer patients" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

*Fluid Grant Allocation:*

*A sum of 48,500/- INR (Rupees Forty Eight Thousand Five Hundred Only) will be granted for 10 months.*

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min No: 10209 [OBSERVE] dated 08.08.2016



Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

# CONTENTS

# INTRODUCTION

The sense of smell is a multidimensional event (1). Olfaction acts as a pleasurable stimulus and has been shown to affect quality of life. It plays a major role in modifying dietary behaviour and also acts as an important surveillance system in safety and prevention (2). During the process of mastication of food, flavour released is transmitted to the olfactory cleft via the nasopharynx. This pathway of retronasal olfaction is essentially involved for appreciating flavour of food. The perception of olfactory stimuli is emotionally linked. Odours relating to memories of the past, are capable of evoking strong emotions (3).

Olfactory impairment has historically been overlooked as a public health problem. Olfactory dysfunction exposes patients to potentially life-threatening events such as increased risk of cooking accidents, inability to detect fires and gas leaks and ingestion of toxic or spoiled substances. These are hazards and collectively pose a significant public health risk (2,4). Several studies indicate that frequent exposure to different odours can lead to improvement of olfactory function. The stimulation of olfaction is based on the ability of the olfactory system to regenerate. An olfactory training programme requires exposure to each odorant for 10 seconds for a duration of 4 to 6 months. The odours usually suitable for the training include lemon, eucalyptus, rose and cloves, which belong to odour categories fruity, floral, resinous, and aromatic (3).

There are various physiological and pathological conditions that affect the sensation of olfaction. In the present study, the chemosensation of patients with primary head and neck malignancies is assessed at different intervals of radiotherapy.

Head and neck malignancies involving the nasopharynx, oropharynx, oral cavity, and sinonasal region are often treated with radiation therapy. In patients undergoing conformal radiotherapy, the radiation fields include the olfactory cleft region. Such patients usually complain of deteriorating chemosensory function and quality of life during the course of treatment. Following therapy, there is reportedly gradual improvement in the olfactory function as the olfactory system regenerates. In some patients, the recovery is delayed and the deterioration in function seems to persist. However there is contradicting literature on this subject. Hence we decided to do a study to make a subjective and objective assessment of the olfactory function, mucociliary clearance and quality of life after initiation of radiotherapy in head and neck cancer patients.

## AIMS & OBJECTIVES

**Aim:**

To assess the effect of radiotherapy on olfaction in patients with head and neck malignancies treated with radiotherapy (RT).

**Objectives:**

1) To compare olfaction before, mid RT, end of RT and 3 months after radiotherapy

2) To evaluate the effect of radiotherapy on mucociliary clearance time using saccharin test before radiotherapy, mid RT, end of RT and 3 months after radiotherapy

3) To compare the quality of life using Appetite, Hunger and Sensory Perception (AHSP) Questionnaire before radiotherapy, mid RT, end of RT and 3 months after radiotherapy

## DEVELOPMENT OF NASAL CAVITY AND OLFACTORY REGION

There are a number of mesenchymal processes surrounding the primitive stomatodeum from which the nose develops. The frontonasal process arises between the central aspect of the forebrain and the epithelial roof of mouth. A highly specialised ectodermal tissue called olfactory placode develops during the 5th week of intrauterine life on each side of the ventral surface of the frontonasal processes which separate it into median and lateral nasal processes. The olfactory placode forms a depression called the olfactory pit (5,6). The stratified placodal base of the invagination forms the olfactory epithelium. The lateral walls around the invaginating pits form the surface ectodermal covering of the nasal cavities. The placodal cells of the olfactory epithelium differentiate into neurosensory cells within the thickness of the epithelium and eventually give origin to olfactory nerve fibres. At the end of third month, the mesenchyme between the sensory epithelium and the bulb gives rise to the lamina cribrosa of the ethmoid bone which is eventually organized around the olfactory nerve networks and separates them into a number of bundles. The lamina ossifies here to form the cribriform plate of the ethmoid through which the nerves pass to enter the olfactory bulbs. At about 5 months, the axons of the superficial cells cross the epithelium and the mesenchyme and reach the olfactory area of the cerebral hemisphere. The axons then connect with the specialized structures of the central nervous system corresponding to the olfactory system. The olfactory bulb elongates, and eventually the extension of the ventricular cavity into it becomes obliterated. Cells in the bulb around which the olfactory nerve fibres terminate and synapse, give origin to secondary olfactory fibres which grow centrally and form the olfactory tract. The

olfactory tract terminates in the region of the piriform. In lower mammals, the olfactory nerve is distributed to the vomero nasal organ found in the lower part of the nasal septum (7). On the lateral wall of the nose a series of elevations appear within the nasal cavity within the 6th week of intrauterine life which ultimately forms the turbinates (5,6).

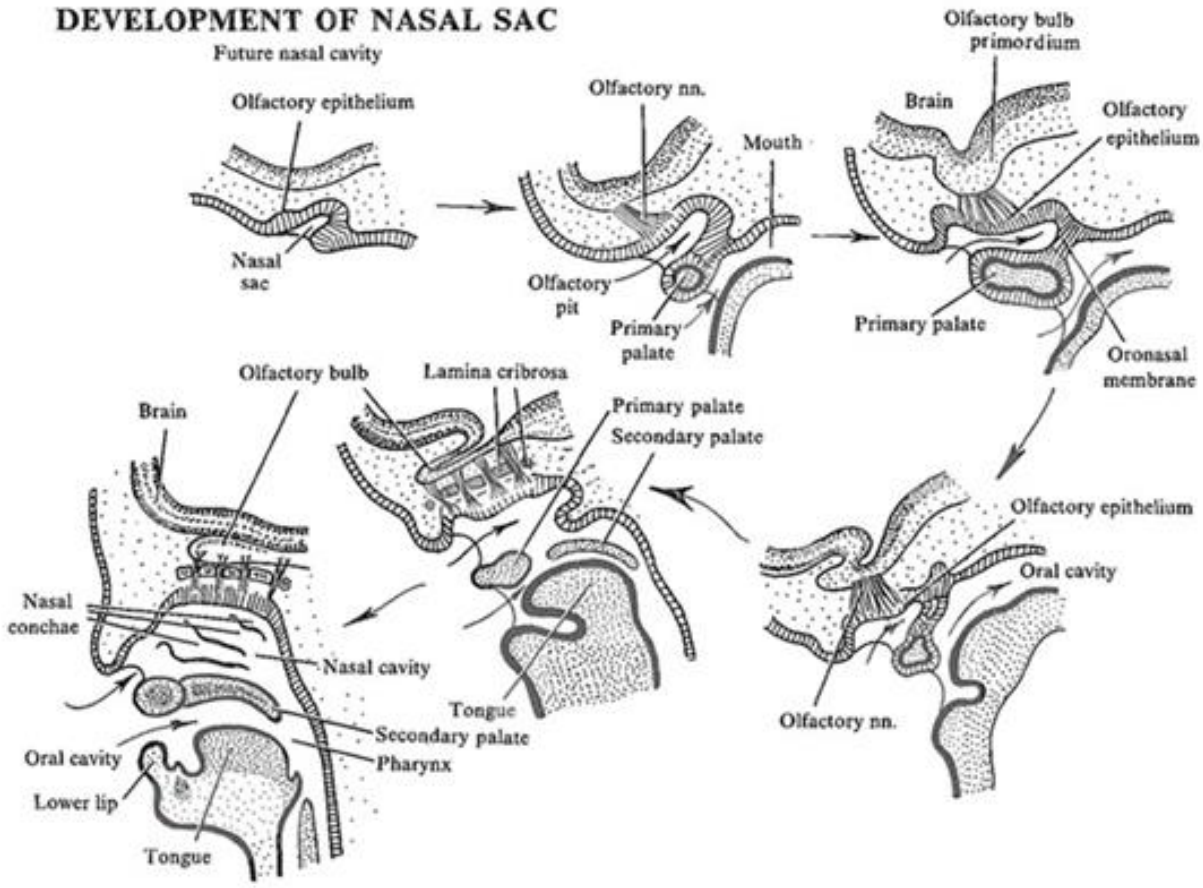



**Fig 1 : Development of nasal cavity and olfactory region**

## ANATOMY OF NOSE

## EXTERNAL FRAMEWORK OF NOSE

The external nose is a pyramidal shaped structure made of cartilages and bones. It is a delicate organ which serves the cosmetic function and act as the gateway of respiratory tract.

### Nasal bones

The nasal bone is wedge-shaped and its surface is grooved by neurovascular bundles (5,7). The 2 nasal bones articulate with each other in the midline forming the bridge of the nose. Superiorly the nasal bone is attached with the frontal bone, inferiorly with the upper lateral cartilage and laterally with the frontal process of the maxilla at the nasolacrimal suture. The nasal bone ossifies from a membranous centre which lies over the anterior part of cartilaginous nasal capsule.

### Cartilages of the external nose and columella

The nasal cartilages are hyalinised structures which prevent collapse of the vestibule on inspiration. There are 2 triangular shaped upper lateral cartilages which articulate superiorly with the nasal bones and are overlapped by them, by the adjacent frontal processes of the maxillae and inferiorly by the lower lateral held by the fibrous tissue. The junction between the upper and lower cartilages is known as the limen nasi, which is the site of intercartilaginous incisions. The lower lateral cartilage has medial and lateral crura which form the dome of the tip. Columella is formed by the medial crura of the 2 lower lateral cartilages in the midline, anterior to the

quadrilateral cartilage (7). The minor sesamoid cartilages are present between the upper and lower nasal cartilages. Nasal bones and cartilages are lined by periosteum and perichondrium (5). The skin and soft tissues over the dorsum of nose and along the nasal bridge is thin and loosely adherent while it is thicker and more adherent over the tip (7).

**Blood supply**

Branches of the facial artery supply the alar region while the dorsum and lateral walls of the external nose are supplied by the dorsal branch of the ophthalmic artery and the infraorbital branch of the maxillary artery (7,8).

**Nerve supply**

The skin of the external nose receives its sensory supply from the two upper divisions of the trigeminal nerve; ophthalmic and maxillary. The anterior ethmoidal nerve traverses the dorsum of the nose to supply the tip. The infraorbital nerve supplies the lateral nasal walls, columella, and vestibule (7).

**VESTIBULE**

The external nose has a dilated pathway called the vestibule which leads into the nasal cavities. It is demarcated by the limen nasi, at the superior margin of the lower lateral cartilage (5). The vestibule is lined by skin containing hair follicles, sebaceous glands and sweat glands.

## NASAL CAVITY

The nasal cavity is divided into 2 halves by the nasal septum. Each nasal cavity extends anteriorly from the external nares to the choanae posteriorly, which is continuous with the nasopharynx. The nasal cavity is narrower anteriorly and widens as it extends posteriorly (7). The surface area of the nasal cavity is about 160 cm2, or 96 m2 if the microvilli are included (9).

Vertically, it extends from the palate to the cribriform plate, being broader at its base and narrows to the olfactory cleft superiorly. Each half has a floor, a roof, a lateral wall and a medial (septal) wall. The floor is formed by the palatine process of maxilla and the horizontal process of the palatine bone. A depression in the mucous membrane above the incisive canals 12mm posterior to the anterior end of the floor transmits the branches of nasopalatine nerve, the greater palatine artery and a short mucosal canal (Stenson's organ) (7). The roof is formed by the cribriform plate of ethmoid and this area lined by the olfactory epithelium is considered as the olfactory area. It is the dangerous area of nasal cavity as it is through the cribriform plate which has perforations that the olfactory nerve fibres pass directly into the anterior cranial fossa and infection can spread intracranially following surgery or trauma or with associated CSF rhinorrhoea (5,10). There are about 20 perforations called foramina on each side of the nose. This is the only site in the body where the central nervous system is in direct contact with the outer surface (7).

The olfactory neuroepithelium is distributed in 3 major areas: the superior septum, the superior aspect of the superior turbinate, and to a slightly lesser degree the

superior aspect of the middle turbinate. These structures define the olfactory cleft (11). The olfactory cleft is a paired orifice located in the medial and upper regions of the nasal cavity. This cleft is limited by the middle turbinate laterally, the nasal septum medially, the cribriform plate and the superior turbinate superiorly, the inferior margin of the middle turbinate inferiorly, and the anterior face of sphenoid sinus posteriorly (12).

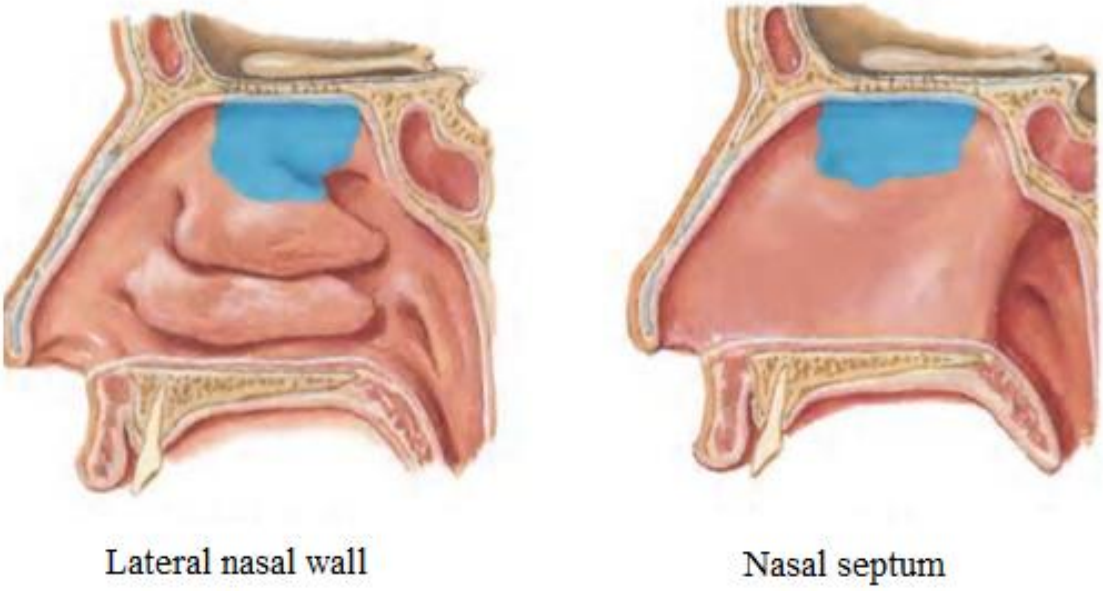



**Fig 2 : Olfactory area**

**NASAL SEPTUM**

The nasal septum is made up of bony and cartilaginous framework. The cartilaginous framework of the nasal septum consists of a quadrilateral cartilage with contribution from the lower and upper lateral cartilages. The membranous columella is the part of the nasal septum formed between the medial crus of the lower lateral cartilage and the quadrangular cartilage.

The perpendicular plate of the ethmoid bone forms the superior and anterior bony septum, extends above to attach to the cribriform plate and crista galli. The vomer forms the posterior portion of the septum and articulates with the rostrum of the sphenoid. The inferior border of the vomer articulates with the nasal crest of maxilla and the palatine crest. The anterior border articulates with the perpendicular plate above and the quadrilateral cartilage inferiorly. The posterior edge of vomer remains free. The surface area of the septum measures between 30 and 35cm2 in adults (7).

## LATERAL WALL OF NOSE

It is an irregular surface formed by scrolls of bones which is the site of drainage of sinus secretions (5,7).

### Inferior turbinate

This structure is composed of the inferior concha which is a separate bone having an irregular surface, lined by respiratory epithelium and its subepithelium containing cavernous venous plexus with large sinusoids under autonomic control which provides the major contribution to nasal resistance. It also articulates with the ethmoid, palatine and lacrimal bones, completing the medial wall of the nasolacrimal duct. The turbinate possesses an impressive submucosal cavernous plexus. The turbinate is covered by a large number of goblet cells which decrease in density towards the posterior end (7).

**Inferior meatus**

The inferior meatus lies lateral to the inferior turbinate and extends along the entire length of the nasal cavity. The opening of the nasolacrimal duct which is at the anterior third of the inferior meatus is guarded by a mucous membrane called Hasner's valve (13,14).

**Middle turbinate**

The middle turbinate forms the medial wall of the middle meatus and is attached superiorly to the cribriform plate. At the middle third of the middle turbinate, it forms the basal lamella which separates the anterior and posterior ethmoidal air cells and inserts in to the lateral wall of nose. The posterior end of the turbinate forms a boundary of the sphenopalatine foramen (9).

**Middle meatus**

The middle meatus is one of the most important areas of the nose that lies between the middle turbinate and lateral wall of nose. The anterior group of sinuses that is the frontal, maxillary and anterior ethmoidal sinuses drain into the middle meatus. A thin piece of bone known as the uncinate process is a wing or boomerang shaped piece of bone forming the first layer or lamella of the middle meatus. It is related anteriorly to the posterior edge of the lacrimal bone, and inferiorly to the superior edge of the inferior turbinate. Superior attachment of the uncinate process is highly variable, may be attached to the lamina papyracea, or the roof of the ethmoidal sinus, or sometimes to the middle turbinate. The maxillary sinus ostium is bounded by the mucous membrane of the maxillary sinus. The membranous area lying anterior to

the uncinate process is the anterior fontanelle while membranous area posterior to the uncinate is posterior fontanelle. Accessory ostia are found most frequently in the posterior fontanelle which occurs as a result of recurrent chronic sinusitis in 25% cases while it may be present naturally also (7,13).

**Superior turbinate**

The superior turbinate is attached to the skull base and forms boundary to the olfactory cleft (11).

**Superior meatus**

This meatus is again defined by its relationship to the superior turbinate. The posterior ethmoidal cells open into this region (11).

**Sphenoethmoidal recess**

The ostium of the sphenoid sinus opens into the sphenoethmoidal recess lying medial to the superior turbinate.

## PARANASAL SINUSES

The paranasal sinuses are air-filled cavities within the skull lined by a thin layer of respiratory mucosa of the nose from the nasal cavity. They are divided into an anterior and a posterior group.

The anterior group including frontal, anterior ethmoidal and maxillary sinuses drain into the middle meatus of the nose. In the posterior group , the posterior

ethmoidal cells drain into the superior meatus and the sphenoid sinus drains into the sphenoethmoidal recess (9,10).

**Maxillary sinus**

The maxillary sinus (antrum) is a paired pyramidal structure formed by the malar process, lower part of the lateral wall of the nose and the floor of the orbit. The roots of the canine, molars and premolars produce different eminences over the maxilla. The maxillary ostium is located at the junction of anterosuperior and posteroinferior aspect of infundibulum, hence drainage is dependent on ciliary action and not gravity. The average adult size of the maxillary sinus is 35 mm high, 30 mm anteroposteriorly and 25 mm wide with a volume of 15 ml (9,10,13).

**Frontal sinus**

These are a pair of funnel shaped structures situated within the frontal bone above the supraorbital margin and root of the nose with their ostia directed downwards. They are asymmetric and divided by a vertical bony septum called interfrontal septum (7,9,10).

**Ethmoidal sinuses**

The ethmoid sinus labyrinth is a cavity made up of honey comb network of small cells that vary in number and size. It is related laterally to the medial wall of the orbit (lamina papyraceae) and medially to the nasal cavity. Superiorly, it is attached to the anterior cranial fossa, near the midline, on either side of the cribriform plate (fovea ethmoidalis). The anterior ethmoidal air cells are small and numerous and drain

into the middle meatus. The posterior ethmoidal air cells are fewer in number and drain into the superior meatus (6,8).

**Sphenoid sinus**

The sphenoid sinuses lie within the body of the sphenoid bone, divided by a vertical septum. They are rudimentary at birth and true growth of the sphenoid sinus only occurs at puberty. Laterally, the sinus is related to the internal carotid artery, the optic nerve and the cavernous sinuses which contain the IIIrd, IVth, ophthalmic and maxillary divisions of Vth and Vlth cranial nerves. The olfactory apparatus and the frontal lobes lie superiorly and the pituitary fossa lies posteriorly (10).

**HISTOLOGY**

The nasal septum is lined by the mucoperichondrium and mucoperiosteum. The nasal mucosa is predominantly respiratory epithelium with olfactory epithelium lining the roof of nose adjacent to the cribriform plate. Respiratory epithelium is composed of ciliated and nonciliated pseudostratified columnar cells, basal pluripotent stem cells and goblet cells. Each cell bears 300–400 microvilli. There are a number of finger-like cytoplasmic extensions called cilia which serve to increase the surface area and prevent drying of nasal mucosa. The cilia beat in a specific direction such that the secretions are directed posteriorly into the nasopharynx and can be swallowed (5). The cilia consists of multi – structural classical axonema of nine peripheral doublet and two central single microtubules (9+2 pattern). Of the paired microtubules peripheral pair (A and B) connects to the next doublet and to the central microtubule with hexin links. The A microtubule contains 2 arms, an outer and inner dynein arm, composed

of ATPase which extends to the B microtubule. This is responsible for the ciliary movement. Several seromucinous glands present in the submucosa are involved in mucus production. Within the sinuses are numerous goblet cells. In newborns, the septal mucosal surface is 450mm2 with 17–18 glands/ mm2, compared with the adult septum of 1700mm2 and 8.5 glands/mm2.

