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Performance Of Different Radiological Imaging Modalities For Estimation Of Tumor Thickness Of Oral Cancer- A Systematic Review

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Abstract
This systematic review seeks to provide high-quality evidence on the performance of different radiological imaging modalities for estimation of tumor thickness of oral cancer. Until 2021, a systematic electronic literature search was undertaken utilizing keywords and MESH search phrases in the PubMed/Medline, Cochrane Central, Scopus, and EBSCO databases, as well as Google Scholar. In addition, the reference lists of the systematic reviews included in the study were manually searched. Patient satisfaction and complications were collected from prospective and experimental studies that provided the greatest degree of evidence. Articles were evaluated critically, and the MINORS scale was used to determine the risk of bias. This systematic review suggested that ultrasonographic examination offers the advantages of being more accurate, noninvasive, quick, and repeatable, and offers increased number of prospective applications. On the other hand MRI provides better structural resolution than CT and USG, but remains limited for the detection of lesions > 3mm.

Keywords: *MRI, PET, Ultrasonography, oral cancer, tumor thickness*

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I. Introduction:

Oral cancer, which accounts for >90% of all oral cavity malignancies and is characterized by oral squamous cell carcinomas (OSCC), is a leading cause of cancer mortality globally, with an estimated 177,000 fatalities each year [1]. It's a cancer that's considered aggressive, with a 5-year overall survival rate of about 50%, declining to less than 30% in advanced stages [2]. The most common reasons for death in OSCC patients are tumor extension, lymph node metastases, and the formation of second primary tumors [3]. Survival rates differ between developed and developing nations, owing to late diagnosis and insufficient access to the most recent breakthroughs in therapy choices in developing countries [4].

Surgery along with adjuvant radiation with or without chemotherapy is now the standard of care for OSCC [5]. The disease stage is still used to manage OSCC patients; however it doesn't accurately reflect the biological behaviour of this heterogeneous collection of tumors. Tumors of the tongue and mouth floor, in particular, can be aggressive even early in their development, with a higher risk of invasion, metastasis, and, as a result, a poor prognosis [6].

In 2017, the 8th edition of the Union Internationale Centre le Cancer (UICC) TNM classification and the 8th edition of the American Joint Committee on Cancer (AJCC) T classification included the notion of depth of invasion (DOI) to the T classification, in addition to the superficial spread of the tumour. DOI is a histological term that refers to the vertical distance between the virtual plane linking the foundation membrane of the normal mucosa next to the tumour and the deepest section of the tumour. It is not the same as tumour thickness. However, clinical measurement procedures, such as diagnostic imaging, have yet to be fully defined and articulated. Although CT or MRI is effective for preoperative evaluation, there is no standard procedure for preoperative DOI measurement.

Ultrasonographic diagnostics has become increasingly employed as a diagnostic imaging of the head and neck region in recent years. Despite the fact that the UICC and AJCC declare that ultrasonography is not appropriate for the examination of primary lesions, several studies have used intraoral ultrasonography (US) to evaluate primary lesions and shown a high connection with histological thickness or DOI. To date, various papers have been published on CT, MRI, and US preoperative radiological DOI evaluations, but no study has been published in which all of these tests were performed at the same time [7].

Tumor thickness (TT), DOI and tumor volume (TV) are important determinants used for prognostic performance, increasing depth of invasion and microvascular proliferation is associated with recurrence and ability to metastasize. It has been mentioned that increased tumor thickness is directly associated with cervical node metastasis. Here, we intend to report a systematic review of the literature pertaining to the use of radiological modalities for determination of tumor thickness.

Aim

To analyses the performance of different radiological imaging modalities for estimation of tumor thickness of oral cancer.

Objectives

To assess

- The diagnostic efficacy of imaging techniques for tumor thickness determination in oral cancer.

Methods

The search protocol is designed based on the PRISMA (Preferred reporting Items for systematic Reviews and meta-analysis) guidelines 2009.

SEARCH STRATEGY

The electronic MEDLINE, Embase, Cochrane, Google Scholar, Scopus and PubMed databases were searched. Additionally, the bibliography of all relevant articles and textbooks were manually searched. Based on the inclusion and exclusion criteria, 2 reviewers) independently selected the relevant articles. Any disagreement was discussed between the 2 reviewers until a consensus was reached.

