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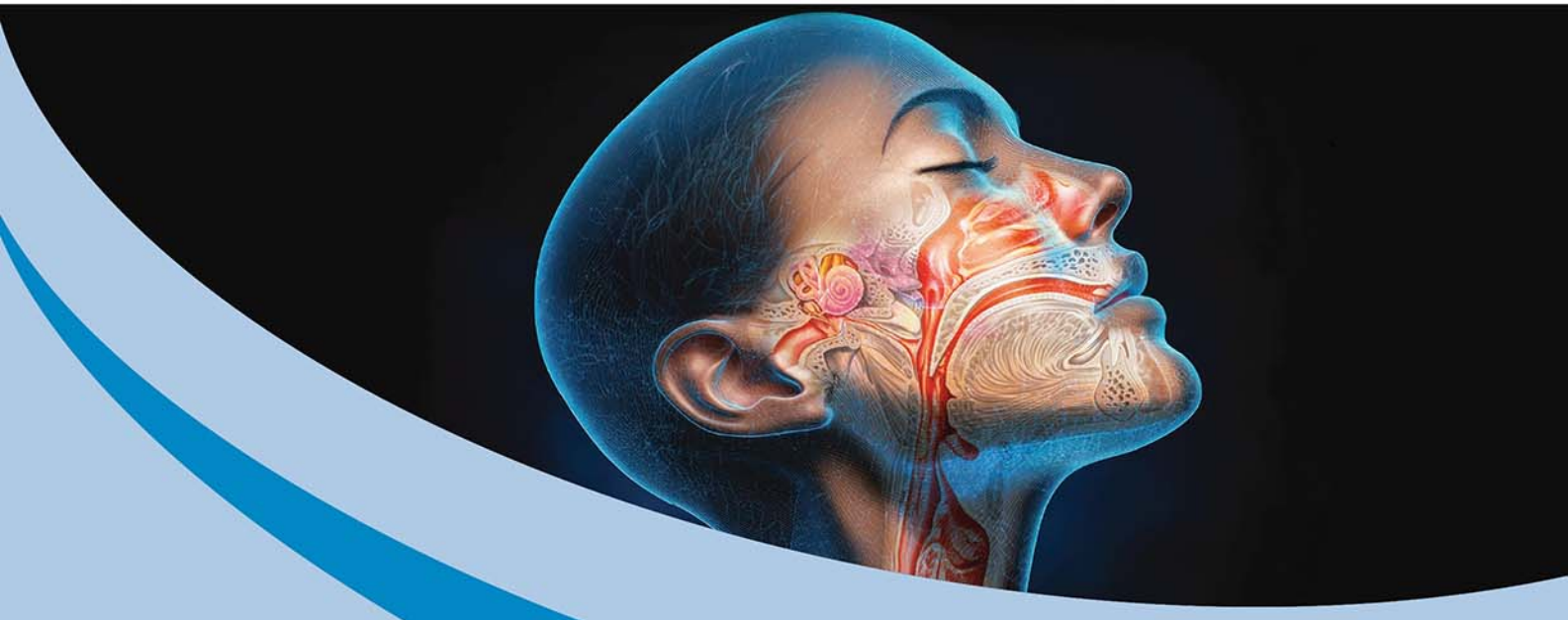

Solved Papers
Otorhinolaryngology
for PG Students

A must for MS, DLO & DNB Students

Last 20 years Questions from several Universities like AIIMS, PGI Chandigarh, DNB, RGUHS, KUHS, WBUHS, Tamil Nadu MGRMU, MUHS, NTRUHS, Bharati Vidyapeeth Pune, etc.

Tithi Debnath • Subhadeep Chowdhury

Foreword **Professor (Dr) Sumit Kumar Basu**

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SECTION 11

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CHAPTER 38

Recent Advance, General and Miscellaneous

Q. Newer modes of radiotherapy

MUHS 2016, PGI 2022, WBUHS 2008, 2020, NTRUHS 2014, DNB APR 2016, DNB JUN 2017, KUHS NOV 2014, OCT 2019, NOV 2021, TNMGRMU NOV 2001, MAR 2002, MAY 2011, APR 2013, 2016, 2024, DEC 2023

Q. Minimal invasive video-assisted thyroidectomy

WBUHS 2015, DNB JUN 2019

MIVAT (Minimally Invasive Video-Assisted Thyroidectomy)

Overview:

MIVAT is a surgical technique that has gained popularity for thyroidectomy procedures due to its minimally invasive nature. It is also known as Miccoli's technique.

Principles:

- **Adequate exposure:** Ensuring clear and unobstructed visibility of the surgical area.
- **Proper retracting:** Effective use of retractors to hold back tissues and provide better access to the thyroid.
- **Optimal lighting:** Utilizing adequate lighting to illuminate the surgical field for precision.

Procedure:

- **Incision:** A small 2–3 cm midline incision is made.
- **Endoscopic dissection:** The superior pole of the thyroid gland is dissected endoscopically.
- **Delivery:** The thyroid is gently delivered into the neck.
- **Completion:** The dissection of the lower pole and completion of the thyroidectomy are done conventionally.

Advantages:

- **Small incision:** The small incision reduces scarring and recovery time.
- **Avoiding complications:** The technique avoids potential complications related to insufflation (introducing gas into the surgical site).
- **Excellent visualization:** Provides excellent visualization of the recurrent laryngeal nerve (RLN), external laryngeal nerve, and parathyroid glands, reducing the risk of injury.

Indications:

- **Nodule size:** Suitable for nodules up to 3 cm in size.
- **Selected Graves' disease:** Can be used in specific cases of Graves' disease.
- **Total thyroid volume:** The total thyroid volume should not exceed 20 mL for this technique.