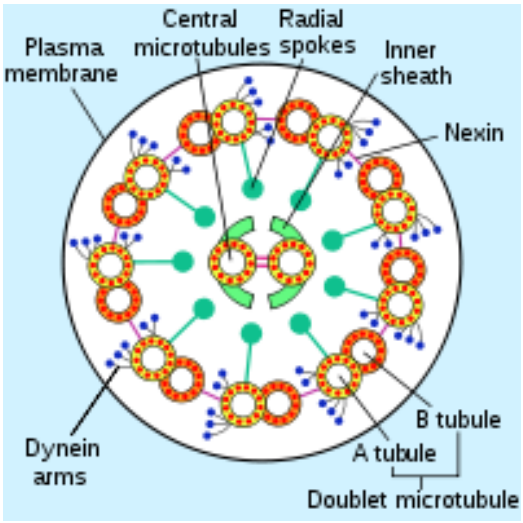



**Fig 3 : Cross section of an Axoneme**

The olfactory epithelium lines the cribriform plate onto the corresponding part of the septum medially. Olfactory region is a small area of 2.5 $mm^2$on each side containing approximately 50 million primary sensory receptor cells. This region consists of olfactory bipolar receptor cells, supporting cells with microvilli and basal stem cells conferring on olfactory epithelium the capacity for regeneration. Each receptor cell has approximately 17 cilia. Dynein arms are absent between the microtubules. The sensory endings have a characteristic knob-like vesicular structure from which olfactory fibres join the axonal bundle. There is a sharp transition zone between the olfactory and respiratory epithelium though the relative area of each

varies with age and reflects the decrease in olfactory acuity. Secretion for the olfactory epithelium is provided by Bowman's glands (5,7).

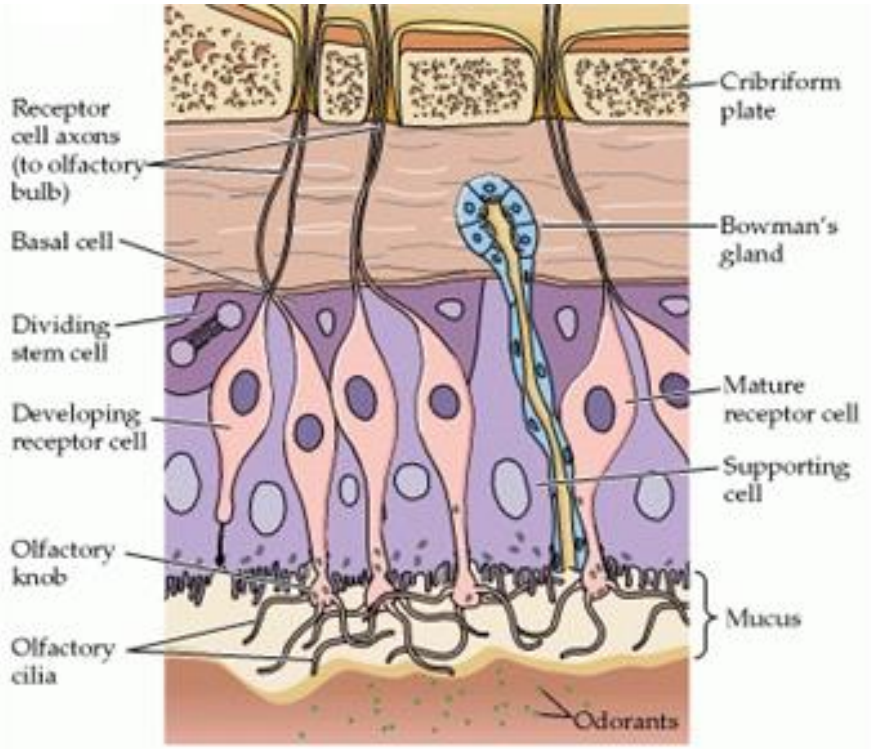



**Fig 4 : Types of olfactory cells**

## PHYSIOLOGY OF NOSE

The primary function of the nose is respiration and olfaction. The nose acts as an air conditioning unit of inspired air and performs three functions: humidification, heat transfer and filtration. The sense of smell is essential in our daily existence and its deterioration is the earliest signs of several diseases. It is also required for ability to taste and determines the flavour of food items (10).

## GENERAL PHYSIOLOGY OF NOSE

Different functions of the nose are:

Airway for respiration

Filters suspended particulate matter from inspired air

Air –conditions (humidifies and regulates temperature) the inspired air

Bactericidal to organisms in inspired air

Transports mucus posteriorly to lubricate the pharynx

Collects the moisture from expired air to prevent excessive loss

Provides the voice with a pleasing resonant quality

Integral part of the olfactory system.

## OLFACTION

Olfaction is one of the distal senses from ancient times which initiates and modifies behaviour in many creatures. Though much emphasis is given to cosmetic and visual appearance of an individual, yet much money is spent modifying body odour. It is a source of livelihood for several workers such as cooks, homemakers, fire fighters, plumbers, wine merchants, perfumers, cosmetic retailers, chemical plant workers (10).

Olfaction requires odorant molecules in air flow to reach olfactory mucosa in the roof of the nose. These receptor molecules need high water and lipid solubility. Diffusion of odorant molecules through the mucous on the mucous membrane excite the bipolar olfactory receptor neurons (ORNs). The solute in mucus is presented to the sensory mucosa. Olfactory mucosa and pathway easily fatigues and regenerates quickly at the same which facilitates man's ability to differentiate several smells (15).

Olfactory tests usually look at the threshold and suprathreshold (7). Suprathreshold tests include odour identification and odour discrimination which are related to the cognitive function. While sniffing there is a rapid change in airflow velocity which allows the trigeminal nerve to alert the olfactory nerve fibres that an odorant molecule is coming. It is the universally performed manoeuvre when presented with an olfactory stimulus although the best stimulus is prolonged inspiration (10).

**Olfactory area**

The olfactory surface area is the region involving the superior third of the superior turbinate corresponding part of the nasal septum and the cribriform plate 200–400$mm^2$ with a density of receptor cells of approximately 5104 receptor cells/$mm^2$. The receptor cells derived from the basal cells bear modified cilia, which increase the surface area and regenerate every month.

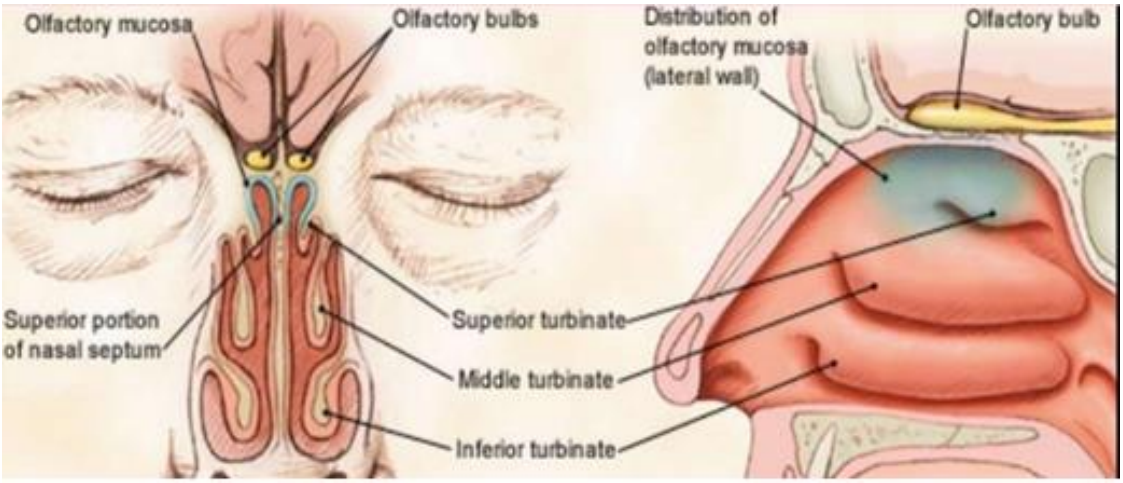



**Fig 5 : Olfactory cleft of nose**

**Stimulus**

Absorption of molecules by the mucosa from the air occurs which influences the spectrum of chemicals reaching the olfactory cleft. Highly absorbable chemicals may have minimal or no odour as they never reach the olfactory cleft. Odours react with the lipid bilayer of the receptor cells at specific sites, which causes potassium and chloride to flow out and thus depolarize the cells and a slow action potential is recorded on the electroolfactogram (EOG) (7).

**Receptors**

Receptors are first order neurons derived from ectoderm. Glial-type cells that ensheath olfactory neurons support axonal growth of both olfactory and non-olfactory neurons. Each receptor cell expresses a single odorant receptor gene. There are more than 1,000 different types of receptors which are responsive to a wide range of stimuli. Receptors are confined to non-overlapping strip like zones. Olfaction is

mediated by G-protein coupled receptors in the cells which interact with a specific adenylcyclase within the neuroepithelium.

**Threshold**

Olfactory responses show both variations in thresholds and adaptation. Threshold depends on the chemical nature of stimuli and the level of inhibitory activity from the higher centres. The threshold of perception is lower than identification that is a smell is sensed before it is recognized and it increases with exposure. Thresholds are affected by changes in nasal mucus and its pH, age and hormones.

**Adaptation**

Adaptation of olfactory responses is a peripheral and central phenomenon. Cross adaptations are present between odours at high concentration (7,16).

**Pathways**

From the olfactory neuroepithelium, bipolar receptor cell projects from the nasal cavity into the brain without an intervening synapse. Odour perception involves the interaction of odorant molecules with highly specialised and specific receptor sites. Receptor cells are connected to the olfactory bulb by nonmyelinated nerve fibres which synapse on olfactory glomeruli. Conduction time between the receptor cells and the glomerulus is 50ms. The impulse is transmitted from the glomeruli by an all or none response into mitral or tufted cells whose axons transport the signal through the

lateral olfactory tract. Normal life span of olfactory neurons ranges from 30 to 90 days (17).

The olfactory pathway can be broadly divided into a peripheral system which receives the odorant stimuli and a central pathway that processes the stimulus so generated.

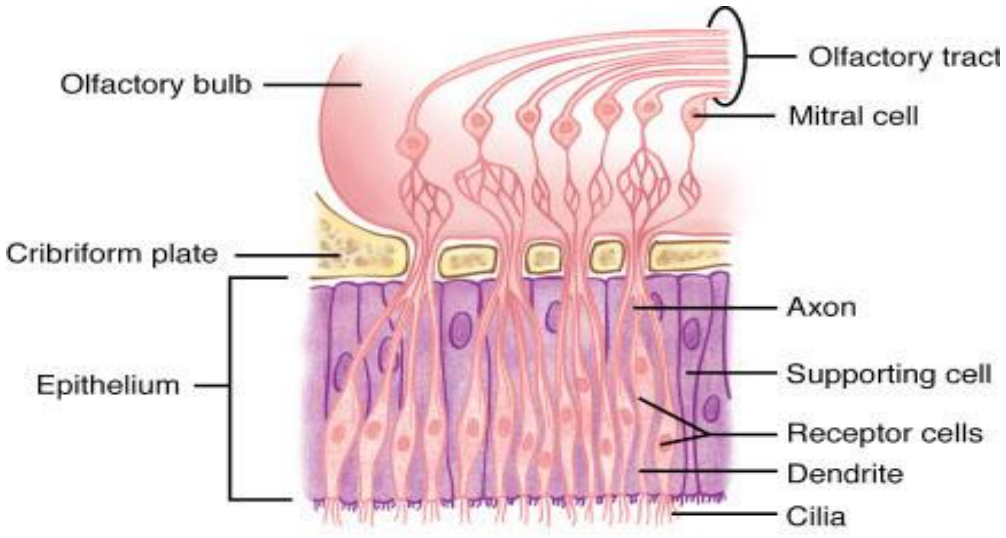



**Fig 6 : Peripheral olfactory pathway**

**Higher centres**

The olfactory bulbs lie on the ventral aspect of the frontal lobes. The olfactory nerves synapse on mitral cells whose axons project directly to the olfactory cortex. The olfactory tract connects the olfactory bulb with the cerebral hemispheres. Axons of mitral cells pass directly back to the olfactory cortex on the ipsilateral side that receives direct sensory input without an interposed thalamic connection

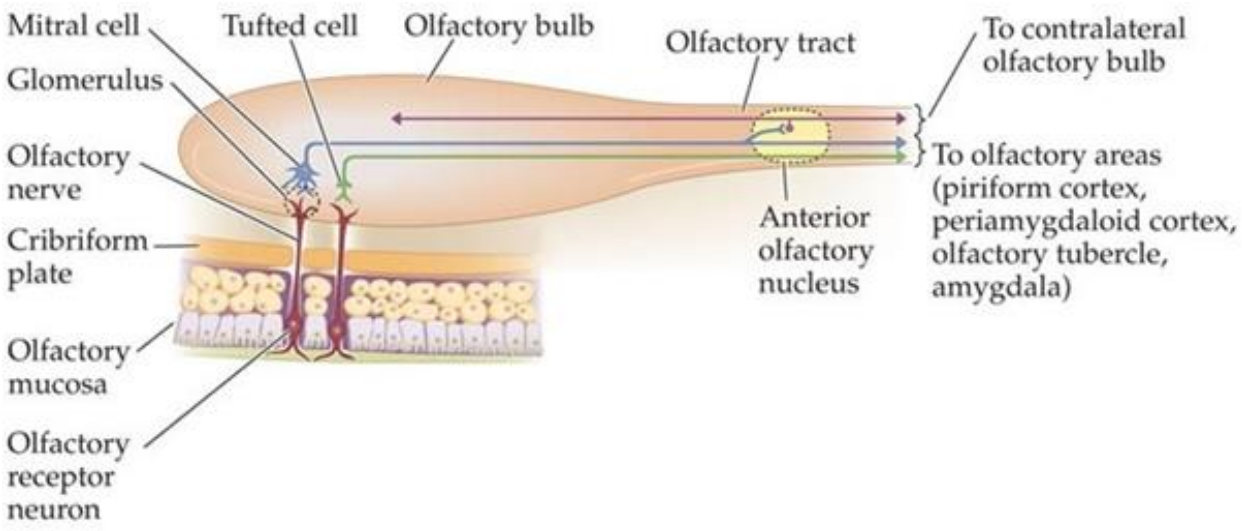



**Fig 7 : Central olfactory connections**

Most of the olfactory cortex is of a primitive 3-layered type, located on the base of the frontal lobe and medial aspect of the temporal lobe overlying the anterior perforated substance through which the striate arteries enter the interior of the brain. On the temporal lobe the olfactory cortex covers the rostral portion of the parahippocampal gyrus including a medial bulge known as the uncus or uncinate gyrus. From the olfactory cortex, olfactory information is relayed via the mediodorsal nucleus of the thalamus to the insular and orbitofrontal cortex. The insular cortex within the Sylvian fissure, also receives taste input from the medial part of VPM and is believed to be the site where olfactory and taste information is integrated to produce the sensation that can be termed flavour. Inhibition comes from feedback from high cortical centres (7,8,15).

**Trigeminal input**

Trigeminal nerve perceives upto 30 % of odours, but at high concentrations irritation occurs and can detect substances such as butyl acetate. Irritation contributes to the nature of smell.

**Theories of olfaction**

- The Steric Theory of Odour– stated air borne chemical molecules are smelled when they fit into certain complementary receptor sites on the olfactory nervous system. This "lock and key" approach was an extension from enzyme kinetics.
- Vibrational theory – Postulated that there is a difference in vibrational frequency for every perceived smell. Odorant molecules that produce the same vibrational frequency produce the same smell
- Luca Turin's theory of smell - reduced to its most basic nature is that the receptors in the nose respond to the different fundamental vibrations of a molecule and that produces the sensation of smell. There are most likely a number of different types of receptors responding to different ranges of vibrations.

**EFFECT OF OLFACTION ON**

**a) Eating**

Olfaction helps two aspects of eating: the recognition of food types and the initiation of digestion. Initiation of digestion is mediated via the lateral and

ventromedial hypothalamus, causes salivation and increases output of gastric acid and enzymes (7). Flavour perception is closely related to olfaction. Flavours released during mastication reach the olfactory cleft via nasopharynx (3).

**b) Sexual behaviour**

Pheromones are chemicals released by one member of a species and received by another member resulting in a specific action or developmental process. These were initially described in animals and insects. Several anatomic and behavioural studies support the possibility of human communication through odorants. Three types of pheromones have been described: releaser pheromones; primer pheromones; and imprinting pheromones.

**FACTORS AFFECTING OLFACTION**

(1) **Age** - Younger persons have thousands glomeruli which decrease in number with age and becomes nearly absent in the elderly after the age of 80 years (10).

(2) **Gender** – In general, many studies have consistently shown that women have a better olfactory ability than men both in threshold and identification.

(3) **Hormonal** - Menstrual cycle influences women's olfaction threshold levels, being best at ovulation and reduced during menstruation (8).

(4) **Neurodegenerative conditions** – Decline in olfaction is seen in Alzheimer's disease, Parkinson's and cognitive degeneration.

(5) **Genetic variability** - Wide range of variability in olfactory performance may reflect different expression patterns of sets of olfactory receptor genes, central processing effects, or genetic variability in the olfactory receptor (OR) genes

(6) **Smoking** – Current smoking was linked to olfactory dysfunction

(7) **Sinonasal diseases** (18)

## DISORDERS OF SMELL

Olfactory disorders are classified according to standard schemata. It is important to differentiate between a patient's chemosensory complaint and the findings of objective testing, which are not always in congruence.

**Anosmia**- refers to an inability to detect qualitative olfactory sensations (i.e. absence of smell function).

**Partial anosmia**- ability to perceive some, but not all odours

**Hyposmia /microsmia**- refers to decreased perception of odours.

**Hyperosmia**– increased sensitivity to common odours.

**Dysosmia** - (sometimes termed cacosmia /parosmia) is distorted or perverted smell perception to odour stimulation.

**Phantosmia** - is a dysosmic sensation perceived in the absence of an odour stimulus Also known as olfactory hallucination

**Olfactory agnosia**- refers to an inability to recognize an odour sensation, even though olfactory processing, language and general intellectual functions are essentially intact

**Heterosmia** – a condition where all odours smell the same

**Presbyosmia** – a decline in smell sense with age

**Osmophobia** – a dislike or fear of certain smells (11).

## MUCOCILIARY CLEARANCE (MCC)

Respiratory mucosa runs in continuity from the nose to the paranasal sinuses. Goblet cells and cilia are less numerous in general but more frequent near the ostia and the blood supply is less well developed with no cavernous plexuses, which give the sinus mucosa a pale colour. Since the nerve supply is less well developed, the sinus mucosa is able to give only a basic vasomotor response and increase mucus production with parasympathetic stimulation.

### Nasal secretions

Nasal secretions contain mucus and water. Mucus glands produce glycoproteins while water and ions are produced by the serous glands and from transudation from the capillary network. There are several mixed glands in the submucosa which are arranged around ducts. Serous cells contain discrete electron dense granules producing neutral glycoproteins, enzymes such as lysozymes and lactoferrin as well as immunoglobulins of the IgA2 subclass. Goblet cells are more numerous in maxillary

sinus than other sinuses. The microbes and particulate matter if any gets entrapped in the secretions and are transported out.

**Drainage**

Mucociliary clearance in the maxillary sinus is spiral or stellate and towards the natural ostium. The secretions from the maxillary sinus start in a star shape from the floor of the maxillary sinus along its wall and opens into the ostium in the lateral wall of nose from where it is actively transported through the ethmoidal infundibulum posterior to the uncinate onto the medial surface of inferior turbinate and towards the nasopharynx.

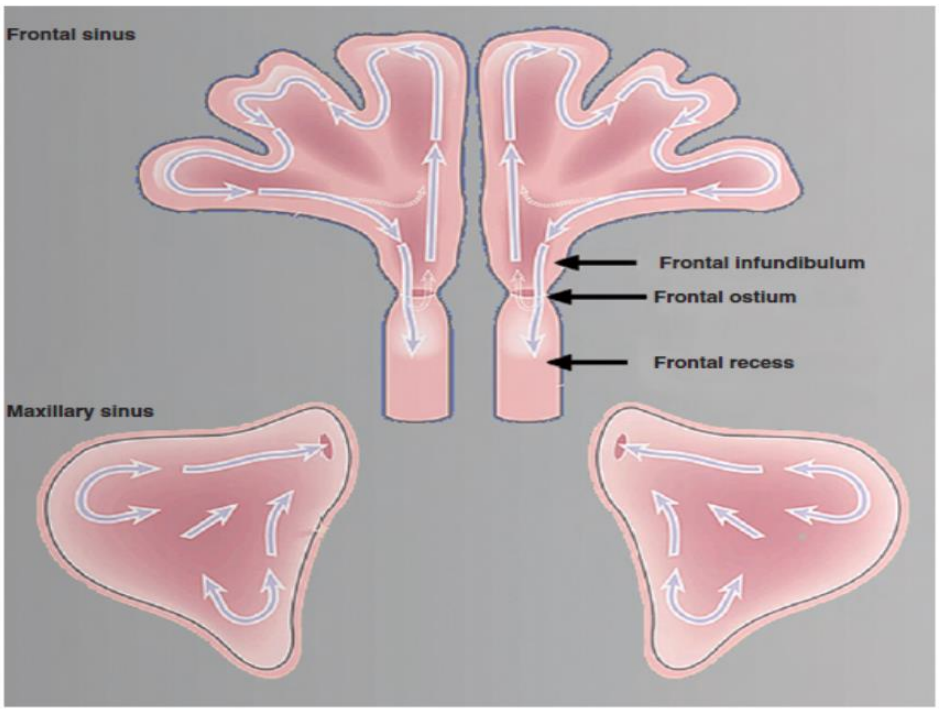



**Fig 8 : Drainage of Paranasal Sinuses**

Drainage of the frontal and sphenoid sinuses is downwards and is aided by gravity, the blood supply is better developed in the frontal sinuses and the ostium is

relatively large in the sphenoid sinus. Messerklinger described the transport of the mucous in the frontal sinus.

Mucus from the sinuses joins that flowing on the lateral nasal wall, with most mucus going through the middle meatus towards the nasopharynx (5). Mucus blanket consists of a superficial viscous mucus layer and a deeper aqueous serous layer, floating on the top of cilia which are constantly beating to carry it like a "conveyer belt" towards the nasopharynx (16). Secretions passing below the eustachian tube orifice is called infratubal stream. Secretions from the superior meatus and sphenoethmoidal recess pass superior to the tubal orifice and is called as supratubal flow.

