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Patterns and Prevalence of Post-Radiation Changes in Head & Neck Cancer Detected by 18F-FDG PET/CT

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ABSTRACT

Objectives: The purpose of this retrospective study was to evaluate patterns and prevalence of post-radiation changes to decrease the false positive results in Positron emission tomography/ computerized tomography (PET/CT) scans. **Methods:** 140 fluorine-18 fluorodeoxyglucose (18F-FDG)-PET/CT scans of 30 patients with head and neck cancer without prior surgical intervention were retrospectively reviewed. Baseline and follow-up PET/CT scans were reviewed. The main period of follow-up was 18.3 months. According to abnormal FDG uptake or abnormal CT findings nine categories of post-radiations changes were selected: cervical spinal cord uptake, esophageal uptake, Lung changes, reactive lymph node, neck muscles uptake, vascular uptake (carotid or subclavian arteries), soft tissue uptake at the radiation field, uptake at the dental regions and miscellaneous (parotid uptake, shoulder drop as a result of radiation induced nerve injury). All these changes were proved to be benign process either by repeated PET/CT follow-up scans or by pathological examinations. We calculated the percentage and the time of appearance and disappearance of each category. **Results:** Soft tissue uptake was present in 21 (70%) of patients. Muscles uptake was present in 20 (66.7%) of patients. 17 patients (56.7%) had uptake at the dental regions. 16 patients (53.3%) had esophageal uptake. 13 patients (43.3%) had cervical spinal cord uptake. of 11 patients (36.7%) had Lung changes. 10 patients (33.3%) had vascular uptake. 8 patients (26.7%) had reactive lymph node. Bilateral parotid uptake was in three patients (10%) and shoulder drop was in one patient (3.3%). All studied patients had at least two post radiation changes. **Conclusions:** We conclude that significant post-radiation changes were encountered. Muscle uptake, soft tissue uptake and uptake in dental region were the most common changes. It is important to be aware of these changes to avoid false interpretations of PET/CT scans.

Key words: PET/CT-Post radiation changes – Head & neck cancer.

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INTRODUCTION

18F-FDG PET scan is effective for staging of previously untreated head & neck squamous cell carcinoma (HNSCC) and in the detection of recurrence after treatment because it has higher sensitivity than anatomical imaging modalities such as CT or MRI [1]. Patients with HNSCC usually treated with radiotherapy either alone or in conjunction with chemotherapy and/or surgery. The current limitations of CT and MRI in detecting recurrent head and neck cancer after radiotherapy mainly result from radiation- induced tissue distortions[2]. Residual or recurrent lesions and treatment-induced changes show similar characteristics on both CT and routine MRI [3]. One of the most effective uses of FDG–PET in HNSCC is to evaluate the results of radiotherapy [2-4]. However, in post radiotherapy FDG PET/CT scan, false positive results may occur as a result of change in cellular glucose metabolism with radiation therapy [5] as well as increase FDG uptake in areas of post radiation inflammation because of glucose metabolism of increased leukocytes in these areas [6]. Any tissue type, including skin, muscle, ligament, tendon, nerve, viscera, and even bone can affected and damaged by radiation fibrosis [7-9].

MATERIALS AND METHODS

This study was approved by the institutional review board. Informed consent was not required for this retrospective analysis.

Patient Population 140 baseline and post radiotherapy FDG-PET/CT scans of 30 consecutive patients with head and neck cancer without prior surgical intervention were retrospectively reviewed. All patients were treated by radiotherapy alone or radio/chemotherapy. The final study population consisted of 30 patients (Table 1).

