The radiological and pathological response co-relation of head and neck squamous cell carcinomas after conventional radiotherapy with concurrent platinum based chemotherapy

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ABSTRACT.

INTRODUCTION.

Head and neck cancers the most common malignancies in developing countries like India due to tobacco in both men and women. Recurrence rate after a definitive or adjuvant chemo radiation in stage III Or IVA-B ranges from 20—45%.

Apart from clinical examination, imaging modality like MRI plays a pivotal role in detection of loco regional recurrence, which replaces biopsy

OBJECTIVES

To co-relate the radiological and pathological response of squamous cell carcinoma of head and neck after conventional radiotherapy with weekly Cisplatin.

METHODOLOGY

We conducted single arm prospective study with 60 patients of head and neck carcinoma in two groups and treated with radiation of 66 Gy in 33 fractions with concurrent weekly cisplatin and evaluated with pre treatment and post treatment MRI scan and biopsy

RESULTS

Out of 60 patients 15 patients presented with residual tumor clinically but biopsy proven were 14 and MRI detected were 15 with false positive one case and sensitivity and specificity of 93 and 97 percent

CONCLUSION

Study of response assessment after conventional radiotherapy with weekly Cisplatin in head and neck cancer showed good correlation clinically with radiological image findings

- So imaging may be considered for primary assessment for follow-up

An invasive procedure may be avoided and it may be considered at times when imaging is inconclusive

Title: The radiological and pathological response co-relation of head and neck squamous cell carcinomas after conventional radiotherapy with concurrent platinum based chemotherapy

INTRODUCTION

Head and neck cancers constitute the most common malignancies[1] in developing countries like India due to tobacco[2] in both men and women. Overall 57.5% of global head and neck cancer occur in Asia, especially in India. Head and neck cancer in India accounted for 30% of all cancers. In India 60-80 % of patients presented often they present in advanced stages[3] due to lack of knowledge or far off from a good source of health care contact.

Recurrence rate after a definitive or adjuvant chemo radiation in stage III Or IVA-B [4] ranges from 20—45%.Most of the patients recurrence occurs within the first 2 years of treatment when on follow up[5]. In Andhra Pradesh according to cancer registry data,70 to 80% are head and neck cancer, with men of about 29% incidence and women of about 11% incidence

Apart from clinical examination, imaging modality like MRI[6] plays a pivotal role in detection of loco regional recurrence. Invasive procedure Biopsy can be replaced[7] by MRI scan in many instances.

MRI

MRI is a non invasive imaging method which gives three dimensional detailedanatomicalimages.Itusesstrongmagneticfieldandradio-waves toproduceimages.ThebiggestadvantageofMRIisnoriskofexposure

Mechanism of MRI

Human body is mostly composed of water, the proton in water (hydrogen nuclei) align themselves in the magnetic field (0.2 – 3teslas).The scanner produces a radiofrequency current which also create savoring magnetic field. When the field is turned off the proton return to their normal position known as precession.

The protons in different body tissues return to normal at different rates, which produce contrast between different body tissues., blood flow, micro-vessel permeability and diameter, tissue oxygenation and metabolism.

Histopathology after radiotherapy[8,9]:

Radiation treatment leads to endothelial damage and fibrosis, impairing lymphatic and vascular flow producing hypo vascular, hypo-cellular and hypoxic tissue. These tissues will not be able to maintain normal tissue turnover leading to necrosis, ulceration and infection. Within first two weeks after radiotherapy edema and mucosal irritation occurs thickening of neck muscles occur. Breakdown of collagen and cell death will overcome the ability of replication of affected tissue and leads to failure of healing.

AIMS &OBJECTIVES

Primary Objectives (s):-To co-relate the radiological and pathological response of squamous cell carcinoma of head and neck after conventional radiotherapy with weekly Cisplatin.

Materials &Methods

Study Centre:

Department of radiation oncology,

King George hospital-Andhra medical

college, Visakhapatnam

Duration of the Study: september2022 to May2023

Study Design: Single arm prospective study

Sample Size: 60 patients.