Disadvantages:

- **Requires two competent assistants:** The procedure requires two skilled assistants to ensure success.
- **Video stacks:** Dependence on video stacks and equipment, which may not always be available.
- **Hypopigmentation and hypertrophy:** Potential risks include skin changes like hypopigmentation and tissue hypertrophy around the incision area.

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Contraindications:

- **Thyroiditis:** Inflammation of the thyroid gland (thyroiditis) may complicate the procedure.
- **Cancer or previous surgery:** Patients with thyroid cancer or a history of previous neck surgery may not be ideal candidates for this technique.

Q. Cryosurgery in ENT

WBUHS 2009, KUHS MAY 2022

Q. Cryotherapy

WBUHS 2009, KUHS MAY 2022

Cryotherapy involves the selective exposure of tissue to extreme cold to destroy or eliminate abnormal tissue. It is used in various medical fields for treating benign and malignant lesions.

Methods:

- **Open method:** Utilizes liquid nitrogen spray or CO_2 snow to directly freeze the targeted tissue.
- **Closed system:** Uses cryoprobes and operates based on the Joule-Thompson effect, where rapid expansion of gas through a small hole produces cooling, reaching temperatures of –70°C or below. Common gases used include liquid nitrogen (N_2), nitrous oxide (N_2O), or carbon dioxide (CO_2).

Mechanism:

- **Dehydration:** The freezing process causes dehydration of the cells, leading to an increase in electrolyte concentration. The pH of the medium also changes, causing toxic concentrations of urea and dissolved gases, which result in cell death.
- **Denaturation:** The freezing and subsequent thawing make cell membranes permeable to cations, causing cell lysis.
- **Thermal shock:** Rapid cooling disrupts the respiratory functions of cells, contributing to cell death.
- **Vascular stasis:** The arterial and venous supply is occluded, leading to an ischemic infarct, which further aids in tissue destruction.
- **Cryoimmunization:** Exposure to cryotherapy can sometimes stimulate an immune response, with the production of autoantibodies specific to the treated tissue.

Technique:

- **Anesthesia:** Depending on the size and location of the lesion, either local or general anesthesia may be used. In some cases, anesthesia is not required as the cold can numb the area.
- **Procedure:**
  - The area to be frozen is isolated, and a suitable cryoprobe is applied to or inserted into the tissue.
  - The tissue is quickly frozen for 3–8 minutes and then allowed to thaw slowly.
  - This freeze-thaw cycle is typically repeated one or two more times.
  - It is crucial to include a margin of normal tissue around the lesion to ensure complete treatment.
  - A thermocouple can be implanted to monitor the temperature and ensure adequate freezing depth.

Uses of cryotherapy:

- **Benign vascular lesions:**
  - *Hemangioma:* Commonly treated in areas such as the skin, oral cavity, or oropharynx.
  - *Adjunct treatment:* Used alongside other treatments for vascular tumors like angiofibroma and glomus tumors.
- **Premalignant lesions:**
  - *Leukoplakia:* Treated in areas such as the cheek, tongue, and floor of the mouth.
  - *Solar keratosis:* Effective for treating solar keratosis on the skin, a precancerous condition caused by sun damage.
- **Malignant lesions:**
  - *Bowen's disease:* A type of skin cancer that can be treated with cryotherapy.
  - *Basal cell carcinoma:* Cryotherapy can be used to treat superficial basal cell carcinoma.

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  - *Primary malignant lesions of the oral cavity and oropharynx:* Limited to early-stage cancers where the lesion is well-defined and accessible.
  - *Recurrent or residual cancer:* Used palliatively in advanced cancer cases where other treatments, like a second course of radiation, are not advisable.
- **Other uses:**
  - *Nasal turbinate reduction:* Helps reduce the size of nasal turbinates, providing relief from nasal obstruction.
  - *Allergic rhinitis:* Used to shrink inflamed nasal tissues and alleviate symptoms.
  - *Tonsil reduction:* An alternative to traditional tonsillectomy, particularly in cases of hypertrophy or chronic infection.

Advantages of cryotherapy:
- **Suitable for high-risk patients:** Can be used with local anesthesia or even without anesthesia, making it suitable for patients with high surgical risk.
- **Bleeding disorders:** Particularly useful for patients with bleeding disorders as the procedure minimizes blood loss.
- **Multiple or recurrent cancers:** Effective for palliative treatment when further radiation is not recommended.
- **Minimal pain and discomfort:** Generally associated with low levels of pain and discomfort during and after the procedure.
- **Minimal scarring:** Often results in minimal scarring compared to other surgical procedures.
- **Outpatient procedure:** This can be performed on an outpatient basis, reducing the need for hospital stays.

Disadvantages of cryotherapy:
- **No tissue for biopsy:** Does not provide tissue samples for histological examination, which is critical for definitive diagnosis and staging.
- **Difficulty in assessing margins:** It can be challenging to determine if all the abnormal tissue has been removed.
- **Control over freezing depth:** Limited control over the depth of freezing, which can result in incomplete treatment or damage to surrounding healthy tissue.
- **Depigmentation and hair loss:** There may be cosmetic changes like skin depigmentation or hair loss in the treated area.
- **Anesthesia required near nerves:** Anesthesia may be necessary if the lesion is close to a nerve to prevent pain during the procedure.

Q. Polysomnography

WBUHS 2009, RGUHS 2004, TNMGRMU OCT 2022

Introduction
- Polysomnography (PSG), a term proposed by Holland Dement and Raynal in 1974, is a comprehensive test used primarily for diagnosing *obstructive sleep apnea syndrome (OSAS)*.
- It involves the simultaneous recording of multiple physiological parameters related to sleep and wakefulness, providing a detailed overview of the patient's sleep patterns and any disturbances.

