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SYSTEMATIC REVIEW

Accuracy of imaging methods for detection of bone tissue invasion in patients with oral squamous cell carcinoma

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The objective of this review is to evaluate the diagnostic accuracy of imaging methods for detection of mandibular bone tissue invasion by squamous cell carcinoma (SCC). A systematic review was carried out of studies in MEDLINE, SciELO and ScienceDirect, published between 1960 and 2012, in English, Spanish or German, which compared detection of mandibular bone tissue invasion via different imaging tests against a histopathology reference standard. Sensitivity and specificity data were extracted from each study. The outcome measure was diagnostic accuracy. We found 338 articles, of which 5 fulfilled the inclusion criteria. Tests included were: CT (four articles), MRI (four articles), panoramic radiography (one article), positron emission tomography (PET)/CT (one article) and cone beam CT (CBCT) (one article). The quality of articles was low to moderate and the evidence showed that all tests have a high diagnostic accuracy for detection of mandibular bone tissue invasion by SCC, with sensitivity values of 94% (MRI), 91% (CBCT), 83% (CT) and 55% (panoramic radiography), and specificity values of 100% (CT, MRI, CBCT), 97% (PET/CT) and 91.7% (panoramic radiography). Available evidence is scarce and of only low to moderate quality. However, it is consistently shown that current imaging methods give a moderate to high diagnostic accuracy for the detection of mandibular bone tissue invasion by SCC. Recommendations are given for improving the quality of future reports, in particular provision of a detailed description of the patients' conditions, the imaging instrument and both imaging and histopathological invasion criteria.
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Introduction

Even though the incidence of oral cancer had diminished from 1975 up to the mid-1990s, this trend has now been reversed, particularly in young adults.[1] And although oral cancer represents 3% of all malignant tumours,[2] it has a high fatality rate, with a 5 year survival rate of less than 60%.[3] The most common cancer in the oral region is squamous cell carcinoma (SCC), which represents 90% of malignant lesions in the oral cavity,[4] particularly in the mandible, with more than 300 000 new cases diagnosed each year worldwide.[5]

For malignant tumours such as SCC, rapid growth may occur even though there are no previous clinical signs.[6] For this reason, clinical examination must be complemented by radiological examination[7] for the assessment of size, thickness and depth of the tumour[8] as well as the degree of bone tissue invasion.[9–11] This bone tissue invasion detection, cortical or medullary, is indicative of a T4 tumour stage.[12] At this stage, the 5 year survival rate is close to 50%, whether treatment is surgical resection (47% survival)[13] or chemotherapy

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(56% survival).[14] For this reason, detection of bone tissue invasion significantly improves patient prognosis.

Complementary to the staging based on biopsy[15] new technologies for non-invasive diagnostic imaging have appeared, which, among other things, have permitted assessment of bone tissue invasion. Such new technologies include: ultrasonography,[16] cone beam CT (CBCT)[17] and single photon emission CT (SPECT) scintigraphy.[18] Existing imaging techniques have been adapted to allow for detection of bone tissue invasion. For example, using gadolinium-diethylenetriaminepentaacetate (Gd-DTPA)[19] as a contrast medium in MRI, reduction of artefacts in CT[20] and the combined use of imaging tests such as positron emission tomography (PET)/CT[21] and SPECT/CT.[22]

In 2001, Brown and Lewis-Jones[23] published a narrative review of different imaging technologies available at that time for the detection of SCC bone tissue invasion. Although it is true that a narrative review allows for a general evaluation of the state of the art, it does not permit a quantitative evaluation of diagnostic accuracy of the distinct imaging techniques nor an assessment of method quality. Thus, our aim is to assess, with a systematic review, the quantity and quality of the evidence available and then to synthesize this in a quantitative manner that will allow us to respond to the following clinical question: what is the accuracy of different imaging methods to detect bone tissue invasion in patients with SCC in the mandible?

Table 1 Inclusion and exclusion criteria of studies

Inclusion criteria
1. Studies of diagnostic accuracy that compare imaging tests in single or multiple form with histopathology examinations, the latter being the reference standard
2. Imaging tests include: panoramic radiography, orthopantomography, CT, cone beam CT, MRI, ultrasonography and/or scintigraphy (positron emission tomography and/or single photon emission CT)
3. Patients diagnosed with oral squamous carcinoma
4. Squamous carcinoma located only in the mandible
5. Must indicate the protocol for each applied imaging test (type of equipment, T_1/T_2 window and the planes used, slice thickness in millimetres) and the imaging criteria used for diagnosis of bone tissue invasion
6. Must describe or give sufficient information to be able to calculate the sensitivity and specificity of the imaging test, to construct a 2×2 contingency table
7. Histopathology examination obtained by bone resection or partial resection or by bone stripping, indicating the criteria for diagnosis of bone tissue invasion
Exclusion criteria
A. Previous treatment of the squamous carcinoma whether unimodal or multimodal, in >10% of the study population
B. Study of metastasis or invaded lymph node
C. Duplicated studies: the older version will be excluded
D. Recurrent squamous carcinoma, in >10% of the population
E. Studies with <10 participants
F. Studies of pharyngeal cancer

Materials and methods

Protocol

The collection, inclusion and analysis methods according to which this review was carried out have been established in a previous unpublished protocol. This can be requested from the corresponding author. This systematic review has been compiled according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (http://www.prisma-statement.org/).

Selection criteria

Seven inclusion criteria (1–7) and six exclusion criteria (A–F) were used for this systematic review (Table 1). Each paper was reviewed for these criteria in a sequential manner. In those studies that were excluded for more than one criterion mention is only made of the first unfulfilled criterion.

Study participants were patients of any age, with a histopathological diagnosis of SCC. Index tests were panoramic radiography, CT, CBCT, PET/CT, SPECT and MRI (all suitable sequences). The condition to be detected was mandibular bone tissue invasion, taking the histopathology reference as the reference standard.

Search strategy

A search was performed for studies of diagnostic accuracy in the databases MEDLINE, SciELO and ScienceDirect with selected index terms, from the year 1960 to 28 February 2012. This search was limited to the literature published in English, German or Spanish. Details of the search strategies are shown in Table 2.