Inclusion Criteria:

- Biopsy proven newly diagnosed locally advanced (Stage III, IV A, IVB) Squamous cell Carcinoma of head and neck not treated previously

- Karnofsky performance status>60%,Age–between18-60years

- Blood parameters and vitals normal

Exclusion Criteria:

- Non Squamous Histopathology.

- Tumors of Unknown Primary, Parotid and other Salivary Gland tumors.

- Pregnant and lactating women

- Metastatic [Stage IVC] or recurrent disease

-Pre radiation dental prophylaxis will also be done.

Patients are planned for Conventional RT schedule delivering 66 Gy in 33 fractions at 2Gy per fraction over 6 ½ weeks

To treat the primary and the draining lymph node regions at a dose of 40Gy per 20 fractions over 4 weeks delivered 5 days in a week 2 Gy per fraction (Monday to Friday)

After off cord reduction, additional dose of 26 Gy per 13 fractions per 2.5 weeks at 2 Gy per fraction is delivered 5 days in a week (Monday to Friday

MRI scans from base of skull to roof of neck–pre-treatment and post treatment after 6 weeks of completion of chemo RT

Chemotherapy:

Inj. Cisplatin 40mg/m2 administered weekly as radio sensitizer with proper

pre medications for a total of 5 cycles.

Biopsy will be taken after 6weeks of completion of chemo-RT

Response assessment will be made both radiologically and pathologically as per RECIST criteria (1.1 version)

Data Collection and Methods:

- Pre treatment and post (6 weeks)MRI scan done to know the extent of tumor
- Biopsy from the pre treatment diagnostic biopsy site done after 6 weeks
- Toxicity assessment and local tumor control was also assessed.
- Response assessment will be made both radiological and pathologically as per RECIST criteria (1.1 version).

ANALYSIS / RESULTS.

Data were described as mean and standard deviation (SD) for quantitative variables and number and percentage for qualitative variables. Sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) with 95% confidence intervals (CIs) were calculated.

Age wise distribution

Members	Age group
4	20-30
12	31-40
19	41-50
25	51-60

Out of 60 patients most of them were in 5th decade accounting to 25 members (41%) Least is 2nd decade (6.6%)

SUBSITE

Oral cavity	28

Oropharynx	8
Larynx	12
Hypopharynx	12

GENDER

Male	43
Female	17

Male is to female ratio was 2.5

TOBACCO ABUSE

Tobacco chewer	16
Smoker	12
Smoker and chewer	22
Reverse smoking	3
Non tobacco	7

STAGE

Locally advanced head and neck squamous cell carcinomas are taken into consideration.

STAGE	NUMBER
III	13
IV-A	24
IV-B	23

Stage 3- 13 cases are of stage III (20%)

Stage IV-A 24 cases (43%)

Stage IV-B 23 Cases (37%)

RADIATION TOXICITY POST RADIATION

Radiation dermatitis

Grade -2	3
Grade-3	53
Grade-4	4

Most of the patients experienced Grade-3 acute dermatitis toxicity immediate post RT.

6 weeks post radiation- Acute radiation reactions subsided and residual disease was noted in some patients.

RESIDUAL DISEASE

	NO	YES
Oral cavity	28	10
Oropha rynx	8	nil
Larynx	12	02
Hypo pharynx	12	02

Residual disease subsites and stage.

Tongue	06
Retro molar trigone	03
Buccal mucosa	01
Supraglottis	02
Pyriform fossa	01
Post cricoid	01

Oral cavity subsites with tongue primary-06 cases .(42%)

Stage-IV-A -04 cases

Stage-IV-B-02 cases

Retro molar trigone-3 cases-Stage IV-A-02 IV-B-01

Buccal mucosa-01 case stage-IV-A

Supraglottis-02 Stage-IV-A 02

Pyriform fossa-01-stage-IV-B

Postcricoid-01-stage—IV-B

Clinic-pathological and radiological correlation

Observation	Clinical presentation	MRI Presentation	BIOPSY
No of patients		60	60
Patients presenting withsymptoms	16		
Patients presenting with Residual tumor clinically	15		
Positive for residual growth		15	14

Negative for residual growth		45	46

True positives	13
True negatives	45
False positives(MRI)	1
False negative(MRI)	1
Sensitivity	93%
Specificity	97%

Discussion

Most of the residual disease after Radical radiation will be addressed by salvage neck dissection[8],the pattern of residual disease and burden of disease is often misleading [9]due to post radiation changes in the pathological specimans.