Table 1: Patient Characteristics

Characteristics	Value
Age (year)	
Mean	56 ± 7.8
Range	24-78
Sex	
No. of male	24
No. of female	6
No. of primary tumor sites	
Oropharynx	11
Larynx	10
Hypophayrnx	4
Nasopharynx	3
Unknown	2

PET/CT scanning

Patients fasted at least 4 hours before the tracer injection and received an intravenous injection of approximately 5.18 MBq/Kg (0.14 mCi/Kg) of 18F-FDG, with a maximum of 444 MBq (12 mCi). Blood glucose level was measured immediately prior to FDG injection and was < 200 mg in all studied cases. Patients were instructed to sit in a quiet injection room without talking during the subsequent 40-60 min of the FDG uptake phase and were allowed to breathe normally during image acquisition without specific instructions. All scans were acquired using a Gemini TF PET/CT scanner (Philips Medical Systems) with an axial co-scan range of 193 cm enabling a head-to-toe represent true whole body (TWB) imaging in one sweep.

CT scanning; The CT scan of the PET/CT scanner consisted of a 64 slice multi-detector helical CT. Gantry allows for a patient port of 70 cm. CT Parameters: It is a single sweep: 120–140 KV and 33–100 mAs (based on body mass index), 0.5 second per CT rotation, pitch of 0.829 and 512 × 512 matrix. CT acquisition was performed before emission acquisition. CT data were used for image fusion and the generation of the CT transmission map. No oral or IV contrast was used.

PET scanning and image processing

Emission data were acquired for 18-22 bed positions (193 cm coverage, identical to the CT protocol). Emission scans were acquired at 1 – 3 minutes per bed position, dependent on the body mass index (BMI). The FOV was from the top of the head to the bottom of the feet in all patients. The 3-dimentional (3D) TWB acquisition parameters consisted of a 128 x 128 matrix and an 18 cm FOV with a 50% overlap. Processing consisted of the 3D Row Action Maximum Likelihood Algorithm (RAMLA) method [10].

Image analysis: Both of the baseline and post radiotherapy FDG-PET/CT scans of each patient in our study were reviewed by board certified nuclear medicine physician. According to abnormal FDG uptake or abnormal CT findings nine categories of post-radiation changes were selected: cervical spinal cord uptake, esophageal uptake, Lung changes, reactive lymph node, neck muscles uptake, vascular uptake (carotid or subclavian arteries), soft tissue uptake. at the radiation field, uptake at the dental regions and miscellaneous (parotid uptake, shoulder drop as a result of radiation induced nerve injury). All these changes were proved to be benign process either by repeated PET/CT follow-up scans or by pathological examinations. We calculated the percentage and the time of appearance and disappearance of each category.

RESULTS:

Soft tissue uptake was present in 21 (70%) of patients with main time of appearance and disappearance was 2.2 and 5.7 months respectively **(Fig.1).** Muscles uptake was present in 20 (66.7%) of patients with main time of appearance and disappearance were 2.3 and 6.7 months respectively **(Fig. 2,3).** 17 patients (56.7%) had uptake at the dental regions with main time of appearance and disappearance was 2.1 and 5.7 months respectively**.** 16 patients (53.3%) had esophageal uptake with main time of appearance and disappearance were 2.3 and 10.3 months respectively **(Fig. 4).**

13 patients (43.3%) had cervical spinal cord uptake with main time of appearance was 1.75 months and fluctuation course of increased and decreased uptake through follow-up period**.** 11 patients (36.7%) had Lung changes with main time of appearance and disappearance was 2.3 and 7 months respectively **(Fig. 5).** 10 patients (33.3%) had vascular uptake with main time of appearance and disappearance was 2.4 and 7.4 months respectively**.** 8 patients (26.7%) had reactive lymph node with main time of appearance and disappearance was 1 and 6 months respectively (**Figure 6**). Bilateral parotid uptake was in three patients (10%) and shoulder drop was in one patient (3.3%). Every patient in our study had at least two post radiation changes.