In addition, the reference section of selected articles was reviewed manually. The final search, both manually and in the databases, was performed on 31 March 2012.

Article selection

Two independent reviewers (SU and LAR) selected published articles by reading the study title and the summary. Papers considered pertinent were obtained as complete texts to which the inclusion and exclusion criteria were applied. One of the authors (LAR) extracted the data, which were then checked by the other authors (SU and CFR). When necessary, the authors of the original research papers were contacted for more information. We resolved any disagreements by consensus or arbitration.

We designed a data abstraction form specifically to collect details from the selected studies. Diagnostic accuracy results were grouped according to the type of imaging test and used to construct a 2×2 contingency table. In those studies with multiple imaging methods in which some of them lacked a defined imaging and/or histopathology invasion criterion, only the test with all information was included and any test without the information was excluded. Also excluded were those cases in which it was not possible to break down relevant data for this review, as it was impossible to calculate sensitivity and specificity of such data.

Table 2 Index terms

Database	*Index terms*
MEDLINE (PubMed)	("diagnostic accuracy" or "specificity" or "sensitivity") and ("imaging" or "radiography, dental" or "CT" or "tomography, X-ray computed" or "cone beam CT" or "MRI" or "positron-emission tomography" or "single-photon emission CT" or "panoramic radiography" or "orthopantomography" or "ultrasonography") and ("oral cancer" or "carcinoma, squamous cell" [MeSH] or "mouth neoplasm") and "invasion"
SciELO	(oral cancer or buccal cancer or squamous carcinoma cells) and (panoramic radiography or MRI or CT or scintigraphy or cone beam or ultrasonography) and (sensitivity or specificity or diagnostic accuracy) available from: http://www.scielo.cl or http://www.scielo.org.pe or http://www.scielo.org.ar or http://www.scielo.br or http://www.scielo.org.co or http://scielo.sld.cu or http://scielo.isciii.es or http://www.scielo.oces.mctes.pt or http://www.scielo.org.ve or http://www.scielo.org.mx or http://www.scielo.sa.cr or http://scielo.iics.una.py or http://caribbean.scielo.org
ScienceDirect (ScienceDirect expert search)	("diagnostic accuracy" or "specificity" or "sensitivity") and ("radiography, dental" or "panoramic radiography" or "orthopantomography" or "CT" or "cone beam CT" or "MRI" or "single-photon emission CT" or "ultrasonography") and ("oral cancer" or "mouth neoplasm" or "carcinoma, squamous cell") and ("oral cavity" or "mouth" or "oral") or not (metastasis or oropharyngeal)

Methodological quality and risk of bias

Two independent reviewers (SU and LAR) assessed the risk of bias of the studies included in each article using criteria given by the quality of diagnostic accuracy studies tool, QUADAS-2,[24] that evaluates the risk of bias in four key domains: (1) patient selection, (2) index test, (3) reference standard and (4) flow and timing. A domain was considered as having a low risk of bias if all questions had been answered: "yes"; risk of bias was "unclear" when at least one question was answered: "unclear"; and a high risk was attributed to having answered at least one question: "no". Articles that showed a high risk of bias in the "(2) index test" or the "(3) reference standard" domains were excluded. Data obtained with the QUADAS-2 tool were noted, ready to subsequently prepare a graph with the quality of the included studies using an electronic spreadsheet in a format suggested by Whiting et al.[24]

Data analysis

We calculated the sensitivity and specificity with a 95% confidence interval (CI) for each imaging test in each study and drew Forest plots to show the variation in sensitivity and specificity estimates together with their 95% CIs.

Analysis of heterogeneity

Between-study heterogeneity was visually assessed with a paired Forest plot of sensitivity and specificity and was evaluated statistically with a χ^2 test, considering $p < 0.10$. Heterogeneity was considered to be present if the statistical value of χ^2 was greater than the degrees of freedom. Possible causes of clinical heterogeneity were identified by exploring the following factors: age, gender, severity of the disease and co-interventions. Methodological heterogeneity was visually assessed by comparing data from the table of study characteristics. The impact of heterogeneity on the results was tested using the I^2 statistic. Heterogeneity was considered to be present for a p-value of greater than 50%. The decision to perform a meta-analysis depended on the clinical, methodological and statistical heterogeneity together with the agreement of the authors of this review.

Results

Search results

The total number of articles found through the electronic database search was 338 (MEDLINE, 138; ScienceDirect, 173; SciELO, 27). One article was added following a manual review. The grey literature found, which was not pertinent to our area of study, was classified as "Other".

Selection process

After the screening process, 42 articles remained. We contacted authors for articles to which we did not have access. Only one author replied positively.[25] After reading these articles in full and application of the selection criteria, 35 articles were then excluded as shown in Table 3 plus two additional studies, which were not available.

Five articles were included for the qualitative analysis of this review. Details of this selection process are given in Figure 1.

Study characteristics

All five of the articles selected correspond to studies of diagnostic accuracy, with one of them being prospective[26] and four retrospective.[27–30] There are a total of 271 participants, 130 diagnosed with SCC and 141 without SCC. The technical aspects of the different imaging modalities as well as the diagnostic and validation criteria can be seen in Table 4.

The frequency of primary imaging tests according to the number (in brackets) of studies was: panoramic radiography (1) with 23 participants, CT (4) with 243 participants, MRI (4) with 164 participants, CBCT (1) with 23 participants and PET/CT (1) with 46 participants.