**Ciliary action**

- Between temperature of $32^0$ and $40^0$C ciliary beat frequency is 7 - 16Hz and remains constant.
- Ciliary beat consists of a rapid propulsive stroke and a slow recovery phase.
- Propulsive ( Rapid ) phase - Initiation of ciliary beat occurs, the cilium is straight and the tip points into the viscous layer of the mucus layer (5,19).
- Recovery (Slow ) stage - the cilium is bent over in the aqueous layer in a tangential direction and returns to steady state position to initiate the next beat cycle.

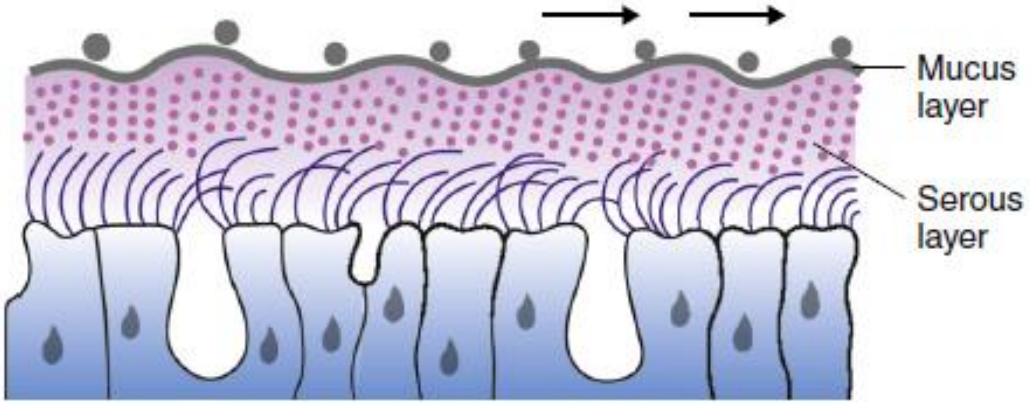



**Fig 9 : Conveyor belt mechanism**

Energy is produced by conversion of ATP to ADP by the ATPase of the dynein arms and the reaction is dependent of magnesium ions. The mucus blanket is thus propelled backwards by metachronous movement of cilia so that mucus flows from the front of the nose posteriorly (13). Mucociliary transport occurs at the rate of 1cm/min, although normal range may have wide variations. (11)

## FACTORS AFFECTING CILIARY ACTION

- Active and passive tobacco smoke exposure
- Gastroesophageal reflux
- Narrowed nasal passages
- Nasal septal deviation
- Turbinate malformations
- Nasal tumours
- Nasal polyps
- Foreign bodies

- Ciliary defects from beta blockers, viruses, dry environment, sulfur dioxide and genetic defects
- Drying stops the cilia
- Temperature > $101^0$ C and < $45^0$C
- pH > 6.4 and <8.5.
- Age : Ciliary function may deteriorate with age. There is significant increase in the occurrence of microtubular defects, including disarrangement of microtubules and the presence of extra microtubules or single microtubules, with aging (20).
- Oxygen tension – Oxygen tension is reduced in the sinuses if the ostium is blocked. Ciliary motion is compromised if the blood supply is inadequate and leads to reduced motility and stasis of secretions.

**TESTS FOR MUCOCILIARY CLEARANCE**

Various tests that can be performed to evaluate mucociliary clearance :

Saccharin test

Rhinoscintigraphy / Nuclear testing

Mucus flow rate with 99m Tc-labelled resin particle

Mucociliary transit time with colouring substances

Nasal Nitric Oxide

Mucus flow rate with radiopaque Teflon disks

**Saccharin test**

This test is done to assess physiological mucociliary clearance and is considered the standard technique. Saccharin test was described by Anderson et al in 1974 (21). Test is performed with patient in sitting position. A 0.5mm particle of saccharin is placed 1 cm behind the anterior end of the inferior turbinate and the time is noted. Patient is advised to not to sniff or sneeze and to breathe normally through the nose and swallow saliva every 30 seconds (22,23). Patient is told to refrain from eating or drinking during the test. When a sweet sensation was perceived the nasal mucociliary transport time is recorded in minutes. Saccharin test is easy to perform, inexpensive and can be done in an outpatient setting (23,24). If the sweetness was not perceived after 30 min, the procedure can be abandoned and the saccharin particle placed on the tongue to check ability for taste (25).

Alternatively, a colouring agent (methylene blue, indigo blue, charcoal) may be added to the saccharine particle which serves as a visual control and its presence can be visualised in the pharynx. While the normal mucociliary transport time is about 10 minutes, a mucociliary transport time of up to 30 minutes is still considered normal. Prolonged time interval of more than 30 minutes is considered abnormal.

Reasonable cooperation of the patient is required as the patient must report the sweet taste. Prohibition of sniffing, sneezing, and blowing the nose during the test limits the use of the test in children. The saccharine has to be placed on respiratory (ciliated) epithelium. On combining this procedure with nasal endoscopy, the coloured particles can be visualised to evaluate the transport pattern with the perception of the

sweet taste (11).Saccharin test is a useful screening technique. It is inexpensive, non-invasive, readily available, results are reproducible and simple to perform (17).

| | |
|---|---|
| Normal | Up to 20 minutes |
| Prolonged | 21 to 3o minutes |
| Severely Prolonged | 31 to 60 minutes |
| Grossly Prolonged | Over 60 minutes |

**Table 1 : Nasal mucociliary clearance time**

**Rhinoscintigraphy / Nuclear testing**

The measurement of mucociliary transport velocity by rhinoscintigraphy with 99m Tc- labelled macroaggregated albumin (99mTc-MAA) is a reliable measure of MCC. A small amount of radiolabelled Tc99m albumin colloid particles is placed on the nasal septum or on the inferior turbinate and the migration is followed with a γ-camera. Normally, most of the radioactivity would have disappeared within 30 minutes. The percentage of radioactivity that remains in the nasal cavity can be calculated, and in sagittal views, the migration of the spot can be measured. Rhinoscintigraphy test is more reliable than the saccharine test and is not affected by sneezing unlike the saccharine test, but it requires expensive equipment and can only be done in specialized centres (8,21).

**Mucus flow rate with 99m Tc-labelled resin particle**

A radiotracer such as 99mTc is used placed on the upper surface of the inferior turbinate, 0.5-0.8 cm behind the anterior end. Serial Polaroid pictures are taken at regular intervals using a gamma camera till the resin particles reach the nasopharynx. This also aids in the calculation of the distance travelled by the particles from their original position and the time at the beginning of the exposure and the exposure time must also be recorded (8).

**Mucociliary transit time with colouring substances-**

This is a simple, non invasive and inexpensive technique of assessment in which a droplet of a dye such as indigo carmine is placed in the anterior part of the nasal cavity. Periodic inspection of the pharyngeal wall is done and the time taken between placement of the dye and its appearance in the pharyngeal wall is noted (8).

**Nasal Nitric Oxide**

Nasal nitric oxide test is a noninvasive and easy screening test for the diagnosis of primary ciliary dyskinesia. This test requires the cooperation of the patient in breath holding for stable plateau measurements which limits its use in children (8).

**Mucus flow rate with radiopaque Teflon disks**

Mucociliary transport is determined by imaging of radiopaque teflon disks introduced into the nose using a Fluroscope image intensifier (17).

## TESTS OF OLFACTION

In the assessment of a patient with chemosensory dysfunction, three major steps are encountered: (a) obtaining a detailed clinical history; (b) testing olfactory function quantitatively; and (c) physically examining the head and neck. The cause of olfactory loss is elicited in history, events such as head trauma, upper respiratory tract infections, toxic exposures, or iatrogenic interventions. Specific history concerning the nature, timing of onset, severity, progression, duration and pattern of fluctuation is to be noted. Sudden olfactory loss suggests head trauma, infection, ischemia, or a psychogenic condition. Gradual loss can reflect the development of degenerative processes or progressive obstructive lesions within (11).

There are several tests designed to test olfaction from three-item Pocket Smell Test to the 40-item University of Pennsylvania Smell Identification Test (UPSIT). Olfactory function can be assessed using numerous psychophysical tests and some subjective scales, such as visual analogue scales (VAS) and the six-item Hyposmia Rating Scale. The UPSIT is commercially known as the Smell Identification Test and is the most widely used and highly reliable olfactory test, having been administered to an estimated 400,000 patients. The test can be self administered in 10–15 minutes by the patient while waiting in the outpatient department. The scoring can be done subsequently in less than a minute by any nonmedical personnel. There are several versions and the test in available in regional languages American, British, Chinese, French, Italian, German, Spanish and Japanese versions. It consists of four booklets containing ten microencapsulated (‘scratch and sniff ’) odorants apiece (7,11,26).

Test results relate to a percentile score of a patient's performance as compared to age- and sex-matched controls.

***Olfactory function can be interpreted as :***

normosmia

mild microsmia

moderate microsmia

severe microsmia

anosmia

probable malingering.

**Olfactory event-related potentials ( OREP )**

The recording of olfactory event-related potentials (OREP) has been done in specialized medical centres to assess the integrity of the olfactory system which is a complex, specialized and expensive equipment capable of delivering a odorant pulse into the nose with continuous flow of warmed and humidified air (7). Although, OERPs are sensitive and can detect malingering, it lacks the ability to localize any anomaly in the olfactory pathway (9).

**Electroencephalography (EEG )**

Brain electroencephalography (EEG) elicits synchronized brain activity recorded from overall EEG activity during brief presentations of odorants (7). This technique involves the placement of surface electrodes under endoscopic guidance on the surface of the olfactory mucosa which gathers reflected summated generator potentials mainly from olfactory receptor neurons (11).

**Sniffin' sticks test**

It is a standardized, re-usable, validated test based on odour filled felt-tip pens. It consists of three parts: odour threshold, odour discrimination, and odour identification. The threshold task reflects the function of the olfactory periphery, while the suprathreshold tests (discrimination and identification) are more related to cognitive function (3,27).

**Connecticut Chemosensory Clinical Research Centre test ( CCCRC )**

Connecticut Chemosensory Clinical Research Centre (CCCRC) test is administered using n – butyl alcohol, a sweet smelling agent as odorant for threshold. It is an inexpensive, portable and can easily be administered test. Butanol is a widely used odorant as it is a water soluble, readily available, neutral odorant with low toxicity. CCCRC test is a 2 component test were olfactory threshold and odour identification are assessed.

***Threshold testing***

Threshold testing is assessed using serial dilutions of 60 ml 4% n- butanol in polythene squeeze bottles in such a way that the spout of the bottle is placed in a specified nostril and squeezed and sniff simultaneously. Test is initiated with the lowest concentration paired with a blank bottle. If an incorrect response was given, next higher concentration paired with a blank bottle was given until four correct responses were elicited in a row.

To accurately assess olfaction unilaterally, the naris contralateral to the tested side should be occluded without distorting the patent nasal valve region. Occlusion not only prevents air from entering the olfactory region from the naris (orthonasal stimulation), but prevents active movement of odour-laden air into the occluded side from the rear of the nasopharynx (retronasal stimulation). Microfoam tape cut to fit the contralateral naris borders may also be used. The patient is instructed to sniff the stimulus normally and to exhale through the mouth (28,29).

***Odour identification***

A test kit with 10 plastic containers of 180 ml capacity with sachets of odorants is presented unilaterally while the opposite side is occluded. Commonly used day to day items were used, namely, Cinnamon, asafoetida, coffee, tea, pepper, cloves and Johnson's baby powder.

Another 3 chemical items also used ( Eucalyptus, Rose, Lemon ). From a 20 item list containing the 10 test items along with 10 distractors, patient attempts to recognise the right odour. Test is done unilaterally while occluding the opposite side.

If a patient is unable to identify, the response was corrected by the examiner and the missed items were given a second trial in random order.

***Composite Score***

The olfactory threshold and identification was combined to get composite score. A composite score of 6 and above accounts for 90 % of the normal individuals (16).

> 6 – Normosmia

5 – 6 – Mild hyposmia

4 – 5 – Moderate hyposmia

2 – 4 – Severe hyposmia

< 2– Anosmia (16)

**Olfactory dysfuntion**

There are 3 types of olfactory dysfunction

Conductive loss- Obstruction of nasal passages. Eg : chronic inflammation, polyposis

Sensorineural loss – Damage to olfactory neuroeithelium Eg :viral, air borne toxins, radiation

Central olfactory neural loss – CNS damage. Eg : tumours, neurodegenerative disorders (11,30)

## RADIOTHERAPY

Radiation therapy refers to treatment of cancer using ionising radiations which when employed releases energy in a localised area that is within a target cell and breaks the chemical bonds in the nucleus. Free radical such as H and OH and oxidising agents react with genes and breaks them.

Effects of radiation – Irradiation is most effective when the G2 – M mitotic phase of a cell cycle is targeted. It causes early cell death, prevents or delays cell division, permanently damages the cell which is then passed on to daughter cell.

Radiotherapy (RT) is a common treatment modality for patients with head and neck malignancies as a potentially curable primary modality or as adjuvant RT. A large number of early stage tumours have a high response rate to this treatment. The radiation treatment of the patients with head and neck cancer is considered one of the most challenging treatments in radiotherapy. This is because the volume that should be irradiated has a convex shape encompassing the spinal cord, which is the most critical organ at risk (OAR) at this site. Also the anatomy of the body itself, where the volume that should be irradiated is located, ranging from the thick bony structures at the face, thin contour of the upper neck and to the thick surface of the supraclavicular areas poses a challenge in delivering the adequate dose. The maximal dose tolerated by the spinal cord is 45 Gy - 50 Gy. The presence of the other OAR like the oral cavity and the parotid glands, complicate the treatment further (31). In most cases, addition of radiotherapy to surgery improves 5-year survival when compared to RT alone or surgery alone. Preoperative radiation may obscure the initial extent of

disease, surgery resection may not control the microscopic extensions of the tumor , increases the infection rate and the risk of post- operative wound complications. Postoperative radiation therapy is started 4 to 6 weeks after surgery.

Post op radiotherapy dose indicated –

Negative margin – 60 Gy in 30 #

Positive / close margin - 66 Gy in 33 #

Gross residual disease – 70 Gy in 35 #

Three-dimensional conformal radiotherapy (3D-CRT) which has become recently available has the potential for tailoring the isodose surfaces to the shape of the tumour (i.e., the planning target volume [PTV]) in all three dimensions (31).

The classical approach in the treatment of the planning target volume (PTV) is to irradiate it up to the maximal allowable dose with two lateral photon fields (usually of 6 MV) and then to reduce the fields from the dorsal side in order to spare the spinal cord. In this way the target radiation dose to the tumour is not compromised, with a low maintained "volume-weighted" dose burden to normal tissues. The irradiation doses used in radiation for tumour control in H&N cancer are usually 60 – 70 Gy which is much more than the tolerance of the radiation-sensitive structures such as the spinal cord, optic nerves, or salivary glands. The cause of such disturbances can be due to direct radiation-induced damage to taste cells and buds, salivary glands, and taste nerve fibres. The xerostomia secondary to salivary gland damage can influence food transport, protection from bacterial invasion, and salivary proteins potentially

involved in taste transduction and can aid in the promotion of opportunistic oral infections, for example, oral candidiasis (20). Permanent injury to the salivary glands occur even at subtherapeutic radiation doses in the range of 22–24Gy in 2-Gy fractions causing fibrosis, hyposecretion, and xerostomia. Xerostomia may predispose to infections, caries and disturbed speech and swallowing.

Radiotherapy leads to transient hypogeusia (especially for bitter and salty tastes) or even ageusia, which is most pronounced approx. 2 months after irradiation. The taste disturbance can persist for 1 to 2 years after radiotherapy. Dental prophylaxis if not addressed may lead to osteoradionecrosis of mandible.

Parotid gland salivary flow deteriorates after a cumulative dose of 30–50 Gy given with conventional fractionation. This can be prevented in by using a conformal parotid-sparing RT technique.

## CONFORMAL THERAPY

This is the radiotherapy treatment modality that creates a high dose volume that is shaped to closely " conform" to the desired target volumes while minimizing the dose to critical normal tissues.

### *Advantages of Conformal Radiotherapy*

1) Three dimensional contouring on CT images can be drawn so that target volumes can be obtained.

2) Multiple beam directions are used to crossfire on the targets.

3) Individual beams are shaped or intensity modulated to create a dose distribution that conforms to the target volume and desired dose levels.

4) Use of image guidance, accurate patient setup, immobilization and management of motion to ensure accurate delivery of the planned dose distributions to the patient.

**Types of Conformal Radiation**

- Techniques aiming to employ geometric field shaping alone( 3D-CRT)
- Techniques to modulate the intensity of fluence across the geometrically-shaped field (IMRT)

**3-D CRT**

Treatment based on 3D anatomic information such that radiation dose distribution is maximised to the target volume that the tumour receives while minimising treatment of adjacent normal tissues. This is achieved by designing beam shapes and beam orientations to improve dose conformation.

**IMRT**

It is an advanced form of 3D CRT. IMRT refers to a radiation therapy technique using computer-aided optimization to modulate the intensity of incoming

radiation beams to a higher degree of special agreement so that specified dosimetric volume is obtained in targeted areas. It is more advanced than 3D CRT and can alter the margins between planning target volume and target volume.

***Advantages of IMRT***

Improved precision and accuracy using 9 + beams and thousands of segments

Lower rate of complication

Lower cost of patient care following treatment

Large fields and boosts can be integrated in single treatment plan

Radiobiologic advantage.

***Limitations of IMRT***

Variation in positioning

Intrafraction motion

Changes of physical and radiobiologic characteristic of tumour and normal tissue

## VOLUMES

Two volumes should be defined prior to treatment planning

**Gross tumour volume (GTV)** – all known gross disease which is visible / palpable including its extension and location. This includes primary tumour and metastatic lymphadenopathy

**Clinical target volume (CTV)** - It is the volume surrounding the gross tumour volume including the areas of potential microscopic spread

**Planning target volume** - is a geometrical concept which provides a margin around the clinical tumour volume to allow variations may be intra-fractional or inter-fractional due to number of factors like – movement of tissues/patient, variations in size & shape of tissues, variations in beam characteristics. It considers the net effect of the geometrical variations to ensure that the prescribed dose is actually absorbed in the CTV.

The boost volume consists of areas at greatest risk for recurrence, such as close or positive resection margins, regions of perineural invasion, extracapsular spread, advanced T stage and multiple cervical metastasis.

## RADIOTHERAPY INDUCED PATHOPHYSIOLOGICAL CHANGES

In primary head and neck tumours such as oral cavity, oropharyngeal, nasopharyngeal and brain tumours radiation with substantial doses to the olfactory epithelium is inevitable. Several studies have shown impairment of olfactory function

as a side effect of radiotherapy (9). In tumours arising from the olfactory cleft, olfactory groove meningiomas, frontal lobe gliomas and suprasellar ridge meningiomas arising from the dura of the cribriform plate, due to the olfactory nerve's close location to the roof and medial wall of the orbit, as well as the optic nerves and tracts, lesions may affect vision also. Olfactory tumours may extend into the frontal lobes resulting in symptoms of dementia.

Mass lesions need not be in the olfactory tracts to cause smell impairment. In radiotherapy for nasopharyngeal cancer, radiation exposure is local and can affect only the receptor cells and nerve endings in the olfactory region of the upper nasal vault. Suprathreshold olfactory discrimination and identification involve higher brain centers, which are spared from radiation delivered to the nasopharynx.

Deterioration of olfaction following radiation may occur due to changes in the nasal mucosa and mucositis which alter the perception of olfactory stimuli (32). At higher doses of 60 Gy, alterations of the cell cycle and depletion of basal cells of the olfactory epithelium occurs. A decreased turnover of olfactory neurons may occur due to the arrest of mitosis in the basal cell layer which is essential for differentiation of mature olfactory nerve cells. However, olfactory neurons are believed to have a turnover time of approximately 30 days, and hence recovery of olfactory dysfunction is expected sooner. Irradiation also causes damage to the Bowman's glands in the olfactory epithelium which dissolve odorants and present them to bipolar receptor cells. Mucosal oedema secondary to irradiation can block the access of odorants to the olfactory area, causing a conductive type hyposmia. Patients may not necessarily perceive nasal airway obstruction, but this could restrict air flow to the roof of the

nose. Alternatively, nasal mucositis leads to changes in airflow and the mucociliary clearance which may have drastic effects on olfactory function and prolonged sinusitis in irradiated persons (33–35).

Finally, olfactory dysfunction may have resulted from temporary neuronal demyelinization which can occur in some patients receiving brain irradiation known as the "early" delayed reaction to radiation therapy. This reaction generally improves within six to 36 weeks, corresponding to the turnover time of myelin. Histologic sections of human adult olfactory mucosa reveal tissue degeneration and cell depletion as well as replacement of the olfactory mucosa by nasal respiratory mucosa. It is possible that even this moderate amount of radiation was enough to cause significant damage to the mucosa, such that it did not fully recover even six months after treatment(35).

RT to the head and neck region in frail elderly patients can result in serious consequences because important tissues are often included in the field of irradiation. Dental problems, xerostomia, gustatory dysfunction and mucositis eventually contribute to poor nutritional status and cancer cachexia and consequently lead to low quality of life in patients.

Patients undergoing radiation experience disturbance in taste and smell causing loss of appetite. Taste aversions can be long lasting and can produce generalized anorexia and cachexia (11). Radiation-induced dysguesia can occur as a result of changes such as depletion of neural progenitor cells, damage to central neural pathways and sensory mechanism along with depletion of sensory cells by scatter or

exit radiation dose (36). Parotid gland salivary flow is severely impaired in conventional fractionation with a cumulative dose of 30–50Gy. More recently, using conformal parotid-sparing RT technique moderate to severe xerostomia may be prevented in most patients (29, 32).

Good QOL is a state of physical, psychological and social well-being, in which the individual is able to perform everyday activities and reports satisfaction with daily function. While overall QOL following radiotherapy has been assessed, little is known about the quality of oral function and taste and olfaction. Patients experience reduced taste (ageusia) or altered taste (dysgeusia) while undergoing radiation therapy or chemoradiation, which can significantly impact on the quality of life. They develop oral mucositis, cachexia, significant weight loss due to decreased appetite and nutrient absorption(37).

