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Diagnostic Efficacy of Computed Tomography and Magnetic Resonance Imaging in Detection of Cervical Lymph Node Metastasis among Patients with Oral Cancer

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Abstract

Background: Oral cancer in India accounts two-third of global incidence. 90% are squamous cell type that prone for neck lymph mode metastasis. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are common imaging methods for this purpose in our clinical practice to determine treatment plan, prognosis and after treatment follow up.

Aim: To assess the diagnostic efficacy of CT and MRI in detecting cervical lymph node metastasis among oral cancer patients in India using systematic review and meta- analysis.

Method: Literature search was be conducted by manual search as well as in academic databases such as Scopus, PubMed, Medline, science direct, and Google scholar from 2000-2021. Based on inclusion and exclusion criteria and studies were be analysed and tabulated. Qualitative assessment of included studies was done with QUADAS 2 which assessed the risk of bias. Further meta- analysis was done the to know the efficacy of CT and MRI in identifying lymph node metastases.

Results: A total of 14 studies including 561 participants were involved. With over all pooled sensitivity and specificity in meta- analysis, CT showed sensitivity of 92% and specificity of 70% and MRI had sensitivity of 75% and specificity of 91%, was identified in ROC curve in detecting the cervical lymph node metastasis. The diagnostic criteria for MRI and CT in identifying

cervical lymph node metastasis showed increases size, round shape, structural changes and extra nodal extensions are key features**.**

Conclusion: CT has good sensitivity and MRI has good specificity which is essential for selective neck dissection.

Keywords: Computed Tomography, Magnetic Resonance Imaging, Cervical Lymph node, Oral carcinoma, Lymph node metastasis, Diagnostic efficacy.

Introduction

Oral carcinomas are 11th most common cancer in Asia, with 66% of global incidence and mortality rate of 74% according to Global Observatory of Cancer (GLOBOCAN) 2020. Significant incidence is seen around the world due to environmental changes, life style as well as habit of using smoke and smokeless tobacco, reverse smoking or betel quid chewing. 90% of oral cancers are squamous cell type which disseminate via regional lymphatics to cervical lymph node. Metastasis of node reduces survival rate by 50% and when its contralateral side it further reduces survival by 25%.[3] Hence, identification of lymph node metastasis and staging of oral carcinomas are critical for appropriate management like selective or radical neck dissection, followed by radiotherapy and/or chemotherapy depending on the pathological findings of the nodes. Computed tomography (CT) and magnetic resonance imaging (MRI) are common imaging methods prescribed for this purpose which can determine treatment plan, prognosis and after treatment follow up. Imaging science has improved accuracy compared to clinical palpation and plays an important role in identifying occult metastasis. However, to determine whether which one these two techniques is higher than the other is critical for providing guidance in clinical practice. Meanwhile, relevant studies utilized different diagnostic criteria in identifying these metastatic lymph nodes, hence a comprehensive criterion that is most appropriate for identification has to be determined. India accounts for one third of global cancer incidence according to WHO 2018. About 70% of the cases are reported in the advanced stages (American Joint Committee on Cancer, Stage III-IV). Detection in the late phase, the chances of cure are very low, almost negative; leaving five-year survival rates around 20% only. Hence, the incidence of reported cases drew interest for comprehensive evaluation in Indian population.

The aim of this study was to assess the diagnostic efficacy of CT and MRI for detecting cervical lymph node metastasis among oral cancer patients in India and to establish the unified diagnostic imaging criteria from these studies in identifying cervical lymph node metastasis using systematic review and meta-analysis.

Materials and Method

Inclusion Criteria

The inclusion criteria were as follows: 1) types of study: diagnostic accuracy test studies designed as cohort studies in humans; 2) participants: Indian patients with biopsy proven oral cancer as primary site; 3) index tests: CT and/or MRI; 4) target condition: cervical lymph node metastasis; 5) reference standard: histopathology examination; 6) outcome: rates of sensitivity, specificity and diagnostic accuracy or true positive (TP), false positive (FP), false negative (FN), and true negative (TN) that could be used to calculate them. 7) Full article available

Exclusion Criteria

Exclusion criteria were (1) animal studies; (2) Diagnostic accuracy of other imaging modalities other than CT or MRI, 3) studies not done in Indian population 4) evaluation of conditions other than

cervical lymph node metastasis, 5) cancers other than oral cancer or secondaries in oral cavity 6) lack of confirmed evidence by pathological examination; 7) studies where the data like sensitivity, specificity, accuracy or TP, FP, FN, and TN are not available 8) review or meta-analysis or short communication, abstract.