Table 3 Excluded studies

Reason for exclusion	*References*
Lack of Criterion 1	Albuquerque MA, Kuruoshi ME, Oliveira IR, Cavalcanti MG. CT assessment of the correlation between clinical examination and bone involvement in oral malignant tumors. *Braz Oral Res* 2009; **23**: 196–202 Sigal R, Zagdanski AM, Schwaab G, Bosq J, Auperin A, Laplanche A, et al. CT and MR imaging of squamous cell carcinoma of the tongue and floor of the mouth. *Radiographics* 1996; **16**: 787–810
Lack of Criterion 3	Crecco M, Vidiri A, Angelone ML, Palma O, Morello R. Retromolar trigone tumors: evaluation by magnetic resonance imaging and correlation with pathological data. *Eur J Radiol* 1999; **32**: 182–188 Dreiseidler T, Alarabi N, Ritter L, Rothamel D, Scheer M, Zöller JE, et al. A comparison of multislice computerized tomography, cone beam computerized tomography, and single photon emission computerized tomography for the assessment of bone tissue invasion by oral malignancies. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011; **112**: 367–374 Huntley TA, Busmanis I, Desmond P, Wiesenfeld D. Mandibular invasion by squamous cell carcinoma: a computed tomographic and histological study. *Br J Oral Maxillofac Surg* 1996; **34**: 69–74 Talmi YP, Bar-Ziv J, Yahalom R, Teicher S, Eyal A, Shehtman I, et al. DentaCT for evaluating mandibular and maxillary invasion in cancer of the oral cavity. *Ann Otol Rhinol Laryngol* 1996; **105**: 431–437 Zupi A, Califano L, Maremonti P, Longo F, Ciccarelli R, Soricelli A. Accuracy in the diagnosis of mandibular involvement by oral cancer. *J Craniomaxillofac Surg* 1996; **24**: 281–284
Lack of Criterion 4	Araki K, Ariji E, Shimizu M, Kanda S, Ozeki S, Shinohara M, et al. Computed tomography of carcinoma of the upper gingiva and hard palate: correlation with the surgical and histopathological findings. *Dentomaxillofac Radiol* 1997; **26**: 177–182 Castelijns JA, van den Brekel MW. Magnetic resonance imaging evaluation of extracranial head and neck tumors. *Magn Reson Q* 1993; **9**: 113–128 Kushraj T, Chatra L, Shenai P, Rao PK. Bone tissue invasion in oral cancer patients: a comparison between orthopantamograph, conventional computed tomography, and single positron emission computed tomography. *J Cancer Res Ther* 2011; **7**: 438–341 Zieron JO, Lauer I, Remmert S, Sieg P. Single photon emission tomography: scintigraphy in the assessment of mandibular invasion by head and neck cancer. *Head Neck* 2001; **23**: 979–984
Lack of Criterion 5	Acton CH, Layt C, Gwynne R, Cooke R, Seaton D. Investigative modalities of mandibular invasion by squamous cell carcinoma. *Laryngoscope* 2000; **110**: 2050–2055 Brown JS, Griffith JF, Phelps PD, Browne RM. A comparison of different imaging modalities and direct inspection after periosteal stripping in predicting the invasion of the mandible by oral squamous cell carcinoma. *Br J Oral Maxillofac Surg* 1994; **32**: 347–359 Lewis-Jones HG, Rogers SN, Beirne JC, Brown JS, Woolgar JA. Radionuclide bone imaging for detection of mandibular invasion by squamous cell carcinoma. *Br J Radiol* 2000; **73**: 488–493 Ord RA, Sarmadi M, Papadimitrou J. A comparison of segmental and marginal bony resection for oral squamous cell carcinoma involving the mandible. *J Oral Maxillofac Surg* 1997; **55**: 470–477; discussion 477–478 Rao LP, Das SR, Mathews A, Naik BR, Chacko E, Pandey M. Mandibular invasion in oral squamous cell carcinoma: investigation by clinical examination and orthopantomogram. *Int J Oral Maxillofac Surg* 2004; **33**: 454–457 Schimming R, Juengling FD, Lauer G, Altehöfer C, Schmelzeisen R. Computer-aided 3-D ^{99m}Tc-DPD-SPECT reconstruction to assess mandibular invasion by intraoral squamous cell carcinoma: diagnostic improvement or not? *J Craniomaxillofacial Surg* 2000; **28**: 325–330
Lack of Criterion 6	Curran AJ, Toner M, Quinn A, Wilson G, Timon C. Mandibular invasion diagnosed by SPECT. *Clin Otolaryngol Allied Sci* 1996; **21**: 542–545 Escott EJ, Rao VM, Ko WD, Guitierrez JE. Comparison of dynamic contrast-enhanced gradient-echo and spin-echo sequences in MR of head and neck neoplasms. *AJNR Am J Neuroradiol* 1997; **18**: 1411–1419 Jungehülsing M, Scheidhauer K, Litzka N, Wagner M, Dietlein M, Ernst S, et al. ^{99m}Tc-MDP-SPECT for detection of subclinical mandibular infiltration of squamous epithelial carcinoma. *HNO* 1997; **45**: 702–709 Millesi W, Prayer L, Helmer M, Gritzmann N. Diagnostic imaging of tumor invasion of the mandible. *Int J Oral Maxillofac Surg* 1990; **19**: 294–298
Lack of Criterion 7	Babin E, Desmonts C, Hamon M, Bénateau H, Hitier M. PET/CT for assessing mandibular invasion by intraoral squamous cell carcinomas. *Clin Otolaryngol* 2008; **33**: 47–51 Brockenbrough JM, Petruzzelli GJ, Lomasney L. DentaScan as an accurate method of predicting mandibular invasion in patients with squamous cell carcinoma of the oral cavity. *Arch Otolaryngol Head Neck Surg* 2003; **129**: 113–117 Higashi K, Wakao H, Ikuta H, Kashima I, Everhart FR. Bone scintigraphy in detection of bone tissue invasion by oral carcinoma. *Ann Nuclear Med* 1996; **10**: 57–61 Kushraj T, Chatra L, Shenai P, Rao PKK. Bone tissue invasion in oral cancer patients: a comparison between orthopantamograph, conventional computed tomography, and single positron emission computed tomography. *J Cancer Res Ther* 2011; **7**: 438–441 Rajesh A, Khan A, Kendall C, Hayter J, Cherryman G. Can magnetic resonance imaging replace single photon computed tomography and computed tomography in detecting bony invasion in patients with oral squamous cell carcinoma? *Br J Oral Maxillofac Surg* 2008; **46**: 11–14 Vidiri A, Guerrisi A, Pellini R, Manciocco V, Covello R, Mattioni O, et al. Multidetector row computed tomography (MDCT) and magnetic resonance imaging (MRI) in the evaluation of the mandibular invasion by squamous cell carcinomas (SCC) of the oral cavity. Correlation with pathological data. *J Exp Clin Cancer Res* 2010; **29**: 73 Yamamoto Y, Nishiyama Y, Satoh K, Ohbayashi Y, Iwasaki A, Miyabe K, et al. Dual-isotope SPECT using ^{99m}Tc-hydroxymethylene diphosphonate and ^{201}Tl-chloride to assess mandibular invasion by intraoral squamous cell carcinoma. *J Nuclear Med* 2002; **43**: 1464–1468

