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Review

Are we ready to use ultrasounds in the clinical assessment of depth of invasion and tumor thickness in oral squamous cell carcinoma? Results from a systematic review, meta-analysis and trial sequential analysis

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ABSTRACT

Objectives: To investigate the accuracy of ultrasound in the quantification of tumor thickness (TT) and depth of invasion (DOI) of oral potentially malignant disorders and oral squamous cell carcinoma.
Materials and methods: A systematic review search was conducted in PubMed, Scopus, and Web of Science to answer the PICO question: "What is the correlation and the mean difference between ultrasound and histopathological assessment of tumor thickness and depth of invasion in patients with oral squamous cell carcinoma and oral potentially malignant disorders? The risk of bias was assessed, meta-analysis and trial sequential analysis was conducted on the available quantitative data, followed by trial sequential analysis.
Results: Of 2089 results, 48 studies were considered suitable for inclusion.
Meta-analysis showed a low heterogeneity for tumor thickness mean difference ($I^2 = 0.00$ %) with an overall standardized mean difference (SMD) of 0.13 (95 % CI: −0.07 to 0.33, $p = 0.214$). Tumor thickness correlation showed high heterogeneity ($I^2 = 93.41$ %). For depth of invasion, the mean difference had moderate heterogeneity ($I^2 = 8.98$ %) with an overall SMD of 0.27 (95 % CI: 0.06 to 0.48, $p = 0.013$). However, correlation analysis showed moderate heterogeneity ($I^2 = 56.22$ %). Trial sequential analysis confirmed the tumor thickness results but indicated more studies are required for depth of invasion to meet the required information size.
Conclusion: There were no statistically significant differences between the results of ultrasound and histological examination, the clinical use of this device cannot yet be confirmed.

Introduction

Oral squamous cell carcinoma (OSCC) is a global health problem, affecting about 390,000 people worldwide [1].This is the most common type of head and neck neoplasm and recently, its incidence has increased, representing approximately 90 % of all oral cancer types [2]. Despite the oral cavity being an anatomical site easily accessible for the evaluation and inspection of the mucosa, to date, the diagnosis of OSCC is still delayed, and consequently the prevalence, incidence, and mortality rates are still reported to be high and are not improving [3]. Moreover, before developing the tumor, some patients may be affected by an oral potentially malignant disorder (OPMD). These include conditions that may be linked to an increased risk of cancer development. Usually, clinical manifestation is heterogeneous and includes red, white, or ulcerated areas [4], with exophytic or endophytic pattern [5]. Clinical manifestations may also include heterogeneous patterns for bigger lesions, with deeper areas, which could not be clinically evaluated during preliminary diagnostic bioptical sampling. Thus, choosing the best location, which could be the most informative and representative of these lesions, can be difficult. In this scenario, the patient can undergo different biopsies, with increased discomfort. Moreover, evidence supports that the ulcerated and endophytic forms can easily infiltrate and spread [6], correlating even small tumors to advanced stages, with lymph node involvement [7]. The American Joint Committee on Cancer (AJCC) improved the prognostic accuracy of the staging system by releasing the 8th edition, including depth of invasion (DOI) as prognostic criteria in the histological tumor thickness assessment [8]. These are respectively related to locoregional recurrence rates and higher

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Table 1
Characteristics of included studies.