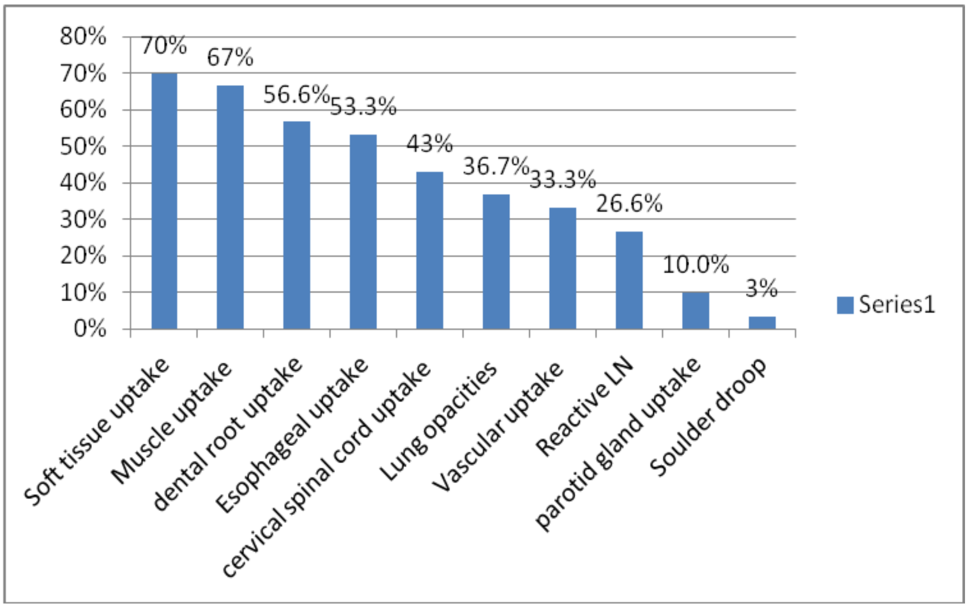

Fig.1: Percentage of FDG PET/CT detected post-radiation changes in 30 head and neck cancer patients.

