K.M. SHAH DENTAL COLLEGE & HOSPITAL
Estd. 1999
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Subject: Oral Medicine and Radiology
Topic: Oral cancer- II

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LECTURE CONTENT

- Staging of oral cancer
- Management
- Complications
- References

TABLE 8-1 TNM Classification of Tumors of the Oral Cavity

T (Size of Primary Tumor)	N (Cervical Lymph Node Metastases)	M (Distant Metastases)	Staging
T1s: carcinoma in situ	N0: no node involvement detected	M0: no known metastases	Stage 1: T1 N0 M0
T1: tumor < 2 cm	N1: single ipsilateral node < 3 cm	M1: metastases present	Stage 2: T2 N0 M0
T2: tumor > 2 cm and < 4 cm	N2a: single ipsilateral node < 6 cm		Stage 3: T3 N0 M0; T1,T2, or T3 N1 M0
T3: tumor > 4 cm	N2b: multiple ipsilateral nodes > 3 cm and < 6 cm		Stage 4: T4 any N M0; any T N2 or N3 M0; any T or N, with M1
T4: tumor > 4 cm with invasion of adjacent structures (ie, through cortical bone; deep into extrinsic muscles of tongue, maxillary sinus, and skin)	N2c: bilateral or contralateral lymph nodes < 6 cm		
	N3a: ipsilateral node > 6 cm		
	N3b: bilateral nodes > 6 cm		

Reproduced with permission from American Joint Committee on Cancer. Manual for staging of cancer. 3rd ed. Philadelphia: J.B. Lippincott; 1988.

Different mode of Therapies

- **Conventional**
- Surgery
- Radiotherapy
- Chemotherapy
- Combined

- **Newer therapies**
- Photodynamic
- Immunotherapy
- Gene therapy
- Cancer vaccines
- Nanoparticles therapy
- Intralesional chemotherapy
- Intraarterial chemotherapy

TREATMENT

General Management Guidelines for H & N Cancers

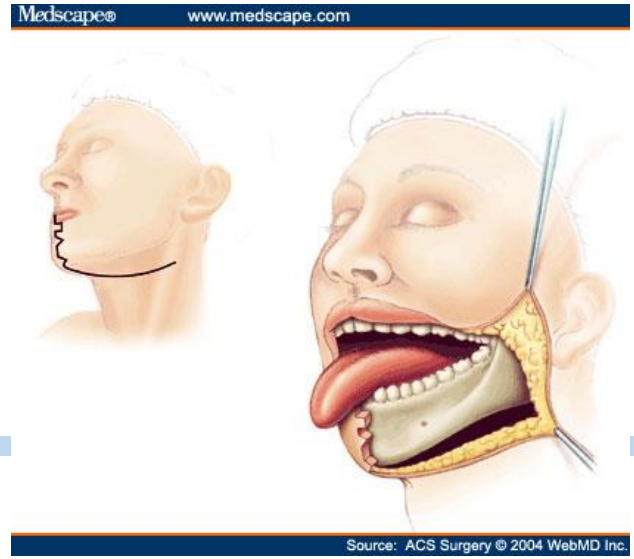
- Aim
- Highest loco- regional control
- Anatomical with functional preservation
- Stage I / II Single modality (Surgery or RT)
- Stage III / IV Combined modality
  Surgery + RT (in most patients)
  Chemotherapy + RT in selected patients

- When different modalities available, one with maximum chance of cure should be used

- When different modalities have same results, one offering better quality of life, with organ, function preservation and good cosmetic results should be used

Surgery

- **Indications**
- For tumors involving bone
- When the side effects of surgery are expected to be less significant than those associated with radiation
- for tumors that lack sensitivity to radiation
- for recurrent tumor in areas that have previously received a maximum dose of radiotherapy.



- Surgical management of clinically positive cervical nodes is the treatment of choice.

- Future advances in treatment may include
- Surgery+ systemic chemotherapy
- Immunotherapy, and there also may be advances in reconstruction.
- Radical neck dissection may be conducted as part of an en bloc resection of tumor with lymph node metastases and can be combined with radiation therapy when the primary tumor is treated by radiotherapy.

Neck dissection

- Neck dissection : cancer that has recurred in the neck.
- Tumors with node involvement due to poorer prognosis
- Surgical excision of dysplastic and malignant lesions can be accomplished with laser therapy.
- Advances: Vascularized flaps and free microvascular reconstruction

Radiation Therapy

Indications

- T1,T2 lesions –smaller lesions
- T3,T4 lesions- locally advanced lesions
- To improve operability of a primary lesions
- Close margins of resection
- Perineural/ vascular invasion
- High grade histology

Classification

- **Radical:** cure the disease
- **Palliative:** relieve symptoms
- **Adjuvant:** with surgery/ chemotherapy

Radiation Therapy mechanism

- Radiation induced damage result in cell death by damaging DNA
- Two mechanism

❖ **Direct**

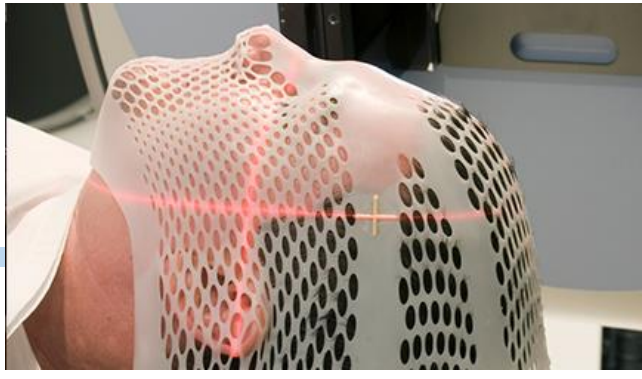
❖ Directly damage DNA

❖ Mainly proton rays (particulate radiation)

❖ **Indirect**

❖ Hydrolysis of water produces free radical – that damage the DNA

❖ Mainly by X-rays



Radiation Therapy Doses

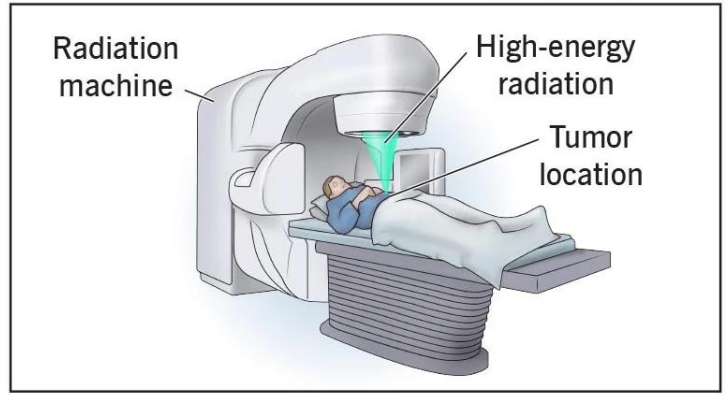
- Dose varies depend on type and stage of cancer
- **Curative dose:** Solid epithelial tumor- 65-75Gy
- Lymphomas- 20-40Gy
- **Palliative dose:** 30-40Gy
- **Adjuvant dose:** 45-60Gy