The AHSP questionnaire aims to assess taste, smell, hunger and appetite for such patients prior to commencement of treatment and after treatment to study the impact on the patients' quality of life during the course of their therapy. This questionnaire is based on assessing the nutritional status of a patient not only on enquiries made regarding the quality and quantity of food intake but also based on subjective analysis of patients perception of hunger and appetite besides taste and olfaction (38).

Two potential pathways were described by Croy et al regarding impairment of quality of life by olfactory dysfunction. Reduced food appetite and enjoyment , worries about personal hygiene and reduced social interaction predisposes patients to

depression. Further more, olfactory loss affects the brain's functioning and, especially, emotional control due to reduced input from the olfactory bulb via amygdala into the limbic circuit (39).

# METHODOLOGY

A study on the "**Effects Of Radiotherapy On Olfaction And Nasal Function In Head And Neck Cancer Patients"** was proposed, and it was put forward to the Institutional Research Board. After obtaining the approval from the ethics committee, IRB dated -08/08/2016, Min no. : 10209, the study was initiated from September 2016

**Study Design:**

This is an observational prospective cohort study.

**Study Population**:

Patients who presented to the ENT OPD diagnosed with primary malignancy of head and neck and planned for radiotherapy fulfilling the inclusion and exclusion criteria were recruited in the study.

**Inclusion Criteria:**

1. Patients above 16 years, diagnosed with malignancy of head and neck planned for conformal radiotherapy

2. Radiotherapy field includes olfactory cleft region

3. Normal olfaction before radiotherapy

4. No prior radiotherapy or surgery of the olfactory region

**Exclusion Criteria:**

1. Patients below 16 years

2. Malignancy involving the olfactory cleft and anterior skull base

3. Nasal cavity tumours

**Study Period**:

This prospective study was conducted between September 2016 and August 2017.

**Statistics**

**Sample Size Calculation**

The sample size was calculated using nMaster 2.0 software.

To study the parameter change between baseline and post RT (3 months), the sample size calculation is done here.

| **Single Mean - Paired t-test** | | |
|---|---|---|
| | **OT** | **MCT** |
| Pre-test mean | 6.4 | 9.4 |
| Post-test mean | 5.5 | 30.6 |
| Standard deviation in Pre-test | 0.4 | 0.4 |
| Standard deviation in Post-test | 1.1 | 1.1 |
| Effect size | 1.2 | 28.26667 |
| Power (%) % | 80 | 80 |
| Alpha Error | 5 | 5 |
| 1 or 2 sided | 2 | 2 |
| Required sample size | 7 | 2 |

The calculated minimum sample size for this study is 7. Anticipating a few drop outs and lost to follow ups we decided to conduct the study with three times the sample size, 21 subjects.

*References: Veyseller et al (2014) and Gupta et al (2006).*

**Prospective Study Recruitment**:

This study is a hospital based prospective observational study on patients with head and neck malignancies who were planned for conformal radiotherapy for whom the olfactory cleft region is included in the radiation portal with normal baseline olfactory function.

Patients who presented to the ENT OPD diagnosed with primary head and neck cancer after discussion in the MDT planned for radiation therapy were included for the study. A baseline olfaction was assessed for all patients and only patients having a normal olfactory threshold were recruited in the study. The CCCRC (Connecticut Chemosensory Clinical Research Center ) test consisting of Odour threshold and Odour Identification was performed.

Simultaneously, mucociliary clearance time using saccharin test and assessment of quality of life using a AHSP questionnaire were done prior to initiation of radiotherapy. These patients were followed up mid RT, immediate post RT and at 3 months after radiotherapy and the tests were repeated.

Connecticut Chemosensory Clinical Research Center Test (CCCRC) test was used in which, the threshold of subjects for butanol was elicited by means of squeeze-bottles using the method of ascending limits. After occluding one nostril, testing was started with the lowest concentration. The participant was presented with a bottle with the test concentration and a blank bottle with water and had to decide which smelled stronger. Four correct choices in a row led to cessation of testing and the concentration at which this occurred was taken as the olfactory threshold. Similarly,

the test was repeated in the opposite side. Odour identification was performed by means of eight bottles containing different odorants with a multiple choice from a list of 16 items identical for all odorants. Seven bottles were with items that exclusively stimulate sense of smell and one with an item that appeal to common chemical sense by trigeminal stimulation. The score for the test comprised of the number of olfactory items out of seven correctly identified. A composite score was calculated with the average of olfactory threshold score and odour identification scores.

Saccharin test is a simple test to assess nasal mucociliary clearance where a small 1mm particle of saccharin was placed approximately 1 cm behind the anterior end of the inferior turbinate. The patient was instructed not to sniff, sneeze, or cough during the test and to report a taste as soon as it was noted. In the presence of normal mucociliary action, the saccharin sweeps backwards to the nasopharynx and a sweet taste is perceived. Failure of sweetness to be detected within 20 minutes signifies delayed mucociliary clearance.

Quality of life assessment was done using Appetite, Hunger and Sensory perception questionnaire which is a validated, 29-item, multidomain appetite assessment tool that was scored with a 5-point (A to E) Likert-type scale with verbally labelled categories.

Questions are divided in to 5 sections:

1) Present odour perception (3 items, score range 3 – 15)

2) Present odour perception compared to the past (3 items, score range 3 – 15)

3) Present taste perception (8 items, score range 8 – 40)

4) Appetite (6 items, score range 6 – 30)

5) Daily feeling of hunger (9 items, score range 9 – 45)

The score for each domain was calculated as the sum of scores on the individual items. The total AHSP score is the sum of scores on all the domains. Possible scores ranged from 29 (worst) to 145 (best) (38,40).

All the study patients were planned for RT simulation with immobilisation and the reference CT isocenters marked on the immobilisation device. After that the planning CT scan was done as per the institutional protocol with the radio opaque marker in the CT isocenters. The CT images were transferred to the contouring work station in the Radiotherapy treatment planning system (RT-TPS). The tumour volume, organs at risk and the olfactory cleft region were marked by the Radiation Oncologist in the CT images and the images were transferred for treatment for inverse treatment planning after prescribing the doses to the organs at risk and Tumor volumes.

After proper optimization the best plan was used for the treatment delivery after the quality assurance tests. The maximum dose, Mean dose and other dose volume effects to the olfactory cleft region will be analysed with the change in the olfactory and nasal function.

**Statistical Analysis**

The descriptive analysis was used for the data description at baseline. Pre post testing was performed using Paired samples t test. p value <0.05 was considered as statistically significant.

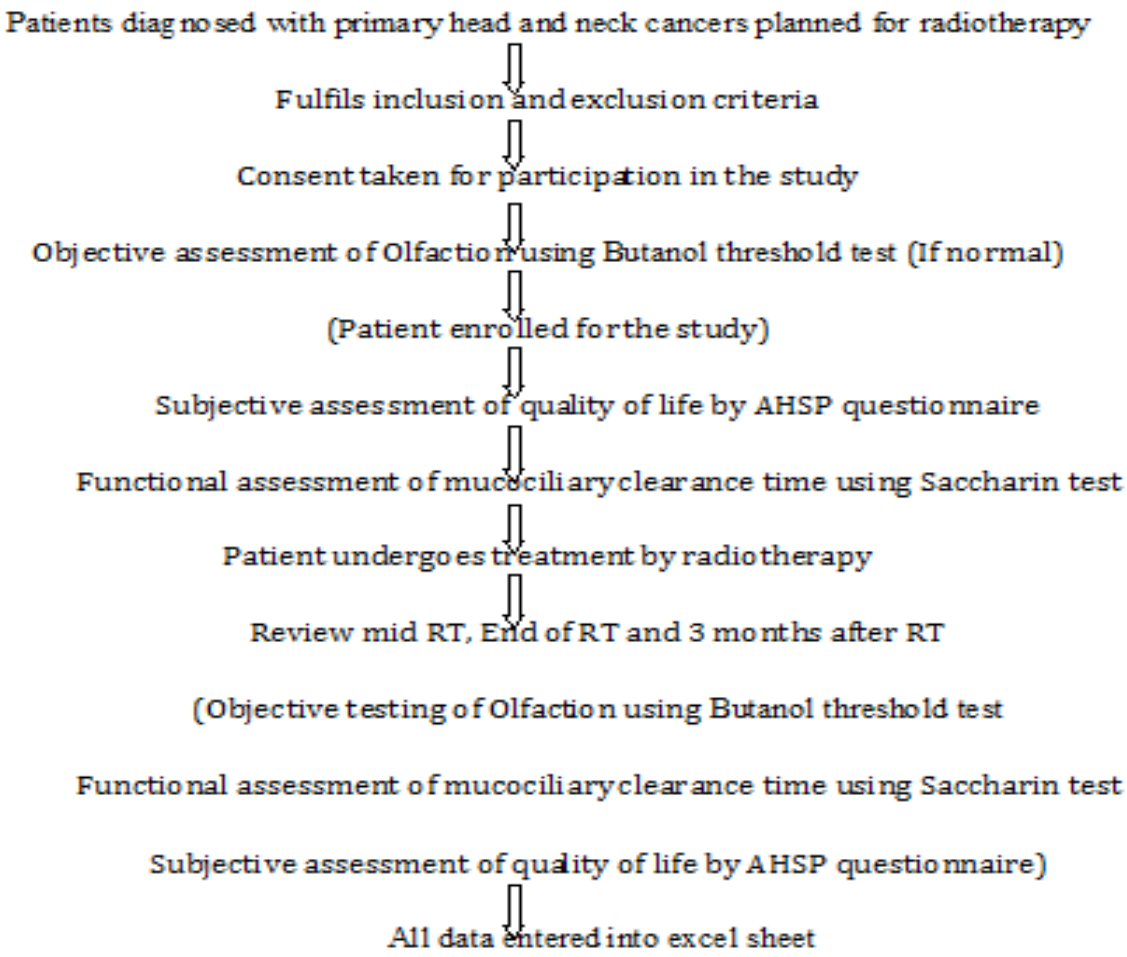



**Fig 10 : Flow chart showing study methodology**

## RESULTS

A total of 21 patients who fulfilled the inclusion and exclusion criteria as per the study protocol were recruited in the study. Three patients were lost to follow up as 1 patient had disease progression on follow up and dropped out and two other patients were unwilling to continue in the study.

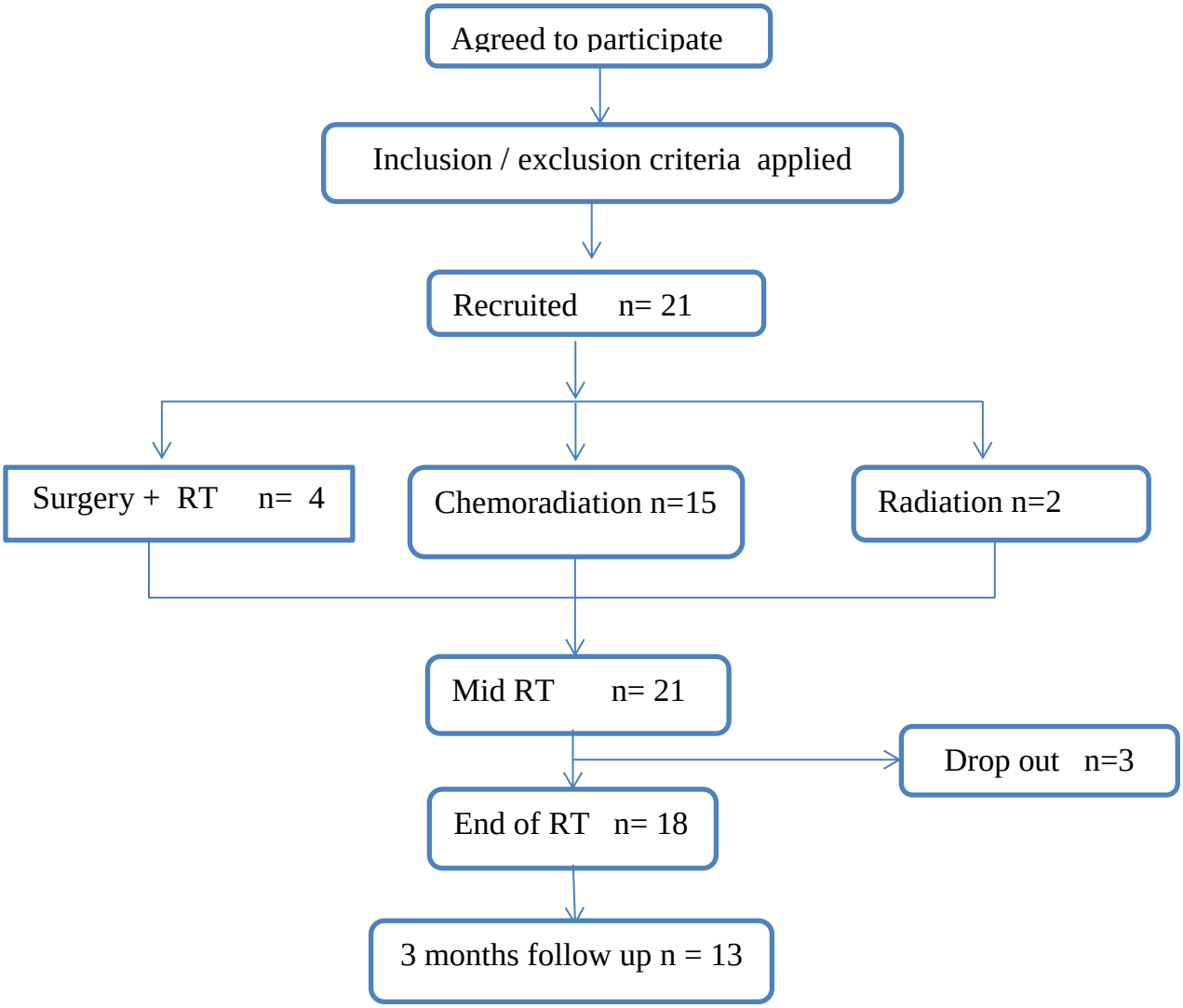



**Fig 11 : Flowchart of recruitment of study cases**

## Age Distribution

The age of the patients recruited in the study ranged from 16 – 75 years ( mean – 42.62, Standard deviation – 17.40 ). Most of the patients were within the 16 – 30 year and 46 – 60 year age groups. There was no significant difference in the distribution in different age groups.

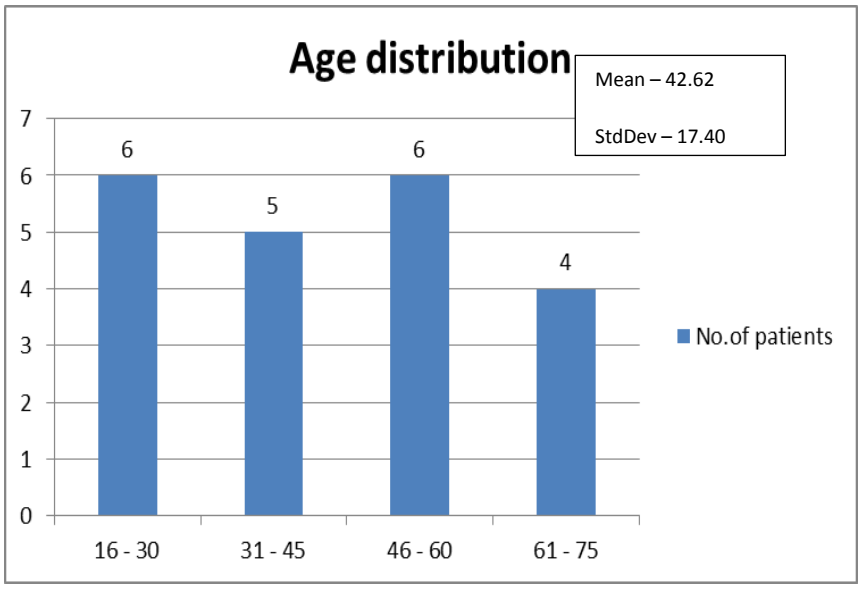



**Fig 12 : Age distribution (n = 21 )**

## Gender distribution

16 ( 76.20% ) of our patients were male while only 5 (23.80% ) were female.

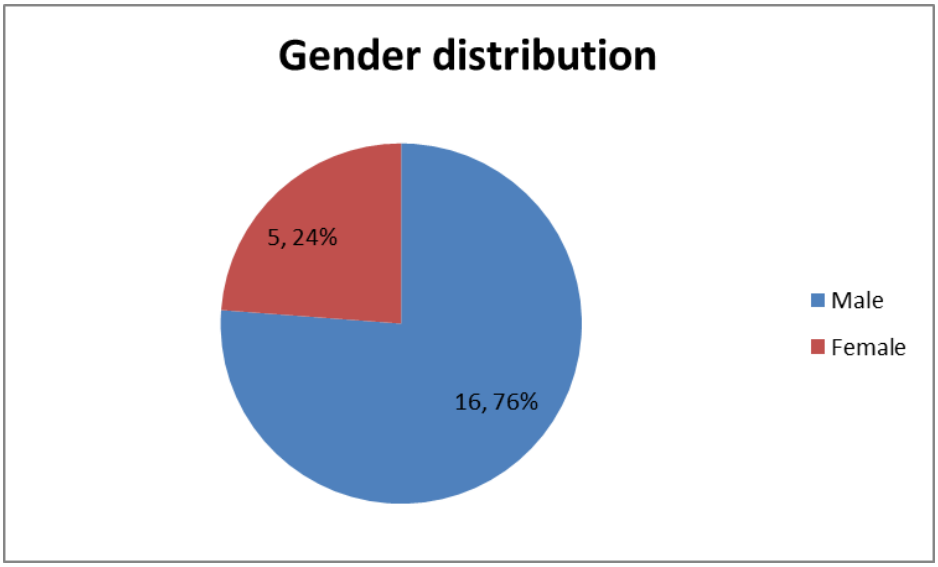



**Fig 13 : Gender distribution ( n = 21 )**

## Comorbidities

A majority of our patients (81% ) did not have any comorbidities. 2 patients were diabetic and 2 patients were hypertensive on regular medication.

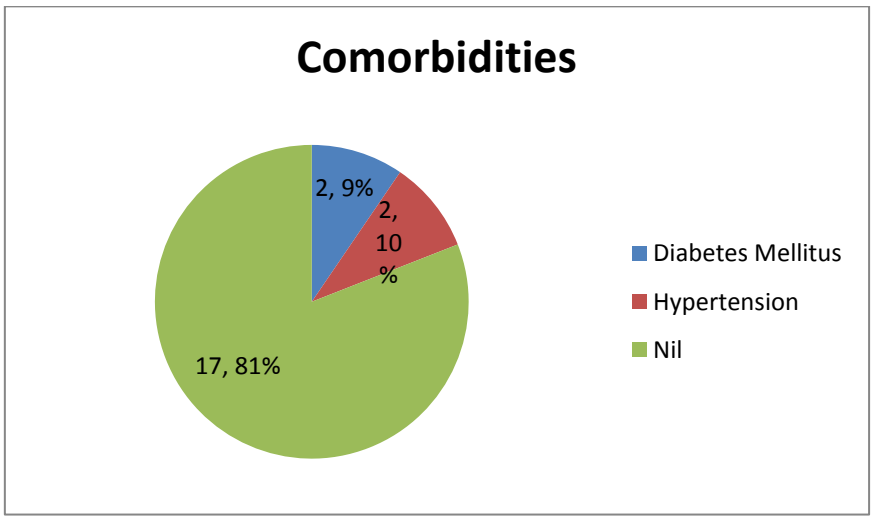



**Fig 14 : Comorbidities (n = 21 )**

**Diagnosis**

In the study as the inclusion criteria required olfactory area to be included in the radiation field, most of the cases were malignancies involving nasopharynx (61.9%) followed by oropharynx (19%), oral cavity (9.5%) and sinonasal region ( 9.5% ).

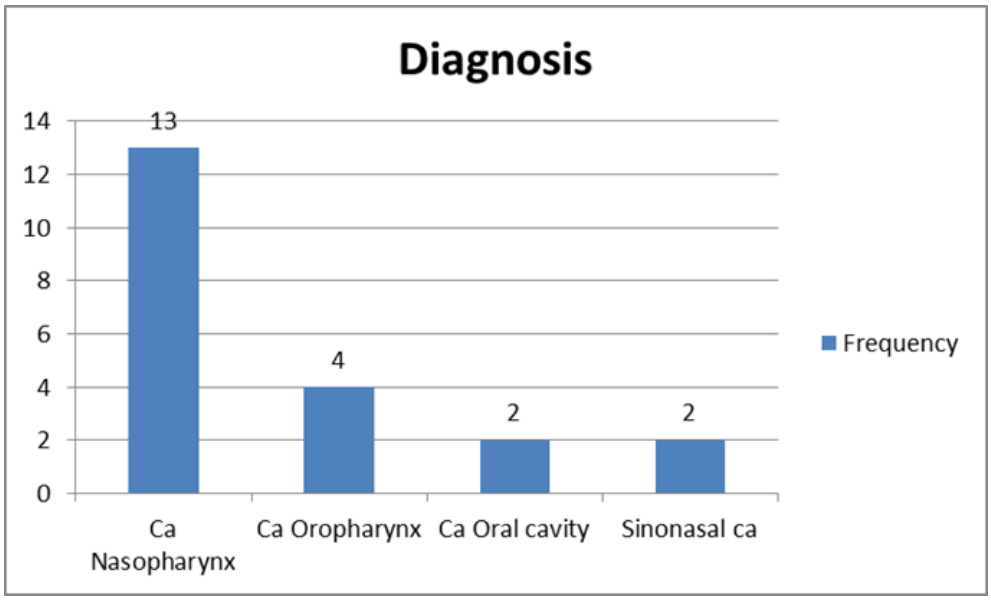



**Fig 15 : Diagnosis / primary site of disease ( n = 21 )**

**Treatment**

Considering the different primary sites, treatment modality of these patients varied from neoadjuvant chemotherapy followed by radiotherapy in 15 patients ( 71.5 % ), surgery followed by adjuvant radiotherapy in 4 patients ( 19% ) and radiotherapy alone in 2 patients ( 9.5% ).