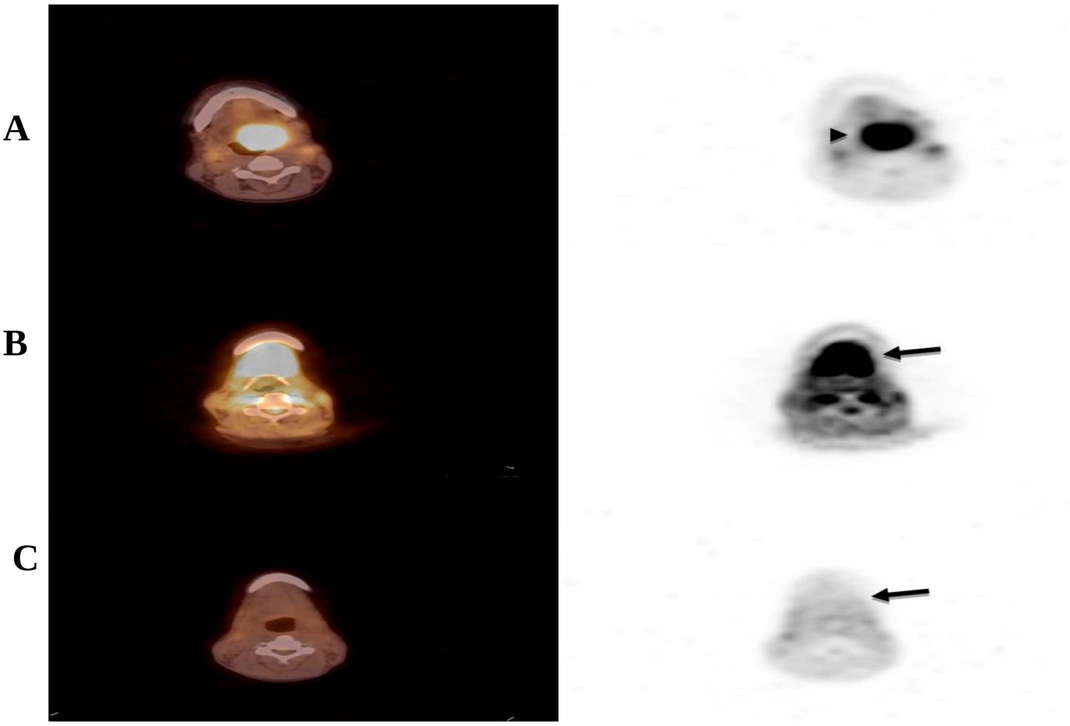

Fig. 2: A 56-year-old female with a history of squamous cell carcinoma of the left tongue base. A: baseline FDG PET/CT showed intense uptake in the primary tumor (arrow head). B: 5 weeks post radiotherapy showed intense soft tissue uptake in the floor of the mouth along with bilateral neck muscles uptake suggested of post radiation changes. C: 6 months post radiotherapy there was complete resolution soft tissue uptake (arrow).

A
B
C

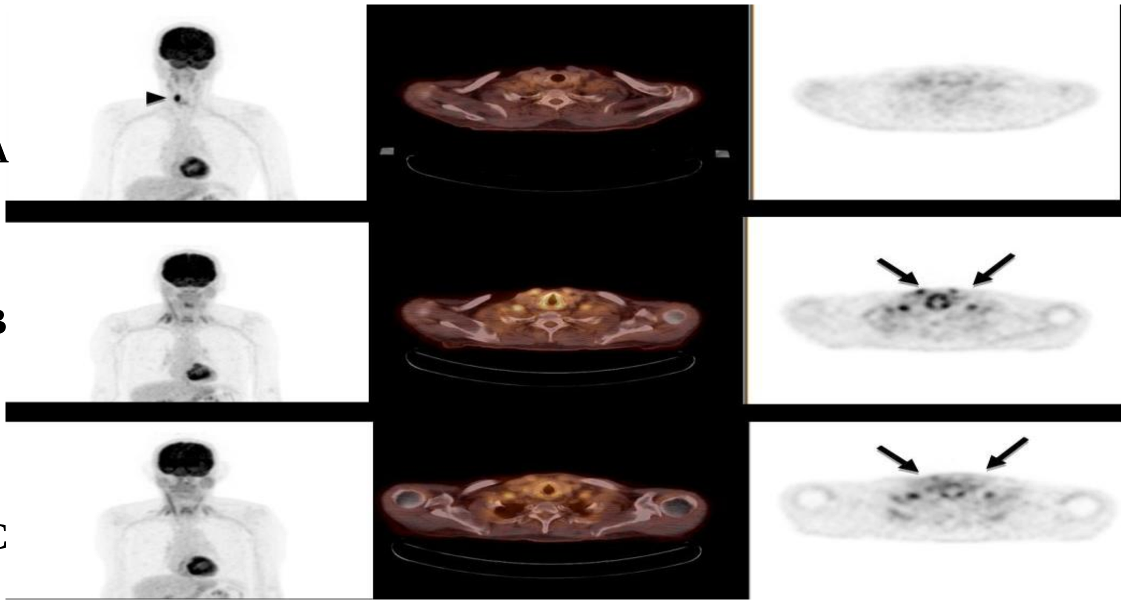

Fig. 3: A 72-year-old male patient with right pyriform sinus SCC. A: baseline FDG PET/CT showed intense FDG uptake in the primary tumor (arrow head). B: follow-up scan 5 weeks after radiotherapy showed bilateral neck muscles uptake (sclene and sternocledomastoid) more in the right side (arrows). C: FDG PET/CT scan 5 months after radiotherapy showed interval increased of muscle uptake (arrows).