Using the PICO-format question, methodological Medical Subject Heading (MeSH) terms were generated to make the search strategy more sensitive in the identification of studies. These terms included ("Computed Tomography" [MeSH] AND (Contrast Enhanced Computed Tomography" [MeSH]) AND ("MRI" [MeSH] AND (“PET” [MeSH]) AND ("Ultrasonography" [MeSH]. Studies that met these inclusion criteria underwent critical analysis. The qualities of the included studies were evaluated according to a proposed specific quality assessment scale.

INCLUSION CRITERIA

The following types of studies were considered:

1. Studies published in English language peer reviewed scientific journals upto January 2022.
2. Randomised controlled trial
3. Case Control study
4. Cohort study
5. Quasi Trials
6. Single Arm Intervention
7. All the articles published till 30 November 2021 were included
8. Full articles in English were included

EXCLUSION CRITERIA

The exclusion criteria included the following:

1. Retrospective Studies
2. case reports, case series,
3. cross-sectional studies,
4. or animal studies,
5. Reviews
6. Abstracts,
7. Technical reports
8. Expert opinions
9. Articles with incomplete data were excluded.

The references of selected articles were also analyzed for additional studies. and any study that did not meet the inclusion criteria.

FORMULATING THE REVIEW QUESTION

The research question was set in accordance with the PICO format (Population, Intervention, Comparison, and Outcome). (Table-1)

SELECTION

The study selection was done in a three step process. All the titles were reviewed and based on the inclusion and exclusion criteria, appropriate studies were selected. For all the selected titles, abstracts were obtained and reviewed, from which appropriate abstracts were selected based on the criteria. For all the selected abstracts, full text articles were obtained and analysed, and the final set of articles were obtained keeping in mind the selection criteria. (Table-2)

DATA EXTRACTION

After the final study sample was determined, data from all studies were extracted into an Excel data sheet. This included: first author, year of publication, study design, number of subjects, mean age, tumor location and stage and image modality used of the subjects.

QUALITY ASSESSMENT

A quality assessment of the included articles was conducted to evaluate their methodological quality. Therefore, the validated Methodological Index for Non-Randomized Studies (MINORS) was used. This instrument was originally developed to review surgical research, where randomization is not always feasible. However, it was still useful to systematically review the existing literature and answer questions in that particular field. Taking into account all the above, we considered the MINORS index as the most appropriate quality assessment index

to evaluate the articles of this systematic review. According to this scale, the articles were divided into comparative and non-comparative studies with different scoring for both groups. Each item of the scale was given a score of 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). For non-comparative studies, 8 items have to be scored, so the global ideal score is 16, while for comparative studies, there are 4 additional items, so the global ideal score for comparative studies is 24. The first author (A.L.) scored all the included articles and the second author (M.C.) was consulted in case of doubt. Judging of the used statistical analysis of the comparative studies was performed by the two main reviewers (A.L and M.C), consulting a professional statistician in case of doubt.

Results: On initial search 200 articles were obtained. Out of a total of 200 articles of the database search, after removal of duplicates and elimination based on eligibility criteria, a total of 16 studies were included for analysis.

SYNTHESIS OF RESULTS

Narrative synthesis has been provided for the findings obtained from the studies. The data extracted has been presented in the tabular form (Table no- 3)

RISK OF BIAS ASSESSMENT

Risk of bias was assessed using Cochrane Risk of Bias Assessment Tool. Bias is assessed as a judgement (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other). Risk of selection, reporting, and other bias are assessed in the Quality Assessment Form Part I. Risk of performance, detection, and attrition bias are assessed using the Quality Assessment Form Part II.