- Methods:
- **Single dose**: small epithelioma of skin
- **Multidose(Fractionation):** Allows normal cell to recover, allows tumor cell to come in radiosensitive phase from radioresistant phase, Improves patient tolerance
- Helps in repair, reoxygenation, repopulation, redistribution of cells

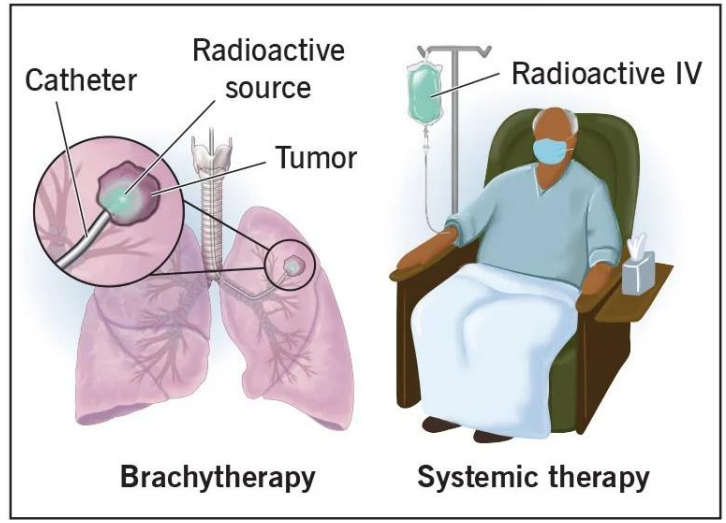
Mode of delivery of radiation therapy

- **External beam therapy/teletherapy**
- Photon therapy (x ray photon linear accelerator, gamma ray photons cobalt 60)
- Electron therapy
- Particle therapy- proton, neutron
- **Brachytherapy**
- **Newer forms**
- Three dimensional conformal radiation therapy
- Intensity-modulated radiotherapy IMRT
- Image Guided radiotherapy IGRT
- Thermo- radiotherapy
- Stereotactic radiation therapy

External beam radiation therapy (EBRT)

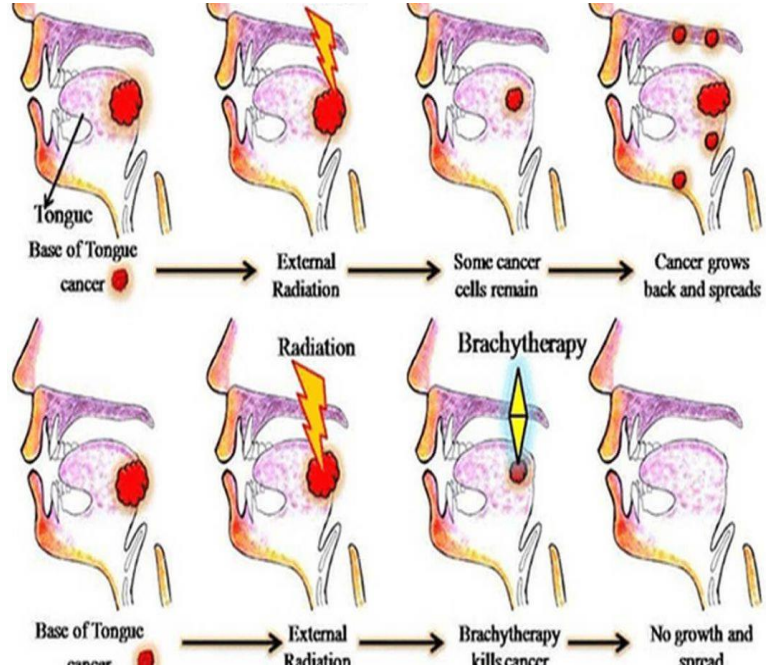


Internal radiation therapy



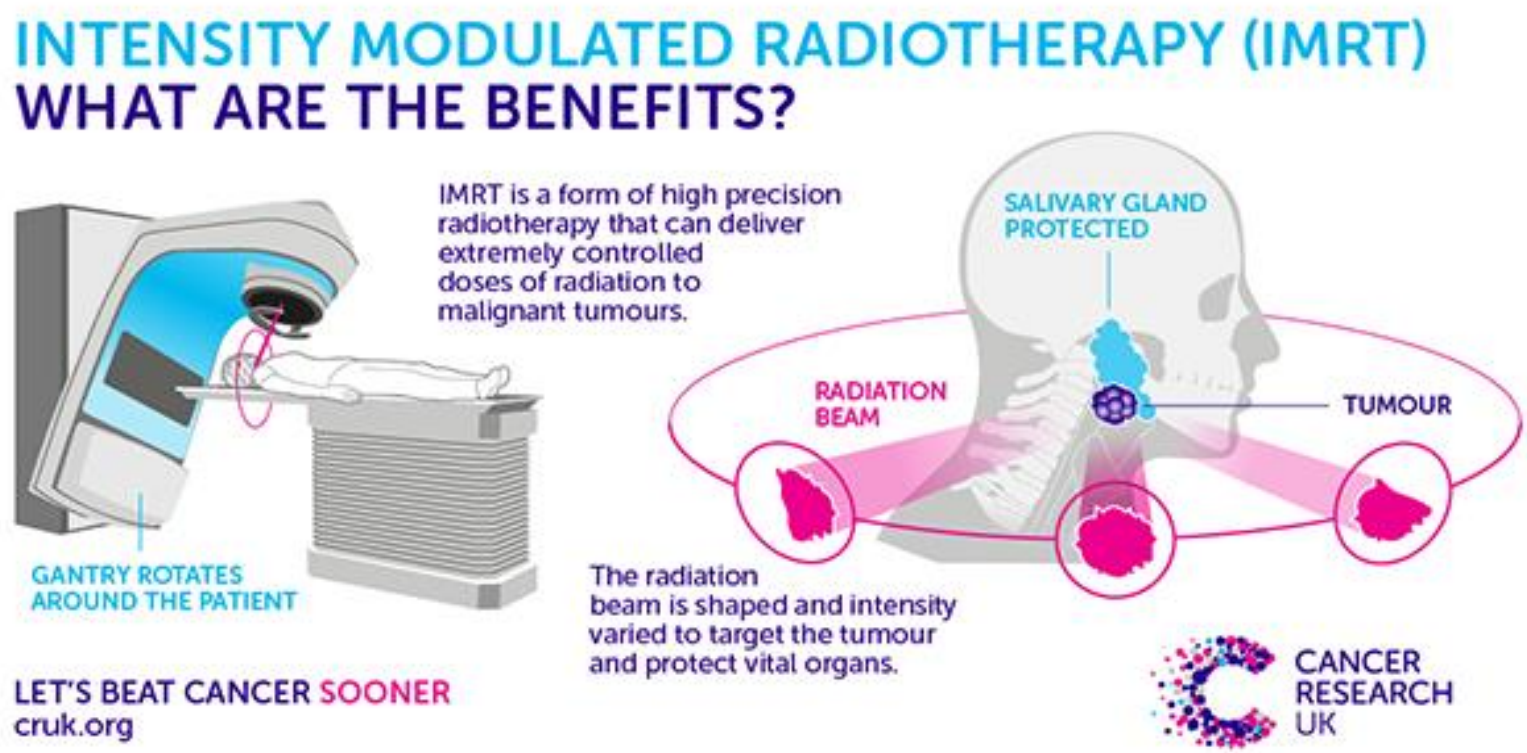
BRACHYTHERAPY (BRACHY=near)

