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Role of Magnetic Resonance Imaging in Differentiating Post Radio-Therapy Changes and Recurrent Lesions of Buccal Mucosa Malignancy

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I. Introduction:

The management of head and neck cancer involves multidisciplinary evaluation and treatment, in which surgery, radiation therapy, and chemotherapy are included. There are various approaches to surgical resection and tissue reconstruction, the types of neck dissection, different radiation therapy techniques, and the addition of concurrent and neo-adjuvant chemotherapy regimens may complicate imaging findings after treatment. **Differentiating post treatment changes from tumor recurrence with the use of imaging is challenging because of the presence of altered anatomy secondary to resection and flap reconstructions and post surgical scarring**. Furthermore, radiation therapy may induce tissue distortions such as inflammation, edema, and fibrosis which make post-treatment images more difficult to evaluate. That's why it is important to be familiar with the characteristics of common post-treatment changes and to distinguish these characteristics from those of tumor recurrence and treatment related complications.

Various imaging modalities, such as radiography, fluoroscopy, endoscopy, ultrasonography (US), computed tomography (CT), magnetic resonance (MR) imaging and dual-modality imaging with2-(fluorine 18)fluoro-2-deoxy-d-glucose (FDG) positron emission tomography (PET) with CT (PET/ CT), (1-4) are used to evaluate the post-treatment status in patients treated for head and neck cancer. **However, the evaluation performed by using PET less than 10–12 weeks after completion of radiation therapy leads to a high false positive rate because of the presence of post-irradiation inflammation, edema, or distortion (4, 6).**

MR imaging provides better soft-tissue contrast details. **Diffusion-weighted MR imaging has been reported to be a useful tool to differentiate tumor recurrence from normal post-treatment changes in the early period after treatment (4,7,8).** The purpose of this publication is to demonstrate post-treatment MR imaging findings in the view of the various methods of surgical and radiation. Key post-treatment imaging appearances are presented for tumor recurrence, postsurgical complications, mucosal necrosis, osseous complications, vascular complications, radiation induced lung disease, radiation induced brain necrosis, and radiation induced neoplasm are discussed.

II. Material And Methods:

The current study is a prospective study conducted in the department of radio diagnosis at **GCS Hospital , Ahmedabad, includes 50 patients (30 females & 20 males) over a period of 12 months from January 2020 to December 2020, Their clinical, and imaging findings of "MRI – Neck Contrast" done using 1.5 Signa explorer are assessed for evaluation of matter in interest.**

INCLUSION & EXCLUSION CRITERIA:

- ✓ **Inclusion criteria:** Patient having history of buccal mucosa malignancy & POST – RT status.
- ✓ **Exclusion criteria :**
- Implanted electric and electronic devices are a relative contraindication to the magnetic resonance imaging, and in particular.
- Heart pacemakers (especially older types) ,Insulin pumps, implanted hearing aids, neurostimulators .
- Intracranial metal clips, metallic bodies in the eye.

MRI PROTOCOL AND ITS IMPORTANT IMAGING FEATURES -

➢ ***T1-weighted imaging (T1WI):*** T1WI is very important in the evaluation of bone marrow , bony involvement in buccal mucosa malignancy. T1WI also provides excellent contrast among the cortical, marrow and surrounding tissues.

➢ **Fat suppression and T2WI :** The use of fat suppression (PDFS) in MRI can confirm or exclude the presence of fat in a lesion. Water shows higher signal than fat on T2WI, but suppressing the fat signal can allow an even better evaluation of the extent of oedema. Short tau inversion recovery (STIR) sequences effectively and homogeneously suppress all fat signals but sometimes it can lead to overestimation of the tumoral extension and compromise its characterization.

➢ **Gadolinium-based contrast study :** Gadolinium-based contrast medium also allows an accurate determination of the degree of vascularisation. Contrast-enhanced imaging is said to be approximately 80 % accurate in differentiating benign tumors from malignant ones.