Using the guidance provided at the end of the form, risk of bias was selected as "high", "low" or "unclear" for each judgment. (Table-4)

II. Discussion

Several studies have been conducted in the past to assess the various elements that influence a cancer's prognosis. Epidemiological, histopathological, and clinical factors could all play a role. Personal history and living situations are epidemiological factors that are highly dependent on the patient's compliance. Clinical parameters, such as TNM staging and tumour location, must be determined. Histopathological markers include perineural and perivascular invasion, tumour thickness, grading, and invasion pattern. These histological criteria should be evaluated prior to treatment, particularly if surgery is the treatment plan. Preoperative information on TT and DOI is extremely useful in deciding treatment decisions, allowing two-step surgery to be avoided. Pathological DOI bigger than 4 mm has been linked to cervical lymph node metastases, and neck dissection is recommended in such instances by the National Comprehensive Cancer Network (NCCN). Histopathology is still the gold standard for evaluation. CO2 laser resections and photodynamic therapy have shown good results in tumours with decreased tumour thickness [26]. Various approaches for determining preoperative thickness have been tried in the past. Studies comparing the tumour thickness estimated from preoperative tumour biopsy with the final postoperative pathologic measurement have found that thick tumours have a higher risk of nodal metastasis, and Bundgaard et al [27] reported that they were unable to obtain tumour thickness measurement from biopsy in their study. Clinical palpation for thickness measurement has similarly yielded varied and unsatisfactory results, with little evidence of its utility. As a result, these modalities have limitations in terms of ensuring total removal of a tumour mass. [28]. The depth of invasion (DOI) was added to the T category of oral cavity cancer in the 8th edition of the American Joint Committee on Cancer's (AJCC) Cancer Staging Manual [29]. The most appropriate method, surgically extracted specimen, has the primary downside of delaying decisions about neck therapy until reports are available, potentially leading to a second stage surgery that is more harmful to the patient.

TT and DOI are words that are not interchangeable but have been used interchangeably in earlier investigations [30,31]. The deepest invasion of the tumour in the tissue from the tumour surface is described as tumour thickness, and the distance from the surrounding epithelial surface to the deepest point of invasion of the tumour is defined as DOI. [32,33] Tumor volume is estimated by multiplying the sum of all transverse section areas by the thickness of the section. [34] For MRI-based measurement, a study was done in which DOI was replaced with TT. [35]

As a result of these vital issues, selecting an appropriate preoperative diagnostic approach becomes crucial. In this study, articles were read and analysed to identify the tumour depth for each imaging modality. The diagnostic capabilities of CT, MRI, CECT, and USG were compared. Each study was examined separately for its design, quality, tumour site, age, and modality employed. Despite the fact that pathological examination remains the gold standard for assessing thickness, formalin preparation and paraffin embedding have been proven to cause some shrinkage.

MRI can be used to determine the extent and stage of primary oral cavity malignancies. Because tumours have higher signal intensity than normal tongue tissue, MRI can accurately detect OTSCC. Previous research has discovered a strong link between MRI-based TT and pathological TT[23]. Different magnetic strengths have been used in studies, and it has been suggested that T1-weighted imaging is better for measuring preoperative tumour thickness and staging, as well as planning case management. A difference of 3.3 mm and 3.9 mm was reported between tumour thickness on CET1WI and pathological DOI with 1.5 T and 3T MRI, respectively, in a research by Baba et al. [10] In the investigation, stretching with a rubber plate reduced processing shrinkage.

Heterogenous results were also seen when a study was conducted by Chen et al, on T4a-staged tongue carcinoma isolately, but a significant correlation was present with correlation coefficient R = 0.905. It was found that the mean MRI thicknesses were significantly greater than histologic thicknesses in various studies. Differences between histologic and MRI thicknesses were found to be small (about 10%)[14]. Preda et al, mentioned that overestimation of MRI thickness is due to the presence of peritumoral edema which leads to the increased signal intensity surrounding the lesion. So, they measure the thickness in T2-weighted images with fat suppression over tongue cancers which are not usually surrounded by conspicuous edema [12]. They have also mentioned that in relation to tumor size and degree of vascularization, contrast agent gets distributed variably.

In their retrospective investigation, Koning et al found that TT is more accurately evaluated with US than MRI when compared to other imaging modalities. They employed an intraoral ultrasonography tool that was placed on the lesion directly. The mean difference between TT measured on US and histology was 0.05 mm (STD 2.7 mm) and 1.3 mm (STD 3.7 mm) between MR and histopathology [13]. Similarly, Lodder and colleagues observed that USG (R=0.87) had a greater correlation with histology than MRI (R=0.54)[17].