Indications for Polysomnography
- *Sleep-related breathing disorders:* Essential for diagnosing conditions like obstructive sleep apnea (OSA).
- *CPAP titration in OSA:* Used to determine the optimal level of continuous positive airway pressure (CPAP) therapy in patients with OSA.
- *Assessment of treatment results:* Evaluates the effectiveness of interventions for sleep-related disorders.
- *Sleep-related behavioral disorders:* Helps in diagnosing unusual behaviors during sleep, such as atypical parasomnias.
- *Narcolepsy and neuromuscular disorders:* Assesses sleep patterns and symptoms related to these conditions.
- *Paroxysmal arousal or seizure phenomena:* Identifies abnormal brain activity during sleep.
- *Periodic limb movements and parasomnias:* Monitors limb movements and sleep disorders that do not respond to conventional therapy.

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Patient Evaluation and Instructions

- *Initial assessment:*
  - Involves taking a detailed medical and psychiatric history, including an assessment of medications, smoking, alcohol use, and daily activities.
  - Sleep history for the last 24 hours is reviewed using tools like the *Stanford Sleepiness Scale, Epworth Sleepiness Scale,* and *Pittsburgh Sleep Quality Index (PSQI)*.
- *Patient instructions:*
  - Patients are advised to report to the sleep lab one hour before their usual sleep time and to visit the lab beforehand to become familiar with the environment.
  - They should have a relaxed day, avoiding naps, strenuous exercise, caffeine, and alcohol on the day of their studies.
  - Patients are encouraged to continue their usual medications, including sleep aids, unless otherwise directed, and any medication use should be recorded by the technician.

Components of Polysomnography

- *Electroencephalography (EEG):*
  - Used to differentiate between wakefulness and various sleep stages.
  - A minimum of three channels is recommended to record electrical activity from different brain regions.
- *Electro-oculography (EOG):*
  - Monitors eye movements, which helps in identifying rapid eye movement (REM) sleep and other eye-related sleep phenomena.
  - Electrodes are placed near the eyes to capture vertical and horizontal movements.
- *Electromyography (EMG):*
  - Assesses muscle activity to determine sleep stages and diagnose parasomnias.
  - Includes chin EMG channels for monitoring facial muscles and leg EMG channels for detecting periodic limb movements.
- *Respiratory monitoring:*
  - Involves assessing upper airway airflow, thoracoabdominal movement, intrathoracic pressure, and snoring.
  - Tools include oronasal thermal devices, nasal prongs with pressure transducers, and respiratory inductive plethysmography.
- *Snoring monitors and intrathoracic pressure monitoring:* Snoring is recorded using a microphone placed on the neck, and intrathoracic pressure is measured with an endoesophageal pressure probe to detect heightened respiratory effort.
- *Capnography and oxygen saturation:* Measures expired carbon dioxide levels and continuous oxygen saturation, respectively, to evaluate respiratory function during sleep.
- *Electrocardiogram (ECG):* Detects cardiac abnormalities that may occur during sleep, such as sinus arrhythmia, extra systoles, and nocturnal angina.
- *Body position monitoring:* Tracks body position throughout the night using sensors to determine if position affects sleep abnormalities.

Types of Polysomnography

Polysomnography (PSG) is classified into different types based on the complexity of the monitoring systems and the environment where the study is conducted. Each type has specific uses, advantages, and limitations.

Level I Polysomnography: In-laboratory, attended polysomnography

- *Description:*
  - This is the *gold standard* for sleep studies, conducted in a sleep laboratory setting.
  - It is an *attended study*, meaning a sleep technician is present throughout the night to monitor the patient and ensure data accuracy.

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- *Parameters monitored:*
  - Comprehensive monitoring including EEG (brain activity), EOG (eye movements), EMG (muscle activity), ECG (heart activity), respiratory parameters (airflow, oxygen saturation, snoring, and respiratory effort), and body position.
  - Additional monitoring may include capnography (CO2 levels), video recording, and esophageal pressure measurements.
- *Advantages:*
  - Provides a *thorough and detailed analysis* of sleep architecture and associated disorders.
  - Ideal for diagnosing complex sleep disorders such as obstructive sleep apnea (OSA), narcolepsy, REM sleep behavior disorder, periodic limb movement disorder, and other parasomnias.
  - Allows for *continuous observation* and immediate response to emergencies, such as severe apneas or cardiac arrhythmias.
- *Limitations:*
  - High cost due to the need for specialized equipment and trained personnel.
  - Requires the patient to sleep in a potentially unfamiliar environment, which can impact sleep quality and results (*first-night effect*).

Level II Polysomnography: Unattended, comprehensive polysomnography

- *Description:*
  - Similar to Level I PSG in terms of parameters monitored, but conducted outside the sleep lab, typically at the patient's home.
  - It is an *unattended study*, meaning there is no technician present during the recording.
- *Parameters monitored:*
  - Almost identical to Level I, including EEG, EOG, EMG, ECG, respiratory parameters, and body position. However, the setup is simplified for home use.
- *Advantages:*
  - It is more convenient and comfortable for the patient as it is done in their own home.
  - Less expensive than in-laboratory studies and avoids the first-night effect associated with sleeping in a lab.
- *Limitations:*
  - Data quality may be compromised without a technician adjusting equipment and monitoring the patient.
  - Less control over the environment leading to potential issues with data reliability.

Level III Polysomnography: Limited channel portable monitoring

- *Description:*
  - Known as *cardiorespiratory sleep studies*, these are performed at home and focus mainly on respiratory parameters.
  - Does not typically include EEG, so it does not measure sleep stages directly.
- *Parameters monitored:* Generally, it includes oxygen saturation, heart rate, airflow through the nose or mouth, and respiratory effort using belts around the chest and abdomen.
- *Advantages:*
  - Easy to use and relatively inexpensive, making it accessible for screening large numbers of patients.
  - Useful for diagnosing moderate to severe OSA in high-risk patients without the need for a full sleep study.
- *Limitations:*
  - Cannot differentiate between sleep and wake states due to the lack of EEG; thus, sleep architecture cannot be assessed.
  - Risk of missing or underestimating other sleep disorders that require EEG or more comprehensive monitoring.