➢ **Diffusion-weighted imaging (DWI) and Apparent diffusion coefficient:** High signal intensity on diffusion- weighted MR images with a decreased value for the apparent diffusion coefficient (ADC) is suspicious for recurrence . This low value for the ADC is thought to be caused by the restriction of proton movement in the extracellular extravascular space, secondary to tumor hypercellularity.

We at GCS hospital ahmedabad follow the following protocol **MRI – Neck Imaging** –

Non contrast sequences:

➢ T1-WI in the axial plane.

➢ T2- in the axial and sagittal planes.

➢ T2W STIR (Short tau inversion recovery sequence) AND proton density fat suppression (PDFS) in the axial, coronal and/or sagittal planes.

➢ DW MRI acquired in the axial plane. Images were obtained using b values of 0, 400, and 800 s/mm2. The ADCs are expressed numerically and were calculated by manually placing a region of interest (ROI) over the solid portion of the tumor and exclude cystic areas.

Post-intravenous contrast sequences:

➢ Post contrast sequences (in the axial, sagittal, and coronal planes) using intravenous gadolinium (Gd - DTPA) approximately 0.1 – 0.2 mmol/kg body weight, at least one fat-saturated sequence was obtained.

III. Results:

Treatment Methods and Expected Post-treatment Imaging findings:

Surgery with or without Reconstruction: Curative resection requires a wide local excision to obtain negative surgical margins. Reconstructive techniques are mainly classified into three types of flap reconstruction (1, 13-20).

Local flap reconstruction involves a geometric repositioning of adjacent tissue. ***Pedicle flap*** reconstruction involves rotation of donor tissue to cover a defect, with preservation of the original arterial and venous systems. Finally, the ***free flap*** reconstructive technique involves the transfer of tissue that is vascularized by local vessels, with anastomosis to the tissue defect by using microvascular techniques.

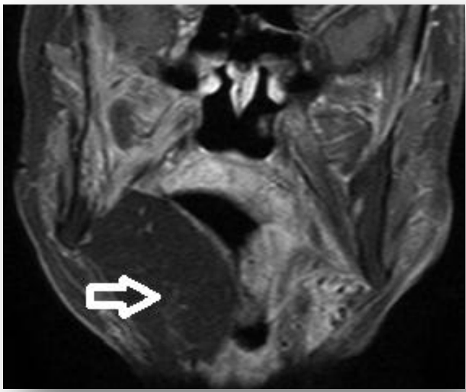


Fig. 1 Reconstruction of the floor of the mouth and the right side of the tongue with a rectus abdominis Myocutaneous free flap (white arrow) in a 68-year-old female. Coronal contrast-enhanced fat-saturated T1-weighted MR image depicts the flap filling the surgical defect. The flap shows reduced signal intensity, which represents fatty replacement, without abnormal enhancement.

Myocutaneous flaps are initially perceived as a mass with soft tissue attenuation & soft tissue intensity, indicating muscle (1, 13-17). Eventually these flaps will show denervation atrophy, which causes volume loss and fatty replacement of the muscle (1,13-17,22). ***Sharp boundaries exist (Preservation of fat planes) between the flap and the surrounding normal structures, which is an important sign indicating benignity (1,13-17)***. Assessment of superior and inferior margins of the flap (16,18), where local recurrence most commonly occurs is therefore very important. Myocutaneous flaps show enhancement after contrast material administration, ranging from almost no contrast enhancement to diffuse intense enhancement (16 , 22).