Post-Radiation treatment changes[10] cannot be usually delineated from tumor recurrence and it is quiet challenge due to alterations in the anatomy after radiotherapy where recurrence may not be clinically evident until it is large enough to be clinically palpable

Hence imaging plays a major role in follow-up cases of head and neck cances..Imaging is of great value in surveillance [11]in addition to clinical follow up.

Post RT changes[13] are acute inflammatory reaction within the deep tissues, increased permeability of blood vessel and lymphatics resulting in interstitial edema and fibrosis which are difficult to interpret ,It is therefore very important to be familiar with the common characteristics of post treatment changes..

Progressive thickening of connective tissue and blood vessel[14] obstruction and fibrosis. Fibrosis causes contracture and hardening of soft tissues. Laryngeal cartilages do not show much of changes after radiation. Tumor recurrence appears as soft tissue mass in the resected margin after surgery. Cartilage and bone erosion is seen in large recurrent tumor Acute reaction in skin and mucosa appear during or after treatment, it depends on radiation dose and rate , radiation tissue volume, time elapsed since the end of radiation therapy. Changes seen include thickening of skin and muscle , Reticulation of subcutaneous fat and deep tissue fat layers ,Edema in the retropharyngeal space, Atrophy of lymphatic tissue ,in both the lymph-nodes and waldeyer's ring,, Thickening and increased enhancement of the pharyngeal walls, Thickening of the laryngeal structures with increased density of fat in the pre epiglottic and paralaryngeal space,.

Tissue necrosis after radiotherapy may be difficult to differentiate from residual tumor, in such circumstances patient management depends mainly on the combination of clinical and imaging findings .These changes are more pronounced during the first few weeks after the end of radiation therapy

These should not be misinterpreted as evidence of persistent tumor. Diagnostic surveillance should aim to detect potential persistent disease before it becomes clinically evident .Early detection of persistent or recurrent disease may at least in part, determine success of salvage therapy possibly with a better chance for successful salvage.

For primary tumor response after RT, MRI imaging variables include tissue asymmetry or mass

Grade I- no detectable focal abnormality

Grade II- anatomic asymmetry or a discrete mass<10mm.

Grade III-mass>10mm,Less than 50% reduction of largest dimension.Lymphadenopathy were evaluated based on diameter-1.5 cm along longest transverse diameter and 1cm along short axis diameter, presence of intra nodal focal defects, necrosis and calcifications.

In a study done by Esteban Brenetet al[15], study makes compelling arguments for the use of pre- and post-chemo-radiotherapy diffusion-weighted MRI in head and neck cancers. This technique brings about differentiation of patients with high potential for recurrence who necessitate intensive post-CRT monitoring. It also facilitates detection of early recurrence or disease progression, thus enabling faster, more efficient implementation of salvage treatment. Finally, diffusion-weighted MRI could be a useful tool to predict failure before CRT

Post treatment MRI imaging is of value when a residual tumor is suspected to confirm the presence of such a lesion and to determine its extent. Differential diagnosis for tumor recurrence includes a vascularized scar, which indicates early fibrosis and it appears as a soft tissue mass with ill defined margins and enhancement which is similar in MRI- retraction and decreased signal intensity on T2 weighted images is suggestive of fibrosis, diffusion weighted images is the best tool to differentiate tumor recurrence from normal post RT 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. ADC has a high sensitivity and Specificity with no overlap between tumor all and non-tumoral tissue. Low ADC is due to restriction of proton movement in extracellular matrix due to tumor hyper-cellularity.

Necrosis, inflammation and sub-mucosal fibrosis show high values of ADC due to low cell density and increase interstitial space. Mucosal necrosis show lack of mucosal enhancement and gas pockets in MRI. Diffusion weighted MRI imaging is useful in persistently enlarged lymph nodes after treatment ,lymph node recurrence has high signal intensity with a decreased ADC in diffusion weighted images.