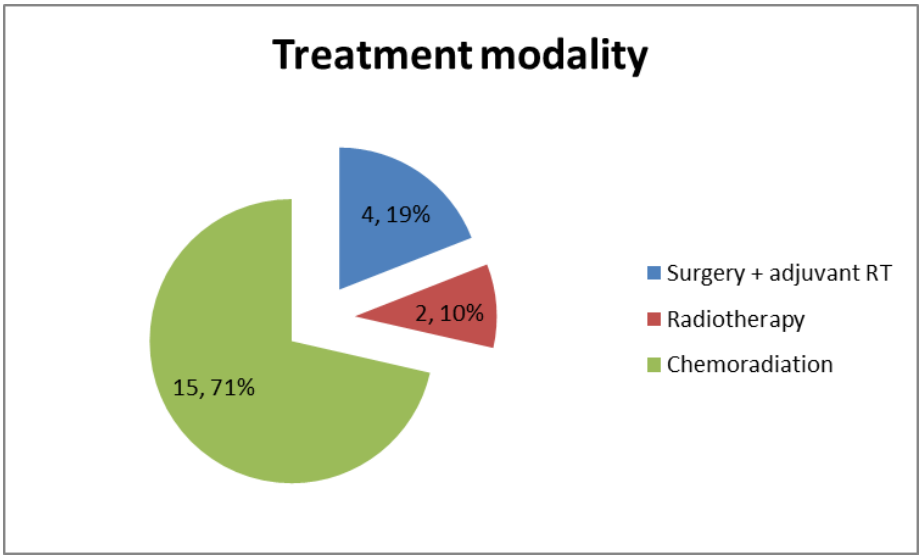



**Fig 16 : Treatment modality**

**Histology**

The study group showed a wide range of histological variants with poorly differentiated carcinoma being the most common.

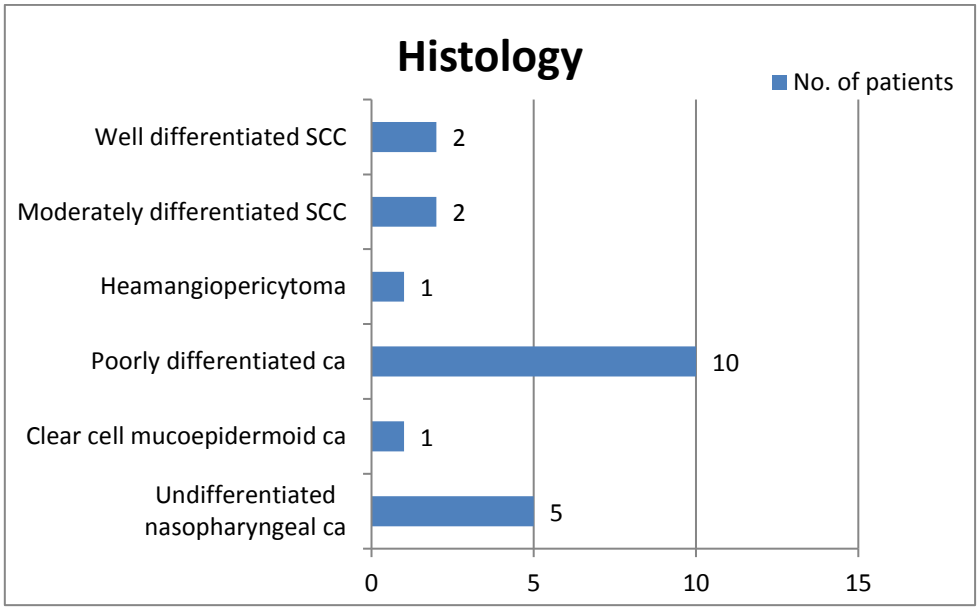



**Fig 17 : Histological types in the study**

## Olfactory threshold

The olfactory threshold of both sides nasal cavities were analysed separately adhering to strict inclusion criteria of normal olfactory threshold to start with. Hence only 39 of the 42 nasal cavities (21 patients) were taken for analysis. A diagrammatic representation of the olfactory threshold at different timepoints show a deteriorating trend in the threshold as the radiation exposure increases.

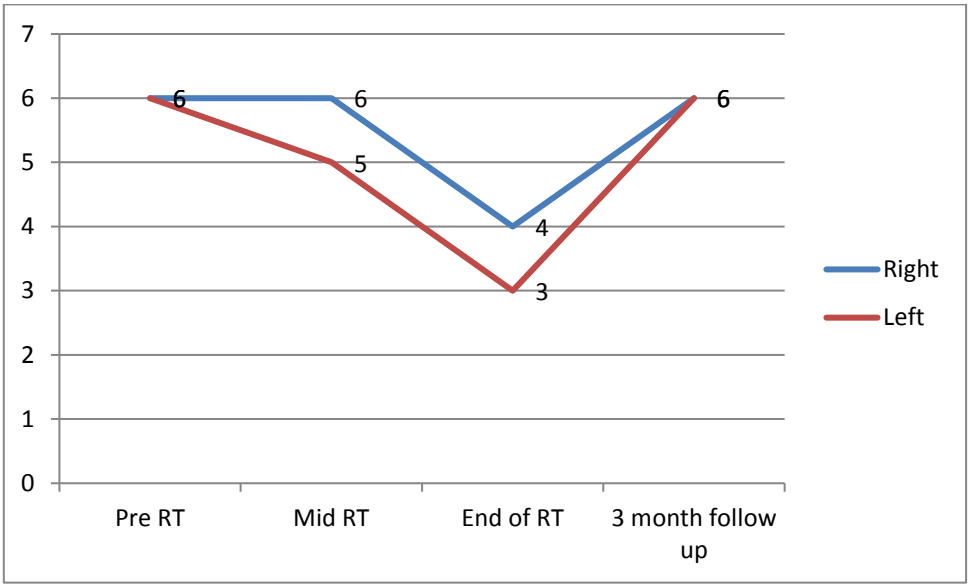



**Fig 18 : Performance based on olfactory threshold scores**

On further analysis the decrease in the olfactory threshold was significant at each time period, including the 3 month follow up as compared to the baseline as shown in the test of significance. Both right and left sides were analysed separately.

| Olfactory threshold ( Right ) | Median ( IQR ) | p value ( overall ) | Paired | |
|---|---|---|---|---|
| | | | | p value |
| Pre RT | 6 | | Pre RT – Mid RT | 0.004 |
| Mid RT | 6 | | | |
| End of RT | 4 | 0.001 | Pre RT – End of RT | 0.002 |
| 3 months post RT | 6 | | Pre RT – 3 month follow up | 0.026 |

**Table 2a : Olfactory threshold scores ( Right side ) during radiotherapy – Test of significance**

| Olfactory threshold ( Left ) | Median ( IQR ) | p value ( overall ) | Paired | |
|---|---|---|---|---|
| | | | | p value |
| Pre RT | 6 | | Pre RT – Mid RT | 0.005 |
| Mid RT | 5 | | | |
| End of RT | 3 | 0.001 | Pre RT – End of RT | 0.001 |
| 3 months post RT | 6 | | Pre RT – 3 month follow up | 0.038 |

**Table 2 b : Olfactory threshold scores ( Left side ) during radiotherapy – Test of significance**

Patients were subcategorized into three groups viz, neoadjuvant chemotherapy followed by radiotherapy group, surgery and adjuvant radiation therapy group and radiation alone group. Subsequently the olfactory threshold of patients who underwent neoadjuvant chemotherapy followed by radiotherapy as compared with the patients belonging to the surgery and adjuvant radiation therapy group and radiation alone group was analysed. The results show delayed recovery of olfactory threshold in the chemoradiation subgroup.

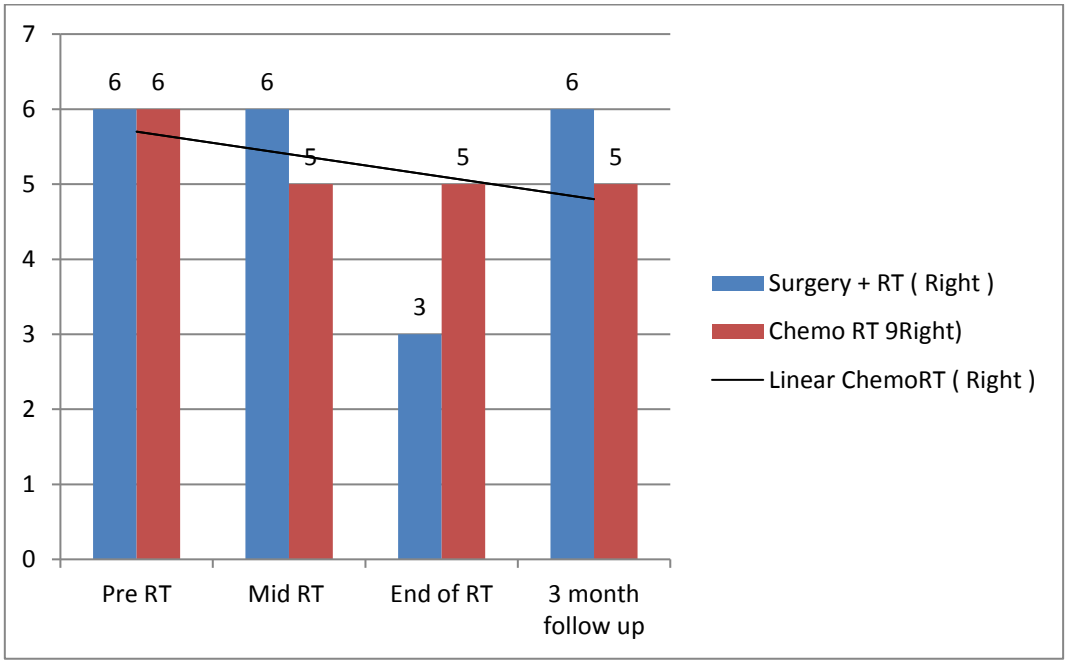



**Fig 19 : Olfactory threshold RT+/- Surgery Vs Chemo RT subgroups (Right)**

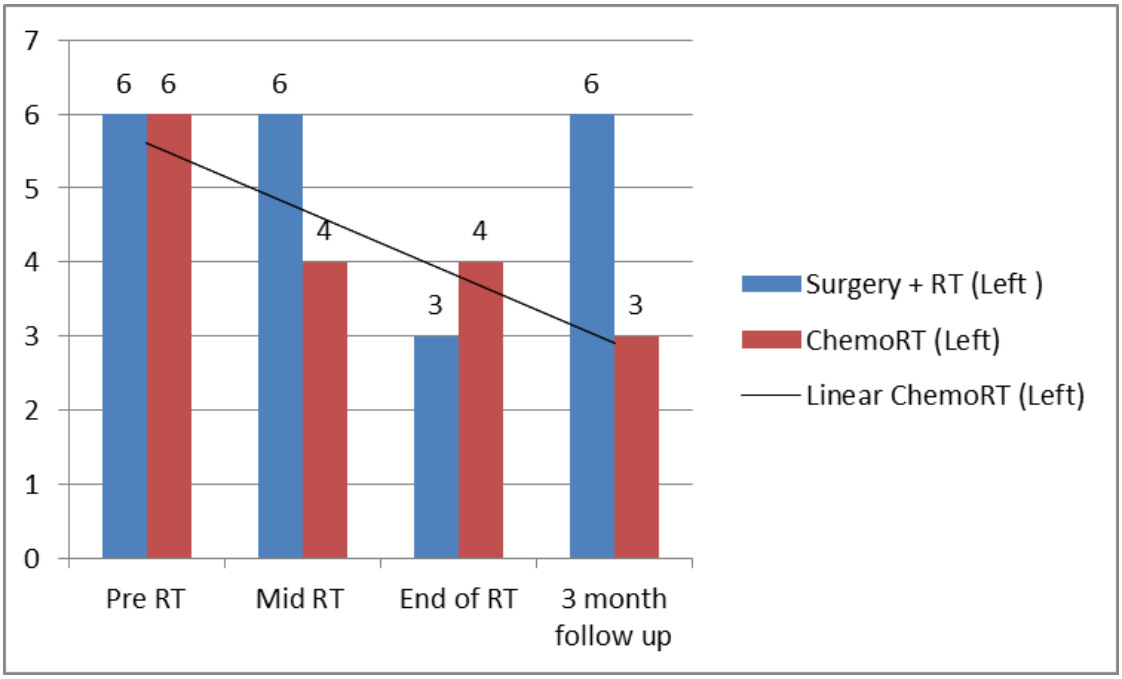



**Fig 20 : Olfactory threshold RT+/- Surgery Vs Chemo RT subgroups ( Left )**

**Odour identification**

In comparison to the olfactory thresholds, there seemed to be a similar descending trend in the odour identification over the course of RT. At 3 month post RT follow up, there was improvement in the score, however was not back to normal. The olfactory identification on both sides is described with its median value in the line diagram.

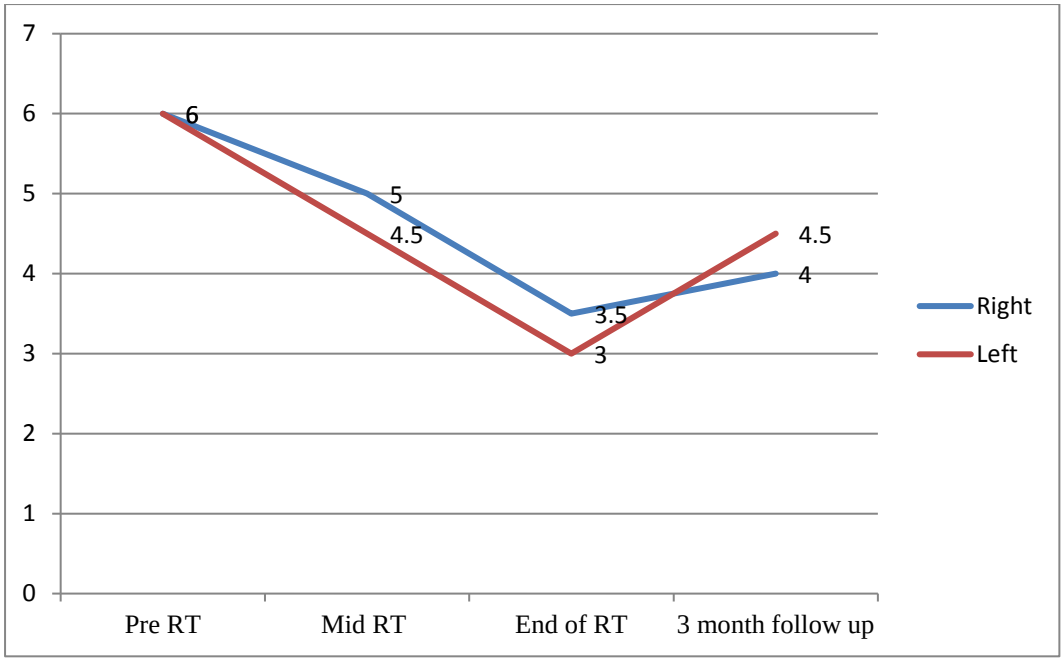



**Fig 21 : Odour identification (Median ) of right and left sides**

The following table shows the mean and standard deviation of odour identification score.

| **Odour identification** | **Pre RT** | | **Mid RT** | | **End of RT** | | **3 months post RT** | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Right | 5.95 | 1.284 | 4.29 | 1.521 | 3.06 | 1.392 | 4.38 | 1.387 |
| Left | 5.78 | 1.215 | 4.00 | 1.879 | 2.88 | 1.364 | 4.67 | 1.073 |

**Table 3 : Mean Odour Identification scores**

**Composite score**

The composite score at various time periods were significantly reduced. The mean and standard deviation of composite scores on the right and left side is represented in figures 22 & 23.

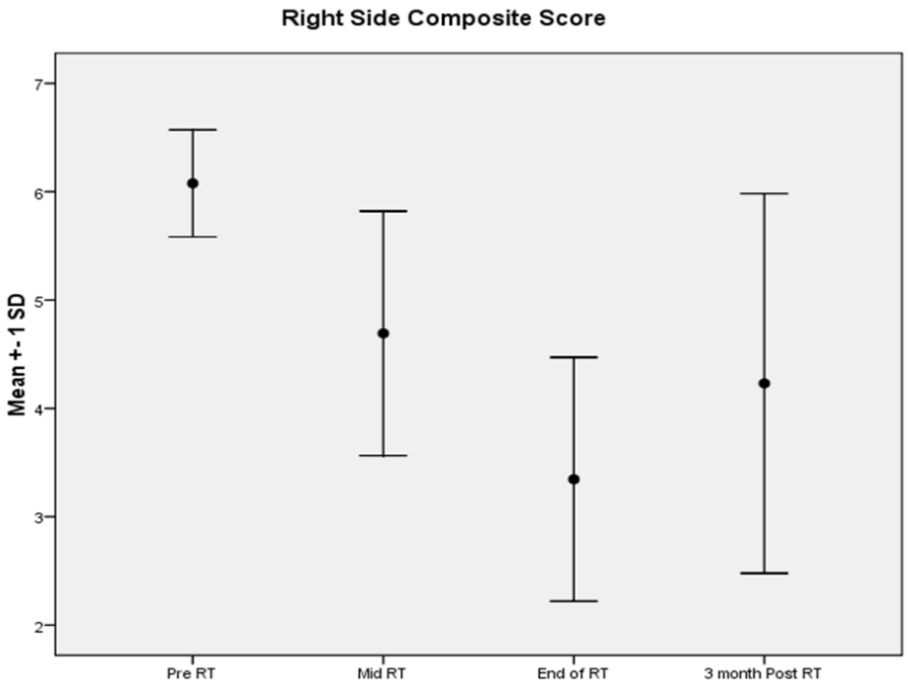



**Fig 22: Mean composite score on the right side**

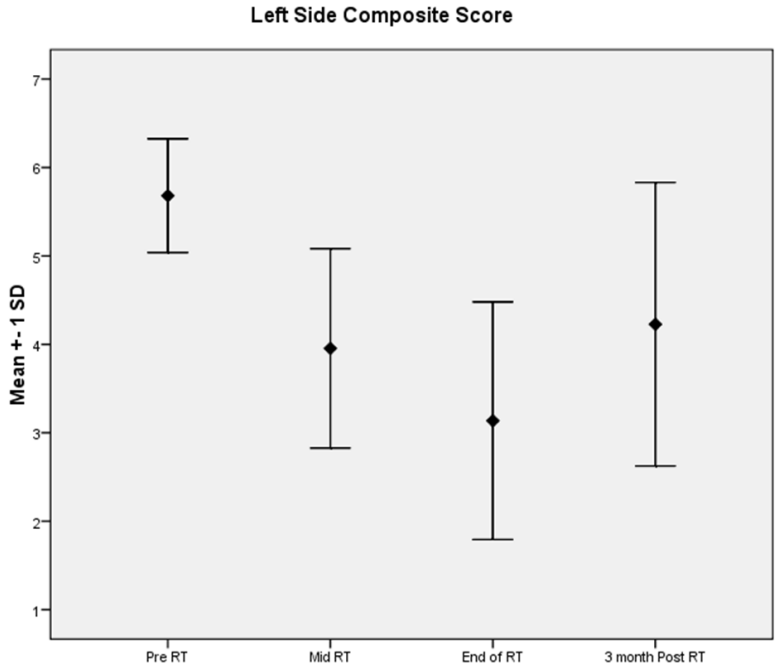



**Fig 23: Mean composite score on the left side**

The composite scores before and after radiotherapy were analysed and it was found that there was a significant deterioration in the mean scores and the difference was statistically significant (P<0.001).

| **Composite score ( Right )** | **Mean ± SD** | **p value ( overall )** | **Paired** | |
|---|---|---|---|---|
| | | | | **p value** |
| Pre RT | 5.90±0.66 | <0.001 | Pre RT – Mid RT | **< 0.001** |
| Mid RT | 4.52±1.35 | | Pre RT – End of RT | **<0.001** |
| End of RT | 3.44±1.32 | | Pre RT – 3 months post RT | **0.002** |
| 3 months post RT | 4.23±1.75 | | | |

**Table 4a : Composite scores at each time interval (Right ) : Test of significance**

We also analysed the mean at each time interval separately in comparison to the base line mean of composite score, and was found to be statistically significant.

| **Composite score ( Left )** | **Mean ± SD** | **p value ( overall )** | **Paired** | |
|---|---|---|---|---|
| | | | | **p value** |
| Pre RT | 5.79±0.68 | | | |
| | | | Pre RT – Mid RT | < 0.001 |
| Mid RT | 4.36±1.28 | | | |
| | | < 0.001 | Pre RT – End of RT | < 0.001 |
| End of RT | 3.14±1.27 | | | |
| | | | Pre RT - 3 months post RT | 0.014 |
| 3 months post RT | 4.37±1.61 | | | |

**Table 4b : Composite scores at each time interval ( Left ) : Test of significance**

The distribution of olfactory dysfunction based on olfactory scores at the end of radiotherapy on right and left sides were calculated .

| | | Right ( n= 18 ) | Left ( n =17 ) | Total( n=35 ) |
|---|---|---|---|---|
| Normosmia | > 6 | 1 ( 5.55% ) | 0 ( 0.00% ) | 1 ( 2.85% ) |
| Mild hyposmia | 5 -6 | 2 ( 11.11% ) | 1 ( 5.88% ) | 3 ( 8.57% ) |
| Moderate hyposmia | 4 - 5 | 7 ( 38.90% ) | 5 ( 29.41% ) | 12 ( 34.28%) |
| Severe hyposmia | 2 - 4 | 6 (33.33% ) | 9 ( 52.94% ) | 15 (42.85% ) |
| Anosmia | < 2 | 2 (11.11% ) | 2 ( 11.76% ) | 4 (11.42% ) |