In the past, ultrasonography was used to evaluate tumor thickness in a variety of ways, including intra-oral, transbuccal, and submental [36]. While the majority of the studies in this review used the mode in the preoperative period, Songra et al used intraoperative intra-oral ultrasound imaging to measure surgical margin clearance of tumor and found good reliability [20]. Weimer et al. conducted a study blinded to pathology to evaluate the radiologic tumour thickness using preoperative CT or MR imaging, and observed a significant rTT-pTT correlation (P0.001) with somewhat greater correlation with MRI. The involvement of the mucosal epithelium, lamina propria, and muscles can be seen clearly on MRI. [21] It has a higher structural resolution than CT and sonography.

Because of the concomitant extreme discomfort experienced by patients, particularly with the floor of mouth, it is more difficult to keep the USG probe in touch with lesions, and the technique is more operators reliant. Madana et al. discovered a highly significant association between pathological tumor thickness of 11.60 mm and mean CT tumor thickness of 12.88 mm, but cited MRI as a better modality in the evaluation of soft tissue lesions [18].

The literature is divided on whether 3.0-T MR performs better than 1.5-T MR. According to Moreno et al. [37] and Lu et al. [38], the most interesting feature of 3.0-T MR is an expected signal-to-noise ratio increase proportional to magnetic field strength, but other features such as increased T1 relaxation time, decreased T2 relaxation time, increased magnetic susceptibility contrast, and increased spectral resolution for MR spectroscopy may also provide important benefits. Neumann et al. [39], on the other hand, noticed certain important difficulties with 3.0-T MR due to the greater magnetic susceptibility, which led to probable spatial distortion, according to the authors. Singh et al. [40] found good agreement (K=0.79) between MR and histology for T staging, with only 14% of patients changing their fnalpT category.

In tiny tumours, the partial volume effect of FDG PET is a significant drawback. PET scanners, along with its modifications, have been discovered to be significantly associated with MRI based TT, which is not available with non SiPM pet based long axis. In T1 and T2 tumours, MRI-based tumour thickness is not connected with both PET and SIPM PET, but it is correlated with both SIPM PET and non SIPM PET in T3 and T4. The study also demonstrated that pathological and SiPM-based PET had a substantial association when compared to non-Si PM PET.

Tenderness, trismus, or anatomic location that prevents proper ultrasound probe positioning is all limitations of intraoral ultrasonography. Furthermore, in bigger tumours (i.e. >20 mm), discordances between pathological and ultrasound-derived tumour thickness have been observed, which can be explained by transducer limitations as well as tissue shrinkage due to histological processing.

III. Conclusion

This review demonstrates that ultrasonographic examination provides better accuracy than MRI and CT, with major advantage of being non-invasive, quick, and repeatable and increased number of prospective applications. Selection of the way to perform, ultrasonography should be made on the basis of location of tumor. On the other hand, MRI provides better structural resolution than CT and USG, but remains limited for the detection of lesions > 3mm.

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TABLE 1: PICO FORMAT

S.No	Category	Search items
1	Population	Patient with Oral cancer
2	Intervention	Imaging Techniques
3	Comparison	Between different imaging techniques
4	Outcome	Estimation of tumor thickness of oral cancer

TABLE NO: 2 DATA SELECTION

Initial search	200
Duplicates and non-relevant	75
Case reports and series	42
Reviews	40
Abstract	18

Table no: 3 EXTRACTED DATA

Study	**Design of study**	**Study group**	**Mean age**	**Tumor location and stage**	**Imaging modality used**	**Comparison**
Kojima et al (2020) [8]	Retrospective	46 (25- SiPM PET/CT 21- conventional PET/CT)	65.9 years (26 men, 20 women)	OTSCC T1- 6 T2- 9 T3-6 T4-4	(PET) scanner using a silicon photomultiplier (SiPM PET) and conventional PET/CT/ MRI/HP	SiPM PET better detection sensitivity tumors
Yoon et al(2020) [9]	Prospective	26	NA	OTSCC	Sonography	Intraoral Sonography provides better results
Baba et al(2021) [10]	Retrospective	30	67±10.3 years (18 males and 12 females)	Floor of mouth	Coronal fat-suppressed CET1W /coronal T2WI/ HP	Undetectability on MRI -superficial lesions with a DOI <3 mm.
Boland et al (2010) [11]	Retrospective	40	(24 men, 16 women) had a mean age of 57 years (23–86 years)	OTSCC	T2 weighted fast spin-echo images with fat suppression	NA
Preda et al (2006) [12]	Retrospective	33	52 years (21 men 12 women)	OTSCC	T2-weighted fat-suppressed images	MRI- accurate and reproducible
Koning et al (2019) [13]	Retrospective	83	61 years (45 men 38 women)	tongue (58), floor of the mouth (24), palate (2), lip (1)	USG/ MRI	TT is best estimated with the use of USG
Chen et	Retrospective	58	(54 male	OTSCC	1.5T MRI axial T1-	NA