Study Selection

All the articles were independently examined for the titles and abstracts of each search record to remove obviously irrelevant ones, not statistically analysed. Latter full text articles of potentially eligible ones were retrieved and further examined according to the inclusion criteria.

Data Extraction

All the articles were independently reviewed and extracted the key information of each eligible paper (such as first author name, year, study design, oral cancer site, diagnostic criteria, imaging modality used, rates of sensitivity, specificity, accuracy, positive predictive value and negative predictive value, TP, TN, FN, and FP based on "inclusion and exclusion criteria" mentioned above.

Types of Bias in Diagnostic Accuracy Test Studies

The quality of diagnostic accuracy studies assessment is determined by their design, sampling methods, testing involved, blinding in the process of interpreting tests and integrity of study report. Bias found in these studies are selection bias, spectrum bias in patient selection; Information bias in Index test; Misclassification bias, Partial verification bias in reference test; and Disease/ Condition progression bias, Differential verification bias, Information bias, Incorporation bias in flow and timing; These can be assessed using The Quality Assessment Diagnostic Accuracy Studies statement-2 (QUADAS-2)

Quality Assessment

The methodological quality of included studies was assessed by (QUADAS-2), which included four domains: patient selection, index test, reference standard, and flow and timing. Each domain was assessed in terms of risk of bias and the first three headings were assessed in terms of concerns regarding applicability. Signalling questions were included to assist judgments on risk of bias. [Table 1]

Results

Selection of Literature: 241 articles were identified in data base and manual search. Of this after removing the studies that did not determine diagnostic accuracy, statistically irrelevant, other modalities other than CT or MRI, reviews and meta-analysis, 67 studies were identified. In 67 studies, those that were done outside India were excluded and further complete reading of full article and considering our inclusion criteria we finally got 14 full text articles for systematic review. Figure 2 shows the PRISMA GUIDELINES followed in our systematic review and meta-analysis.

Study Characteristics

Of these 14 studies included, [Figure 3] 1 study included both MRI and CT, 2 studies were only MRI and 11 studies were only CT. Total participants involved in these studies is 516 among the 20 underwent both MRI and CT, 85 underwent only MRI and 431 underwent CT. The site of oral cancer involved in these studies includes buccal mucosa, lip, tongue, gingiva, gingiva buccal complex, soft and hard palate and floor of the mouth. Tongue cancer was the common cancer in all the studies included. [Graph 1] Mostly T2 and T4 stage in TNM staging was found in these studies. [Graph 3] The 14 studies which were included in systematic review are enlisted in Table 2. Among these studies, 13 studies were prospective and 1 study was both prospective and

retrospective. Lymph node metastasis was unit analysis. CT studies were done with contrast enhancement. MRI studies used T1W and T2 W fast spin echo sequence in two studies (Puhani et al 2017 and Goel et al in 2017) and along with these sequences Short tau inversion recovery sequence and Diffusion Weighted imaging (DWI) was identified in one study where ADC value was be calculated. For MRI the sensitivity ranged from 33%-94.4% and specificity ranged from 96%- 100% of MRI ranged. Study done with DWI gives a better sensitivity (94.44%), specificity (96%) and diagnostic accuracy (95.08%) of lymph node metastasis of and compared with other two studies in MRI. In 12 studies done in Contrast Enhanced Computed Tomography (CECT) ranges of the sensitivity was 11%-92%, specificity was 42- 100% and diagnostic accuracy was 61% - 96.1 % in our study. Mishra et al [17] 2016 study among CECT gave a highest accuracy of 96.1 %.

Quality of Included Studies

All the studies had fairly good applicability. For risk of bias assessment five studies (Suryavanshi et al 2021, Abishek et al 2018, Kallalli BN et al 2017, Mishra at al 2016 and Chaukar et al 2014) had low risk of bias, two study (Punhani et al 2017, Sharma et al 2021) had high risk of bias and seven studies (Tuli et al 2008, Pandeshwar et al 2013, Abdul et al 2015, Goel et al 2017, Geetha et al 2010, Hallur et al 2021, Shetty et al 2016) had an unclear risk of bias. [Table 3]