- Radiation source is to close to the tissue being treated
- **Interstitial and Intracavitary implants** are used to treat primary cancers in the head and neck.
- Brachytherapy may the primary treatment modality for localized tumors in the **anterior two-thirds of the oral cavity,** for boosted doses of radiation to a specific site, or for treatment following recurrence.
- The isotopes used include **cesium, iridium, and gold**.
- Directly implanted sources may be used to deliver radiation, or an after loading technique may be used in which the radiation source is placed by using previously inserted guide tubes.



Intensity-modulated radiotherapy (IMRT)

- Improved mode of high-precision radiotherapy
- Utilizes computer controlled linear accelerators to deliver precise radiation doses to specific areas within the tumor.



- It allows for the radiation dose to conform to the three-dimensional shape of the tumor, by modulating or regulating the intensity of the radiation beam in multiple trivial volumes.
- This permits increased radiation doses to be focused to regions within the tumor, while decreasing the dose to surrounding normal critical structures.

Image Guided Radiotherapy (IGRT)

- Images acquired in perpendicular/orthogonal planes(2D) to confirm the position of the isocenter, as well as the distinct fields.
- These images are obtained prior to treatment.
- IGRT is used to treat Head and Neck cancers and tumors in areas of the body that are prone to movement, such as the lungs, as well as tumors located close to critical organs and tissues.
- Advantages of Newer faster forms
- Reduce the size of the high-dose field of irradiation
- Limit the exposure of adjacent vital structures

Chemotherapy

- Chemotherapy is largely palliative in patients with recurrent or metastatic disease.
- Prevents the division of abnormal cell different mechanism
- Chemotherapy is combined with radiotherapy &/or surgery to increase local regional control, decrease distant metastasis and improve survival

- Chemotherapy may be used as
  - **Induction therapy** prior to local therapies (shrinking tumor allow to be treated easily with surgery/ radiation
  - Concurrent chemo-radiotherapy (CCRT)-for unresectable cases
  - Adjuvant chemotherapy after local treatment- as maintenance

DRUGS USED FOR CHEMOTHERAPY

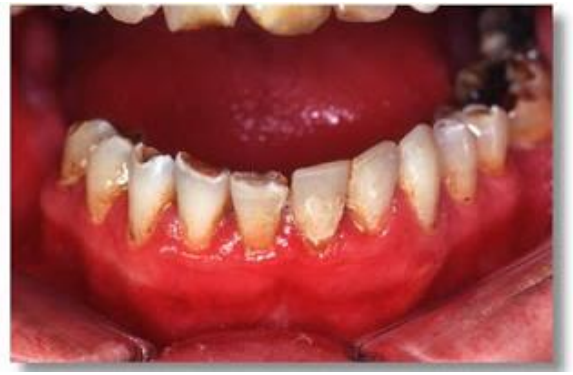
- Methotrexate
- Bleomycin
- Cisplatin & its analogue carboplatin
- 5-fluorouracil
- Taxanes (Paclitaxel, docetaxel)
- Gemcitabine
- Topotecan

- **Intralesional chemotherapy**:drug is injected directly into the tumour
- **Intra-arterial chemotherapy**: drug is injected directly to the feeding arteries of into the tumour cells
- **Immunotherapy:** designed to repair , stimulate and enhance bodies own immune response
- 1.Immunologic gene therapy: interleukinz-2,4,6,12 ,INF-alpha, gamma, TNF-alpha use
- 2.Radioimmunotherapy : cytotoxic nucleotides yattrium-90, iodine -131 linked to antibodies in order to deliver toxins directly to tumour
- **Gene therapy**: introduction of genetic material into target cell to replace or supplement defective genes
- **Cancer vaccine**: protein or carbohydrates on cancer cell surface act as an antigen and stimulate immune response

COMPLICATIONS OF CANCER TREATMENT

- Mucositis
- Xerostomia
- Candidiasis
- Caries
- Tissue Necrosis
- Speech and Mastication
- Nutrition
- Mandibular Dysfunction
- Dentofacial Abnormalities
- Pain

RADIATION EFFECT ON ORAL TISSUE



- Radiation mucositis:
- Inflammation of oral mucosa due to radiotherapy
- Mechanism:
- Injury to Basal cell layer (Radiosensitive)—atrophy—fibrosis—arteries obliteration and avascularity

- End of 2nd week: Area of redness / inflammation (mucositis)
- Therapy continue: Mucous membrane being breakdown with formation of white yellow pseudomembrane
- At end of therapy: Mucositis sever, discomfort is max, food intake is difficult / poor

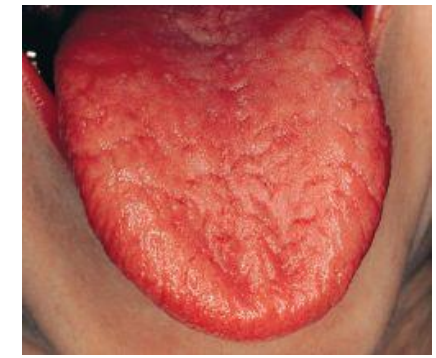
ORAL MUCOUS MEMBRANE

- Common complication 2ndry infection by Candida albicans
- Management:
- Saline, frequent rinse with water
- Lip lubrication : lanolin
- Coating agent: aluminum chloride, sucralfate
- Topical anesthetic at meal time: xylocaine, benzocaine

RADIATION EFFECT ON ORAL TISSUE

- Taste buds :
- Sensitive to radiation
- Cause extensive degeneration of normal histologic patter

- Patient notice
  - Loss of taste during 2nd/3rd week of therapy
  - Loss of bitter/ acid when post 1/3rd irradiate
  - Loss of Salt/ sweet when ant 2/3rd irradiate



- Alteration of saliva --reduction in taste sensitivity
- Recovery 60-120 days

RADIATION EFFECT ON ORAL TISSUE

- Salivary Gland (xerostomia)
- Major salivary gland
  - Unavoidable exposure during the radiation of oral cavity
  - Parenchymal component is rather sensitive
- Parotid more than submandibular and sublingual
- Acute inflammatory response/ soon after therapy (particularly serous acini)
- During early period of acute inflammation marked increase in serous amylase
- As the therapy progresses
- Inflammatory response more chronic--Progressive fibrosis --Adiposis--Loss of vasculature

- During first few weeks:
- Marked parenchymal degeneration--Progressive loss of salivary secretion
- Extent of decreased flow is dose dependent
- Reaches 0 at 6000 rads
- Scanty saliva secreted
- Increased concentration of Na, K, Mg ions & proteins
- Loses lubricating properties
- pH 1 unit below normal 5.5 (normal 6.5)

- Pt complaints of dry mouth, burning sensation if bilaterally irradiated
- Increased S. mutan, lactobacilli, Candida
- Dryness of mouth subsides in 6-12 months because of compensatory of residual salivary gland tissue
- Xerostomia beyond 1 year Less chance to return to normal function
- Treatment :
- Amifostine approved as a radioprotective agent
- Preserve salivary function
- Reduction of dry mouth in patients undergoing radiation treatment for head and neck cancer

- Mechanism of action:
- Scavenging of free oxygen radicals
- Amifostine is dephosphorylated in the circulation by alkaline phosphatase to a pharmacologically active free thiol metabolite.
- The thiol metabolite scavenges free oxygenspecies generated by radiation.