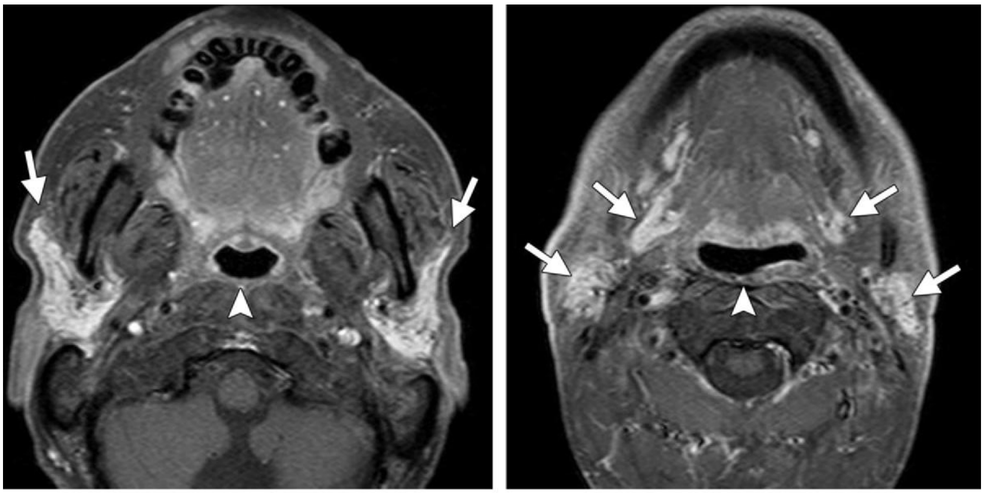
Neck Dissection :
The **three** major types of neck dissection (1,23):

Radical neck dissection involves the removal en bloc of all of the ipsilateral lymph nodes (levels I–V), including the sternocleidomastoid muscle, internal jugular vein, submandibular gland, and spinal accessory nerve (1,23).
Modified radical neck dissection is the same as radical neck dissection but with preservation of one or more structures described above. Modified radical neck dissection has some advantages; for example, preservation of the spinal accessory nerve prevents the development of adhesive capsulitis (frozen shoulder) (1,18).
Selective neck dissection: The supra-omohyoid type (levels I–III), the lateral type (levels II–IV), the postero-lateral type (levels II–V), and the anterior compartment type (levels VI and VII). Extended radical neck dissection is the same as radical neck dissection but includes the removal of additional nodes (levels VI and VII) and/or non-lymphatic structures such as the internal carotid artery, hypoglossal nerve, and vagus nerve (1).
The main MR imaging finding after neck dissection is the absence of the tissues resected with the cervical lymph nodes. Another imaging finding after neck dissection is in MR imaging, this postoperative area shows low to intermediate signal intensity on T1- andT2- weighted MR images, representing fibrosis or scar (23).

Radiation Therapy
External beam radiation therapy includes (24):
(1) Three dimensional conformal radiation therapy.
(2) Intensity modulated radiation therapy.
(3) Stereotactic radio surgery.
Early reactions or complications are seen during the course of radiation therapy or within 90 days after treatment and in majority of cases they are reversible in nature. ***Late complications*** defined as effects of treatment that manifest more than 90 days after the completion of radiation therapy, may take months to years to emerge and are often irreversible in nature (25).

The early complications of radiation therapy are seen frequently; particularly oral mucositis and skin desquamation, and completely resolve within a few weeks after completion of radiation therapy. Late complications of radiation therapy for head and neck cancer include xerostomia, dysphagia, accelerated dental caries, soft-tissue necrosis, osteo-radionecrosis; radiation induced vascular complications, and, rarely, radiation-induced neoplasm (1,28).

Early reactions that persist may also lead to subsequent late reactions. The severity and duration of radiation reactions are related to the technique, the total cumulative dose, and the volume of irradiated structures and may be exacerbated by smoking and alcohol consumption habits and the inherent radiosensitivity of the patient.



A. B.

Fig.2 . Late post irradiation changes at 1year after completion of radiation therapy in a 70-year-old man with squamous cell carcinoma of the buccal mucosa and hypopharynx. Contrast-enhanced fat-saturated T1-weighted MR images (A. At the level of the oropharynx and B. At the level of the base of the tongue) show atrophy of the parotid and sub-mandibular glands (arrows) and thickening of the pharyngeal constrictor muscle (arrowhead) and skin.

MR imaging findings of early reactions to radiation therapy are thickening of the skin and platysma, reticulation of the subcutaneous fat and edema associated with increased enhancement of the major salivary glands. Late reactions to radiation therapy include atrophy of the salivary glands and thickening of the pharyngeal constrictor muscle, platysma, and skin (1,20).