**Table 5 : Severity of olfactory dysfunction at the end of radiotherapy**

Table 6 shows the distribution of severity of olfactory dysfunction based on olfactory scores at 3 months post radiotherapy on right and left sides.

| | | Right ( n=13 ) | Left ( n= 12 ) | Total( n= 25 ) |
|---|---|---|---|---|
| Normosmia | > 6 | 4 ( 30.76% ) | 2 (16.66% ) | 6 (24% ) |
| Mild hyposmia | 5 -6 | 3 ( 23.07% ) | 5 ( 41.66% ) | 8( 32% ) |
| Moderate hyposmia | 4 - 5 | 2 ( 15.38% ) | 1 (8.33% ) | 3 (12% ) |
| Severe hyposmia | 2 - 4 | 2 ( 15.38% ) | 4 (33.33% ) | 6 (24% ) |
| Anosmia | < 2 | 2 ( 15.38% ) | 0 ( 0.00% ) | 2(8% ) |

**Table 6 : Severity of olfactory dysfunction 3 months post radiotherapy**

**Saccharin perception time –**

The nasal function in terms of mucociliary clearance was evaluated with the saccharin perception test. At the beginning of RT, only 12 ( 57.14% ) patients had a normal saccharin perception time which became increasing prolonged towards the mid RT and end of RT where 52.38 % and 55.55% of the patient's mucociliary function was clearly deranged, respectively.

| | 0 – 20 min | 21 – 30 min | > 30 min |
|---|---|---|---|
| Pre RT ( n= 21 ) | 12 ( 57.14 % ) | 3 ( 14.28 % ) | 6 ( 28.57% ) |
| Mid RT ( n = 21 ) | 6 (28.57 % ) | 4 ( 19.04 % ) | 11 ( 52. 38 % ) |
| End of RT ( n = 18 ) | 5 ( 27.77 % ) | 3 ( 16.66 % ) | 10 ( 55.55 % ) |
| 3 months post RT<br><br>( n= 13 ) | 8 (61.53 % ) | 1 ( 7.69 % ) | 4 ( 30.76% ) |

**Table 7: Number of patients with mucociliary dysfunction at different time points**

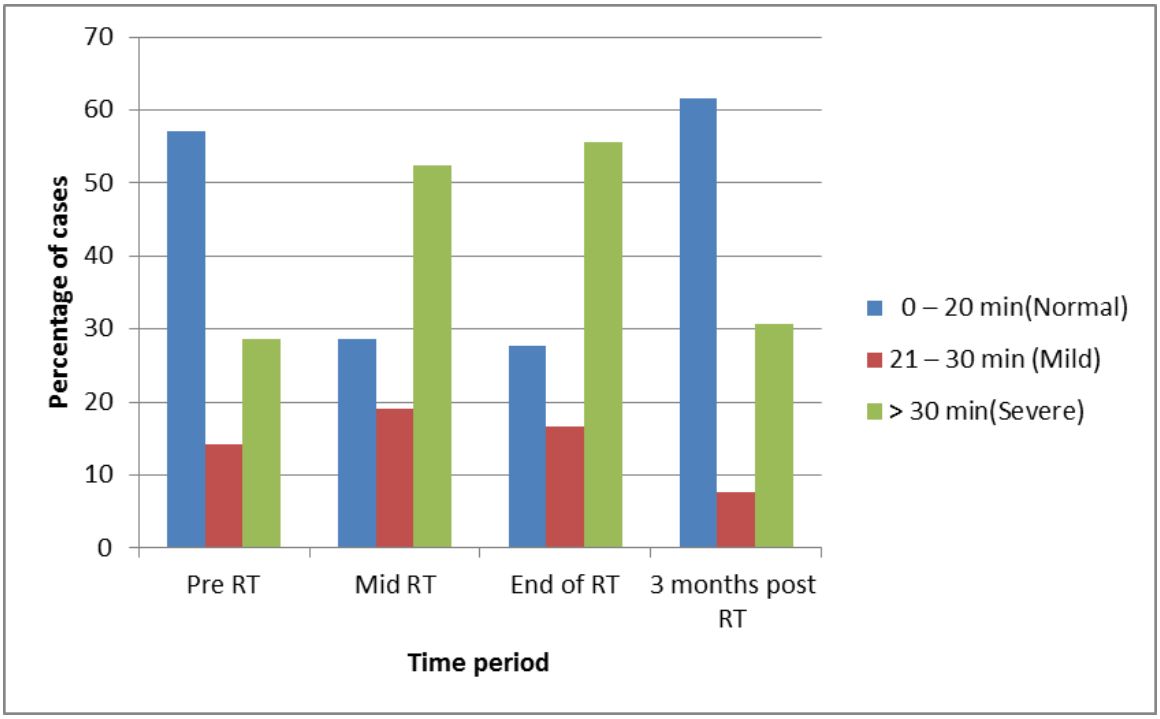



**Fig 24 : Percentage of cases with mucociliary dysfunction**

Since about one third of the patients already had impaired mucociliary clearance before treatment, patients with normal saccharin perception time at the beginning of the study were analysed separately. There were 12 patients with normal mucociliary clearance prior to treatment. Table 8 shows the results in these patients. 58.32% patients developed prolonged mucociliary clearance time at mid RT and at end of RT 70% patients had prolonged clearance time with 60 % showing significantly prolonged mucocilicary clearance time ( > 30 min ). At 3 months follow up, 62.5% patients continued to have prolonged mucociliary clearance time.

| | **0 – 20 min** | **21 – 30 min** | **> 30 min** |
|---|---|---|---|
| Mid RT ( n= 12) | 5 ( 41.66% ) | 2 (16.66% ) | 5( 41.66 %) |
| End of RT ( n = 10 ) | 3 (30% ) | 1 (10% ) | 6 (60 % ) |
| 3 months post RT ( n= 8 ) | 3 ( 37.5% ) | 1 ( 12.5% ) | 4 ( 50% ) |

**Table 8: Change in mucociliary clearance in patients with normal pre RT mucociliary clearance time (n = 12)**

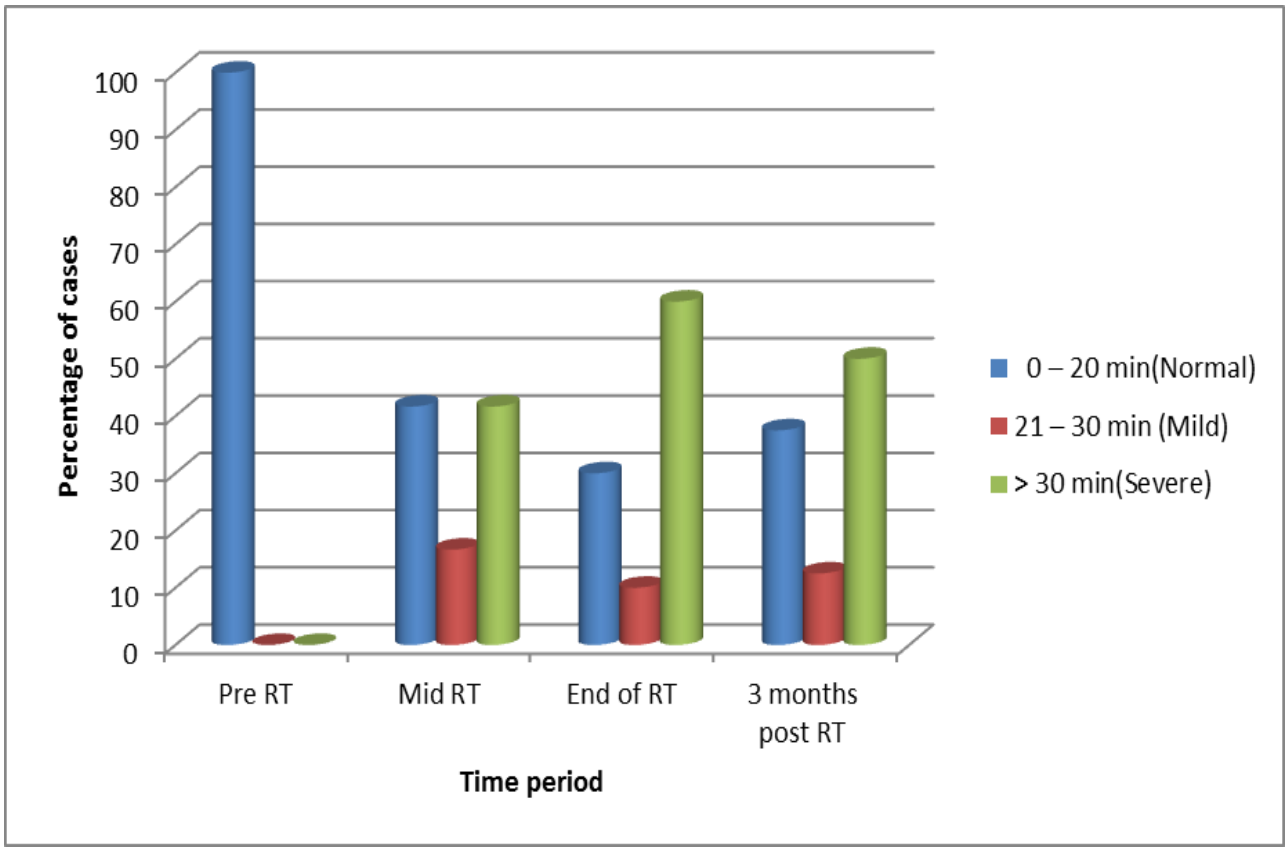



**Fig 25 : Percentage distribution of patients with initial normal mucocilicary clearance at various time points in RT**

**AHSP questionnaire**

The quality of life in terms of appetite, hunger, taste and smell perception was studied at all 4 time periods and results analysed.

| **Domain** | **Pre RT** | **Mid RT** | **End of RT** | **3 months post RT** |
|---|---|---|---|---|
| | **Mean ± SD** | **Mean ± SD** | **Mean ± SD** | **Mean ± SD** |
| Appetite ( 6 – 30 ) | 20.35 ± 3.602 | 17.43 ± 4.069 | 17.56 ± 3.518 | 17.85 ± 3.648 |
| Present smell perception ( 3 – 15 ) | 9.05 ± 2.089 | 9.05 ± 3.339 | 8.17 ± 2.875 | 7.62 ± 1.981 |
| Present smell perception as compared to past ( 3 – 15 ) | 8.10 ± 2.315 | 8.05 ± 2.479 | 8.50 ± 2.036 | 8.38 ± 1.557 |
| Taste ( 8 – 40 ) | 24.60 ± 4.957 | 20.76 ± 3.590 | 22.11 ± 3.104 | 23.31± 3.772 |
| Hunger ( 9 – 25 ) | 33.50 ± 4.617 | 29.05 ± 7.201 | 27.28 ± 6.461 | 33.77 ± 6.623 |
| Total QOL score | 95.50 ± 10.407 | 88.00 ± 13.462 | 83.50 ± 9.488 | 90.00 ± 10.883 |

**Table 9 : Mean of each domain in the AHSP QOL questionnaire**

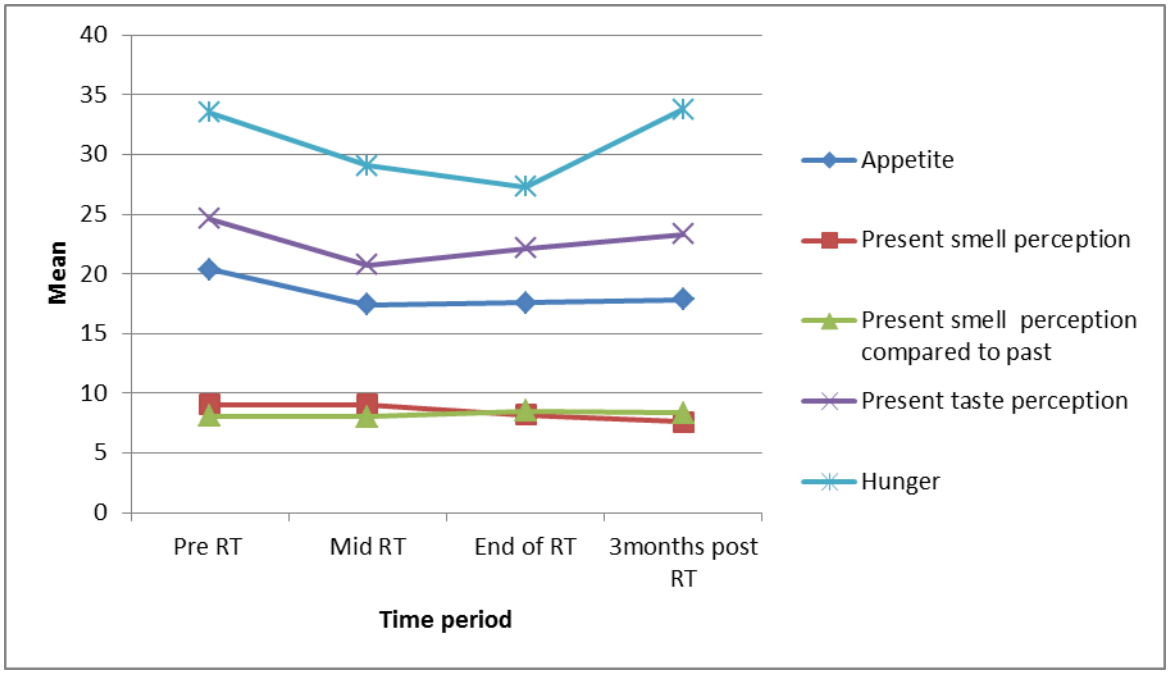



**Fig 26 : Trend of each domain in the AHSP questionnaire**

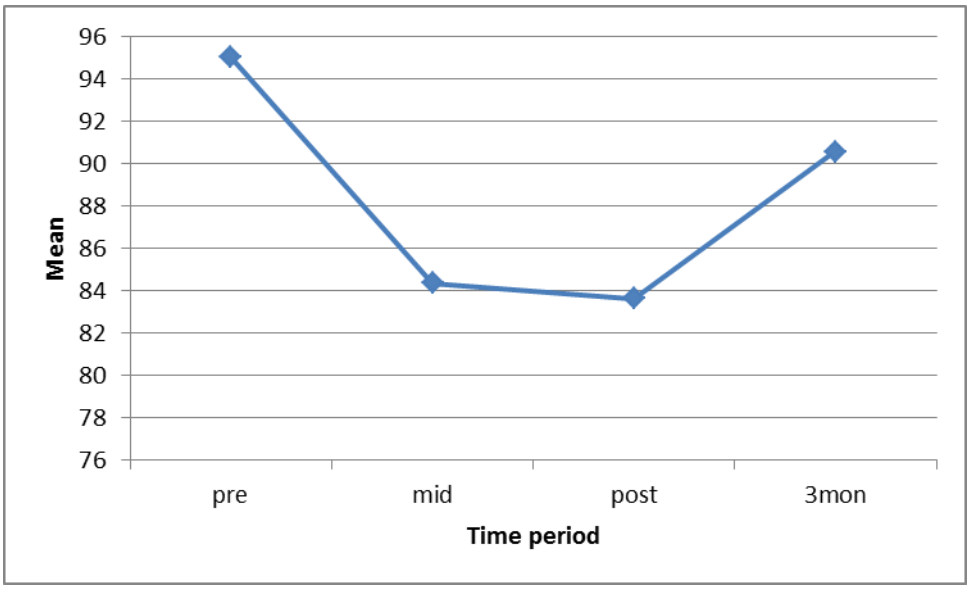



**Fig 27: Mean total QOL score over various time points of RT**

Although, there is no gross variation in the smell, appetite, hunger, taste perception scores, when the total QOL scores were compared before and after therapy, there appeared to be a fall in the overall total QOL score post therapy.

| Domain | Time point | P value |
|---|---|---|
| Appetite | Pre RT – Mid RT | **0.044** |
| | Pre RT – End of RT | **0.047** |
| | Pre RT – 3 months post RT | 0.087 |
| Present smell perception | Pre RT – Mid RT | 0.719 |
| | Pre RT – End of RT | 0.319 |
| | Pre RT – 3 months post RT | 0.225 |
| Present smell perception as compared to past | Pre RT – Mid RT | 0.795 |
| | Pre RT – End of RT | 0.320 |
| | Pre RT – 3 months post RT | 0.480 |
| Taste | Pre RT – Mid RT | **0.025** |
| | Pre RT – End of RT | 0.099 |
| | Pre RT – 3 months post RT | 0.192 |
| Hunger | Pre RT – Mid RT | **0.049** |
| | Pre RT – End of RT | **0.010** |
| | Pre RT – 3 months post RT | 0.639 |
| Total QOL score | Pre RT – Mid RT | **0.020** |
| | Pre RT – End of RT | **0.004** |
| | Pre RT – 3 months post RT | 0.147 |

**Table 10: AHSP QOL score at each time interval: Test of significance**

Patients were often unaware of the olfactory loss as evident in the threshold scores which directly did not significantly affect the quality of life. However, gustation and appetite related quality of life seemed to be significantly affected.

# DISCUSSION

Radiation therapy is an integral component in the management of head and neck malignancies and the radiation fields often include the olfactory cleft region. Such patients sometimes complain of deteriorating chemosensory function during the course of treatment. Olfactory impairment is most often overlooked even though it could expose patients to potentially life-threatening events. In order to look at this aspect of effect of radiotherapy on nasal functions, the present study was designed and conducted.

We assessed olfaction in 33 head and neck cancer patients, planned for IMRT, who agreed to participate in the study. Strictly adhering to normal olfaction at baseline, 21 patients could be recruited in the study. At the time of analysis, 18 patients had completed radiotherapy and 13 were followed up 3 months post treatment.

The age group ranged from 16 – 75 years. Generally, the overall incidence of head and neck cancers is much more common in men as compared to women. In our study also there was a male predominance noted.

Our study is based on the Connecticut chemosensory clinical research centre test (CCCRC) in patients diagnosed with primary head and neck cancers after irradiation. In the selection of cases, patients with head and neck cancer in whom the irradiation field included the olfactory cleft were only studied. Standardized irradiation techniques and head and neck cancer treatment guidelines according to institutional protocols were followed.

All patients in the study were treated with intensity modulated radiotherapy. After determining the exact site, dose and tumour volume to be irradiated, 200 cGy (2 Gy) of irradiation per day was given for 5 days a week in all the cases over a period of 6 – 7 weeks in 33 to 35 fractions. Total dose ranged from 60 – 70 Gy ( Mean total dose – 65.75 Gy ). The mean olfactory region dose volume varied from 0.00 – 2.36 $cm^3$ ( Mean – 1.47 $cm^3$).

Although, the CCCRC test is a fairly simple procedure, some of the odorants in the study could be perceived but not identified by some patients. Our study shows a gradual decline in both olfactory threshold and odour identification in individuals with normal olfaction following 2 weeks of radiotherapy which progressed until the end of radiotherapy ( $p < 0.001$). This could be a conductive defect due to oedema of the nasal mucosa and also partly sensorineural due to effect of radiation on the olfactory receptors and nerve fibres. In patients in whom treatment was complete, when assessed during their 3 month follow up, there was recovery of olfaction to normal in a few while olfactory loss still persisted in others. Olfactory thresholds alone were analysed in the subgroups that underwent chemoradiation and surgery with adjuvant radiotherapy or radiation alone groups. Similar results were obtained, however patients undergoing chemoradiation reported a delayed recovery or the olfaction did not return to normal. This was in contradiction to the findings in a study by Yakirevitch et al where he reported cisplatin has no deleterious effects on olfactory function (27).

In a study by Jalali et al where 54 patients with head and neck cancer treated by radiotherapy were assessed, the mean olfactory threshold scores were found to

deteriorate significantly at various time points after radiotherapy (11.7 before radiotherapy versus 4.0 at 3 months general linear model, ( $P<0.0001$). Olfactory threshold was significantly decreased 2–6 weeks after initiation of therapy. However, this study showed no recovery of olfaction upto 6 months follow up (31).

In a similar study by Ophir et al , on patients with nasopharyngeal carcinoma or pituitary adenoma treated by radiotherapy, the olfactory function significantly reduced during the course of treatment. However, most patients showed varying degrees of recovery 3 -6 months after treatment (35). This is in agreement with our study where a significant reduction was noted at mid RT assessment. Even though there was an improvement in olfaction at the 3 month post RT evaluation, it continued to be significantly reduced compared to the pre RT baseline.

Ho et al measured olfactory threshold, odour identification, and odour discrimination in 48 patients using the 'Sniffin– Sticks' test at five time points from beginning of RT till 1 year follow up after treatment for nasopharyngeal carcinoma. Contrary to our findings, a mostly negative result was found in this prospective study. Only 12 months after radiotherapy there was a significant deterioration in olfactory thresholds. However, olfactory discrimination and identification did not show any significant change (32).

Hölscher et al studied olfactory function in 44 patients, 25 of whom were followed for 12 months. Based on the dose of radiation to the olfactory epithelium, patients were divided into two groups: median 62.2 Gy (OLF group) and median 5.9 Gy (non-OLF group). This study showed a significant impairment of odour

discrimination or odour identification in the OLF group with no significant changes in olfactory thresholds. The observed changes were attributed to the effects of radiotherapy on the olfactory bulb/orbitofrontal cortex. The authors postulated that the olfactory epithelium is relatively resistant against the effects of radiation (33).

In a study by Veysellar et al, the long-term side effects of radiotherapy on the olfactory bulb volumes and olfactory function in nasopharyngeal cancer patients were evaluated. The olfactory bulb volumes on MRI scan and olfactory threshold of nasopharyngeal cancer patients was significantly diminished as compared to healthy controls. This was attributed to the direct radiation induced damage to the olfactory mucosa or the effect of radiotherapy to primarily the olfactory bulb and other olfactory centers (34).