Table 3 Continued

Reason for exclusion	*References*
Criterion A	Bolzoni A, Cappiello J, Piazza C, Peretti G, Maroldi R, Farina D, et al. Diagnostic accuracy of magnetic resonance imaging in the assessment of mandibular involvement in oral-oropharyngeal squamous cell carcinoma: a prospective study. *Arch Otolaryngol Head Neck Surg* 2004; **130**: 837–843 Imaizumi A, Yoshino N, Yamada I, Nagumo K, Amagasa T, Omura K, et al. A potential pitfall of MR imaging for assessing mandibular invasion of squamous cell carcinoma in the oral cavity. *AJNR Am J Neuroradiol* 2006; **27**: 114–122 Imola MJ, Gapany M, Grund F, Djalilian H, Fehling S, Adams G. Technetium 99m single positron emission computed tomography scanning for assessing mandible invasion in oral cavity cancer. *Laryngoscope* 2001; **111**: 373–381 Momin MA, Okochi K, Watanabe H, Imaizumi A, Omura K, Amagasa T, et al. Diagnostic accuracy of cone beam CT in the assessment of mandibular invasion of lower gingival carcinoma: comparison with conventional panoramic radiography. *Eur J Radiol* 2009; **72**: 75–81 Mukherji SK, Isaacs DL, Creager A, Shockley W, Weissler M, Armao D. CT detection of mandibular invasion by squamous cell carcinoma of the oral cavity. *AJR Am J Roentgenol* 2001; **177**: 237–243 Schimming R, Juengling FD, Altehöfer C, Schmelzeisen R. Diagnosis of questionable mandibular infiltration by squamous epithelial carcinomas. 3-D 99mTc-DPD SPECT reconstruction and 18F fluoride PET study: diagnostic advantages or unnecessary expense?. *HNO* 2001; **49**: 355–360
Criterion C	Lane AP, Buckmire RA, Mukherji SK, Pillsbury HC, Meredith SD. Use of computed tomography in the assessment of mandibular invasion in carcinoma of the retromolar trigone. *Otolaryngol Head Neck Surg* 2000; **122**: 673–677
Not available	Baker HL, Woodbury DH, Krause CJ, Saxon KG, Stewart RC. Evaluation of bone scan by scintigraphy to detect subclinical invasion of the mandible by squamous cell carcinoma of the oral cavity. *Otolaryngol Head Neck Surg* 1982; **90**: 327–336 Close LG, Merkel M, Burns DK, Schaefer SD. Computed tomography in the assessment of mandibular invasion by intraoral carcinoma. *Ann Otolaryngol Rhinol Laryngol* 1986; **95**: 383–388

The ratio of males to females was 1:2.4, with an age range of 39–89 years. Frequency according to localization, from most to least frequent, was: the floor of the mouth, mandible, retromolar trigone, maxillary gingiva, tongue and buccal space. Patient descriptions and values of diagnostic accuracy of the included studies can be seen in Table 5.

Risk of bias in the studies

The signalling question about the case–control design of Domain 1 of the QUADAS-2 tool was eliminated as it was not pertinent to the articles under review.

The risk of bias of the included studies is low to moderate. The greatest risk of bias arises from the fact that the studies lack sufficient information about patient selection, the time between the imaging test and histopathological confirmation and the application of the index test. Table 6 shows the results obtained according to QUADAS-2 for each included article grouped according to the imaging test.

From an imaging point of view, there are discrepancies in application of the tests in these studies, such as differing slice thicknesses for CT[30] and different tesla values for MRI.[27]

Diagnostic accuracy per study

Sensitivity, specificity and diagnostic accuracy values for each test according to the study are shown in Table 5.

Diagnostic accuracy: The test that showed the greatest diagnostic accuracy, 95.7%, was CBCT, followed by PET/CT with 87.0%. Maximum values for MRI are 85.7–87.0%, similar to those of CT, 85.7–86.7%. Panoramic radiography shows a diagnostic accuracy of 73.9%, similar to the lower MRI and CT values.

Heterogeneity analysis

Clinical heterogeneity: Age range was reported in all studies and gender ratio in 57%. Severity of the disease was reported in two studies by tumour–node–metastasis (TNM) classification.[27,28] As for co-interventions, just one article mentioned additional periapical tests in the assessment routine.[26]

Methodological heterogeneity: Most of the studies did not mention case or illness definition for calculation of sensitivity and specificity. For CT, differences in slice thicknesses of between 1.5 mm and 6 mm were observed[27,30] as well as in amperage, with values of between 100 and 200 mAs.[29,30] Slice thickness for MRI also varied, from 3 to 6 mm.[28,29] Receiver operating characteristic (ROC) curves were not prepared because the different scales and criteria used did not permit generation/definition of cutoff points for the different studies.

Result of individual studies

Because of the significant presence of clinical, methodological and statistical heterogeneity, we decided against performing meta-analysis. The individual results of each study grouped according to the imaging technique are displayed in a Forest plot (Figure 2) showing sensitivity and specificity values and the values of the test for statistical heterogeneity.