A
B
C
D

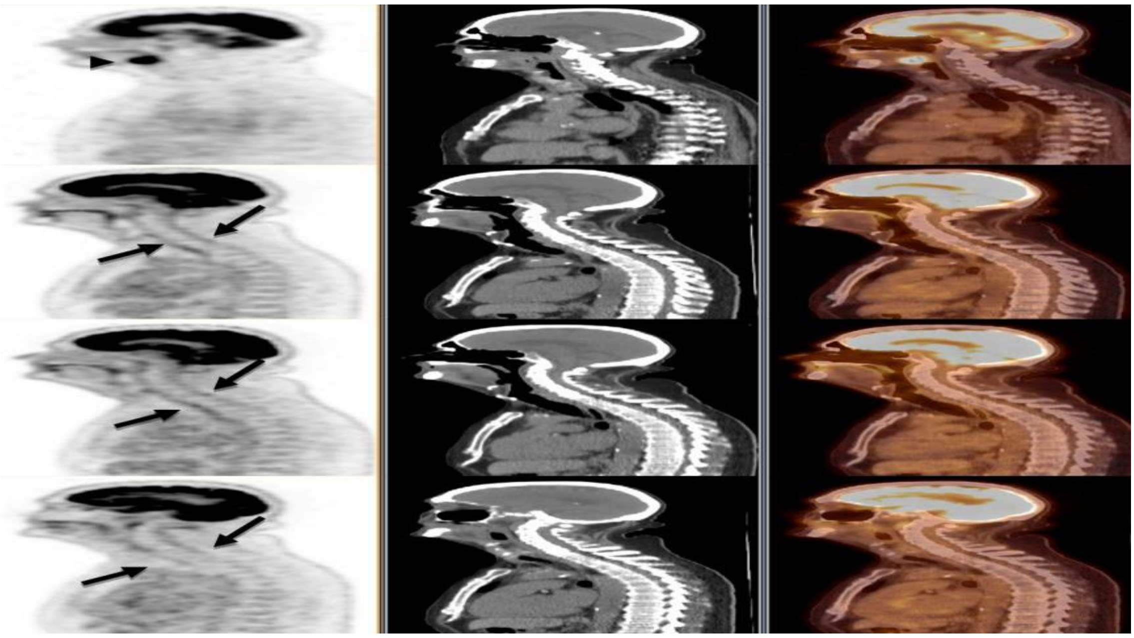

Fig. 4: Right oropharyngeal squamous cell carcinoma. A: 18F-FDG PET/CT at baseline showed intense uptake in the primary tumour (arrow head). B: 6 week after radiotherapy showed interval radiation induced increased cervical spinal cord uptake and radiation induced esophageal uptake (arrows). C: 6 months after radiotherapy showed decreased spinal cord and esophageal uptake (arrows). D: one year after radiotherapy showed spinal cord and esophageal uptake almost return to baseline (arrows).