ID	YEAR	COUNTRY	STUDY DESIGN	MODEL	LESION TYPE	SAMPLE SIZE	SITE	STAGING	EDITION	GENDER	MEAN AGE	MODEL	FREQUENCIES	FEATURE
Adriaansens	2022	Netherlands	Within-person study prospective study	In vivo	OSCC	13	Buccal mucosa	Not indicated	TNM, 8th ed	5 M 8 W	Mean age 73	L16-4Hs, Mindray Bio-Medical Electronics, Shenzhen, China)	16 MHz	Hockey stick
Angelelli	2016	Italy	Within-person study prospective study	In vivo	OSCC	32	Tongue 22; cheeks 6; palate 3; mandibular alveolar bridge1;	T1: 23; T2: 9	AJCC	17 M 15 W	Not indicated	GE Logic 9 equipment	18 MHz	Linear probe Hockey Stick,
Au	2023	Canada	Retrospective study	In vivo	OSCC	Not indicated	Tongue	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated
Baek	2008	Korea	Prospective study	In vivo	OSCC	20	Tongue	T1: 12;T2: 8	Not indicated	10 M 10 W	Mean age 57	UST-9120 convex sector probe, ALOKA America, Wallingford, CT	9 MHz	Linear probe
Brouwer de Koning	2019	Netherlands	Retrospective study	In vivo	OSCC	85	Tongue 58; floor of the mouth 24; palate 2; lip 1	Not indicated	AJCC7 and AJCC8,	45 M 38 W	Mean age 61	EUP-054 J	7–13 MHz	Hockey stick
Brouwer de Koning	2020	Netherlands	Prospective study	In vivo	OSCC	31	Lateral tongue 25; base of the tongue 2; dorsal surface 2; ventral surface 2	T1: 11; T2: 16; T3: 1; T4: 3	Not indicated	Not indicated	Not indicated	ALOKA ProSound SSD-Alpha 5	5–10 MHz	Not indicated
Bruneton	1986	France	Prospective study	In vivo	OSCC	70	42 Tongue; 28 tonsil	T1: 13; T2: 34; T3: 18; T4: 5	Not indicated	64 M 6 W	Mean age 63	Sonel 400; CGR, Columbia	5–7.5 MHz	Not indicated
Bulbul	2021	USA	Retrospective study	In vivo	OSCC	23	Tongue	Not indicated	AJCC8	Not indicated	Not indicated	L15–7io; Philips)	Not indicated	Linear probe
Caprioli	2023	Italy	Retrospective study	In vivo	OSCC	Not indicated	Lateral tongue 24; dorsal tongue 2; floor 4; alveolar crest 4	T1: 11; T2: 11; T3: 8; T4: 4	Not indicated	Not indicated	Not indicated	Not indicated	22–28 Mhz	Hockey stick
Caprioli	2022	Italy	Retrospective study	In vivo	OSCC	41	Tongue	Not indicated	Not indicated	25 M 16 W	Mean age 64.07	Not indicated	22–8 Mhz; 15–7 Mhz (before 2018)	Hockey stick
Chammas	2010	Brazile	Within-person study Prospective study	In vivo	OSCC	19	Tongue	T1: 2; T2:8; T3:1; T4:6;	TNM, 8th ed	11 M 8 W	Mean age 60	H40212LM/ T739 T-Type; GE Medical Systems	5 MHz	T-shaped
de Koning	2020	Netherlands	Retrospective study	In vivo	OSCC	13	Tongue	T1: 3; T2:9; T3: 1	Not indicated	7 M 3 W	Mean age 59.9	L16-4Hs, Mindray Bio-Medical Electronics, Shenzhen, China	16 MHz	Hockey stick

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Table 1 (*continued*)