Discussion

Diagnostic tests are performed when the available information (clinical examination or previous tests) is insufficient to enable a precise diagnosis or to make an informed decision about treatment. Such diagnostic

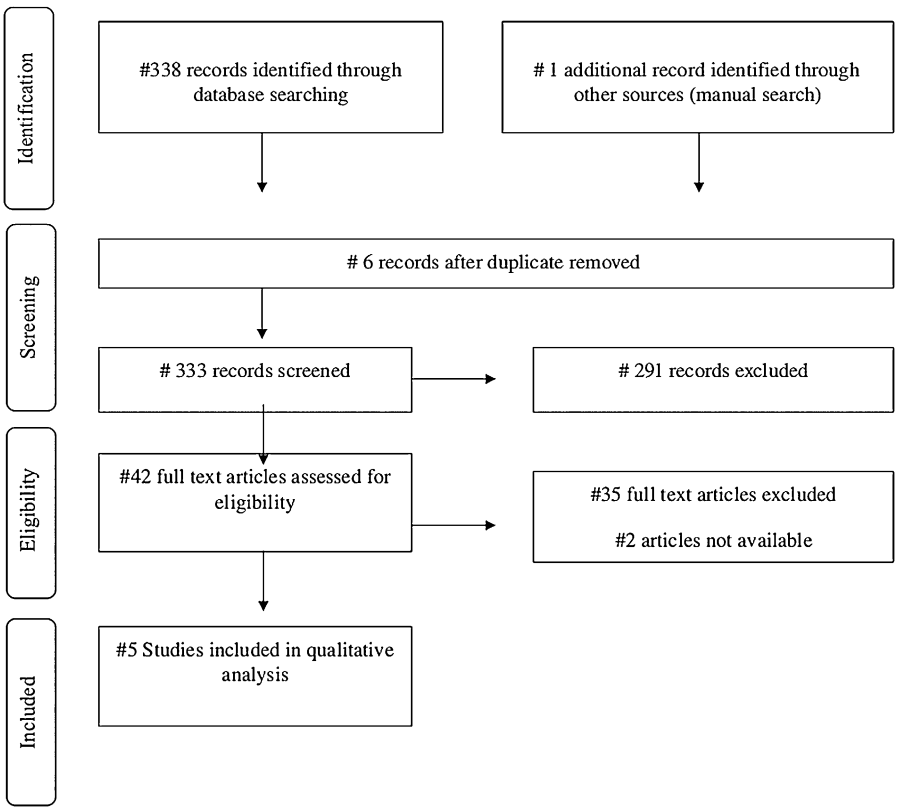

Figure 1 Flow of studies through the selection process

tests should be supported by studies that assess their diagnostic accuracy. This systematic review aimed to assess the published evidence on the diagnostic accuracy of several different imaging methods for SCC assessment. We found five articles that showed an adequate quality of methodology on the diagnostic accuracy of different imaging methods for detection of mandibular bone tissue invasion by SCC. These articles show a low to moderate risk of bias. Brown and Lewis-Jones[23] published a review in which they combined the results of several studies. Since we found a significant heterogeneity across studies, we did not perform a meta-analysis or combination as Brown and Lewis-Jones[23] did. Also, our method differs from the one used by Brown and Lewis-Jones[23] since we used a critical appraisal tool, the QUADAS-2, available since 2003 and recently updated.[24] This explains the difference between the number of included studies by Brown and Lewis-Jones[23] (61) and us (5). But the main difference is that we used a reference standard (*i.e.* histopathological diagnosis) as the criterion used to compare any test index. A comparison between studies, as performed by Brown and Lewis-Jones,[23] is difficult as different studies use different measurement scales, diagnostic criteria and technical parameters. Brown and Lewis-Jones[23] also included two reports about ultrasound, but we had to discard studies of ultrasonography, as these are focused on the detection of cervical metastases[31] or the determination of lingual tumour density at stages T1 and T2.[32]

Although methods such as CT, MRI, panoramic radiography and CBCT have a high capacity for detection of mandibular bone tissue invasion in patients, we found a large variation between minimum and maximum sensitivity values. CBCT shows high sensitivity and specificity values, greater than those seen for panoramic radiography or MRI, but tends to underestimate the extent of mandibular invasion.[28] For this reason, the causes of the false-negative and false-positive high values in these tests require continued research and improvement. However, specificity also shows high values for detection of healthy patients, but, in these cases, the range of specificity is mainly found to be over 50%. On the one hand, these results strongly suggest that the current imaging diagnostics tests included in our review would allow us to more precisely discard mandibular bone tissue invasion than to detect it. This implies that the clinical use of these tests should be oriented towards diagnostically suspect cases of patients with oral SCC, rather than used as a screening method for suspicious or non-diagnosed patients. Our review results reveal information that would allow the clinician to choose, for each particular case, which technique or combination of methods would give the best diagnostic accuracy, *e.g.* the use of a highly specific test such as SPECT would require the use of a complementary and highly sensitive test. On the other hand, our results suggest that diagnostic accuracy varies in a significant

Table 4 Technical characteristics of the imaging techniques used, diagnostic criteria and histopathological validation per study

Reference	*Imaging method*	*Equipment, contrast medium or radionucleotide and setting conditions*	*Tumour localization (number)*	*Imaging invasion criteria*	*Histopathological invasion criteria*	*Histopathological protocol*	*Comments*
Handschel et al[30]	CT	Somatom Sensation 6 (Siemens Healthcare, Munich, Germany). Lohexol 300 mg ml^{-1}. Collimation of 6 × 1 mm at 110 kVp and 100 mAs. Axial slice thickness up to 2007: 3 mm. From 2007 to 2010: 1.5 mm. Bone window: 1400/400 HU. Soft-tissue window: 350/50 HU	Mandible (58), floor of the mouth (43) and tongue (6)	Three-point scale according to the degree of cortical bone erosion Invasion: compromise of periosteum and bone	Three-point classification according to the degree of penetration in cortical bone	n.i.	
Gu et al[29]	CT	MX8000 Infinite Detector Technology, Omnipaque 300 (Philips, Eindhoven, Netherlands), 100 ml. Collimation of 41.5 mm at 120 kVp and 200 mAs. Slice thickness: 3 mm. Axial and coronal reconstruction of 3 mm in a matrix 512 × 512	Tonsils (23)	Interruption or erosion of the peripheral hyperattenuating rim adjacent to a mass of abnormal soft tissue or when the medullary bone is replaced by a hyperattenuating lesion. Four-point scale according to the presence or absence of invasion Invasion: probably present and definitely present	No distinction is made between cortical or medullary invasion. Both are considered positive for invasion	n.i.	
	MRI	Gyroscan Intera 1.5 T. Omniscan (Philips), 0.1 mmol kg^{-1}. Axial, sagittal and coronal slices. FOV: 200–300 mm. Slice thickness: 6 mm. Matrix 256 × 256	Retromolar trigone (8)	Replacement of the hypointense peripheral signal by a signal intensity of the tumour on T_1 and T_2 or replacement of the hyperintense signal by an intermediate tumour signal			
	PET/CT	Discovery STE whole-body PET/CT system (General Electric Medical Systems, Milwaukee, WI). ^{18}F-FDG 370–555 MBq (10–15 mCi). Detector configuration: 8 × 1.25 mm. Tube voltage: 120 kVp and 200 mAs. Slice thickness: 3.75 mm. Reconstruction in the axial and coronal planes with a slice thickness of 6.5–7.8 mm	Base of the tongue (6)	Dark areas correspond to regions with high FDG absorption adjacent to the cortical bone that shows a visible defect in CT or FDG accumulation in the cortical bone and within the medullary bone in the same region, even without detectable cortical erosion			
	CT + MRI		Floor of the mouth (5)	Combined score: score of 4 for more than one imaging test or a combined score of >2			
	CT + PET/CT		Buccal space (3)	As above			
	MR + PET/CT		Gingiva (1)	As above			
	CT + MRI + PET/CT			As above			