Post-treatment Imaging

Tumor Recurrence:

Tumor recurrence cannot be visually examined or clinically palpated which is located deep to flap reconstructions. Hence, imaging evaluations are needed. Tumors mostly recur within the first 2 years after completion of treatment. Tumors may recur within weeks after surgery, before adjuvant radiation therapy, because of accelerated repopulation. ***The most common locations for tumor recurrence are in the operative bed and at the margins of the surgical site. Tumor recurrence is identified as a slightly expansile mass lesion in the operative bed or as progressive thickening of soft tissues deep to the flap*** (1,16,18,20,22,23).

On CT-Scan, it demonstrates recurrence as an infiltrating slightly hyper attenuating mass with enhancement, with or without bone destruction ***Tumor recurrence has attenuation similar to that of muscle. Therefore, if a suspected mass has lower attenuation than that of muscle, it is unlikely to be a malignancy and often is related to edema***. MR imaging demonstrates tumor recurrence as an infiltrative mass with iso T1-weighted signal intensity, iso to highT2-weighted signal intensity, and enhancement (1,18,20,22,23). The differential diagnosis for tumor recurrence includes a *vascularized scar, which represents early fibrosis. Differentiation of a vascularized scar from tumor recurrence is difficult because such a scar appears as a soft-tissue mass with ill-defined margins and enhancement, which is similar to the findings for tumor recurrence at both CT and MR imaging.* Retraction and decreased signal intensity on T2-weighted MR images at the follow-up examination are suggestive of fibrosis. In addition, diffusion- weighted MR imaging has been reported to be a useful tool to differentiate tumor recurrence from normal postoperative changes and fibrosis.

"High signal intensity on diffusion- weighted MR images with a decreased value for the apparent diffusion coefficient (ADC) is suspicious for recurrence."
The use of the ADC has been reported to result in a high sensitivity and specificity, with nearly no overlap between tumoral and non-tumoral tissue. ***This low value for the ADC is thought to be caused by the restriction of proton movement in the extracellular extravascular space, secondary to tumor hypercellularity (4,7,8).*** On the other hand, necrosis, inflammation, and submucosal fibrosis after treatment show high values for the ADC, **a finding which correlates with an increased interstitial space and a low cell density**. *Lymph node recurrence and metastases are detected on the basis of their slightly higher enhancement and their expansive character (7).* Similar to its use in the primary tumor site, diffusion-weighted MR imaging is useful in the characterization of persistently enlarged lymph nodes after treatment. Specifically, lymph node recurrence or metastases have high signal intensity with a decreased value for the ADC on diffusion-weighted MR images.

Complications after Surgery

Most complications related to surgery occur in the early period after treatment , include wound infection, abscess, fistula, flap necrosis, hematoma, chylous fistula, and serous retention. Multiple risk factors have been reported, including preoperative radiation therapy, preoperative chemo-radiation therapy, prior tracheotomy, duration of surgery, type of flap, age, primary tumor stage, medical complications, malnutrition, anemia, tobacco use, and a history of habitual alcohol consumption (37,38). The reported incidences of surgical complications in the head and neck after radiation therapy alone and after chemotherapy with radiation therapy are 37%–74% and 46%–100%, respectively (39).

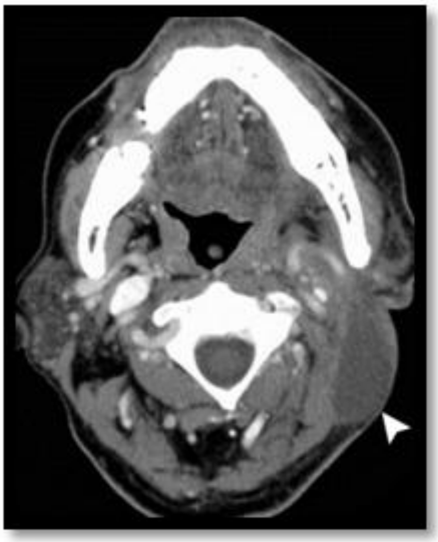


Fig. 3. Serous retention in a 70-year-old man after a left-sided modified neck dissection with reconstruction with a pectoralis major pedicle flap. Axial contrast-enhanced CT image shows a fluid collection (arrowhead) adjacent to the flap, without rim enhancement. Follow-up imaging disclosed that the fluid eventually resorbed.