ID	YEAR	COUNTRY	STUDY DESIGN	MODEL	LESION TYPE	SAMPLE SIZE	SITE	STAGING	EDITION	GENDER	MEAN AGE	MODEL	FREQUENCIES	FEATURE
de Koning	2022	Netherlands	Retrospective study	Ex-vivo	OSCC	40	Tongue	T1: 15; T2: 18; T3: 7;	TNM, 8th ed	23 M 17 W	Mean age 58.9	L16-4Hs, Mindray Bio-Medical Electronics, Shenzhen, China	16 MHz	Hockey stick
Dhoot	2014	India	Prospective study	In vivo	OSCC	40	Tongue	Not indicated	Not indicated	30 M 10 W	Not indicated	Nemio 30 SSA-550A; Toshiba Medical Systems Co, Ltd, Tokyo, Japan	7–12 MHz	Not indicated
Di Stasio	2021	Italy	Retrospective study	In vivo	OSCC	20	Tongue	G1:12; G2 7; G3 1	8th Edition	14 M 6 W	Mean age 65.03	GE Logiq-e R7 device	18 MHz	Linear probe
Filauro	2020	Italy	Prospective study	In vivo	OSCC	49	Buccal mucosa 6; tongue 39; floor 4	T1: 16; T2: 20; T3: 13	8th Edition	27 M 22 W	Mean age 65.06	Philips Healthcare, Philips North America Corpora- tion, Andover, MA, USA	7–15 Mhz	Hockey stick
Fruewhald	1985	Austria	Prospective study	In vivo	OSCC	50	Tongue	T0: 1; T1 6; T2 15; T3 1; T4 27	Not indicated	Not indicated	Not indicated	ATL mark 600, Diasonics DRF 400, Siemens Sonoline SL	5 MHz	Not indicated
Heppt	1992	Germany	Within-person study retrospective study	In vivo	OSCC	33	Floor 16; tonsil 17	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	5–7.5 MHz	Not indicated
Heppt	1991	Germany	Within-person study retrospective study	In vivo	OSCC	21	Floor of the mouth; tongue; oropharynx	Not indicated	Not indicated	Not indicated	Not indicated	CS 9300 Picker	5–7.5 MHz	Picker finger tip
Iida	2018	Japan	Within-person study retrospective study	In vivo	OSCC	56	Lateral edge of the tongue	Not indicated	8 th Edition	34 M 22 W	Mean age 59.	Model UST-5713 T/Intraoperative Electronic Linear Probe;	16 MHz	Linear probe
Izzetti	2019	Italy	Prospective study	In vivo	11 reticular olp; 8 atrophic olp; 8 papular olp; 8 bullous olp; 7 plaque-like; 8 erosive olp	50	Buccal mucosa	Not indicated	Not indicated	25 M 25 W	Not indicated	Vevo® MD. VisualSonics	70 MHz	Linear probe
Izzetti	2021	Italy	Within-person study retrospective study	In vivo	OSCC	10	Tongue 6; mandibular mucosa 2; buccal mucosa 1; floor 1	T1: 3; T2:3; T2 N1: 1;	Not indicated	4 M 6 W	Mean age 68.7	Vevo MD (VisualSonics, Toronto, ON, Canada)	70 MHz	Linear probe
Izzetti	2020	Italy	Within-person study Prospective study	In vivo	OSCC	18	Buccal mucosa	Not indicated	Not indicated	11 M 7 W	Mean age 63.48	Vevo MD; VisualSonics, Toronto, Canada	70 MHz	Linear probe
Izzetti	2020	Italy	Within-person study	In vivo	Leukoplakia and erythroplakia	19	Buccal mucosa	Not indicated	Not indicated	9 M 10 W	Mean age 58.63	Vevo MD; VisualSonics, Toronto, Canada	70 MHz	Linear probe

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Table 1 (*continued*)

ID	YEAR	COUNTRY	STUDY DESIGN	MODEL	LESION TYPE	SAMPLE SIZE	SITE	STAGING	EDITION	GENDER	MEAN AGE	MODEL	FREQUENCIES	FEATURE
			Prospective study											
Joshi	2014	Japan	Within-person study Prospective study	In vivo	OSCC	10	Tongue 3; buccal lesion 4; intraoral 1, neck 1	Not indicated	AJCC	Not indicated	Not indicated	730 Pro BTO8 GE Voluson, USA)	5 MHz	Linear probe
Kaneoya	2009	Japan	Not indicated	Ex-vivo	OSCC	48	Tongue	T1: 25; T2: 20; T3:3	TNM	27 M 21 W	Mean age 57.4	PLM-1202S	12 MHz	Linear probe
Kodama	2010	Japan	Within-person study Prospective study	Ex-vivo	OSCC	13	Tongue	T1: 4; T2:9;	1997 criteria of the International Union Against Cancer.	8 M 5 W	Mean age 61.6	SSD-1200CV ultrasound machine	7.5 MHz	Sector probe
Kumar	2023	India	Within-person study Prospective study	In vivo	OSCC	50	Tongue	T1: 9; T2: 32; T3: 9	8 th Edition AJCC	37 M 13 W	Mean age 47.3	Aixplorer US system (SuperSonic Imagine, Aix-en-Provence, France).	6–13 MHz	Hockey stick
Kurokawa	2005	Japan	Within-person study Prospective study	In vivo	OSCC	28	Tongue	Not indicated	International Union Against Cancer staging system,	18 M 10 W	Mean age 59.4	Echo Camera SSD-1200CV	7.5 MHz	Not indicated
Lodder	2010	Netherlands	Retrospective study	In vivo	OSCC	65	Tongue 38; floor of the mouth 22; other part of the mouth 5	Not indicated	T1: 50;T2 15; N0:59: N1:4; N2 2	34 M 31 W	Mean age 65	Philips IU-22 L 15–7;	7–15-MHz	Linear probe
Manchanda	2022	India	Within-person study Prospective study	In vivo	OSCC	2	Tongue: 1 ulcerative 1 sessile	Not indicated	8th Edition of the AJCC UICC TNM	Not indicated	Not indicated	Not indicated	6–13 MHz	Hockey stick
Nair	2018	India	Within-person study Prospective study	In vivo	OSCC	24	Tongue	T1: 18; T2:6;	AJCC 2010	16 M 6 W	Mean age 55	Not indicated	9–17 MHz	Linear probe
Narayana	1996	India	Within-person study Prospective study	In vivo	OSCC	20	Tongue	Not indicated	Not indicated	Not indicated	Not indicated	B-mode scanner of GE 3600.	5 MHz	Linear probe
Nilsson	2022	Sweden	Within-person study Prospective study	In vivo	OSCC	40	Tongue	T1: 19; T2: 10; T3: 11	8 th Edition	25 M 15 W	Mean age 65	Medical Flex Focus 500 US system	18 MHz	Linear probe
Nilsson	2022	Sweden	Within-person study Prospective study	Ex-vivo	OSCC	34	Tongue	Not indicated	8 th Edition	Not indicated	Not indicated	BK Medical Flex Focus 500 US	18 MHz	Linear probe
Nogami	2020	Japan	Within-person study retrospective study	In vivo	OSCC	69	Tongue	Not indicated	Not indicated	32 M 37 W	Mean age 64.5	LOGIQ 400; GE Medical Systems, Tokyo	10–12 MHz	Not indicated