al(2011) [14]			4 female)		weighted images ,axial & coronal fat-suppressed T2-weightedsequence, contrast-enhanced T1-weighted spin-echo images	
Choi et al(2014) [15]	Prospective	29	52 yearrs (22 men, 7 women)	OTSCC(16) Fibroma(3), hemangioma(10)	Transbuccal USG/ HP	NA
Lam et al(2004) [16]	Prospective	18	63.5 years (16 males 2 female)	OTSCC: 8- T1 (7-N0 and 1-N1; all M0); 8- T2 (6-N0 and 2-N1; all, M0); 2 at T3 (both, N1; both, M0)	MRI (contrast-enhanced T1-weighted and T2-weighted spin-echo sequences) and histologic sections	MRI- satisfactory
Lodder et al (2011) [17]	Retrospective	65	65 years (34 men 31 women)	Tongue (38), Floor of the mouth (22) Other sites (n=5). T1 AND T2 STAGE	Intra-oral US (65) MRI (36)	NA
Madana et al (2015) [18]	Retrospective	116	66 years (range 28–92)	OTSCC	CT/HP	CT scan provide an accurate estimation of true thickness
Shintani et al(1997) [19]	Prospective	24	32 -77 years; (16 men 8 women).	OTSCC T1NOMO to T4NOMO.	I/0 USG/ HP	NA
Songra et al(2005) [20]	prospective	14	N/A	11 OTSCC 1 alveolar mucosa 1 floor of mouth 1 lip	Intraoral USG/ HP	Intraoral USG-assessing the TT and the surgical margin clearance
Weimer et al(2018) [21]	prospective	335	62 years (129 female 206 male)	All OSCC except lip T1-T3	CT/ MRI/HP	Both rDOI and rTTare indepen-dently associated with inferior OS in addition to seventh edition T-category.
Tang et al(2021) [22]	Retrospective	122	62 yrs (78 Male 44 female)	OTSCC	(T2WI), diffusion-weighted imaging (DWI), dynamic enhanced-T1 high-resolution insotropic volume examination (e-THRIVE), (CE-T1WI)	NA
Iwai et al (2002) [23]	Retrospective	30	54.2 years (24 male 6 female)	OTSCC (7 T1 tumors, 18 T2 tumors, and 5 T3 tumor)	T2-weighted sequence in the axial plane	NA
Filauro et al (2021) [24]	Retrospective	49	65.6 Years (22 Female 27 Male)	cT1-T3 OCSCC	1.5 T MR, 3 T MRI, IOUSG	Good correlation with histopathological findings. IOUS- used alone, for preoperative staging of early OCSCC. 3 T MR >1.5 T MR.
Takamura M et al (2021) [7]	Retrospective	48	65.7 years (28 men and 20 women)	T1/T2 tongue cancer	US, CT, and 1.5 T MRI in preoperative image depth of invasion (DOI)	US most accurate preoperative diagnostic tool for T1 and T2 SCC
Noorlag R et al (2020) [25]	Retrospective	83 for MRI 107 for IOUS	64 years (74 males and 72 females)	T1-2 tongue cancer	1.5 T MRI, 3 T MRI, IOUS	Estimation of histopathological DOI in tongue cancers with DOI till 10 mm is very accurate through use of IOUS. MRI tends to overestimate DOI in

						both thin and thick tumours.

Table 4 Risk of bias assessment.