After surgery, a fluid collection is sometimes seen, (1) and serous retention may often resolve spontaneously, requiring no further treatment. Chylous fistula occurs in 1%–2% of patients after neck dissection, especially when level IV nodes are dissected. Chylous fistula is often located in the lower left portion of the neck, so this characteristic location helps raise the suspicion of this complication. It is important to distinguish a benign fluid collection from an abscess or tumor recurrence. Early surgical complications such as serous retention, abscess, hematoma and chylous fistula often show imaging findings similar to those of a fluid collection, with peripheral enhancement at CT and MR imaging. Clinical symptoms, such as fever, pain and swelling and laboratory parameters, such as the white blood cell count and the serum level of C-reactive protein, can be used in distinguishing an abscess from these other types of fluid collections .Fistulas may close spontaneously, but some may require reoperation.

Fig.4 Fistula and abscess after irradiation and surgery in a 61-year-old man with right-sided modified neck dissection with flap reconstruction were performed. Axial contrast-enhanced CT images (obtained at the level of the base of the tongue and b at the lower neck level) show a fluid collection (arrows) with air adjacent to the surgical site and the flap. Note the formation of a pharyngeal fistula (arrowhead in a).

Post- operative anemia, prior tracheotomy, and prior radiation therapy and neck dissection are associated risk factors for fistula formation. The severity and the duration of fistulas are greater in patients who have undergone prior radiation therapy than in those who have not.

Flap necrosis is a rare complication. If the flap is pale or does not blanch with local pressure, the viability of the flap is questionable. When decreased flap perfusion is suspected, re-exploration should be considered without delay (16,22). The risk factors for developing complications after free tissue transfer are the patient's age, tobacco usage, a prolonged or protracted surgical time, and hyper-coagulable states such as polycythemia vera and sickle cell disease, as well as sickle cell trait. Flap failure is associated with vascular thrombosis, and the majority of thrombosis is venous in origin, occurring within 3 days after surgery. Therefore, the detection of thrombus in the artery and vein is important in the evaluation of the viability of the flap (17).

Mucosal Necrosis

Mucosal necrosis is an uncommon but important late toxic effect of head and neck radiation therapy that may cause substantial pain and interferes with the patient's ability to chew and swallow. The risk for mucosal necrosis is greatest during the first 6–12 months after radiation therapy. In more than 95% of cases, soft-tissue necrosis heals spontaneously, but healing may take 6 months or more (30). ***Mucosal necrosis is a separate entity from acute mucositis*; *the latter results from an acute loss of functional cells and temporary lack of replacement from the pools of rapidly proliferating cells (25).*** If the reaction is severe, subsequent fibrosis occurs and leads to impairment of microvascular and lymphatic flow. This impairment produces hypoxic, hypocellular, and hypovascular tissue that is unable to maintain normal tissue turnover, resulting in mucosal necrosis and ulceration (28,29).On CT, pockets of gas identified adjacent to the lesion should raise suspicion for tissue necrosis. If the ulceration is associated with adjacent enhancement, the differentiation between radiation necrosis and recurrent tumor becomes difficult. Tumor recurrence and mucosal necrosis typically occur within 2 years after therapy, so the time of the onset is usually not helpful in distinguishing between radiation-induced injury and tumor recurrence (30).

Osseous Complications

It is a condition in which irradiated bone becomes devitalized and exposed through the overlying skin or mucosa, persisting without healing for at least 3 months (22,23). The reported incidence of osteoradionecrosis varies greatly in the literature, ranging from 0.4% to 22% in patients with head and neck cancer (26,27).