Table 4 Continued

Reference	*Imaging method*	*Equipment, contrast medium or radionucleotide and setting conditions*	*Tumour localization (number)*	*Imaging invasion criteria*	*Histopathological invasion criteria*	*Histopathological protocol*	*Comments*
Hendrikx et al[28]	Cone beam CT Classic i-CAT		Retromolar trigone (8)	Four-point scale according to bone compromise. Positive: slight invasion, clear invasion	Erosion: bone replacement without invasion towards the medullary space, mandibular canal or periodontal ligament space. Mandibular invasion: diffuse growth of the tumour within the medullary bone, root canal and, if present, the periodontal ligament space	Decalcification with 10% formic acid. Slice thickness: 5 μm	
	Digital panoramic	Planmeca Promax (Planmeca, Helsinki, Finland)	Floor of the mouth (9)	As above			
	MRI	1.5 T Siemens Vision whole-body (Siemens Healthcare). Gadopentetate dimeglumine 0.2 ml kg^{-1}. Slice thickness: 3 mm	Inferior alveolar flange (6)	As above			
Van Cann et al[26]	CT	Somatom 3. Iohexol, 150 ml, 350 mg I ml^{-1}. Slice thickness: 1.5 mm. Configuration: soft and hard tissue	Retromolar trigone (20), floor of the mouth (31), inferior alveolar flange (13) and mucous membrane (3)	Absence of cortical bone adjacent to a mass of abnormal soft tissue	(a) Cortical invasion: bone replacement without invasion into the medullary space, mandibular canal or periodontal ligament space (b) Medullary invasion: diffuse growth of the tumour within the medullary bone, root canal and, if present, the periodontal ligament space	Decalcification with 10% formic acid. Slice thickness: 5 μm	Includes diagnostic algorithms for different strategies of imaging method sequences
	MRI	1.5 T Siemens Vision whole body. Gadopentetate dimeglumine 0.2 ml kg^{-1}. Slice thickness: 3 mm		Replacement of the hypointense peripheral signal by a signal intensity of the tumour on T_1 and T_2 or replacement of the hyperintense signal by an intermediate signal from the tumour			
	Panoramic	Planmeca Promax		n.i.			
	Single photon emission CT	^{99m}Tc-methylene-diphosphonate 600 MBq. Dual head gamma camera. Photo peak: 140 keV. Window: 15%. Matrix: 128 × 128		n.i.			
van den Brekel et al[27]	MRI	0.6 T or 1.5 T Siemens systems (Siemens Healthcare). Gadolinium in 24 patients. Slice thickness: 2.5–5.0 mm	Retromolar trigone (9)	Tumour on the inside of the mandible or the normal medulla high signal replaced by an intermediate signal or an inflammatory reaction in T_1 window	Compromise of spongy and medullary bone	Fixed and decalcified	Consider erosion and invasion as positive
	CT	Philips Tomoscan 350 (Philips) or Siemens Plus (Siemens Healthcare). Slice thickness: 5–6 mm	Floor of the mouth (20)	Destruction of the external cortical bone and/or medullary bone			
	Panoramic	Siemens Orthopantomograph (Sirona Dental Company, Bensheim, Germany) 10		Three categories: no compromise, minimal erosion or extensive invasion Invasion: much bone destruction and replacement by tumour			

FDG, fludeoxyglucose; FOV, field of view; n.i., no information/not enough information available; PET, positron emission tomography.

Table 5 Patient characteristics and values of diagnostic accuracy per study and imaging method

Reference	*Type*	*Country*	*N*	*M:F*	*Age range (years)*	*Ethnic origin*	*Imaging method*	*TP*	*TN*	*FP*	*FN*	*Sensitivity*	*Specificity (%)*	*Diagnostic accuracy (%)*
Handschel et al[30]	Retros	Germany	107	n.i.	Average: 62 ± 10	n.i.	CT	38	53	8	8	82.6	86.9	85.0
Gu et al[29]	Retros	South Korea	46	39:7	39–89	n.i.	CT	5	34	0	7	41.7	100	84.8
							MRI	7	33	1	5	58.3	97.1	87.0
							PET/CT	7	33	1	5	58.3	97.1	87.0
							CT + MRI	8	34	0	4	66.7	100	91.3
							CT + PET/CT	8	34	0	4	66.7	100	91.3
							MR + PET/CT	9	34	0	3	75.0	100	93.5
							CT + MRI + PET/CT	10	34	0	2	83.3	100	95.7
Hendrikx et al[28]	Retros	Netherlands	23	n.i.	43–84	n.i.	Cone beam CT	10	12	0	1	90.9	100	95.7
							Digital panoramic	6	11	1	5	54.5	91.7	73.9
							MRI	9	8	4	2	81.8	66.7	73.9
Van Cann et al[26]	Prosp.	Netherlands	66	42:25	43–84	n.i.	CT	25	22	1	18	58.1	95.7	71.2
							MRI	27	23	0	16	62.8	100	75.8
							Panoramic[a]	n.i.	n.i.	n.i.	n.i.	—	—	—
							Single photon emission CT[a]	n.i.	n.i.	n.i.	n.i.	—	—	—
van den Brekel et al[27]	Retros	Netherlands	29	19:10	39–73	n.i.	MRI	17	8	3	1	94.0	73.0	85.7
			23				CT	9	8	1	5	64.0	89.0	73.9
			26				Panoramic[b]	n.i.	n.i.	n.i.	n.i.	—	—	—