S. E. J. Conno et al [16]conducted a study titled-MRI in head and neck cancer following chemo radio therapy: what is the optimal delay to demonstrate maximal response concluded that Apart from HPV-OPC patients with nodal disease, the 6-week post-CRT MRI demonstrates maximal reduction in the linear dimensions of head and neck cancer

Another study by **Y.L Dai et al[17]** titled-State of the art MRI in head and neck cancer The imaging modality should not be overlooked when it comes to its prognostic value, especially more advanced MRI methods, like diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI. On DWI-MRI, the apparent diffusion coefficient (ADC) has often been discussed as a prognostic factor in different head and neck sites

Another study by **roland .p.nooji et al[18]** Review analysed the role of specific functional MRI modalities in differentiating benign post treatment effects from recurrence and or residual malignancy and metastasis in HNSCC Differentiation between malignant and benign post-treatment effects in HNSCC is of importance to guide clinical decisions. Differentiation between malignant and benign post-treatment effects in HNSCC is of importance to guide clinical decisions. As anatomical MRI is not able to reliably differentiate post-therapy effect from tumor, functional techniques have been investigated and shown to be promising. This review showed that DWI can increase the diagnostic accuracy significantly for the primary tumor site and might also increase the diagnostic accuracy for the region lymph nodes after therapy. Diffusion is most easy to implement and is recommended to perform routinely in a clinical setting in HNSCC follow-up. Its use during treatment to predict outcome is interesting, but evidence is too low to implement Adenoid cystic carcinoma salivary glands and Melanoma .PNI Is easily identifiable in MRI which shows nerve enlargement and obliteration of fat planes, but granulation tissue may also mimic this finding which should be correlated with prior images.

Radiation induced vasculopathy may mimic atherosclerotic disease showing intimal proliferation, thrombosis and Accelerated atherosclerosis, radiation induced vasculopathy is often bilateral and related to irradiated field .Imaging plays an important role in early detection of recurrence ,to allow early intervention of salvage treatment. A baseline imaging as a reference for evaluation in the post treatment follow up.