Osteoradionecrosis often occurs 1–3 years after radiation therapy and most commonly occurs in patients who undergo radiation therapy after surgery. Osteoradionecrosis is unlikely to occur if the radiation dose is less than 60 Gy (26,27)delivered by standard fractionation.

Many risk factors for osteoradionecrosis have been reported; these include the irradiation technique, total radiation dose, photon energy, brachytherapy, field size, fractionation, xerostomia, periodontitis , pre-irradiation bone surgery, poor oral hygiene, alcohol and tobacco use, dental extractions, tumor location and stage, and proximity of the primary tumor to bone (25) With intensity-modulated radiation therapy, the dose to the mandible is controlled to reduce "hot spots" , (24) and with the use of parotid sparing techniques, the incidence of osteoradionecrosis should be reduced because xerostomia accelerates periodontal disease.

Sites in the head and neck region are the skull base, temporal bone, mandible, maxilla, and hyoid bone. Of these, the mandible is the most common site of osteoradionecrosis because of its superficial location and relatively poor blood supply. (21,26) Other possible reasons for the higher incidence of osteoradionecrosis in the mandible are *(a)* the direct involvement of the mandibular bone in the radiation fields with old radiation therapy techniques, which resulted in higher doses to the mandible, and *(b)* the aggressive and radical surgical approaches necessary for tumor resection.(29) The symptoms of osteoradionecrosis in the head and neck region are chronic focal pain, swelling, and facial deformation. In the case of the mandible, common signs and symptoms include dysphagia, drainage, and fistulization to the mucosa or skin.

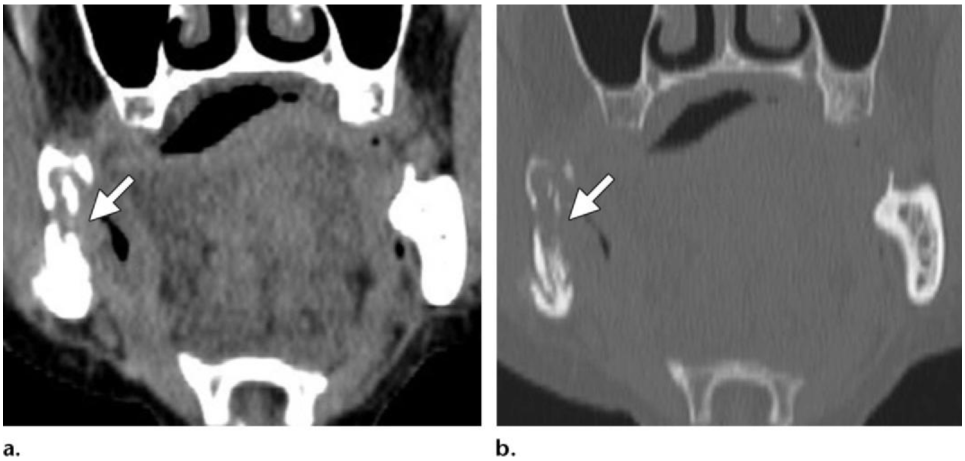


Fig .5 Osteoradionecrosis of the mandible after chemoradiation therapy in a 64-year-old man with squamous cell carcinoma of the right tonsil. Coronal CT images obtained with soft- tissue (a) and bone (b) windows show a focal lytic area with cortical destruction and a pathologic fracture in the right mandibular ramus (arrow).