F, females; FN, false negative; FP, false positive; M, males; n.i.= no information/not enough information available; PET, positron emission tomography; Prosp: prospective; Retros, retrospective; TN, true negative; TP, true positive.
[a]No imaging invasion criteria.
[b]No information about missing patients.

manner according to the criteria used to determine mandibular bone tissue invasion by SCC. Future studies should establish a common criterion for each diagnostic method. Table 7 gives a summary of the advantages and disadvantages mentioned by the authors with respect to the articles selected on imaging techniques.

One limitation of the present study is the exclusion of the grey literature. Although non-published information is used in only 12% of reviews of diagnostic tests[33] it would be useful to assess its impact in further reviews. Also, the language choice of papers was based on author preference, but future studies could usefully include other languages, such as Chinese or Portuguese. Removing language restrictions could improve results.[33]

Even though we managed to extract sensitivity and specificity values from most of the studies, the clinical efficacy of diagnostic accuracy must not be interpreted solely on the basis of these values. Our systematic review gives information about the performance of the diagnostic tests.[34] It should be considered that, although studies of diagnostic accuracy are necessary, they do not suffice for making public policy decisions.[35] However, assessment of new diagnostic techniques must incorporate not only image quality but also the impact of decisions made about treatment.[36]

Use of objective guidelines for methodological assessment of the studies allows us to identify aspects that should be considered in future studies. We recognize the

Table 6 Methodological quality summary: review authors' judgment on each individual QUADAS-2 item for the included studies

		Risk of bias				*Applicability concerns*		
Imaging method	*Study*	*Patient selection*	*Index test*	*Reference standard*	*Flow and timing*	*Patient selection*	*Index test*	*Reference standard*
CT	Van Cann et al[26]	+	+	+	+	+	+	+
	Gu et al[29]	?	+	?	+	+	+	+
	van den Brekel et al[27]	?	+	+	?	+	+	+
MRI	Van Cann et al[26]	+	+	?	+	+	+	+
	Gu et al[29]	?	+	?	+	+	+	+
	Hendrikx et al[28]	?	?	?	?	+	+	+
	van den Brekel et al[27]	?	+	+	?	+	−	+
Panoramic	van den Brekel et al[27]	?	+	+	?	+	+	+
	Hendrikx et al[28]	?	?	?	?	+	+	+
	Van Cann et al[26]	+	−	?	+	+	−	+
Cone beam CT	Hendrikx et al[28]	?	?	?	?	+	+	+
Positron emission tomography/CT	Gu et al[29]	?	+	?	+	+	+	+

+, low risk; −, high risk; ?, unclear risk.