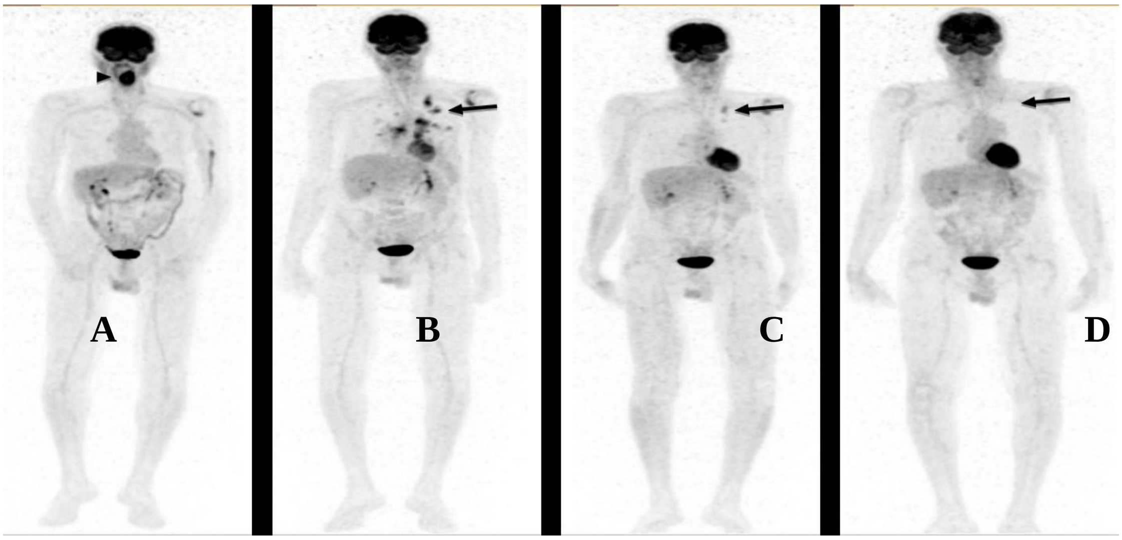

Fig5: A 65-year-old male patient with left tonsilar SCC, A: Maximum intensity projection (MIP) of baseline PET/CT showed intense uptake in the primary tumor (arrow head). B: MIP image after 3 months of radiotherapy showed FDG post radiation lung changes more in the upper left lung near the radiation field (arrow). C: MIP image 6 months after radiotherapy showed interval decreased of these lung changes. D: MIP image after 9 months showed complete resolution of these post radiation lung changes (arrow).

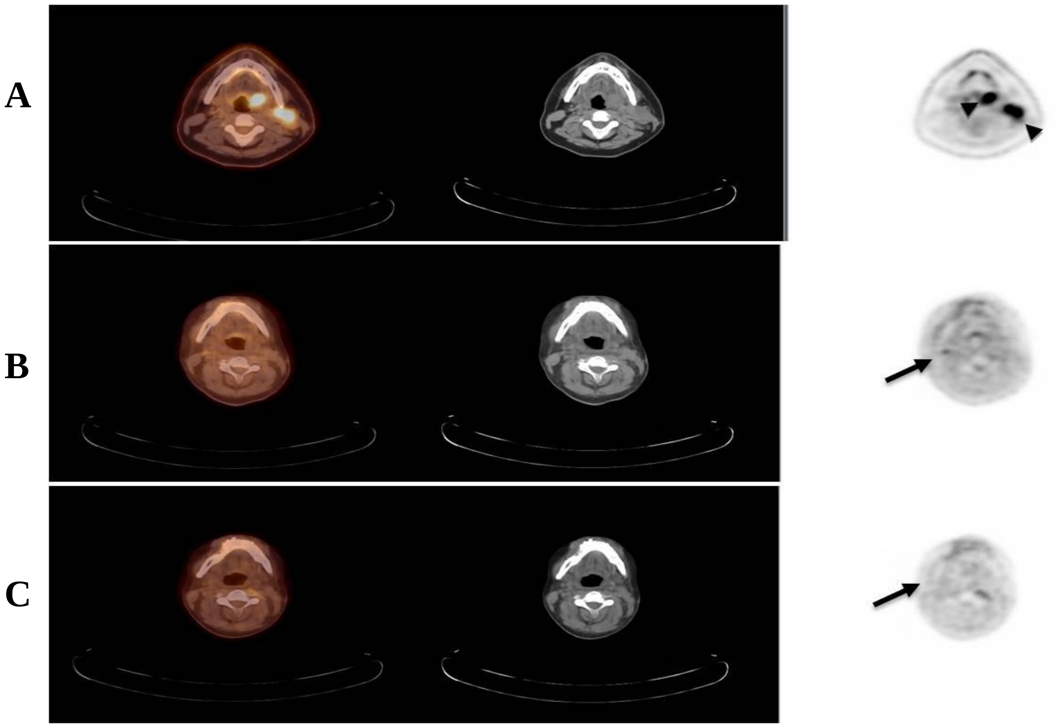

Fig. 6: A 28-year-old male patient with left tonsilar SCC. A: FDG PET/CT baseline scan showed intense FDG uptake in the primary tumor and metastatic lymph node (arrow heads). B: PET/CT scan at 2 months post radiation showed FDG avid reactive right carotid space LN (arrow). C: 6 months after radiotherapy, this reactive lymph node completely resolved (arrow).