Level IV Polysomnography: Continuous single or dual channel recording

- *Description:*
  - Simplest form of polysomnography, often used for initial screening of sleep disorders, particularly sleep apnea.
  - Typically involves only one or two channels of recording, such as pulse oximetry or airflow measurement.

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- *Parameters monitored:* Usually limited to oxygen saturation (SpO2) and pulse rate. Some devices may also measure airflow or snoring.
- *Advantages:*
  - Extremely portable and easy to use, suitable for preliminary assessment or follow-up evaluations.
  - Low cost and can be used in any setting, including home or a primary care office.
- *Limitations:*
  - Provides very limited data, insufficient for a comprehensive diagnosis of sleep disorders.
  - Not suitable for patients with complex sleep disorders or those needing detailed analysis of sleep architecture and other physiological parameters.

Limitations of Polysomnography
- *First-night effect:* Reduced sleep efficiency and increased awakenings due to unfamiliar surroundings.
- *Technological dependence:* The quality of results is highly dependent on the technology used and the technician's expertise.
- *Episodic disorders:* Some disorders, like seizures or parasomnias, may not be captured in a single night's study.
- *Night-to-night variability:* Variations in nasal patency, body position, or environmental factors can affect the results, potentially underestimating the severity of conditions like OSA.

Q. Intensity-modified radiotherapy

PGI 2022, AIIMS 2011, WBUHS 2009, 2010, NTRUHS 2017, DNB JUN 2016, DNB DEC 2021, KUHS NOV 2013, APR 2018, OCT 2018, DEC 2020, JULY 2023, RGUHS 2015, TNMGRMU MAY 2017, OCT 2018, JUL 2021

Overview
- *Type:* Conformal radiotherapy.
- *Function:* Shapes radiation beams to fit the cancer area closely.
- *Machine used:* Standard radiotherapy machine called a linear accelerator (LINAC).

Mechanism
- **Multileaf collimator:**
  - Device in LINAC made of thin lead leaves that move independently.
  - Shapes radiation beams to fit the treatment area precisely.
  - Moves around the patient, adjusting the beam shape and intensity.
- **Radiation delivery:**
  - The tumor receives a high dose while the nearby healthy cells get a lower dose.
  - Each beam is divided into many small beamlets, varying radiation intensity across the tumor.
- **Applications:** Useful in head and neck areas to avoid critical structures like the spinal cord and salivary glands.

Planning IMRT
- **Initial scans:**
  - It begins with a CT scan, possibly including MRI or PET scans.
  - Scan data feeds into the radiotherapy planning computer.
- **Treatment planning:**
  - The treatment team uses advanced computerized calculations to plan.
  - Finds dose strength pattern matching the tumor shape.
  - Planning may take longer compared to other types of radiotherapy.
- **Skin markings:** Radiographers may make marks on the skin as reference points for accuracy in each session.
- **Masks and molds:**
  - Patients needing head or neck radiotherapy may wear a mask (also called a shell or mold).
  - Masks and molds ensure the treatment area remains completely still for accuracy.

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- **Waiting period:** After planning, there may be a waiting period of a few days to two weeks before treatment starts.
- **Treatment setup:**
  - Patient lies on a radiotherapy couch.
  - Radiographers position the patient and attach any necessary molds.
- **Treatment machines:** LINAC or other types like tomotherapy (combines CT scanning with IMRT).
- **Radiographers' role:**
  - Radiographers leave the room during treatment to avoid radiation exposure.
  - X-rays may be taken before treatment (*image-guided radiotherapy* or *IGRT*) to ensure correct positioning.
  - Radiographers monitor the patient via CCTV and communicate through an intercom.
- **Treatment experience:** Radiotherapy itself is painless and typically takes 15–30 minutes.

Volumetric Modulated Arc Radiotherapy (VMAT) or Rapid Arc:
- **Definition:** A type of IMRT where the machine rotates around the patient in an arc shape.
- **Features:**
  - Continuous reshaping and intensity change of the radiation beam.
  - Increases accuracy, shortens treatment time, and uses a lower overall dose of radiation.
  - Treatment usually takes about 10 minutes.

Tomotherapy:
- **Definition:**
  - A type of IMRT where the patient lies on a couch that moves through a donut-shaped machine.
  - The machine's radiation source rotates in a spiral pattern (*helical tomotherapy*).

Complications:
- **Early complications:**
  - *Radiation sickness:* Nausea and vomiting due to radiation exposure.
  - *Mucositis:* Inflammation and ulceration of the mucous membranes.
  - *Xerostomia:* Dry mouth due to reduced saliva production.
  - *Skin reaction:* Redness and irritation of the skin.
  - Laryngeal edema.
  - Candidal infection.
  - *Bone marrow suppression:* Decreased production of blood cells.
  - *Acute transverse myelitis:* Inflammation of the spinal cord.
- **Late complications:**
  - *Permanent xerostomia:* Long-term dry mouth.
  - *Skin changes:* Subcutaneous fibrosis (thickening and scarring of connective tissue).
  - *Tooth decay:* Increased risk of dental caries.
  - Osteoradionecrosis.
  - Cartilage necrosis.
  - Trismus.
  - Transverse myelitis.
  - *Radiation retinopathy:* Damage to the retina from radiation, potentially leading to cataracts.
  - Endocrine deficits.
  - Sensorineural hearing loss.
  - Radiation-induced malignancy.
  - *Brain injury:* Potential cognitive and neurological deficits resulting from radiation to the brain.