Evidence

Authors	Bourhis J et al, 2011
Title	**Effect of amifostine on survival among patients treated with radiotherapy: a meta-analysis of individual patient data.** J Clin Oncol. 2011 Jun 20;29(18):2590-7. Epub 2011 May 16. CEBM level 1a
Aim	to evaluate the impact of amifostine on overall survival (OS) and progression-free survival (PFS) in patients treated with radiotherapy or chemoradiotherapy.
Results	Amifostine did not reduce OS and PFS in patients treated with radiotherapy or chemoradiotherapy.
Interpretation	Quality of life of patients undergoing head and neck radiotherapy is improved as salivary dysfunction will de delayed ----> development of xerostomia and mucositis is delayed --→ psychological benefit

RADIATION EFFECT ON ORAL TISSUE

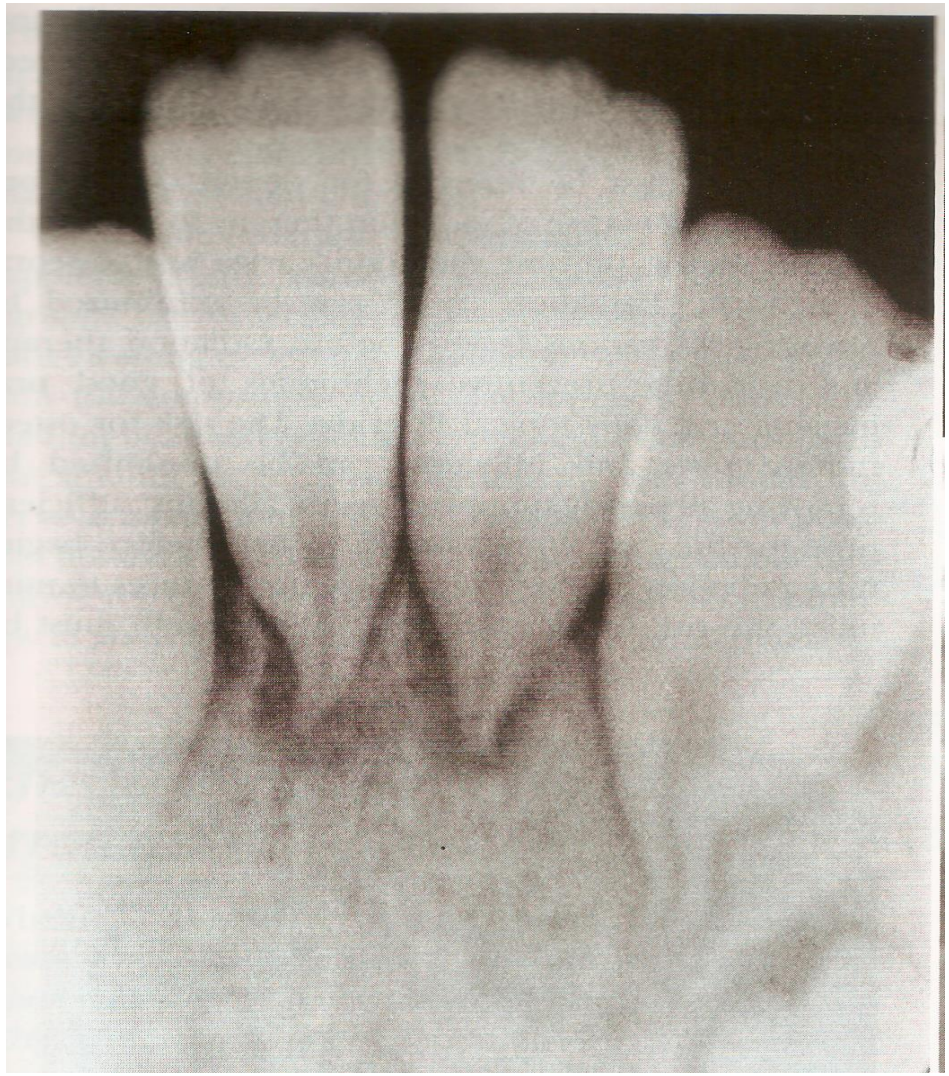
- Adult teeth

- Very resistant to direct effect of IR
- No effect on crystalline structure of enamel, dentin or cementum
- Dose not increase solubility of teeth