In a study by Brammerson et al, the olfactory identification was assessed using the Scandinavian Odor Identification Test (SOIT ) which showed that the identification test given before treatment yielded a mean score of 12.4 in the high-dose group and 12.5 in the low-dose group for which corresponding scores after treatment were 10.2 and 12.4. Before treatment there was no significant difference between groups, but after treatment high dose group showed a significant reduction ($p < 0.05$) (30).

According to the CCCRC composite scores in the present study, 3 months after radiotherapy, patient distribution based on severity of olfactory symptoms was: normosmia 6 ( 24% ), mild hyposmia 8 (32% ), moderate hyposmia 3( 12 % ), severe hyposmia 6 ( 24% ) and anosmia 2 (8 % ).

Veyseller et al reported, composite scores of 11 (45.8%) patients classified as normal, 7 (29.2%) as mildly hyposmic, 3 (12.5%) as moderately hyposmic, and 3 (12.5%) as severely hyposmic in tests conducted 12 months after treatment.

Wang et al, reported the significant decrease in UPSIT scores with a mean of 30.6 before IMRT and a mean of 28 after IMRT. However, 75.6% of patients retained normal olfactory function after IMRT which indicated that most nasopharyngeal carcinoma patients were not affected by IMRT (20) .

Based on the site of lesion on the olfactory pathway, Snow et al has classified olfactory disorders in to 3 types, transport, sensory, and neural disorders. In transport olfactory disorders, there is reduced transmission of odorant particles to the neuroepithelium, whereas sensory olfactory disorders involve lesions of the neuroepithelium itself. In our study patients, the mechanism of olfactory dysfunction may include both transport and sensory olfactory losses. Radiotherapy induced mucosal changes like oedema and mucositis can lead to obstruction of access of odorant particles to the olfactory area resulting in a conductive type hyposmia even though often the patient doesn't feel the nasal obstruction. In addition, irradiation can damage the olfactory epithelial Bowman's glands which dissolve odorants and present them to bipolar receptor cells. Any significant change in the microenvironment around the olfactory receptor neurons is detrimental to the appreciation of smell (12).

The alteration in cell cycle and arrest of mitosis in the basal cell layer of olfactory epithelium leading to a decreased turnover of olfactory neuroepithelium is postulated to be yet another mechanism by which irradiation affects olfaction. The

regenerative capability of olfactory neuroepithelium could be the reason for recovery of olfactory function few months following radiotherapy as noticed in our study too.

According to Jalali et al, variability in the total irradiation dose to the olfactory region can have different effects. Low radiation doses cause olfactory threshold change due to sensory perception. Irradiation in higher doses is hypothesised to cause nerve damage in addition to the mucosal damage. This could account for the contradictory results of different studies (31).

Another important aspect of nasal function is the nasal mucociliary clearance. The process by which the particles inhaled in the nasal mucosa are pushed towards the nasopharynx through the ciliary movement is called mucociliary clearance (MCC). Usually, the mucosal ciliary activity of the nasal cavity sweeps the mucosal blanket posteriorly at a rate of 6 – 7 mm/ min till the nasopharynx where it is swallowed. This is dependent on the physical properties of the mucus and proper function of the cilia. Several studies have been reported to show effects of age, gender, inflammation, temperature changes and drugs on the mucociliary clearance time. Many patients undergoing radiation therapy for head and neck cancers complain of nasal congestion, facial pain and foul smell during treatment. This was attributed to the prolonged mucociliary clearance time and inadequate drainage of secretions. Similar symptoms were reported by Kiliç et al and Stringer et al (41,42).

Damage to the respiratory mucosa and the cilia due to direct effects of irradiation have been reported in animal and human studies following physiological changes such as vacuolation of the ciliary cells, goblet cell secretions, nuclear

pyknosis, decreased ciliary cells and sloughing. Even though there are numerous studies on mucociliary clearance there is paucity of literature on the effect of radiation therapy on this phenomenon. The study aimed to demonstrate how the nasal mucociliary transport times are affected in the patients receiving radiotherapy for head and neck tumours. We assessed the mucociliary clearance time by the saccharin test. In our study, out of the 21 patients, only 12 (57.14%) patients had normal mucociliary clearance time before initiation of radiotherapy. This could be because majority of the study patients had carcinoma of the nasopharynx (61.9% ) having a mass which contributed to the obstruction of mucus clearance. The decrease in mucociliary clearance rate could also be attributed to the toxic effect of the chemotherapy regimen on cilia movement and/or mucus structure since 71 % of the participants had undergone chemoradiation. Another contributing factor impeding the mucociliary clearance could be an in situ nasogastric tube in many of these patients.

There was a prolonged saccharin perception time at the end of radiation (21.44±1.2400 ) as compared to the start of radiation (Mean + SD 14.80±8.637 ). There were wide variations in the results as several patients were unable to perceive saccharin at all. This could be attributed to the fact that several patients were placed on nasogastric tube feeds which further occluded the nasal cavity. Analysis of results in the surgery and RT subgroups as well as chemoradiation subgroups also yielded similar results.

A study by Gupta et al, showed significantly prolonged saccharin perception time in head and neck cancer patients after radiotherapy when compared to their pre

irradiation values [pre RT (Mean + SD-9.45 ± 0.36 minutes) while post RT (Mean + SD - 30.64 ± 1.12 minutes] (24).

Stringer at al evaluated the mucociliary function in 9 patients who had previously undergone radiotherapy. The irradiated patients had a negative saccharin test similar to our study where several patients did not perceive the saccharin following the initiation of radiotherapy.

Kiliç et al, demonstrated significantly prolonged mucociliary clearance time in nasopharyngeal and laryngeal cancer patients who received RT which persisted at 3 months and 6 months follow up in the nasopharyngeal cancer patients (41).

Radiation therapy has a negative impact on the quality of life as reported by many researchers. In a study of patients undergoing chemotherapy, Epstein et al reported, the greatest changes in QOL were seen to be the impact upon physical, emotional, cognitive, and social functions.(37) He reported a reduced taste (ageusia) or altered taste (dysgeusia), which may have a significant impact on QOL in patients undergoing radiation and/or chemotherapy. Decreased food intake could be due to decreased appetite (28)induced by nausea and altered taste or smell, oral ulcers and oropharyngeal mucositis, hyposalivation, and xerostomia and decreased interest in food associated with depression.

Braam et al reported a prospective study of the QOL combined with parotid salivary outflow of 44 patients with head-and-neck malignancies treated with RT. They assessed xerostomia using the EORTC –H&N35 questionnaire which revealed

deterioration of most of the QOL items after completion of radiotherapy compared with baseline, with improvement during 5 years follow-up, even after 12 month (43) .

Leyrer et al performed a dose-volume histogram analysis in 20 patients with gliomas. The patients completed a questionnaire relating to taste and smell disturbances at baseline and at Weeks 3 and 6. Ten of 20 patients reported experiencing some degree of smell disturbance (36).

Kamel et al, conducted serial follow up studies on mucociliary clearance of patients who received RT over a period of 2 – 4 years post therapy. They concluded that the MCC deteriorates for up to 6 months and then stabilizes and persists due to damage to ciliary motility. Serial nasal endoscopies revealed a decrease in the amount of discharge, resulting in thick mucous with adhesions and choanal stenosis causing accumulation of the crusts (44).

We used the Appetite, hunger, taste and smell perception ( AHSP ) questionnaire designed by Dr De Jong. It consisted of 5 domains with a total of 29 questions which made inquiries in to present status of the patients' appetite, smell, frequency on meals, alterations in taste as well as comparisons made to previous disease free period. Each domain was analysed separately (40).

Patients at each visit were also enquired about their general health. Patients complained of generalised weakness, oral ulcers and decreased taste perception but were unaware of deterioration in olfactory function. Mean scores in each domain were comparable to the baseline and did not show drastic differences. Overall total QOL score at the end of RT was reduced (83.50 ± 9.488 ) as compared to the total score

prior to radiotherapy (95.50 ± 10.407 ). However, individual components such as appetite and hunger were also significantly reduced even though olfaction did not show a significant reduction.

**Limitations**

Most patients come from different parts of India with different cultures and tradition. There is no single globally acceptable olfaction assessment tool for all these patients. Patients were sometimes unfamiliar with the components used for odour identification and the test had to be repeated. Some patients were unwilling for repeated follow up because of their physical and emotional condition while undergoing concurrent chemoradiation.

Factors such as nasogastric tubes, nasal packing were confounding. Hence, prolonged effects of mucociliary clearance time could not be effectively assessed. Further more, the less number of studies in this area of interest along with different tests used in the studies did not favour comparison of data.

# CONCLUSION

Radiotherapy has a significant effect on nasal functions of olfaction and mucociliary clearance. Both olfactory threshold and identification showed significant reduction during the course of radiotherapy with partial recovery at 3 months follow up. In patients who underwent chemoradiation recovery of olfactory function was comparatively less. Mucociliary dysfunction persisted even after 3 months following radiation therapy. The patients did not notice olfactory dysfunction subjectively. Impairment of quality of life can be attributed as an indirect impact of olfactory loss.

# BIBLIOGRAPHY


1. Temmel AFP, Quint C, Schickinger-Fischer B, Klimek L, Stoller E, Hummel T. Characteristics of olfactory disorders in relation to major causes of olfactory loss. Arch Otolaryngol Head Neck Surg. 2002 Jun;128(6):635–41.

2. Santos DV, Reiter ER, DiNardo LJ, Costanzo RM. Hazardous events associated with impaired olfactory function. Arch Otolaryngol Head Neck Surg. 2004 Mar;130(3):317–9.

3. Walliczek-Dworschak U, Hummel T. The Human Sense of Olfaction. Facial Plast Surg FPS. 2017 Aug;33(4):396–404.

4. Frasnelli J, Hummel T. Olfactory dysfunction and daily life. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg. 2005 Mar;262(3):231–5.

5. Hazarika P. Textbook of Ear, Nose, Throat and Head and Neck Surgery: Clinical and Practical. Place of publication not identified: CBS Publishers & Distributors; 2013. 936 p.

6. Pansky B. Review of Medical Embryology. New York: Macmillan USA; 1982. 496 p.

7. Gleeson M, editor. Scott-Brown's Otorhinolaryngology: Head and Neck Surgery 7Ed: 3 volume set. 7 edition. London: Jaypee medical; 2008. 3900 p.

8. MD PWF, FACS BHHM, FRCSEd VJLCMF, MD JKN, FACS KTRM, FACS JRTM, et al. Cummings Otolaryngology: Head and Neck Surgery, 3-Volume Set, 6e. 6 edition. Philadelphia, Pa: Saunders; 2014. 3624 p.

9. Gizurarson S. Anatomical and histological factors affecting intranasal drug and vaccine delivery. Curr Drug Deliv. 2012 Nov;9(6):566–82.

10. Turner A. Logan Turner's Diseases of the Nose, Throat and Ear, 10Ed. 10 edition. Oxford: CRC Press; 1987. 468 p.

11. Wackym. Ballenger's Otorhinolaryngology Head and Neck surgery. 17 edition. Shelton, Conn.; Hamilton, Ont.; London: McGraw-Hill Medical; 2009. 1248 p.

12. Biacabe B, Faulcon P, Amanou L, Bonfils P. Olfactory cleft disease: an analysis of 13 cases. Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 2004 Feb;130(2):202–8.

13. Levine H, May M. Endoscopic Sinus Surgery: Rhinology and Sinusology. New York : Stuttgart : New York: Thieme-Stratton Corp; 1993. 272 p.

14. Presutti L, Mattioli F, editors. Endoscopic Surgery of the Lacrimal Drainage System. 1st ed. 2016 edition. New York, NY: Springer; 2015. 99 p.

15. Hummel T, Landis BN, Hüttenbrink K-B. Smell and taste disorders. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2011;10:Doc04.

16. Sagar SM, Thomas RJ, Loverock LT, Spittle MF. Olfactory sensations produced by high-energy photon irradiation of the olfactory receptor mucosa in humans. Int J Radiat Oncol Biol Phys. 1991 Apr;20(4):771–6.

17. Welge-Lüssen A. Re-establishment of olfactory and taste functions. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2005;4:Doc06.

18. Pinto JM. Olfaction. Proc Am Thorac Soc. 2011 Mar;8(1):46–52.

19. Gueron S, Levit-Gurevich K. Energetic considerations of ciliary beating and the advantage of metachronal coordination. Proc Natl Acad Sci U S A. 1999 Oct 26;96(22):12240–5.

20. Washington N, Washington C, Wilson C. Physiological Pharmaceutics: Barriers to Drug Absorption. 1 edition. New York: CRC Press; 2000. 328 p.

21. Corbo GM, Foresi A, Bonfitto P, Mugnano A, Agabiti N, Cole PJ. Measurement of nasal mucociliary clearance. Arch Dis Child. 1989 Apr;64(4):546–50.

22. Pandya VK, Tiwari RS. Nasal mucociliary clearance in health and disease. Indian J Otolaryngol Head Neck Surg Off Publ Assoc Otolaryngol India. 2006 Oct;58(4):332–4.

23. Stanley P, MacWilliam L, Greenstone M, Mackay I, Cole P. Efficacy of a saccharin test for screening to detect abnormal mucociliary clearance. Br J Dis Chest. 1984 Jan;78(1):62–5.

24. Gupta SC, Chandra S, Singh M. Effects of irradiation on nasal mucociliary clearance in head and neck cancer patients. Indian J Otolaryngol Head Neck Surg Off Publ Assoc Otolaryngol India. 2006 Jan;58(1):46–50.

25. Lioté H, Zahm JM, Pierrot D, Puchelle E. Role of mucus and cilia in nasal mucociliary clearance in healthy subjects. Am Rev Respir Dis. 1989 Jul;140(1):132–6.

26. Wang J-J, Liang K-L, Twu C-W, Lin J-C, Jiang R-S. Olfactory change after intensity-modulated radiotherapy for nasopharyngeal carcinoma. Int Forum Allergy Rhinol. 2015 Nov;5(11):1059–62.

27. Yakirevitch A, Talmi YP, Baram Y, Weitzen R, Pfeffer MR. Effects of cisplatin on olfactory function in cancer patients. Br J Cancer. 2005 May 9;92(9):1611–3.

28. Cain WS, Gent JF, Goodspeed RB, Leonard G. Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. The Laryngoscope. 1988 Jan;98(1):83–8.

29. Kilicaslan A, Acar GO, Tekin M, Ozdamar OI. Assessment the long-term effects of septoplasty surgery on olfactory function. Acta Otolaryngol (Stockh). 2016 Oct 2;136(10):1079–84.

30. Bramerson A, Nyman J, Nordin S, Bende M. Olfactory loss after head and neck cancer radiation therapy. Rhinology. 2013 Sep;51(3):206–9.

31. Jalali MM, Gerami H, Rahimi A, Jafari M. Assessment of olfactory threshold in patients undergoing radiotherapy for head and neck malignancies. Iran J Otorhinolaryngol. 2014 Oct;26(77):211–7.

32. Ho W, Kwong DLW, Wei WI, Sham JST. Change in olfaction after radiotherapy for nasopharyngeal cancer—A prospective study. Am J Otolaryngol. 2002 Jul;23(4):209–14.

33. Hölscher T, Seibt A, Appold S, Dörr W, Herrmann T, Hüttenbrink K-B, et al. Effects of radiotherapy on olfactory function. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2005 Nov;77(2):157–63.

34. Veyseller B, Ozucer B, Degirmenci N, Gurbuz D, Tambas M, Altun M, et al. Olfactory bulb volume and olfactory function after radiotherapy in patients with nasopharyngeal cancer. Auris Nasus Larynx. 2014 Oct;41(5):436–40.

35. Ophir D, Guterman A, Gross-Isseroff R. Changes in smell acuity induced by radiation exposure of the olfactory mucosa. Arch Otolaryngol Head Neck Surg. 1988 Aug;114(8):853–5.

36. Leyrer CM, Chan MD, Peiffer AM, Horne E, Harmon M, Carter AF, et al. Taste and smell disturbances after brain irradiation: a dose-volume histogram analysis of a prospective observational study. Pract Radiat Oncol. 2014 Apr;4(2):130–5.

37. Epstein JB, Phillips N, Parry J, Epstein MS, Nevill T, Stevenson-Moore P. Quality of life, taste, olfactory and oral function following high-dose chemotherapy and allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2002 Dec;30(11):785–92.

38. Savina C, Donini LM, Anzivino R, De Felice MR, De Bernardini L, Cannella C. Administering the "AHSP Questionnaire" (appetite, hunger, sensory perception) in a geriatric rehabilitation care. J Nutr Health Aging. 2003;7(6):385–9.

39. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life--an updated review. Chem Senses. 2014 Mar;39(3):185–94.

40. Mathey MF. Assessing appetite in Dutch elderly with the Appetite, Hunger and Sensory Perception (AHSP) questionnaire. J Nutr Health Aging. 2001;5(1):22–8.

41. Kılıç C, Tunçel Ü, Cömert E, Kaya BV. The effect of radiotherapy on mucociliary clearance in patients with laryngeal and nasopharyngeal cancer. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg. 2015 Jun;272(6):1517–20.

42. Stringer SP, Stiles W, Slattery WH, Krumerman J, Parsons JT, Mendenhall WM, et al. Nasal mucociliary clearance after radiation therapy. The Laryngoscope. 1995 Apr;105(4 Pt 1):380–2.

43. Braam PM, Roesink JM, Raaijmakers CPJ, Busschers WB, Terhaard CHJ. Quality of life and salivary output in patients with head-and-neck cancer five years after radiotherapy. Radiat Oncol Lond Engl. 2007 Jan 5;2:3.

44. Kamel R, Al-Badawy S, Khairy A, Kandil T, Sabry A. Nasal and paranasal sinus changes after radiotherapy for nasopharyngeal carcinoma. Acta Otolaryngol (Stockh). 2004 May;124(4):532–5.

# PATIENT INFORMATION SHEET

You are being requested to participate in a study . In this study we will test your olfaction (ability to smell ) before and after radiotherapy. We will assess the ability to smell prior to initiation of radiotherapy. Subsequently, your quality of life and nasal function test will also be done.

Olfaction testing is done using Butanol test. In this test you will be given a solution at different concentrations and you will be asked at which concentration you can identify the smell. You will also be asked to smell different odours and see if you can differentiate between the odours and identify them separately.

Quality of life will be assessed using a questionnaire containing a series of 29 questions for which you will have to choose your answers from 5 different options.

Nasal function will be tested by a saccharine test where in a small particle will be placed in the nasal vestibule and the time taken for you to identify it presence by taste will be noted.

**What are Butanol test, odour identification and odour discrimination?**

Butanol is butyl alcohol (chemical ) which is given at different dilutions and you will be asked to smell the different concentrations and tell us at which concentration you can identify the smell. The test is repeated independently in each of the nostrils. In odour identification and discrimination you are asked to smell different odours we use on a daily basis such as coffee, cinnamon etc. and you are expected to identify the odour and differentiate it.

**Does butanol test have any side effects.**

There are no side effects for these tests. This will only assess the extent of your ability to smell.

**How and where will the nasal tests be done?**

Your nasal examination will be done in the ENT OPD treatment room no. – 27 using a butanol ( chemical ) solution at different concentration and nasal function by the saccharine test.

**Will you be charged for the nasal examination**

You will not be charged for the nasal examination.

**Can you withdraw from this study after it starts?**

Your participation in the study is highly valuable and voluntary. You are free to decide to withdraw from the study at any time. If you do so, this will not affect your usual treatment in the hospital.

**Will you have to pay for the olfactory test and the nasal function test?**

You need not pay for the smell test and nasal function test. Any other treatment that you usually take will continue as usual.

**Will the questionnaire be easy to answer?**

The questionnaire will be easy and answers will be of multiple choice. A doctor will be with you while answering the questionnaire. Any problem in understanding the questions can be clarified with him / her.

**Will the answers of the questionnaire be kept confidential?**

The answers of this questionnaire will not be revealed or published. The questionnaire is only to quantify the problem pre and post radiotherapy. The results will be reviewed by only people associated with the study

**Will your personal details be kept confidential?**

The results of this study will be publishes in a medical journal but you will not be identified by name in any publication or presentation of results.