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Q. Oncogenes

PGI 2022, AIIMS 2012, WBUHS 2010, DNB (DEC & JUN) 2013, DNB DEC 2021, KUHS JUN 2020, TNMGRMU OCT 1997, 2019, DEC 2023

Definition

- Oncogenes are mutated forms of normal cellular genes known as *proto-oncogenes*. These genes play crucial roles in regulating normal cell growth and differentiation.
- When proto-oncogenes become oncogenes due to mutations, their function becomes aberrant, leading to the uncontrolled proliferation of cells, which is a hallmark of cancer.

Mechanisms of oncogene activation

- **Gene amplification:**
  - Leads to an *increase in the number of gene copies*.
  - Results in *overproduction of the encoded protein*, enhancing its effect in promoting cell growth and proliferation.
  - *Example: EGFR (Epidermal Growth Factor Receptor)* amplification causes excessive cell signaling that promotes cancer cell growth.
- **Activating mutations:**
  - Mutations in proto-oncogenes can result in *constitutively active proteins* that are always "turned on."
  - These mutations cause the protein to function independently of normal regulatory signals.
  - *Example:* Mutations in the *RAS* gene family lead to proteins that continuously activate downstream signaling pathways, driving uncontrolled cell proliferation.
- **Chromosomal translocations:**
  - Involves the *rearrangement of genetic material* between nonhomologous chromosomes.
  - Creates *fusion genes* that encode abnormal proteins with oncogenic properties.
  - *Example*: *BCR-ABL* fusion gene, created by a translocation between chromosomes 9 and 22, produces a continuously active tyrosine kinase, promoting leukemia development.
- **Gain of function mutations**:
  - Specific mutations that *enhance the normal function* of a proto-oncogene.
  - Results in *overactive signaling pathways* that lead to increased cell division and survival.
  - *Example: PIK3CA* mutations enhance the PI3K/AKT pathway, promoting cancer cell growth and survival.
- **Noncanonical pathway activation:**
  - Oncogenes can activate *alternative signaling pathways* that are not their typical targets.
  - This mechanism allows cancer cells to *bypass normal regulatory mechanisms*.
  - *Example: GLI* gene amplification leads to activation of noncanonical signaling pathways, contributing to cancer development.
- **Overexpression:**
  - Oncogenes can be *overexpressed due to regulatory changes* that increase their transcription or translation.
  - Results in *excessive amounts of protein* that drive oncogenic signaling.
  - *Example:* Overexpression of *HER2* in breast cancer leads to increased signaling through the HER2 pathway, promoting aggressive tumor growth.

Examples of oncogenes and their mechanisms

- **EGFR (Epidermal Growth Factor Receptor):**
  - *Mechanism:* Amplification, activating mutations, overexpression.
  - *Associated cancers:* Head and neck squamous cell carcinoma (HNSCC >80%), nonsmall cell lung cancer (NSCLC 40%), ovarian cancer (>30%), and breast cancer (14–91%).
- **SMO (Smoothened Homolog):**
  - *Mechanism:* Mutations in the SMO M1/2.
  - *Associated cancers:* Medulloblastoma (MB).

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- **GLI (Glioma-associated oncogene homolog):**
  - *Mechanism:* Gene amplification, noncanonical pathway activation, activating mutations.
  - *Associated cancers:* Gliomas (>50%), some sarcomas.
- **RAS Family (KRAS, NRAS, HRAS):**
  - *KRAS:* Somatic gain of function mutation.
    - *Associated cancers:* Pancreatic cancer (57%), gastrointestinal cancer (33%), lung cancer (26%).
  - *NRAS:* Somatic gain of function mutation.
    - *Associated cancers:* Skin cancer (18%), nervous system tumors (17%).
  - *HRAS:* Somatic gain of function mutation.
    - *Associated cancers:* Salivary gland tumors (15%), urinary tract tumors (10%).
- **RAF Family (BRAF, CRAF, ARAF):**
  - *BRAF:* Somatic activating mutation (e.g., V600E).
    - *Associated cancers:* Nervous system tumors (57%), melanoma (50%), thyroid cancer (38%), colorectal cancer (>15%).
  - *CRAF:* Activating mutation, somatic, rare.
    - *Associated cancers:* Liver cancer (unknown).
  - *ARAF:* Mutation.
    - *Associated cancers:* Ovarian cancer (4%).
- **MET (Mesenchymal-Epithelial Transition Factor):**
  - *Mechanism:* Gene amplifications (somatic > germline) and gain of function mutation.
  - *Associated cancers:* Nonsmall cell lung cancer (NSCLC 10–20%).
- **AKT1 (AKT Serine/Threonine Kinase 1):**
  - *Mechanism:* Somatic activating mutation.
  - *Associated cancers:* Thyroid, small cell lung cancer (SCLC), ovarian cancer, breast cancer (4%).
- **PI3K (Phosphoinositide 3-Kinase):**
  - *Mechanism:* PIK3CA mutation.
  - *Associated cancers:* HNSCC (30%), breast cancer (26%), colorectal cancer (20%).

Impact of oncogene activation on cancer development

- The activation of oncogenes results in the *constitutive activation of downstream signaling pathways* that regulate cell proliferation, survival, migration, and angiogenesis.
- This leads to the transformation of normal cells into cancerous cells and contributes to tumor growth and metastasis.
- Oncogene activation often disrupts the delicate balance between cell death and survival, favoring tumorigenesis.
- *Example:* Mutations in the *RAS* family genes disrupt normal cell signaling and lead to uncontrolled growth and division.