Knowledge of the various treatment methods and their expected and unexpected post treatment imaging findings help to make an accurate diagnosis and avoid unnecessary future diagnostic work up. Post-treatment biopsy may not be a representative in site of lesion ,which may yield a false negative result, MRI gives a full view of picture which is more in favour of correct identification
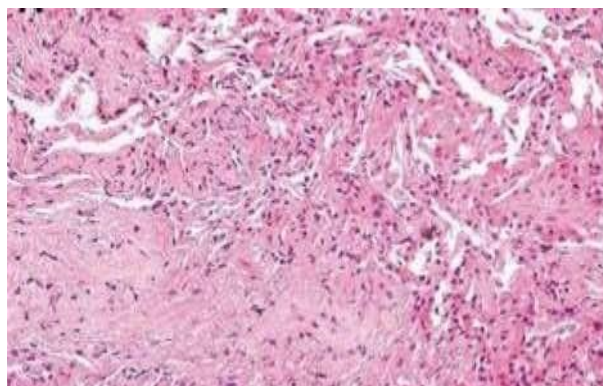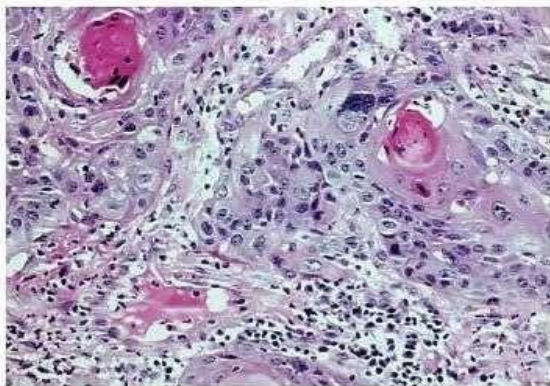
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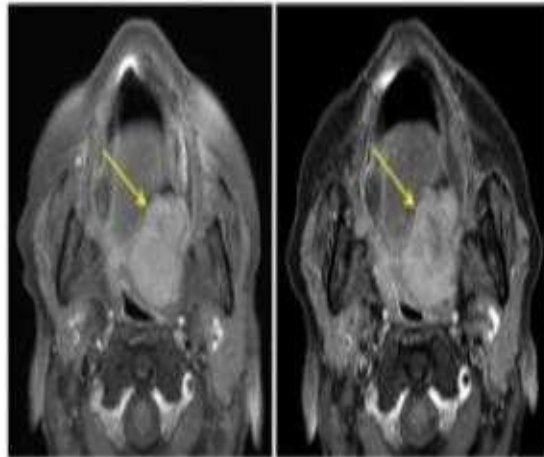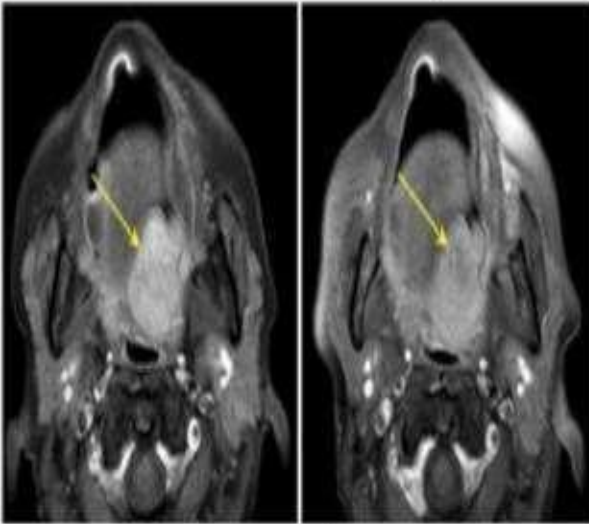
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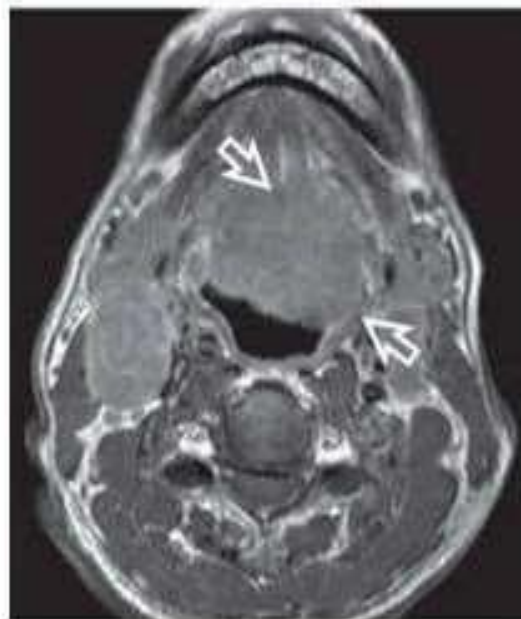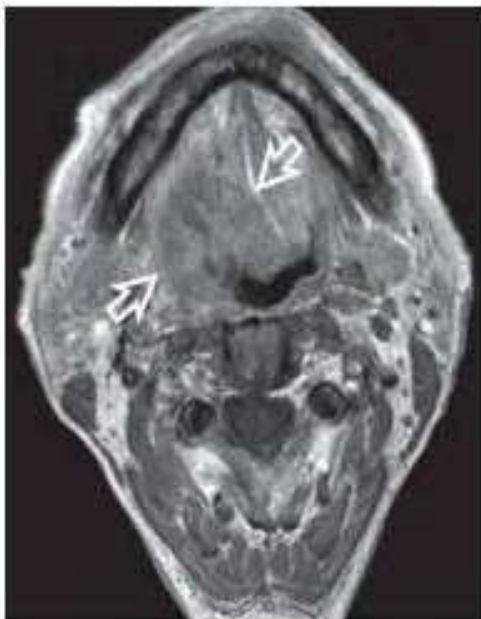
CONCLUSION

Study of response assessment after conventional radiotherapy with weekly Cisplatin in head and neck cancer showed **good correlation clinically**with radiological image findings

- So imaging may be considered for primary assessment for follow-up
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