Quantitative Assessment

Meta-Analysis: Meta-analysis was done for 8 studies out of 14 studies. 6 studies which were not included because of considerable amount of heterogeneity and lack one or more variable of TP, TN, FP, FN. In these 8 articles, 7studies were CT and 1 study in MRI. The summary estimates of sensitivity and specificity of CT and MRI in diagnosis lymph node metastasis in various studies are analyzed with Forest plot with the confidence interval 95%. (CI= 95%) using RevMan software (2014). [Figure4]. Among the studies, Geetha et al 2010 had most skewed distribution with sensitivity 50% (95% CI: 12%- 88%), while the specificity was 100% (95% CI: 40%-100%). Other studies had moderately skewed distribution such as Abishek et al 2018 having sensitivity 90% (95% CI: 55%- 100%) and specificity 88%(95% CI: 75%-95%), Chaukar et al 2014had sensitivity of 76% (95% CI: 59%-88%) and specificity 85% (95% CI: 72%-94%), Pandeshwar et al 2013 showed sensitivity of 92% (95% CI: 74%-99%) and specificity was 84% (95%CI: 64%-95%), Sharma et al 2021 had a sensitivity of 92% (95%CI: 75%-99%) and specificity of 43% (95% CI:28%-59%); Hallur et al 2021showed a sensitivity of 67% (95% CI: 35%-90%) and specificity of 90% (95% CI: 81%-95%) . One study Mishra et al 2016 showed homogenous distribution and good sensitivity and specify of 87% (CI: 68%-98%); 97% (CI: 93%- 99%); Punhani et al 2017 which was MRI study gave sensitivity of 75% (66-100%) while specificity was low as 100% (CI: 6%-61%)

The sensitivity values obtained from these 8 studies were plotted in ROC curve with sensitivity in X axis and specificity in Y axis. It showed a sensitivity of 92% and specificity of 70% for CT and since there was one MRI study, whose corresponding sensitivity of 75% and specificity of 91% was identified in ROC curve in detecting the cervical lymph node metastasis. [Graph 3]

In the above-mentioned studies, there were variable diagnostic criteria used for CT and MRI. So going through these articles with good sensitivity, specificity and diagnostic accuracy, we derive a common holistic criterion for in CT and MRI for identifying a metastatic lymph node. Which are follows:

- Size of the node greater than 10mm in all the levels except IB and IIA (greater than 15mm).
- Round or spherical shape long axis/short axis (L/S) ratio ≤2.
- Irregular border of lymph node.
- Arterial invasion is noted by the degree of obliteration of the normal fat plane surrounding the artery
- Heterogeneity density of node.
- Enhance periphery with central hypo intense area of central necrosis.
- Grouping of three or more nodes, each of 8-15 mm diameters, which are contiguous.
- Extra nodal tumor extension seen as thickened nodal rim with infiltration of adjacent fat planes

Discussion

Oral squamous cell carcinoma is a common malignancy of head and neck leading to lymph node metastasis. Cervical lymph-node status at the time of diagnosis is one of the most important factors affecting long-term survival of the patient. Identification of sentinel lymph node, occult metastasis and skip metastasis is very important in the prognosis of the patient. Cancer cells get disseminated and reach the nearby lymph node through lymphatic drainage and change to metastatic node. The first lymph node in a regional lymphatic basin that receives lymph flow from the primary tumor is called sentinel node. This provides a “road map” of the lymphatic drainage from a tumor site. These metastatic lymph nodes show change in normal “lima beam” shape to round shape, increase in size, gets fixed to underlying structures and conglomeration of nodes occur. These can be evaluated by clinical palpation although there will be still metastatic nodes without showing these features. Hence imaging these nodes draining the area of cancer is essential.

Since 1981, CT has been used to determine neck metastasis in head and neck cancer. CT with hard and soft tissue window can delineate the primary tumor, distance metastasis as well as lymph node metastasis. CECT most commonly used for this purpose of viewing tissues in deeper planes, vascular supply and the disease extent. Disadvantage of CECT is high cost, radiation exposure, risk of anaphylaxis due to intravenous contrast and it cannot be repeated every time. Geetha et al in 2010 in her study using CT found 3 true positive and 3 false negative nodes which resulted in sensitivity of CT to 50%. In this study it was found that size criteria were more reliable for small nodes and rim enhancement with central necrosis is highly specific indicator of metastasis for large nodes. Kallali et al 2016 and Mishra et al[17] in 2017 are similar study to Geetha et al with 20 and 30 patients respectively. Their sensitivity of CT were 81% and 86.7 % respectively, which may be due to sample size and criteria used for diagnosis. Mishra et al found to have highest accuracy (96.1%) ,very low risk of bias and homogenous distribution of data in our study.