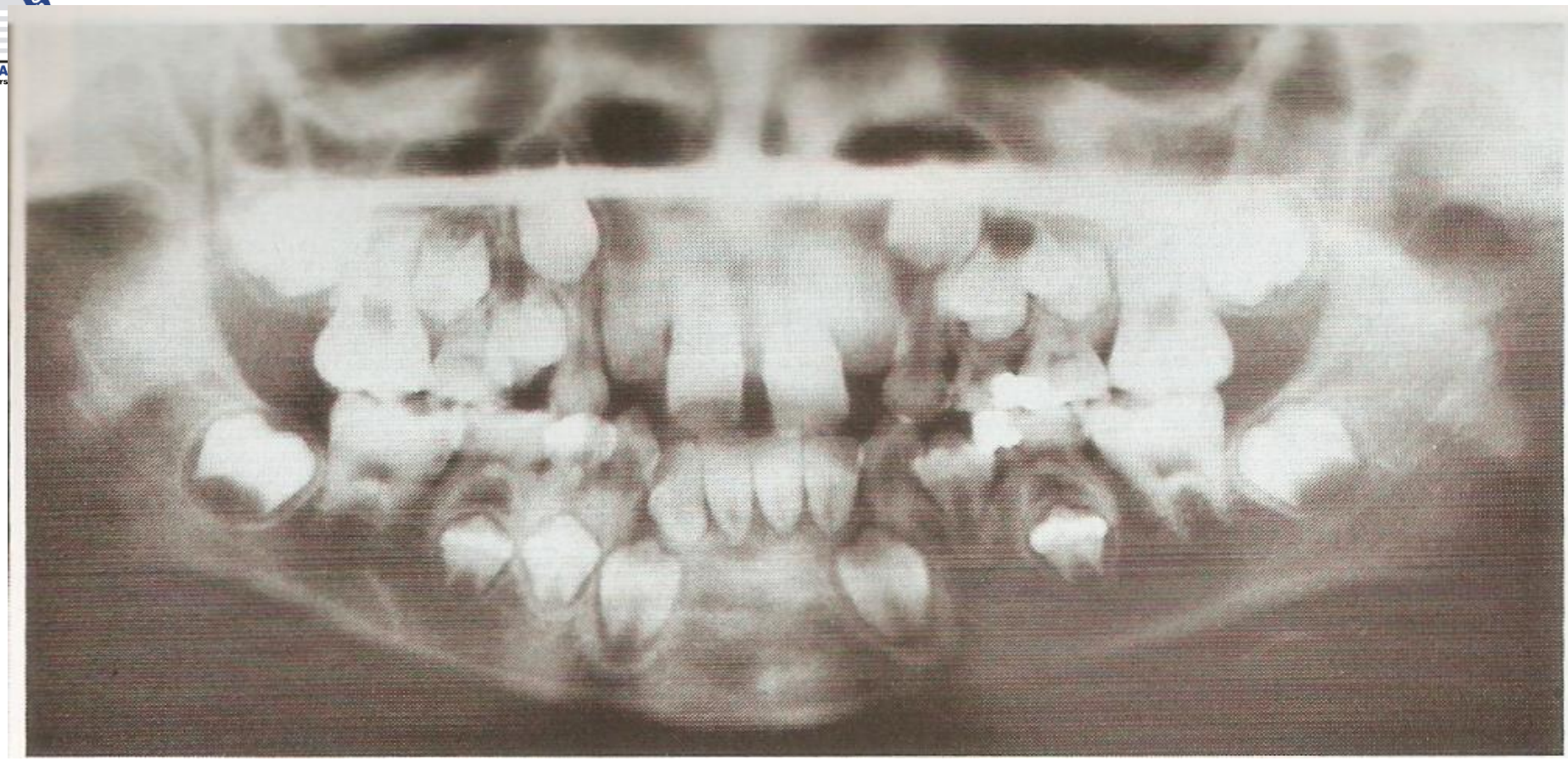
- When irradiated during development
  - Growth may be severely retarded
- Tooth Bud
  - Destroyed if precedes calcification

- Malformation, arresting general growth

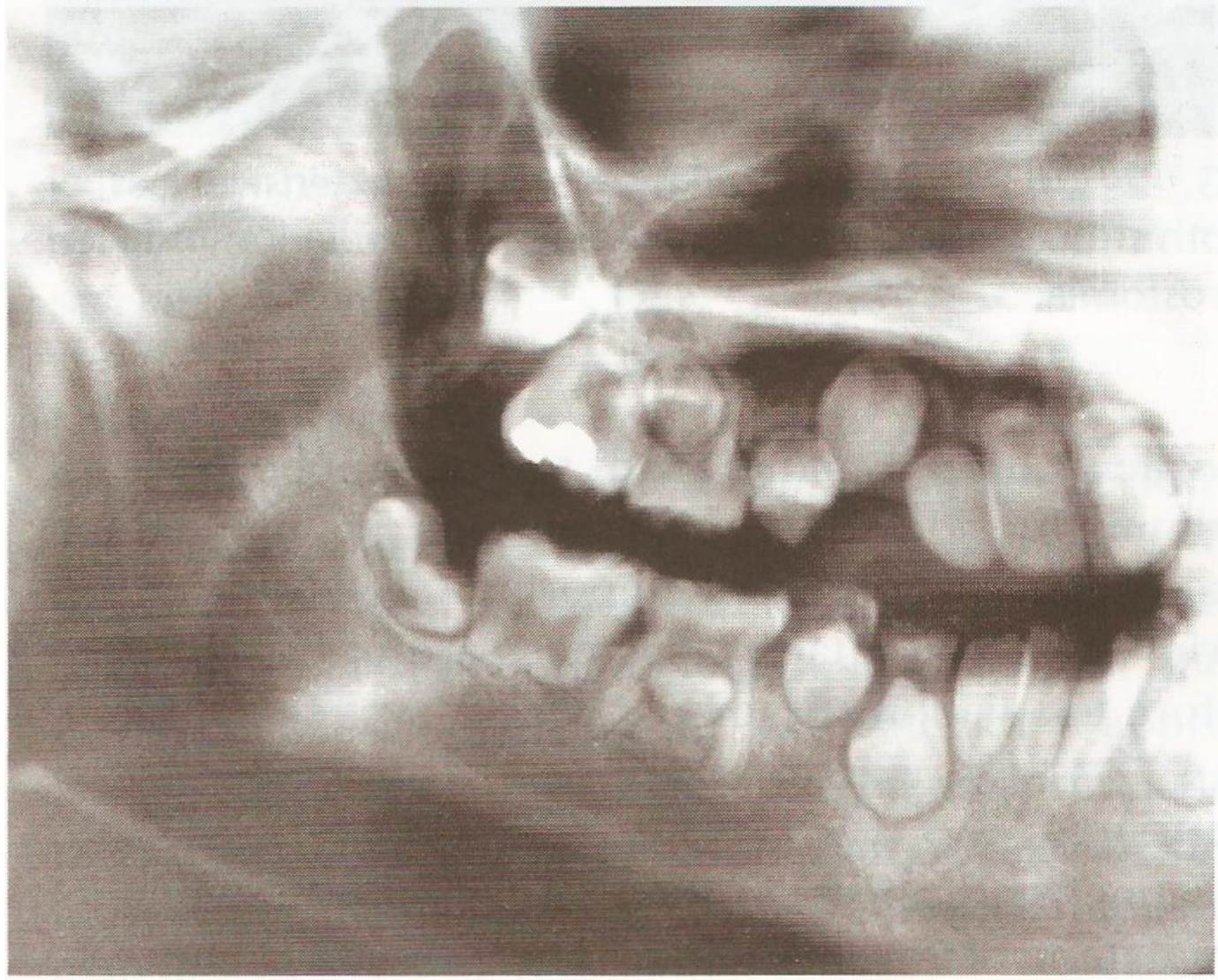
- Children receiving irradiation
  - Retarded root development
  - Dwarfed teeth
  - Hypoplastic enamel
  - Failure to form one or more teeth
  - Retarded root formation but eruption mechanism normal