Authors name	Selection Bias Random sequence generation	Allocation Concealment	Reporting bias	Others	Performance bias Blinding participants and personnel	Blinding Outcome	Attrition bias
Kojima et al (2020)[8]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	High risk
Yoon et al(2020)[9]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Baba et al(2021)[10]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Boland et al (2010)[11]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk
Preda et al (2006) [12]	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk
Koning et al (2019) [13]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chen et al(2011)[14]	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk
Choi et al(2014) [15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lam et al(2004)[16]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	High risk
Lodder et al (2011)[17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Madana et al (2015)[18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Shintani et al(1997) [19]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk
Songra et al(2005) [20]	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk
Weimer et al(2018) [21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Tang et al(2021) [22]	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk
Iwai et al (2002) [23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Filauro et al (2021) [24]	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk
Takamura M et al (2021) [7]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Noorlag R et al (2020) [25]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

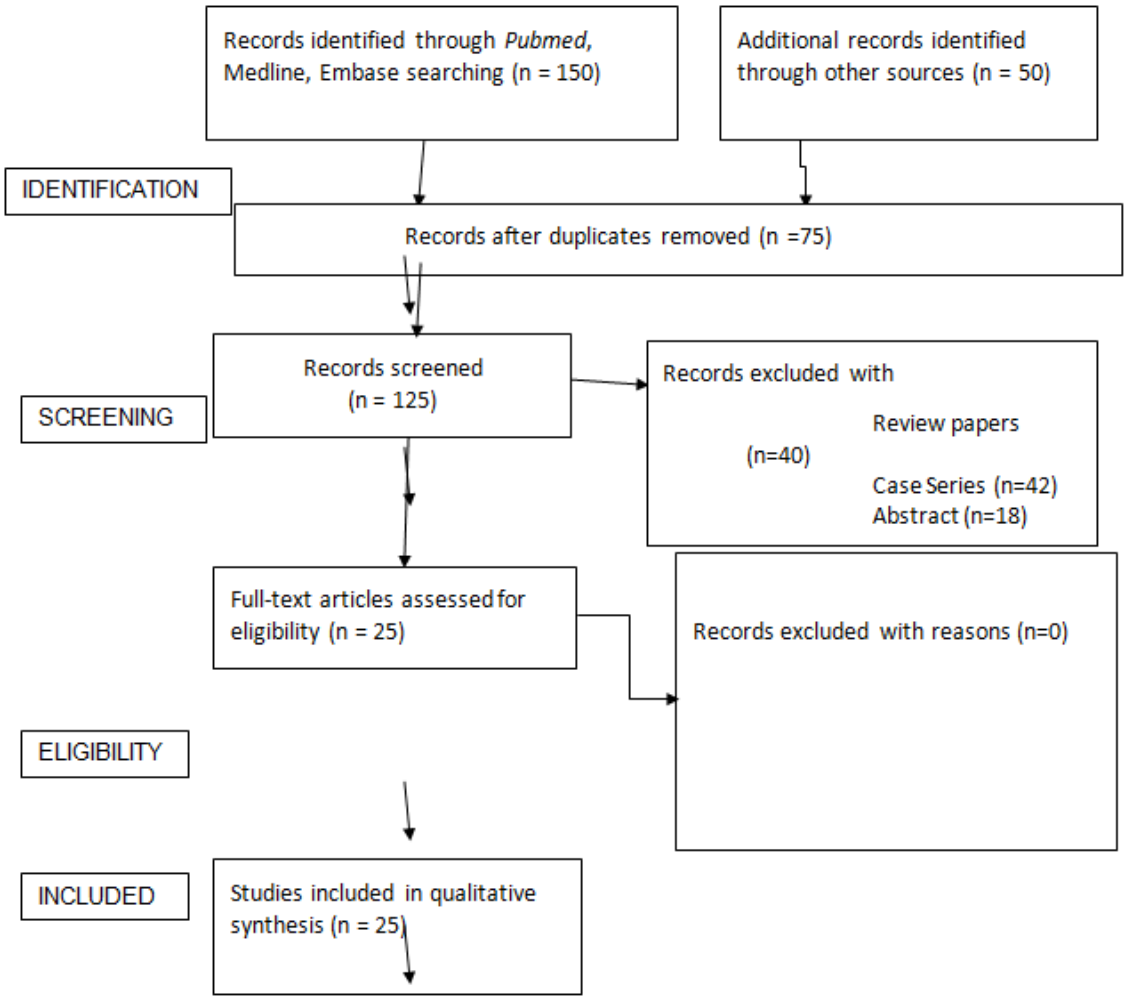

Figure: PRISMA flow chart

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