MRI provides better resolution of detailed soft tissue architecture than either CT or, USG (Ultrasonography), especially, in 3D visualization of the soft-tissue lesions and nodal metastasis. Use of MRI, in the head and neck region, is supported by the facts that oro-facial tissues have variable amount of fat distribution in different regions. Hence, different sequencing will aid in the viewing of tumor site, extent, characteristics ideally. Moreover, MR imaging is free from metal streak artifacts caused due to dental restorations as seen on CT images. Diffusion weighted MRI (DW-MRI) is superior in detecting nodal metastasis. Diffusion weighted image (DWI) is a non-invasive functional technique to study the molecular function and micro-structure of the tissue and lesion. Apparent diffusion coefficient (ADC)

mapping using signal intensity in DWI is based on the analysis of water molecule motion. This is used to differentiate benign and malignant nodes. Goel et al in our study showed ADC cut off value between benign and malignant node as 1.39x10 $^{-3}$mm^2/s. But Amit et al in 2019[22] made a prospective study in patients with lymph adenopathy and found that ADC cut off value 0.93×10-3 mm2/s. The major limitations of MR imaging includes its reduced availability and difficulties in performing MRI scan in patients who are claustrophobic and uncooperative. MR imaging is contraindicated in patients who have pacemakers and vascular clips. Both CT and MRI have their own advantages and disadvantages but they still remain are the reliable modality for investigation and treatment planning in oral cancer patients

In our systematic review and meta-analysis, we have comprehensively evaluated all the evidences from 14 studies whether one of the two imaging modalities (CT/MRI) can have a better efficacy. Our meta- analysis has pooled the results from available studies and found that CT had good sensitivity and MRI had good specificity which was in accordance similar studies done by Sun et al in 2015 and Park et al in 2020 in their systematic review and meta-analysis. Bondt et al in 2007, evaluated the diagnostic performance of Ultrasonography guided Fine needle aspiration cytology (USG- FNAC), USG, CT and MRI and found USG-FNAC is the most reliable imaging technique for identifying metastases in cervical lymph nodes in head and neck cancer patients. This variation may be due to lymph node size and shape criteria were only taken into consideration in these studies to determine whether the lymph nodes are pathonomic. Similar to our systematic review and meta-analysis comparing CT and MRI for lymph node metastasis, studies have been done for uterine cancer by Bipat et al in 2003 and cervical cancer Bin Liu et al in 2017 and they concluded that MRI showed better modality for identifying lymph node metastasis than CT especially DWI sequence. But Cho et al in 2020 for thyroid cancer in his review and meta-analysis exclusively for MRI reported MRI showed moderate diagnostic performance in the diagnosis of metastatic lymph nodes in patients with thyroid cancer in the neck but this may be due all studies which were included seemed to be retrospective and there was high risk of bias.

Finally, irrespective of CT or MRI, the imaging diagnosis of metastatic lymph node showed most of studies had size, shape (L:S >2), central necrosis with peripheral rimming as criteria. Studies done in 2021 had the Extra Nodal Extension as (ENE) as additional criteria which were also included the revised 8th edition AJCC staging of head and neck cancer.

Limitation of the study

The limitations of our study showed firstly, although we conducted meta-analysis, the studies showed that assessed variables largely did not account for heterogeneities between studies, additional undetected heterogeneities warrant further research. Secondly, present study was focused on the only group of Indian of population, hence more MRI studies in order to evaluate its diagnostic accuracy in detection lymph node metastasis in oral cancer among Indian population are need. Thus, we will be able to narrow down the promising diagnostic study. Finally, with more sample size and homogenous data, we will be able to analyze CT and MRI independently for diagnostic accuracy is also required.

Conclusion

Our comprehensive systematic review and meta-analysis have identified both CT and MRI show reasonable

diagnostic performance for detection cervical lymph node metastasis in oral cancer patients in India. Our study seems to be one of first of its kind exclusively in Indian population. In our CT has good sensitivity which is essential to investigate metastatic node. But, nevertheless MRI with good specificity is need for diagnostic confirmation or eliminate non metastatic nodes. This is essential for selective neck dissection which influence the morbidity and mortality in patients. The lymph node size, shape, structural changes like central nodal necrosis and peripheral rim with infiltration in to adjacent fat (ENE) are diagnostic markers of metastasis. Further, more research and literature are to be drawn in this spectrum for more adequate and valuable information on primary or metastatic oral cancer.

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