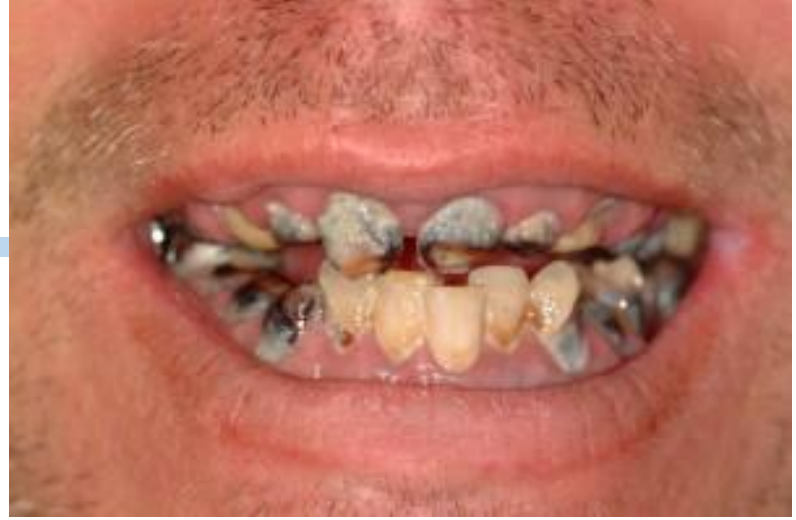
9-year-old girl who received 35 Gy at the age of 4 years because of Hodgkin's disease, had severe stunting of the incisor roots with premature closure of the apices at 8 years



Retarded development of the mandibular second premolar crowns with stunting of the mandibular incisor, canine, and premolar roots at 9 years



10-year-old boy who received 41 Gy to the jaws at age 4 years, had severely stunted root development of all permanent teeth with a normal primary molar



- Radiation caries
  - Rampant form
  - Due to exposure of salivary gland

- Lesion result from changes in salivary gland & saliva
- Decreased salivary flow
- Decreased pH & buffering capacity
- Increased viscosity

- Three types of carious lesion
  - Involved cementum / dentin with loss of crown
  - Buccal occlusal, incisal, palatal surface
  - Dark pigmentation of entire crown

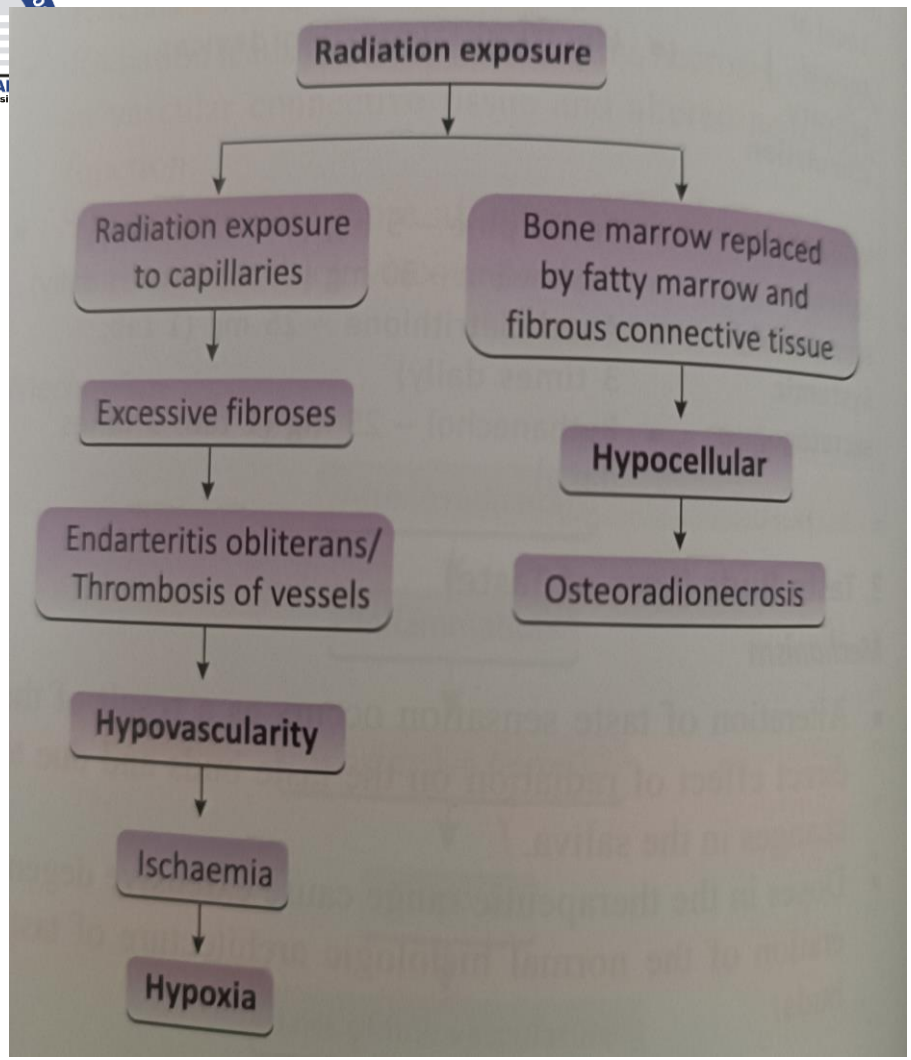
- Reducing radiation caries
  - Application of 1% sodium fluoride gel
  - That delays elevation of S. mutans
  - Oral hygiene instruction