Functions of Oncogenes

- **Promotion of cell growth and proliferation:**
  - Oncogenes enhance signals that promote cell progression, leading to increased cell division and proliferation.
  - They help cells bypass normal growth control mechanisms, allowing for continuous growth.
- **Inhibition of apoptosis (programmed cell death):**
  - Oncogenes can activate pathways that prevent apoptosis, allowing cells with damaged DNA or oncogenic mutations to survive and proliferate.
  - This contributes to the accumulation of genetic mutations and cancer progression.
- **Activation of survival pathways:**
  - Oncogenes activate signaling pathways that enhance cell survival under conditions that would normally induce cell death, such as nutrient deprivation or hypoxia.
  - Example: Activation of the *PI3K/AKT* pathway enhances cell survival and growth.

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- **Stimulation of angiogenesis:**
  - Oncogenes promote the secretion of factors that stimulate the formation of new blood vessels (angiogenesis), providing tumors with a blood supply to sustain growth.
  - This process supports tumor expansion and metastasis by supplying oxygen and nutrients.
- **Enhancement of cell motility and invasion:**
  - Oncogenes can induce changes in the cytoskeleton and cell adhesion properties, increasing the ability of cancer cells to move and invade surrounding tissues.
  - This facilitates metastasis, where cancer cells spread from the primary tumor site to distant organs.
- **Evasion of immune surveillance:**
  - Some oncogenes help cancer cells evade detection and destruction by the immune system.
  - They may downregulate surface molecules that are recognized by immune cells or secrete immunosuppressive factors.
- **Promotion of metabolic reprogramming:**
  - Oncogenes can alter cellular metabolism to support rapid growth and proliferation.
  - They enhance glucose uptake and glycolysis (Warburg effect), even in the presence of oxygen, to generate the energy and biosynthetic precursors needed for cell growth.
- **Regulation of gene expression:**
  - Oncogenes can influence the expression of other genes involved in cell cycle regulation, apoptosis, DNA repair, and metabolism.

They can function as transcription factors or influence signaling pathways that regulate gene expression profiles in cancer cells.

Q. Gene Therapy

MUHS 2015, AIIMS MAY 2012, 2017, NTRUHS APR 2012, 2019, TNMGRMU OCT 2018, DNB JUN 2013, DEC 2015, 2021

Introduction to gene therapy

- **Definition and purpose:** Gene therapy involves the *deliberate introduction of genetic material* into a patient's cells to treat or prevent diseases.
- **Relevance to head and neck squamous cell carcinoma (HNSCC):**
  - HNSCC arises from squamous cells in the mucosal surfaces of the upper aerodigestive tract, salivary glands, paranasal sinuses, and skin.
  - Traditional treatments like surgery, radiotherapy, and chemotherapy have maintained a 5-year survival rate of about 60%.
  - Gene therapy offers a novel approach to potentially improve survival and treatment outcomes, given the localized nature of HNSCC.

Genetic changes in cancer

- **Normal cellular regulation:** In a healthy cell, *proto-oncogenes* and *tumor suppressor genes* maintain a balance that regulates cell proliferation.
- **Oncogenic transformation:** Cancer results when there is an increase in proto-oncogene expression or a reduction in tumor suppressor gene activity, leading to uncontrolled cell growth.

Types of gene therapy

- **Corrective gene therapy:**
  - *Objective:* To block oncogene activity or replace missing or defective tumor suppressor genes.
  - **p53 gene role:**
    - *p53* is a tumor suppressor gene often mutated in cancers like HNSCC.
    - Restoring p53 function through gene therapy (e.g., *Gendicine*) can halt tumor growth and improve sensitivity to radiotherapy and chemotherapy.

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- **Antisense oligonucleotides:** Used to block oncogene expression by binding to messenger RNA (mRNA) and preventing protein production.

- **Cytoreductive gene therapy:**
  - **Objective:** Directly or indirectly kill cancer cells.
  - **Chemotherapy sensitization:**
    - Genes that convert pro-drugs into active forms selectively within tumor cells enhance chemotherapy's effectiveness.
    - Example: *Herpes simplex virus thymidine kinase (TK) gene* used with ganciclovir.
  - **Anti-angiogenic approaches:** Gene therapy can inhibit blood vessel growth that supports tumor development, effectively starving the tumor.
  - **Pro-apoptotic strategies:** Induces programmed cell death (apoptosis) specifically in cancer cells.
- **Immunomodulatory gene therapy:**
  - **Objective:** To modify the immune system's response to recognize and destroy cancer cells.
  - **Tumor antigen presentation:** Genes are introduced to express proteins that make cancer cells more recognizable to the immune system.
  - **Cytokine gene transfer:** Enhances the immune response by introducing genes that produce immune-modulating proteins.

Monitoring and evaluating gene therapy

- **Imaging techniques:** *Cross-sectional imaging* (e.g., CT, MRI) helps assess tumor response indirectly by visualizing size reduction or progression.
- **Molecular and immunohistochemical methods:** Biopsy samples analyzed for specific protein markers indicate the expression and activity of therapeutic genes.
- **Reporter gene systems:** Allow for noninvasive tracking of gene therapy in real-time, helping to monitor the distribution and effectiveness of gene delivery.

Gene delivery methods (vectors)

- **Viral vectors:**
  - Utilized for their efficiency in delivering genetic material into cells.
  - **Retroviruses and lentiviruses:** Integrate into host DNA, providing stable gene expression but with risks of insertional mutagenesis.
  - **Adenoviruses:** Remain episomal, reducing mutagenesis risk, and are capable of high expression levels in dividing and nondividing cells.
  - **Oncolytic viruses:** Engineered to selectively replicate in and destroy cancer cells while sparing normal tissues.
- **Nonviral vectors:**
  - **Physical methods:** *Direct injection, electroporation,* and *biolistics (gene gun)* introduce DNA into cells.
  - **Chemical carriers:** *Liposomes* and other nanoparticles serve as vehicles for delivering genetic material, reducing immune response but often with lower efficiency compared to viral vectors.