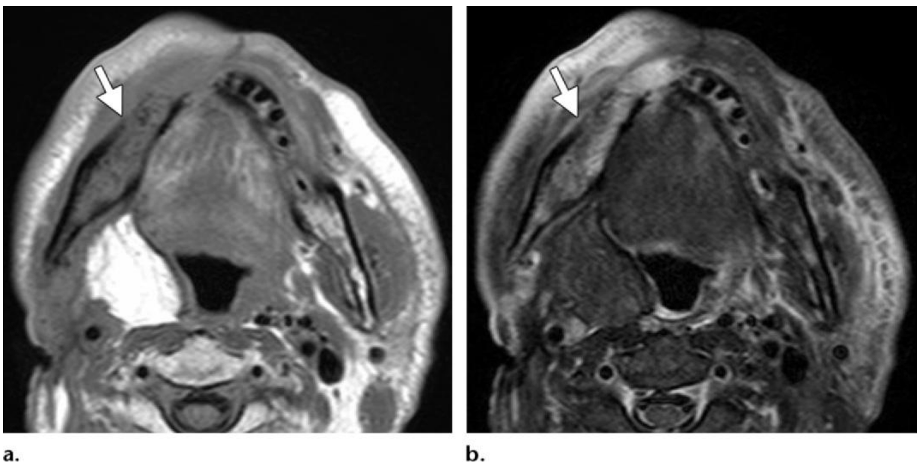


Fig. 6 .Osteoradionecrosis of the mandible in a 70-year-old man with squamous cell car- cinoma of the right tonsil. Tumor resection, right oropharyngeal reconstruction with a rectus abdominis myocutaneous free flap, and radiation therapy were performed. AxialT1-weighted(a) andfat-saturatedT2-weighted(b)MRimagesshowaT1-hypointenseandheterogeneousslightly T2-hyperintense area (arrow) in the right mandibular body.

CT images of osteoradionecrosis demonstrate a focal lytic area with cortical destruction, sequestra formation, and loss of the trabeculation pattern. MR images of osteoradionecrosis show abnormal signal intensity in the bone marrow, with cortical destruction. Pathologic fracture, soft-tissue thickening, and fistula formation are sometimes seen. (1,18,20,28) ***Although these imaging findings mimic those of tumor recurrence, the presence of an associated soft-tissue mass favors a diagnosis of tumor recurrence. The identification of cortical defects remote from the primary tumor site can also help in the diagnosis of osteoradionecrosis.(18,20)***

Vascular Complications

Accelerated atherosclerosis and thrombosis of the internal jugular vein or carotid artery are well- known vascular complications in patients with head and neck cancer treated with radiation therapy (1,18,28).Formation of a pseudo-aneurysm of the internal carotid artery is reported to be a rare complication after radiation therapy.

Radiation induced vasculopathy occurs most often in patients who have undergone high-dose radiation therapy, with a latency period between 4 months and 20 years.(22,28) However, most patients treated for head and neck cancer have pre-existing ischemic vascular disease secondary to alcohol and tobacco consumption and elevated serum cholesterol and lipid levels. The histopathologic changes of radiation-induced vasculopathy are intimal proliferation, thrombosis, and accelerated atherosclerosis. Radiation-induced vasculopathy is often bilateral and related to the irradiated field. (27)

Radiation-induced Neoplasm

Radiation-induced neoplasm is rare, with one group of investigators reporting an incidence rate of 0.037% for post-irradiation osteosarcoma in patients who had undergone treatment for nasopharyngeal cancer (29). These investigators reported that the latency period ranged between 4 and 27 years, with a mean latency period of 13.3 years. Various types of radiation-induced neoplasms have been reported, including meningioma, sarcoma (osteosarcoma, malignant fibrous histiocytoma), osteochondroma, schwannoma, osteoblastoma, squamous cell carcinoma, and lymphoma (29). The diagnostic criteria of post-irradiation osteosarcoma include a lesion centered in irradiated bone without a primary malignant osteoblastic lesion, arising after a latency period of at least 3 years after the completion of radiation therapy (18).

IV. Conclusions :-

Fig.7 Summary of post-treatment findings in patients with head and neck cancer. Diagram shows the common periods for tumor recurrence and for treatment- associated complications.

In patients who have been treated for buccal mucosa cancer, the typical post-treatment changes are based on the various types of therapy, including surgery with and without reconstruction, neck dissection, and radiation therapy. Common periods for tumor recurrence and the treatment-associated complications in patients with head and neck cancer are summarized. Knowledge of the various treatment methods and their expected and unexpected post-treatment imaging findings helps to make an accurate diagnosis and avoid unnecessary further diagnostic work-up.

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