Contact :

Dr. Preethi Rose Gurushekar

PG Registrar

ENT

Ph no. – 8098233772

## Informed Consent form

**Study Title: Study of smell after radiotherapy in head and neck cancer patients**

**Study Number: _____**

**Subject's Initials: _____**

**Subject's Name: _____**

**Date of Birth / Age: _____**

(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 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/Legally Acceptable

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: _____

_____

## PROFORMA FOR DATA COLLECTION

Name:

Age :

M/F:

Hospital number:

Phone number:

Clinical history:

ENT history :

Diagnosis:

Treatment plan:

**CCCRC Test:**

Olfactory threshold -

| Right nostril | | | | Left nostril | | | |
|---|---|---|---|---|---|---|---|
| Pre RT | Mid RT | End of RT | 3 months | Pre RT | Mid RT | End of RT | 3 months |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |

Odour identification test –

| Odorant | Right nostril | | | | Left nostril | | | |
|---|---|---|---|---|---|---|---|---|
| | Pre RT | Mid RT | End of RT | 3 months post RT | Pre RT | Mid RT | End of RT | 3 months post RT |
| Cinnamon | | | | | | | | |
| Asafoetida | | | | | | | | |
| Coffee | | | | | | | | |
| Tea | | | | | | | | |
| Pepper | | | | | | | | |
| Clove oil | | | | | | | | |
| Baby powder | | | | | | | | |
| Total correct | | | | | | | | |
| Eucalyptus ( Trigeminal ) | | | | | | | | |
| Key | √ Correct | | NS – No sensation | | DK – Don't know | | Misidentification to be specified | |

Score -

| | Pre RT | | Mid RT | | End of RT | | 3 months post RT | |
|---|---|---|---|---|---|---|---|---|
| | R | L | R | L | R | L | R | L |
| Olfactory threshold | | | | | | | | |
| Odour identification | | | | | | | | |
| Composite Score | | | | | | | | |

| | Pre RT | Mid RT | End of RT | 3 months post RT |
|---|---|---|---|---|
| Quality of life | | | | |
| Mucociliary Clearance time | | | | |

**Appetite, Hunger and Sensory Perception (AHSP) questionnaire**

**TASTE**

In former days I enjoyed food:

[ ] 1 much more than nowadays

[ ] 2 more than nowadays

[ ] 3 the same as nowadays

[ ] 4 less than nowadays

[ ] 5 much less than nowadays

It seems that all foods have the same taste

[ ] 1 totally agree

[ ] 2 agree

[ ] 3 no opinion

[ ] 4 disagree

[ ] 5 totally disagree

It seems that the taste of food

[ ] 1 seriously declined

[ ] 2 declined

[ ] 3 stayed the same

[ ] 4 improved

[ ] 5 seriously improved

I still eat with relish

[ ] 5 totally agree

[ ] 4 agree

[ ] 3 no opinion

[ ] 2 disagree

[ ] 1 totally disagree

In former days, food was

[ ] 1 much more enjoyable than nowadays

[ ] 2 more enjoyable than nowadays

[ ] 3 as enjoyable as nowadays

[ ] 4 less enjoyable than nowadays

[ ] 5 much less enjoyable than nowadays

In general, I find food taste

[ ] 5 very good

[ ] 4 good

[ ] 3 fair

[ ] 2 bad

[ ] 1 very bad

In former days I enjoyed eating

[ ] 1 much better than nowadays

[ ] 2 better than nowadays

[ ] 3 the same as nowadays

[ ] 4 worse than nowadays

[ ] 5 much worse than nowadays

Nowadays the food is rather tasteless

[ ] 1 totally agree

[ ] 2 agree

[ ] 3 no opinion

[ ] 4 disagree

[ ] 5 totally disagree

**APPETITE**

Nowadays my appetite is generally

[ ] 5 very good

[ ] 4 good

[ ] 3 fair

[ ] 2 bad

[ ] 1 very bad

Nowadays I donot feel too much like eating

[ ] 1 totally agree

[ ] 2 agree

[ ] 3 no opinion

[ ] 4 disagree

[ ] 5 totally disagree

In former days my appetite was

[ ] 1 much better than nowadays

[ ] 2 better than nowadays

[ ] 3 the same as nowadays

[ ] 4 worse than nowadays

[ ] 5 much worse than nowadays

It seems that my appetite

[ ] 1 seriously declined

[ ] 2 declined

[ ] 3 stayed the same

[ ] 4 improved

[ ] 5 seriously improved

Everyday I feel like eating

[ ] 5 totally agree

[ ] 4 agree

[ ] 3 no opinion

[ ] 2 disagree

[ ] 1 totally disagree

I still have a hearty appetite

[ ] 5 totally agree

[ ] 4 agree

[ ] 3 no opinion

[ ] 2 disagree

[ ] 1 totally disagree

**SMELL BEFORE**

In former days my sense of smell was

[ ] 1 much finer than nowadays

[ ] 2 finer than nowadays

[ ] 3 as fine as nowadays

[ ] 4 less fine than nowadays

[ ] 5 much less fine than nowadays

In former days, most of foods smelled

[ ] 1 much better than nowadays

[ ] 2 better than nowadays

[ ] 3 the same as nowadays

[ ] 4 worse than nowadays

[ ] 5 much worse than nowadays

It seems that my sense of smell was better in former days than now

[ ] 1 totally agree

[ ] 2 agree

[ ] 3 no opinion

[ ] 4 disagree

[ ] 5 totally disagree

**SMELL NOWADAYS**

I smell

[ ] 1 very well

[ ] 2 well

[ ] 3 fairly

[ ] 4 badly

[ ] 5 very badly

It seems that everything smells the same

[ ] 1 totally agree

[ ] 2 agree

[ ] 3 no opinion

[ ] 4 disagree

[ ] 5 totally disagree

Nowadays I am not able to identify a lot of odours

[ ] 1 totally agree

[ ] 2 agree

[ ] 3 no opinion

[ ] 4 disagree

[ ] 5 totally disagree

**HUNGER FEELINGS**

How often do you feel like eating your breakfast?

[ ] 5 daily

[ ] 4 often

[ ] 3 sometimes

[ ] 2 seldom

[ ] 1 never

How often do you feel like eating your lunch?

[ ] 5 daily

[ ] 4 often

[ ] 3 sometimes

[ ] 2 seldom

[ ] 1 never

How often do you feel like eating your dinner?

[ ] 5 daily

[ ] 4 often

[ ] 3 sometimes

[ ] 2 seldom

[ ] 1 never

How often do you feel like eating a snack?

[ ] 5 daily/ several times a day

[ ] 4 often

[ ] 3 sometimes

[ ] 2 seldom

[ ] 1 never

How often do you feel like eating something sweet?

[ ] 5 daily/ several times a day

[ ] 4 often

[ ] 3 sometimes

[ ] 2 seldom

[ ] 1 never

How often do you feel like eating something salty?

[ ] 5 daily/ several times a day

[ ] 4 often

[ ] 3 sometimes

[ ] 2 seldom

[ ] 1 never

How often do you have to force yourself to eat something?

[ ] 1 always

[ ] 2 often

[ ] 3 sometimes

[ ] 4 seldom

[ ] 5 never

How often are you looking forward to the next meal?

[ ] 5 always

[ ] 4 often

[ ] 3 sometimes

[ ] 2 seldom

[ ] 1 never

If you have been snacking, do you still feel like eating your next meal?

[ ] 5 always

[ ] 4 often

[ ] 3 sometimes

[ ] 2 seldom

[ ] 1 never

| ID | NAME | HOSP | AGE | GENDER | COMD | DIAG | STAGE | TNM | RX | SX | HISTOLOGY | R | R1 | R2 | R3 | L |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Mihir Chandra Debnath | 497887g | 36 | 1 | 2 | 1 | 4 | T2N3M0 | 3 | | Undifferentiated nasophyngeal ca | 6 | 5 | 4 | 6 | |
| 2 | Sudhamoy Misra | 640434g | 38 | 1 | 3 | 3 | | | 1 | Left inferior partial maxillectomy | Clear cell mucoepidermoid ca | 6 | 6 | 2 | 6 | 6 |
| 3 | Mahendra Singh Prasad | 672169g | 57 | 1 | 3 | 2 | 4 | T4N2M0 | 3 | | Poorly differentiated ca | 6 | 6 | 4 | | 6 |
| 4 | Kharka Bahadur Limboo | 698685g | 52 | 1 | 3 | 1 | 4 | T1N3bM0 | 3 | | Poorly differentiated ca | 6 | 6 | 6 | 6 | 6 |
| 5 | Suvankar Rakshit | 648128g | 16 | 1 | 3 | 4 | | | 1 | Endoscopic excision right nasal mass | Haemangiopericytoma right nasal cavity | 6 | 6 | 3 | 6 | 6 |
| 6 | Bavish Karmakar | 699256g | 17 | 1 | 3 | 1 | 3 | T3N1M0 | 3 | | Undifferentiated nasopharyngeal ca | 6 | 6 | 6 | 6 | 6 |
| 7 | Rajendra Bahadur Chettry | 706189g | 69 | 1 | 3 | 2 | 3 | T3N0M0 | 2 | | Poorly differentiated ca | 6 | 6 | 4 | 4 | 6 |
| 8 | Abdullah Mamoon | 732841g | 59 | 1 | 1 | 1 | 3 | T3N0M0 | 3 | | Poorly differentiated ca | 5 | 4 | | | 5 |
| 9 | Lalzingtluanga | 720263g | 67 | 1 | 1 | 2 | 2 | T2N0M0 | 2 | | Moderately differentiated SCC | 6 | 6 | 1 | 6 | 6 |
| 10 | Sarika Sangdo | 671586g | 31 | 2 | 3 | 1 | 4 | T3N3M0 | 3 | | Poorly differentiated ca | 6 | 6 | 6 | 6 | 6 |
| 11 | Mithun Kumar Kundu | 757521g | 21 | 1 | 3 | 1 | 4 | T4aN2M0 | 3 | | Poorly differentiated ca | 6 | 6 | 6 | | 6 |
| 12 | Matta Nagendra Prasad | 766658g | 39 | 1 | 3 | 1 | 4 | T2N3M0 | 3 | | Poorly differentiated ca | 6 | 4 | 3 | 4 | 6 |
| 13 | Mst Salina Khatun | 770194g | 41 | 2 | 3 | 1 | | | 3 | | Poorly differentiated ca | 6 | 4 | 3 | 3 | 5 |
| 14 | Dileep Kumar | 767699g | 22 | 1 | 3 | 1 | 4 | T1N2M0 | 3 | | Undifferentiated nasopharyngeal ca | 6 | 5 | 6 | 0 | 6 |
| 15 | Babu | 766737g | 50 | 1 | 3 | 1 | 3 | T1N1M0 | 3 | | Undifferentiated nasophayngeal carcinoma | 6 | 1 | 1 | 0 | 6 |
| 16 | Golak Modal | 790529g | 49 | 1 | 3 | 1 | 4 | T2N3M0 | 3 | | Metastatic ca | 6 | 5 | 0 | | 6 |
| 17 | Sunitha Mishra | 783924g | 28 | 2 | 3 | 4 | | | 1 | Endoscopic excision of tumour | Poorly differentiated ca with neuroendocrine differentiation | 6 | 6 | 5 | | 6 |
| 18 | Shyam Sundar Roy | 303890c | 65 | 1 | 3 | 3 | 1 | T1N0M0 | 1 | Right inferior partial maxillectomy + Right SND | Squamous cell ca | 6 | 5 | 3 | 0 | 6 |
| 19 | Munna | 878233g | 24 | 2 | 3 | 1 | 4 | T4N0M0 | 3 | | Undifferentiated nasopharyngeal ca | 6 | 6 | 6 | | 6 |
| 20 | Jayanthi | 878817g | 48 | 2 | 2 | 1 | 4 | T2N2M0 | 3 | | Poorly differentiated squamous cell ca | 6 | 0 | | | |
| 21 | Rajat | 910298g | 66 | 1 | 3 | 2 | 4 | T4N0M0 | 3 | | Well differentiated squamous cell ca | 5 | 2 | | | |

| L1 | L2 | L3 | R4 | R5 | R6 | R7 | L4 | L5 | L6 | L7 | R8 | R9 | R10 | R11 | L8 | L9 | L10 | L11 | SP | SP1 | SP2 | SP3 | APPTPRE | PSPPRE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 7 | 5 | 5 | 7 | | | | | 6.5 | 5.0 | 4.5 | 6.5 | | | | | 8 | 30 | | | 19 | 7 |
| 4 | 2 | 6 | 7 | 6 | 2 | 6 | 6 | 5 | 2 | 7 | 6.5 | 6.0 | 2.0 | 6.0 | 6.0 | 4.5 | 3.5 | 6.5 | 30 | 30 | 30 | 5 | 19 | 9 |
| 6 | 2 | | 6 | 5 | 4 | | 7 | 6 | 3 | | 6.0 | 5.0 | 4.0 | | 6.5 | 6.0 | 2.5 | | 25 | | | | 15 | 11 |
| 6 | 6 | 6 | 6 | 3 | 0 | 3 | 4 | 2 | 2 | 4 | 6.0 | 4.5 | 3.0 | 4.5 | 5.0 | 4.0 | 4.0 | 5.0 | | | 15 | 1 | 26 | 11 |
| 5 | 3 | 6 | 7 | 5 | 4 | 4 | 7 | 6 | 1 | 5 | 6.5 | 5.5 | 3.5 | 5.0 | 6.5 | 5.5 | 2.0 | 5.5 | | | 15 | 13 | 25 | 10 |
| 5 | 5 | 6 | 7 | 5 | 4 | 4 | 7 | 6 | 4 | 4 | 6.5 | 5.5 | 5.0 | 5.0 | 6.5 | 5.5 | 4.5 | 5.0 | 10 | 14 | | 9 | 23 | 9 |
| 6 | 3 | 4 | 4 | 4 | 4 | 3 | 4 | 3 | 1 | 4 | 5.0 | 5.0 | 4.0 | 3.5 | 5.0 | 4.5 | 2.0 | 4.0 | 20 | | 25 | 30 | 16 | 10 |
| 4 | | | 5 | 1 | | | 4 | 1 | | | 5.0 | 2.5 | | | 4.5 | 2.5 | | | 30 | 30 | . | | 22 | 10 |
| 6 | 1 | 6 | 5 | 3 | 2 | 6 | 4 | 1 | 0 | 5 | 5.5 | 4.5 | 1.5 | 6.0 | 5.0 | 3.5 | 0.5 | 5.5 | 15 | 40 | 50 | | 12 | 6 |
| 6 | 4 | 6 | 7 | 2 | 2 | 6 | 6 | 2 | 3 | 5 | 6.5 | 4.0 | 4.0 | 6.0 | 6.0 | 4.0 | 3.5 | 5.5 | 6 | 14 | 15 | 15 | 24 | 8 |
| 6 | 6 | | 5 | 4 | 2 | | 6 | 5 | 3 | | 5.5 | 5.0 | 4.0 | | 6.0 | 5.5 | 4.5 | | 17 | 21 | 13 | | 20 | 7 |
| 1 | 0 | 0 | 7 | 4 | 4 | 4 | 5 | 3 | 4 | 4 | 6.0 | 4.0 | 3.5 | 4.0 | 5.5 | 2.0 | 2.0 | 2.0 | 13 | 45 | | 15 | 17 | 6 |
| 4 | 3 | 3 | 6 | 6 | 4 | 4 | 5 | 5 | 5 | 3 | 6.0 | 5.0 | 3.5 | 3.5 | 5.0 | 4.5 | 4.0 | 3.0 | | 10 | 20 | 20 | 23 | 14 |
| 4 | 6 | 0 | 6 | 6 | 3 | 3 | 5 | 2 | 4 | 4 | 6.0 | 5.5 | 4.5 | 1.5 | 5.5 | 3.0 | 5.0 | 2.0 | 20 | | | | 22 | 6 |
| 2 | 3 | 0 | 5 | 2 | 2 | 4 | 7 | 3 | 4 | 5 | 5.5 | 1.5 | 1.5 | 2.0 | 6.5 | 2.5 | 3.5 | 2.5 | 3 | 1 | 10 | | 24 | 11 |
| 4 | 0 | | 2 | 5 | 1 | | 6 | 4 | 2 | | 4.0 | 5.0 | 0.5 | | 6.0 | 4.0 | 1.0 | | | | | | 18 | 9 |
| 6 | 4 | | 7 | 7 | 4 | | 7 | 6 | 4 | | 6.5 | 6.5 | 4.5 | | 6.5 | 6.0 | 4.0 | | | | | | 20 | 10 |
| 6 | 3 | 6 | 7 | 5 | 3 | 3 | 7 | 6 | 4 | 6 | 6.5 | 5.0 | 3.0 | 1.5 | | 6.0 | 3.5 | 6.0 | | 5 | | 15 | | |
| 4 | 4 | | 7 | 5 | 5 | | 7 | 6 | 3 | | 6.5 | 5.5 | 5.5 | | 6.5 | 5.0 | 3.5 | | 7 | 15 | | | 23 | 7 |
| | | | 6 | 3 | | | | | | | 6.0 | 1.5 | | | | | | | 8 | | | | 20 | 10 |
| | | | 6 | 4 | | | | | | | 5.5 | 3.0 | | | | | | | 10 | | | | 19 | 10 |

| PSPPPRE | PTPPRE | HUNG | TOTALPRE | APPTMID | PSPMID | PSPPMID | PTPMID | HUNG1 | TOTALMID | APPTPOST | PSPPOST | PSPPPOST | PTPPOST | HUNG2 | TOTALPOS | APPT3MON |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 27 | 30 | 93 | 14 | 6 | 7 | 17 | 22 | 66 | 11 | 4 | 7 | 15 | 22 | 59 | 16 |
| 9 | 31 | 37 | 99 | 6 | 4 | 7 | 13 | 15 | 45 | 15 | 6 | 10 | 25 | 37 | 93 | 11 |
| 11 | 21 | 36 | 96 | 20 | 10 | 10 | 25 | 40 | 105 | 19 | 8 | 13 | 28 | 13 | 81 | |
| 9 | 32 | 40 | 118 | 16 | 3 | 9 | 22 | 38 | 88 | 17 | 10 | 7 | 23 | 29 | 86 | 21 |
| 7 | 27 | 38 | 107 | 22 | 10 | 8 | 25 | 34 | 99 | 18 | 5 | 7 | 23 | 35 | 88 | 18 |
| 8 | 29 | 35 | 104 | 17 | 12 | 7 | 21 | 25 | 82 | 19 | 10 | 8 | 20 | 23 | 80 | 15 |
| 11 | 36 | 37 | 100 | 19 | 13 | 7 | 24 | 26 | 89 | 24 | 12 | 11 | 25 | 26 | 98 | 23 |
| 8 | 28 | 38 | 106 | 18 | 12 | 7 | 14 | 30 | 81 | | | | | | | |
| 8 | 20 | 26 | 72 | 22 | 6 | 10 | 25 | 38 | 101 | 17 | 6 | 9 | 25 | 30 | 87 | 19 |
| 6 | 21 | 38 | 97 | 16 | 8 | 9 | 23 | 32 | 88 | 12 | 10 | 10 | 21 | 30 | 83 | 20 |
| 7 | 26 | 21 | 81 | 16 | 15 | 6 | 21 | 35 | 93 | 18 | 13 | 7 | 21 | 29 | 88 | |
| 9 | 21 | 35 | 88 | 14 | 5 | 11 | 19 | 28 | 77 | 15 | 5 | 12 | 18 | 23 | 73 | 19 |
| 7 | 20 | 33 | 97 | 24 | 9 | 7 | 25 | 28 | 93 | 16 | 10 | 7 | 25 | 25 | 83 | 16 |
| 10 | 22 | 35 | 95 | 13 | 9 | 10 | 18 | 13 | 63 | 19 | 5 | 8 | 20 | 27 | 79 | 21 |
| 12 | 28 | 29 | 104 | 16 | 6 | 11 | 18 | 31 | 82 | 26 | 4 | 10 | 24 | 34 | 98 | 12 |
| 4 | 21 | 31 | 85 | 22 | 10 | 4 | 20 | 28 | 84 | 18 | 10 | 7 | 23 | 16 | 74 | |
| 6 | 19 | 30 | 85 | 20 | 7 | 3 | 19 | 40 | 89 | 17 | 8 | 6 | 21 | 32 | 84 | |
| | | | | 14 | 15 | 4 | 20 | 29 | 82 | 17 | 10 | 7 | 19 | 25 | 78 | 21 |
| 3 | 20 | 34 | 87 | 19 | 10 | 10 | 25 | 26 | 90 | 18 | 11 | 7 | 22 | 35 | 93 | |
| 10 | 19 | 33 | 92 | 17 | 11 | 12 | 23 | 27 | 90 | | | | | | | |
| 7 | 24 | 34 | 94 | 21 | 9 | 10 | 19 | 25 | 84 | | | | | | | |

| PSP3MONT | PSPP3MON | PTP3MONT | HUNG3 | TOTAL3MO | DOSE | CYCLES | meantotal dose phase 1 | mean total dose phase 2 | MEANOLFACTORYREGIONDOSEcGy | MEANOLFACTORYREGIONVOLUME - 2 | MEANOLFACTORYREGIONVOLUME 1 | MEANOLFACTORYREGIONVOLUME 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | 7 | 20 | 29 | 80 | 66 | 33 | 6718 | | 2,820.3 | 42.7 | | |
| 6 | 11 | 18 | 21 | 67 | 66 | 33 | 5,625.2 | 6,697.1 | 6,735.4 | 102.2 | 101.5 | |
| | | | | | 70 | 35 | 6,848.5 | 7,037.5 | 601.4 | 0.1 | 7.9 | |
| 7 | 7 | 27 | 33 | 95 | 66 | 33 | 6701.3 | | 5,432.9 | 82.3 | | |
| 9 | 6 | 28 | 35 | 96 | 60 | 30 | 6131.7 | | 6,165.0 | 102.8 | | |
| 10 | 7 | 22 | 41 | 95 | 66 | 33 | 6674.9 | | 5,782.2 | 87.6 | | |
| 12 | 10 | 29 | 32 | 106 | 70 | 35 | 6,254.0 | 7,106.2 | 294.9 | 0.0 | 2.9 | |
| | | | | | 70 | 33 | 7097.1 | | 2,777.0 | 39.7 | | |
| 6 | 9 | 23 | 33 | 90 | 70 | 35 | 5,717.0 | 7,101.8 | 373.7 | 0.0 | 2.6 | |
| 8 | 10 | 27 | 39 | 104 | 70 | 33 | 7132.1 | | 5,837.1 | 83.4 | | |
| | | | | | 63 | 30 | 6070.7 | | 6,139.9 | 102.3 | | |
| 7 | 9 | 21 | 45 | 101 | 70 | 33 | 7079.6 | | 3,788.5 | 63.8 | | |
| 7 | 7 | 25 | 25 | 80 | 66 | 33 | 6,318.8 | 7,084.8 | 5,962.1 | | 82.4 | |
| 7 | 8 | 23 | 30 | 89 | 70 | 33 | 7159.5 | | 2,375.0 | 33.9 | | |
| 8 | 10 | 23 | 37 | 90 | 70 | 35 | 7110.9 | | 2,162.9 | 30.9 | | |
| | | | | | 70 | 33 | 7158.8 | | 3,405.3 | 48.7 | | |
| | | | | | 66 | 33 | 6606.2 | | 6,559.8 | 99.4 | | |
| 4 | 8 | 17 | 39 | 84 | 70 | 35 | 6748.4 | | 1,664.9 | 28.0 | | |
| | | | | | | | 7013 | | 5,690.0 | 95.8 | | |
| | | | | | | | 7036.9 | | 1,414.6 | 20.2 | | |
| | | | | | | | 7106.2 | | 162.5 | 2.3 | | |