DISCUSSION

FDG-PET/CT plays an important role in management of patients with HNSCC; starting from diagnosis, initial staging, treatment monitoring, detection of recurrence, restaging and radiation field planning. One of the most effective uses of FDG–PET in HNSCC is to evaluate the results of radiotherapy [2-4]. However, false positive results in FDG PET/CT are commonly observed in areas of active inflammation or infection [11], with a reported false positive rate of 13% and false negative rate of 9% [12]. Inflammatory cells (neutrophils and activated macrophages) at the sites of inflammation or infection will show increased FDG accumulation [12]. Some of the most common iatrogenic causes of uptake on PET/CT include the response from radiation with development of inflammation/fibrosis [13]. Up to date the optimal timing of post radiotherapy FDG-PET in head and neck cancer patients is a subject of debate. High rates of false positive findings due to post-radiation soft tissue effects and false negative findings because of the residual viable cancer cells that did not have sufficient time to repopulate to a level that can be detected by PET are encountered if PET imaging obtained too soon after radiation. On the other hand early discrimination between post-radiation changes from viable tumor tissue is important because it enables prompt salvage treatment when the size of residual tumor volume is limited [3].

The knowledge of the features of post radiation changes in HNSCC patients is of paramount important to decrease the rate of false positive results and to get more precise interpretation of the FDG PET/CT. To our knowledge up to the date of writing this article there is no articles in the literature take in consideration specifically the features and timing of appearance and disappearance of post radiations changes in HNSCC patients in FDG PET/CT. In our study we studied the pattern and prevalence of post radiation changes in FDG PET/CT scans in HNSCC hoping to help in decreasing the rate false positive result and increasing the accuracy of FDG PET/CT in monitoring radiation treatment in head and neck cancer patients.

Increased soft tissue FDG uptake at the radiation field is due to migration of a great number of leukocytes to this area [8]. This increased soft tissue uptake can affect the interpretation. However, the pattern of this uptake and decreasing intensity over time without interval therapy can be helpful in differentiating post radiation soft tissue uptake from residual/recurrent disease. In our study post radiation increased soft tissue uptake was present in 70% of patients with main time of appearance and disappearance was 2.2 and 5.7 months respectively **(Fig.2).**

Skeletal muscle considered relatively resistant to radiation injury [14]. However in one study of interest, Jentzsch et al. [15] reported on 29 patients with Ewing's sarcoma who were treated with 50 Gy of external beam radiation therapy and chemotherapy. They classified the patients according to the functional limitations which were due to bone injury rather than muscle damage. The results emphasize the potential late effects of radiation on skeletal muscle, especially in pediatric patients. Many other studies described the exaggerated physiologic uptake of FDG involving different muscle groups [16&17]. Neck and upper thorax muscles are the most commonly affected sites. The uptake may be caused by muscle activity before, during, or after the radiotracer injection. However, it also can result from radiation induced myositis. In our study post radiation neck muscles uptake was present in 66.7% of patients. The main time of appearance and disappearance of the post radiation changes was 2.3 and 6.7 months respectively **(Fig. 3).**

Patients with head and neck irradiation usually had alterations in the salivary glands and in the dental structure, which predisposes to progressive periodontal attachment loss, rampant caries and fungal and bacterial infections [18]. These areas of infection are FDG avid and may lead to false positive results in FDG PET/CT scan. In our study 56.7%of patients had uptake at the dental regions. The main time of appearance and disappearance of the post radiation changes was 2.1 and 5.7 months respectively**.**