Challenges in gene therapy

- **Vector safety and efficiency:** Balancing the need for high-efficiency transfection with minimizing risks such as insertional mutagenesis and immune reactions.
- **Targeted delivery:** Achieving specific delivery to cancer cells while sparing normal tissues remains a key challenge.
- **Sustained therapeutic effect:** Developing methods to maintain therapeutic gene expression over time to prevent recurrence and manage chronic conditions.

Future directions

- **New vector development:** Research is ongoing to create more effective and safer vectors for gene delivery, including advances in *CRISPR-Cas9* and other gene-editing technologies.

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- **Combination therapies:** Combining gene therapy with traditional treatments like surgery, radiotherapy, and chemotherapy may enhance overall treatment efficacy.
- **Personalized medicine:** Tailoring gene therapy is based on individual genetic profiles and tumor characteristics to improve outcomes and reduce side effects.

Q. Biomaterials in ENT

PGI 2022, AIIMS 2007, WBUHS 2010, 2020, NTRUHS 2016, DNB DEC 2021, 2022, KUHS NOV 2015, 2017, APR 2018, OCT 2018, OCT 2019

Definition of biomaterials

Biomaterials are synthetic or treated materials used to *replace* or *augment* tissues and organs.

To understand biomaterials, certain factors need to be considered:

- *Biocompatibility*
- *Surface activity*
- *Structure*

Biocompatibility:

Biocompatibility is the *interaction* between the implant and the body in terms of both *local* and *systemic* reactions. These reactions can lead to *degradation* of the implant and *loss* of its function, a phenomenon known as the *biofunctionality* of the implant.

Surface activity:

Surface activity refers to the body's reaction to the implant. It can be of three types:

- *Bio-inert:* The body does not react at all to the implant material, resulting in the formation of a small fibrous capsule around the implant.
- *Bio-tolerant:* The body initially reacts to the implant as a foreign body but ceases to react after encapsulation. This leads to the formation of a fibrous capsule around the implant, sometimes with the presence of giant cells.
- *Bio-active:* The body has an *active surface reaction* to the implant material throughout its life, leading to a firm integration between the body and the implant materials.

Structure:

Biomaterials can be structurally of two types:

- *Solid:* Used when long-term use is required, such as in bone prostheses.
- *Porous:* Used when it is intended to be replaced or remodeled by soft tissue, like in middle ear reconstructions. The size of the pores affects the degradation rate of the materials; larger pores lead to faster degradation.

Types of biomaterials:

Biomaterials may be divided into three major groups:

- *Metals:* Initially used in reconstructive surgery but later declined due to their highly reactive nature, except for two metals, *gold* and *silver*, known for their inert characteristics. Today, alloys of different metals are used, such as:
  - *Cobalt-chromium alloys:* Also termed Vitallium, mainly used in maxillofacial surgery.
  - *Stainless steel:* An alloy of steel and chromium (11–30% chromium), used in middle ear surgery and maxillofacial surgery. These prostheses do not bond with the body.
  - *Titanium:* Titanium alloys are well integrated with the underlying bone, a process called *osseointegration*. Titanium implants are used in ear surgery and maxillofacial surgery.
- *Polymers:* Widely used as biomaterials, such as:
  - *Polyethylene:* Available in low-density (LDPE) and high-density (HDPE) forms.
  - *Polytetrafluoroethylene (PTFE or Teflon)*
  - *Polydimethylsiloxane (Silastic or silicone rubber):* Used due to its integrating capability.

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- *Ceramics:* These are mainly two types:
  - *Bioinert ceramics:* Such as oxide ceramics, also known as *Carborundum*. These are very hard and difficult to shape, often used in maxillofacial surgery.
  - *Bioactive ceramics:* Such as glass ceramics and calcium phosphate ceramics. They are degradable to a certain extent and used in ossicular chain reconstruction in middle ear surgery.

Complications of using biomaterials:
- *Degraded products* may cause severe allergic reactions.
- *Bacterial colonies* may be attracted by the degraded surface of biomaterials.
- Some *metallic components* released from biomaterials may induce malignancy.

Q. Functional MRI

MUHS 2010, WBUHS 2011, 2019, DNB DEC 2015, DNB JUN 2017, 2018, KUHS NOV 2013, DEC 2020, TNMGRMU OCT 2022, MAY 2019

Functional MRI (fMRI)

Definition:

Functional MRI (fMRI) is a neuroimaging procedure that measures brain activity by detecting associated changes in blood flow. It is based on the premise that cerebral blood flow and neuronal activation are coupled: when an area of the brain is in use, blood flow to that region also increases.

Mechanism:

Functional MRI utilizes the *Blood Oxygen Level Dependent (BOLD)* contrast, which exploits the differences in magnetic properties between oxygenated and deoxygenated hemoglobin. The BOLD signal is indirect and relies on the fact that:
- *Oxygenated hemoglobin (Oxy-Hb)* is diamagnetic and does not distort the magnetic field.
- *Deoxygenated hemoglobin (Deoxy-Hb)* is paramagnetic and does distort the magnetic field.

When neurons are active, they consume oxygen, and the local increase in oxygenated blood flow to these regions surpasses the amount of oxygen that the neurons use. This results in a relative decrease in deoxygenated hemoglobin, leading to a stronger MRI signal in these areas. The differences in Oxy-Hb and Deoxy-Hb are detected by the MRI scanner and are used to generate images that reflect brain activity.

How it works:
- The fMRI scanner takes a series of images of the brain in rapid succession, typically every 1–3 seconds.
- Changes in the BOLD signal are monitored to identify active brain regions.
- These images are then processed to produce a map of brain activity, with different colors representing varying levels of activity.