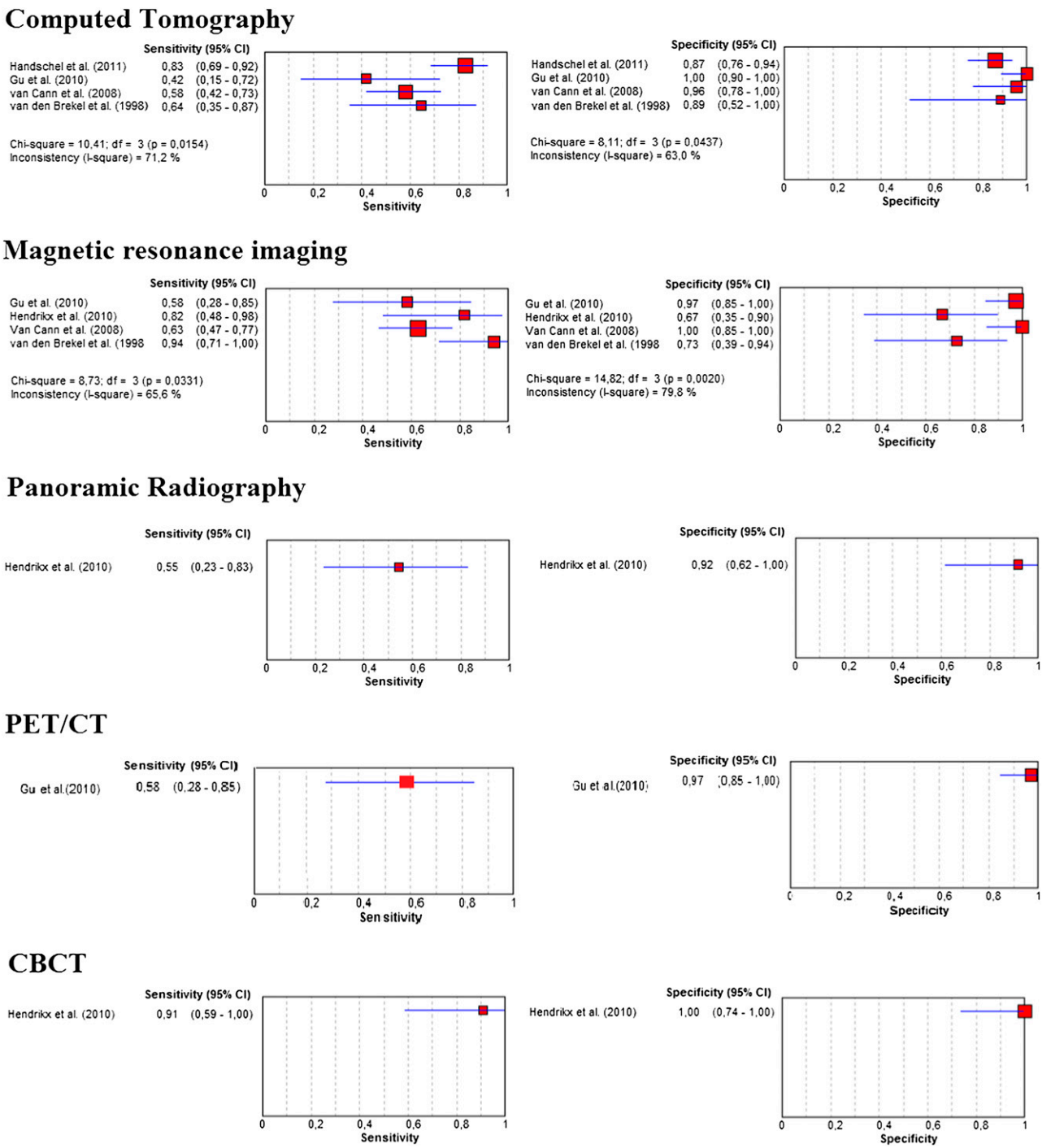

Figure 2 Forest plot of diagnostic test accuracy for detection of mandibular bone tissue invasion per imaging test type. CBCT, cone beam CT; CI, confidence interval; df, degrees of freedom; PET, positron emission tomography

effort and dedication of researchers in performing these valuable investigations and we regret that it was necessary to exclude such a large number of studies. With respect to this, we identified aspects that might be improved in future publications, with the aim of being able to compare the performance of the different technologies in different patient groups. We have divided these recommendations into four aspects: pertaining to the patient, to interventions, to classification and to histopathology.

First of all, we recommend that future studies be accompanied by the ratio of males/females for each study as well as the ethnic origin of patients. As patient selection is based on the TNM classification, we suggest

Table 7 Summary of diagnostic accuracy and the characteristics of different imaging techniques

Technique	*Sensitivity/Specificity*[a]	*Advantage*	*Disadvantage*
Panoramic	55%/92%	Useful for revealing periapical or periodontal infections that may be misinterpreted by other modalities[26]	Low sensibility
		Low patient radiation dose	
CT	83%/100%	High sensibility and specificity	Slice thickness may affect the sensibility
MRI	94%/100%	High sensibility and specificity	In windows at T_1 and T_2, improved with gadolinium, this method overestimates the extent of the tumour if there is adjacent oedema[27]
			Artefacts due to movements or inflammatory periodontal conditions, osteoradionecrosis and partial volume effect[29]
Cone beam CT	91%/100%	High sensibility and specificity	Underestimates the extent of mandibular invasion[28]
		Patient position prevents collapse of soft tissue.	Requires four times more radiation than panoramic radiography[28]
		Requires less radiation than for multislice CT[28]	
Positron emission tomography/CT	53%/97%	Slightly superior diagnostic accuracy to CT	Low specificity
		Identifies hypermetabolic and non-hypermetabolic lesions	Results altered by inflammatory processes or by an increased haematopoiesis[29]

[a]Only maximum values of sensitivity and specificity are shown.

that the number of patients at each stage of the disease be specified, with the aim of discovering the proportion of patients classifiable clinically as "with invasion" or "without invasion". The clinical examination is useful for the first three stages of classification in which the tumour size is evaluated. But stage T4 is more complex, having a diagnostic accuracy of 54–82%.[26,37] In the same way, it is necessary to clarify whether patients who have received previous treatment should be included because, in previously irradiated patients, invasion tends to be more extensive and less predictable.[16] In addition, as part of the patient description, the precise manner of tumour location should be detailed, as there may be differences in diagnostic performance according to the test method used and the area examined.

Second, imaging tests should detail technical parameters with greater precision. This should include information about the equipment, the contrast medium used and its concentration, kilovoltage and milliamperage, among others. Long and Smith[38] reveal causes of false positives and negatives in PET/CT oncology imaging that are due to patient position, artefacts arising as a product of inadequate administration of radionucleotides or behaviour post therapy of chemotherapy patients.

Third, and perhaps the most urgent for future reports: one of the main problems arising from synthesizing results from different research papers is that different criteria are used to define invasion and erosion. Such discrepancies in the criteria made it impossible for us to generate ROC curves with our sensitivity and specificity values. Classification scales for the presence of invasion in CT are, in general, based on cortical bone compromise, though some authors include erosion as an invasion parameter[27] while others do not.[26] To consider erosion as invasion may be influenced by the slice thickness in CT, as this thickness may affect the detection of minimal erosion.[27] The same study is suggested for PET/CT and MRI.[29] Thus, to consider erosion as an invasion criterion requires that an agreement be established on the minimum slice thickness for detection of mandibular bone tissue invasion by SCC. Likewise, every report should be more explicit with respect to the classification scale used such that values will be considered positive (bone tissue invasion) and negative (no bone tissue invasion) for later comparison against the reference standard.

And fourth, the reference standard. Future studies should give a scale with ranges and the histopathological invasion criteria used to calculate the number of patients for each level of the imaging and histopathological assessment scale. This would enable calculation of sensitivity/specificity for different diagnostic levels as well as for transforming different scales into one common scale and thus enable comparison of different studies. However, for rapid growth of pathologies, such as SCC, the time between imaging and histopathological assessment should be reported.

Future research thus requires specific reporting of certain aspects that allow a comparison of results to be performed and, where possible, combined. This will generate a body of evidence based on which studies other than those of diagnostic accuracy may be performed and thus will determine just how the detection of mandibular bone tissue invasion by SCC with different imaging methods affects the clinician's diagnostic decision, the treatment to pursue and the cost–benefit to patients.

Even though we found only a few reports assessing diagnostic accuracy in SCC that fulfilled the inclusion criteria, available published evidence indicates that the diagnostic accuracy of imaging methods is high, with values of 95.7% for CBCT, 87.0% for CT and MRI and 73.9% for panoramic radiography. PET/CT

was reported just once as having a diagnostic accuracy of 87.0%. This implies that current imaging methods do support determination of bone tissue invasion by oral SCC.

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