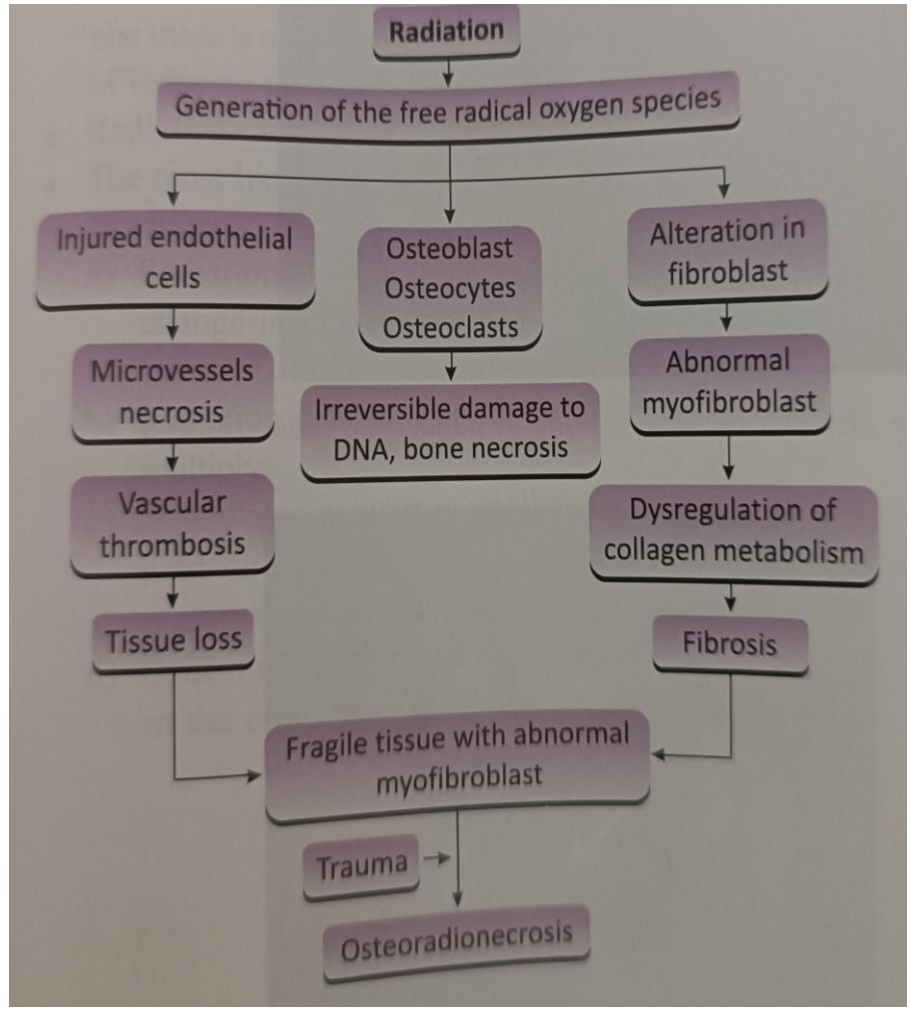
RADIATION EFFECT ON ORAL TISSUE

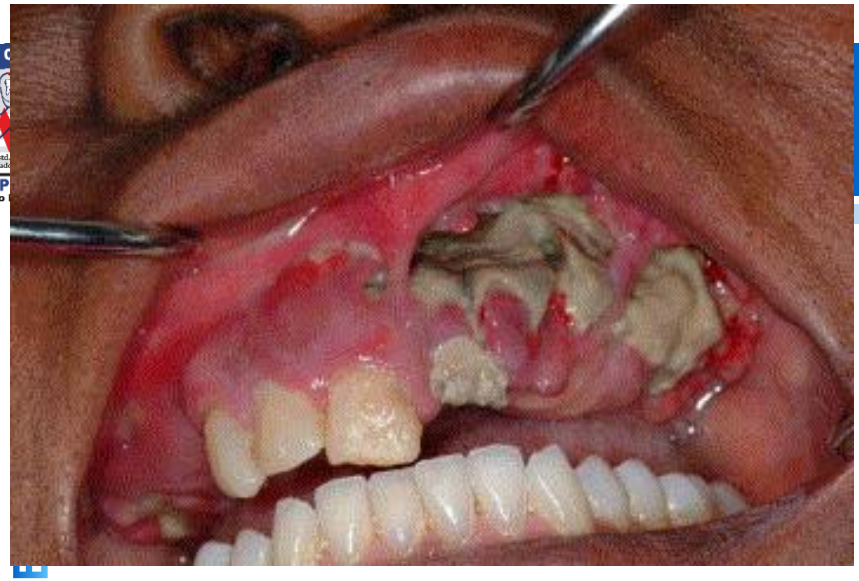
- Bone
- Most frequently irradiates: Mandible
- First damage to mature bone results from radiation induced damage to fine vasculature
- Marrow tissue becomes hypoxic & hypocellular
- Subsequently
  - Replacement of normal marrow with fatty marrow
  - Endosteum
    - Atrophic
    - Lack of osteoclastic & osteoblastic activity
- Decreased capacity of bone to resist infection
  - If injury occurs such as extraction
  - Infection/necrosis of bone

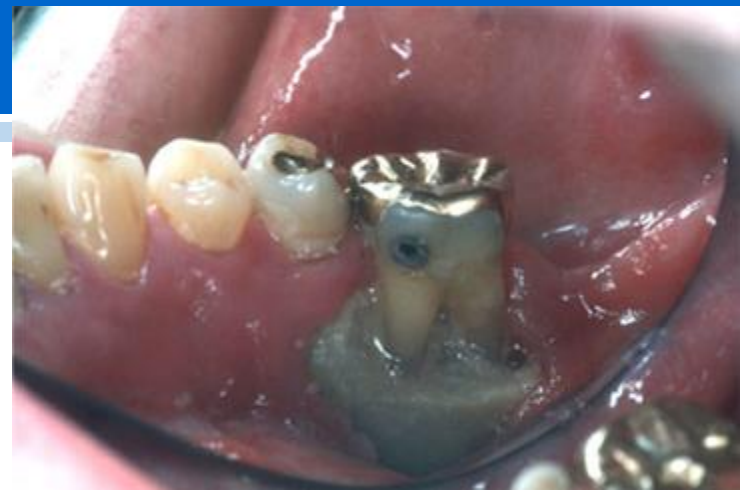
OSTEORADIONECROSIS

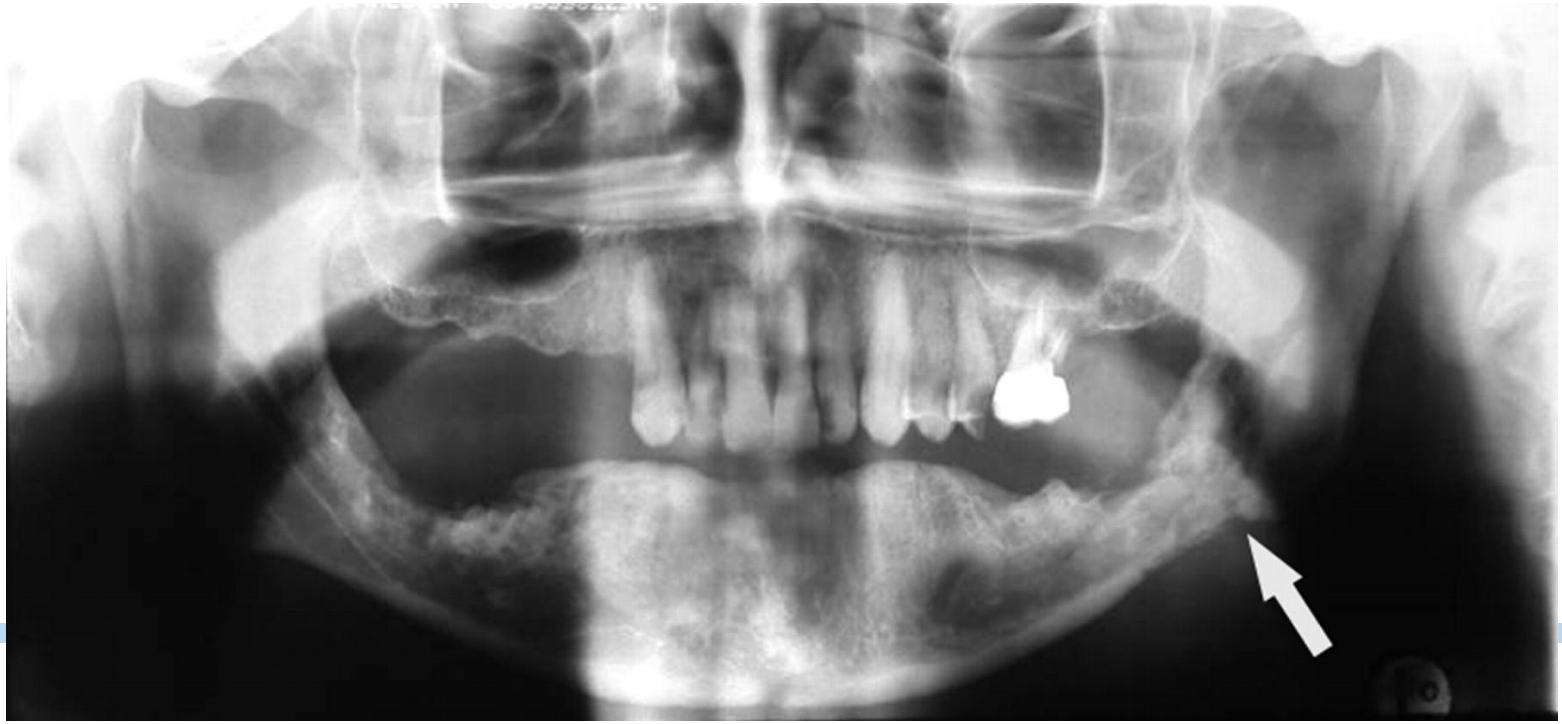
- Radiation induced necrosis of bone
- Clinically: Exposed bone with pus discharge, trismus, bad odor, swelling, painful mucosal ulceration, xerostomia, difficulty in swallowing.
- Commonly seen in mandible (more commonly irradiated)
- Maxilla has rich blood supply
- Factors affecting: Post/pre radiation extraction & Periodontal diseases
- **Management:**
- Risk reduced by performing necessary extractions at least 10-14 days before RT
- Warm saline, 0.4% stannous fluoride gel in custom tray for 15min twice daily
- Treated by Bone graft & Hyperbaric oxygen, Ozone therapy