Applications of fMRI:
- **Tonotopic mapping:** Tonotopic mapping is the spatial arrangement of where sounds of different frequencies are processed in the brain. fMRI can be used to map these regions, which is critical in understanding auditory processing.
- **Language processing:** fMRI helps in understanding the modal presentation of language, particularly in areas like Wernicke's area, which is involved in language comprehension. It is also used to study the dominance of the left hemisphere in language processing.
- **Role of the cerebellum in hearing:** Research using fMRI has determined that the cerebellum, traditionally associated with motor control, also plays a role in auditory processing.
- **Brain plasticity and learning:** fMRI can demonstrate short-term plasticity of the brain, showing how learning and experience can lead to functional changes in the brain over short periods.
- **Drug effects on the brain:** The modality is used to study the effects of various drugs on different brain areas, providing insights into their psychosomatic effects and helping in the development of new treatments.
- **Monitoring brain injury:** fMRI can be used to monitor the brain's recovery after injury by observing changes in brain activity patterns over time.

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- **Investigating Alzheimer's disease:** In Alzheimer's research, fMRI helps in identifying early changes in brain function, contributing to early diagnosis and monitoring disease progression.
- **Emotional processing:** It can be used to find out how different emotions are processed in the brain, which has applications in both research and clinical settings.
- **Detection of malingering:** fMRI can detect malingering (faking illness) by comparing brain activity patterns with those expected in genuine cases, thus aiding in legal and clinical assessments.

Benefits:
- *Noninvasive* and does not involve radiation exposure.
- *High spatial resolution,* allowing for detailed maps of brain activity.
- Can be *repeated multiple times* for longitudinal studies.

Challenges:
- Relatively *low temporal resolution* compared to electrophysiological techniques.
- Susceptible to *motion artifacts,* requiring the subject to remain very still.
- *Data analysis* is complex and requires sophisticated computational tools.

Q. Biofilm

MUHS 2013, AIIMS 2007, AIIMS 2011, WBUHS 2011, 2019, NTRUHS 2015, KUHS APR 2018, JUN 2020, TNMGRMU 2016

Definition
- **Biofilm:** An aggregation of microorganisms in which cells are adhered to each other or a surface. These adherent cells are embedded within a self-produced matrix of extracellular polymeric substance (EPS), which consists of DNA, protein, and polysaccharides.

Biofilm formation

Biofilm formation occurs in three steps:
- **Attachment:**
  - Reversible adsorption of bacteria (seconds)
  - Irreversible attachment of bacteria (seconds to minutes)
- **Growth:**
  - Growth and division of bacteria (hours to days)
  - EPS formation (hours to days)
- **Detachment:**
  - Up to 90% of biofilm cells may detach as planktonic forms (Hall-Stoodley et al., 2004).
  - Triggered by nutrient lack, enzymes (e.g., dispersin B), or shear stress >1 dyn/cm^2.
  - Detached cells are more virulent and antibiotic-resistant, aiding infection spread.

Stages of biofilm formation:
- **Attachment stage:** Accompanied by significant changes in gene expression, resulting in a biofilm phenotype.
- **Growth stage:**
  - Recruitment of other bacteria.
  - Individual cells express quorum sensing genes in response to the environment. These genes allow bacteria to communicate and coordinate through a technique called *quorum tunneling.*
  - Initiation of EPS production.
  - Development of 3D structures of biofilm.
- **Detachment:**
  - Biofilms shed planktonic cells, leading to the potential spread of infection to adjacent sites.
  - This stage is responsible for bacterial spreading and enhances the ability to colonize new environments.

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Organisms involved:

- **Bacteria:**
  - Bacillus
  - Staphylococcus
  - E. coli
  - Pseudomonas
  - Listeria
  - Lactobacillus
- **Fungi:**
  - Candida
  - Cryptococcus
  - Pneumocystis
  - Trichosporon

Features of biofilm:

- **Resistance to external stress:** Less susceptible to UV rays, osmotic stress, and environmental fluctuations.
- **Adaptive environment:** Secretes material to create a suitable local environment for the organism.
- **Evasion of host defense:** Evades natural host defenses effectively.
- **Antimicrobial resistance:** Resists antimicrobial therapy, being 2,000 times more resistant than planktonic cells.
- **Disease contribution:** Contributes to a variety of human diseases.

Mechanisms of resistance to antimicrobial therapy:

- **Physical barriers:** The biofilm acts as a physical barrier to antimicrobial agents.
- **Absorption and disruption:** Antimicrobial agents are absorbed and disrupted within the biofilm matrix.
- **Altered growth rate:** The growth rate of organisms is altered by the exchange of genetic material within biofilm.
- **Reseeding:** The biofilm can reseed itself, contributing to persistent infections.

Biofilm in ENT (Ear, Nose, Throat):

- **Conditions associated with biofilm:**
  - Otitis media with effusion (OME)
  - Infectious cholesteatoma
  - Tonsillitis
  - Rhinosinusitis
  - Adenoiditis
  - Prosthetic device infections (e.g., ET tube, tracheostomy tube, cochlear implant, TORP, PORP)
  - Chronic osteoradionecrosis

Investigation:

- **Microscopy techniques:**
  - Electron microscopy
  - Fluorescent in situ hybridization (FISH)
  - Confocal laser scanning microscopy (CLSM)

Treatment:

- **Physical removal:** Debridement or physical removal of biofilm.
- **Electric current:** Low-level electric current can enhance the efficacy of antibiotics against biofilm.
- **Macrolides:** Use of macrolides (e.g., Clarithromycin).
- **Furanones:** Application of furanones (e.g., butenolide).
- **Topical antibiotics:** More effective against biofilm infections.
- **Laser treatment:** It can be used in methicillin-resistant *Staphylococcus aureus* (MRSA) biofilm infections.
- **Chemical agents:** Gentian violet and ferric ammonium citrate can be used.

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