Radiation esophagitis is the most important dose-limiting acute toxicity during radiotherapy for thoracic malignancies [19]. As an inflammatory process, radiation esophagitis may cause an increase in FDG accumulation [20]. In patients with HNSCC, radiation esophagitis typically results when the esophagus is included in the irradiation field. Most of the studies in the litterateurs look at FDG uptake in radiation esophagitis in patients with thoracic cancer [21&22]. In our study 53.3% had esophageal uptake with main time of appearance and disappearance of the post radiation changes was 2.3 and 10.3 months respectively **(Fig. 4).**

Few studies have been published on PET of the spinal cord and all of them revealed a very low physiological FDG uptake, due to the considerable proportion of white matter with low metabolic activity relative to the small bulk of the gray matter [23-27]. ÉSIK et al. observed a temporarily increased FDG uptake after radiotherapy that may be related to subclinical, transitory demyelination and vascular inflammation. This temporary increase in the FDG uptake of the irradiated spinal cord region had almost completely disappeared by the 44th month of radiotherapy [28]. In our study, 43.3% of patients had cervical spinal cord uptake with main time of appearance was 1.75 months and fluctuation course of increased and decreased uptake through follow-up period**.**

One of the side effects of radiation treatment in thoracic malignancies is radiation pneumonitis (RP) which is an inflammatory reaction within lung tissue in response to radiation injury. Because pulmonary inflammation appears as enhanced 18F-FDG uptake on PET, post radiation inflammatory changes can cause interpretation dilemma in FDG-PET in thoracic malignancies [29-31]. Post radiation lung changes may also occur in HNSCC when upper mediastinum included in the irradiation field, causing false positive results in FDG PET/CT. In our study 36.7 % of patients had upper lung changes. The main time of appearance and disappearance of the post radiation changes was 2.3 and 7 months respectively **(Fig. 5).**

Radiation therapy in patients with HNSCC may result in damaging the nearby carotid arteries, resulting in initiating or accelerating the atherosclerotic process [29] with resultant stenosis and stroke. A prospective study by Font et al demonstrated that low to moderate carotid atherosclerosis can be detected using 18-FDG-PET imaging [32]. Wengen et al; reviewed data from basic sciences as well as animal and clinical studies and concluded that there is an emerging role of FDG-PET/CT in assessing atherosclerosis in large arteries in humans [33]. Radiation accelerating atherosclerosis may appear in post radiation FDG PET scan as interval increased vascular FDG uptake**.**

18 F- FDG PET/CT is used for nodal staging in HNSCC depending on increased FDG uptake in metastatic lymph node, however, it is well known that 18-F- FDG accumulates in areas of inflammation and in reactive lymphadenopathy [33&34]. In patients with HNSCC, post radiation FDG uptake in reactive lymph node may result in

interpretation dilemma as seen in 8 patients (26.6%) of our study population **(Fig.6).**

Parotid glands usually demonstrate minimal-to-low grade FDG uptake. When the parotid glands are included in the irradiation field in HNSCC patients, this may result in disruption of serous acini, which are extremely radiosensitive, with leakage of enzymes into the surrounding salivary tissues resulting in an acute inflammatory process [34]. This inflammation results in increased 18 F-FDG uptake which may return to baseline value after few months as evident in 3 (10%) patients in our study population.

The incidence of cranial nerve palsy appears to be very low and the underlying cause of cranial nerve palsy after radiotherapy is not well documented. The criteria for diagnosis of radiation induced accessory nerve palsy include muscle weakness and inability to elevate the shoulder girdle (shoulder drop) and turn the neck. This diagnosis was limited to patients who had not undergone previous neck surgery [35]. In our study there was only one case with shoulder drop due to radiation induced accessory nerve palsy represent 3% of all cases.

Conclusions:

We conclude that significant post-radiation changes were encountered and muscle uptake, soft tissue uptake and uptake in dental region were the most common changes. It is important to be aware of these changes to avoid false interpretations of the PET/CT exam.

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