Radiation exposure
Radiation exposure to capillaries
Excessive fibroses
Endarteritis obliterans/ Thrombosis of vessels
Hypovascularity
Ischaemia
Hypoxia
Bone marrow replaced by fatty marrow and fibrous connective tissue
Hypocellular
Osteoradionecrosis


Radiation
Generation of the free radical oxygen species
Injured endothelial cells
Microvessels necrosis
Vascular thrombosis
Tissue loss
Osteoblast Osteocytes Osteoclasts
Irreversible damage to DNA, bone necrosis
Alteration in fibroblast
Abnormal myofibroblast
Dysregulation of collagen metabolism
Fibrosis
Fragile tissue with abnormal myofibroblast
Trauma
Osteoradionecrosis







Other Head & Neck malignancies

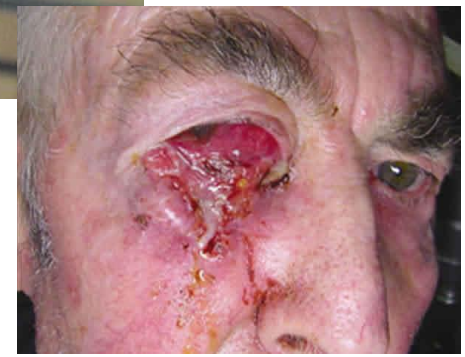
- Malignancies of salivary glands
  - Majority involve parotid
  - Mucoepidermoid carcinoma>adenoid cystic carcinoma>adeno carcinoma>SCC>Malignant pleomorphic adenoma
  - Spread through lymphatics, blood & perineural
  - Swelling may get ulcerated. Facial nerve palsy
  - Majority of minor salivary gland tumors are malignant
  - FNAC/Biopsy
  - Surgery, radiation
  - Poor prognosis for Adeno, Adenoid cystic carcinoma

Other Head & Neck malignancies

- Malignant lesions of jaws
  - Metastases more commonly to posterior portion of jaws
  - Adenocarcinoma (breast, prostrate, GIT) and renal carcinomas commonly metastasize
  - Pain, paresthesia, mobility of teeth & swelling
  - Metastases to soft tissues rare
  - Osteosarcoma, Multiple myeloma

Other Head & Neck malignancies

- Basal cell carcinoma
  - On skin, due to sun exposure in the head and neck region
  - Burrowing ulcer
  - Localized with indurated papule like or ulcer with rolled borders
  - Necrosis and ulceration
  - Metastases rare
  - Local excision

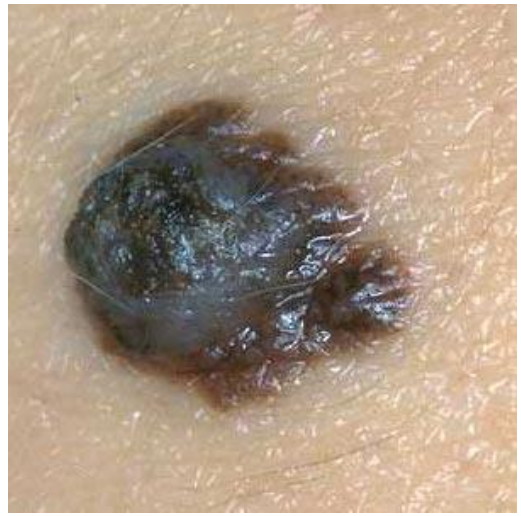


Evidence

Authors	Thissen MR, Neumann MH, Schouten LJ.
Title	**A systematic review of treatment modalities for primary basal cell carcinomas.** **Arch Dermatol. 1999;135:1177-1183** **CEBM Level 1a**
Aim	To systematically review the literature for studies reporting on recurrence rates of basal cell carcinomas (BCCs) after different therapies.
Results	Of 298 studies found in several electronic databases, only 18 met the requirements and could be used for analysis. Tumors treated with Mohs micrographic surgery show the lowest recurrence rates after 5 years, followed in order by those treated with surgical excision, cryosurgery, and curettage and electro-desiccation.
Interpretation	Mohs micrographic surgery should be used mainly for larger, morphea-type BCCs located in danger zones. For smaller BCCs of the nodular and superficial types, surgical excision remains the first treatment of choice. Other treatment modalities can be used in patients in whom surgery is contraindicated. Immunotherapy and photodynamic therapy are still investigative

Other Head & Neck malignancies

- Malignant melanoma
- Intraoral & Head, Neck sarcomas
  - Osteosarcoma, rhabdomyosarcoma, chondrosarcoma
- Malignancies in HIV
  - Hodgkin's & Non Hodgkin's lymphoma
  - Kaposi's sarcoma
    - Multicentric neoplastic proliferation of endothelial cells



MCQs

1. Osteoradionecrosis is more common in
   - A. Maxilla
   - B. Mandible
   - C. both
   - D. None
2. Amifostine is
   - A. Radioprotector
   - B. Radiation source
   - C. Both of the above
   - D. None of the above
3. Single modality treatment is given in
   - A. Stage I cancer
   - B. Stage II cancer
   - C. Stage I & II cancer
   - D. Stage III cancer

4. Severe stunning of root development occurs
   A. Radiation exposure during tooth development
   B. Radiation exposure after tooth development
   C. Radiation exposure to adult teeth
   D. Any of the above

5. Intracavitary implants are used in
   A. External beam therapy
   B. Brachytherapy
   C. Any type of radiotherapy
   D. All of the above

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THANK YOU