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Table 1 (*continued*)

ID	YEAR	COUNTRY	STUDY DESIGN	MODEL	LESION TYPE	SAMPLE SIZE	SITE	STAGING	EDITION	GENDER	MEAN AGE	MODEL	FREQUENCIES	FEATURE
Noorlag	2020	Netherlands	Within-person study retrospective study	In vivo	OSCC	146	Tongue	T1: 84; T2: 62	TNM 7th ed. guidelines from the American Joint Committee on Cancer (AJCC	74 M 72 W	Mean age 64	EpiQ 5, with CL15-7 transducer, Philips Medical Systems, Best, The Netherlands	15 MHz	Hockey stick
Ota	2008	Japan	Within-person study Prospective study	In vivo	OSCC	38	Buccal mucosa	T1: 10; T2:11; T3: 4; T4a: 3; T4b:10	UICC-TNM	23 M 15 W	Mean age 67	Not indicated	7.5–10 MHz	Linear probe
Rocchetti	2020	Italy	Retrospective study	In vivo	OSCC	36	Tongue, floor of the mouth, buccal mucosa	Not indicated	8 th Edition AJCC	23 M 13 W	Mean age 67	E-CUBE 15 EX US scanner (Alpinion Medical Systems, Seoul, Republic of Korea)	a 8–17 MHz b. 3—12 MHz	a) "hockey stick" b) linear oral fitting-shaped probe
Shinozaky	2014	Japan	Not indicated	In vivo	OSCC	29	Tongue	T1: 7; T2: 14; T3: 4; T4: 4	Not indicated	16 M 13 W	Mean age 64	SSD-5500 system (Aloka, Japan)	7.5 MHz	Not indicated
Shintani	1997	Japan	Within-person study retrospective study	In vivo	OSCC	Not indicated	Not indicated	Not indicated	TNM	16 M 8 W	Not indicated	PEF-704LA,	7 MHz	Linear probe
Shintani	2001	Japan	Within-person study Prospective study	In vivo	OSCC	39	Tongue 26, buccal mucosa 9; mouth floor 4	T1:14; T2: 13; T3: 8; T4: 4	UICC	25 M 14 W	Mean age 58.2	PEF-704LA,	7.5 MHz	Not indicated
Smiley	2018	USA	Prospective study	In vivo	OSCC	10	Tongue	T1: 1; T2:4; T3: 2; T4a: 2; T4b:1	Not indicated	7 M 3 W	Mean age 62.7	Not indicated	7–12 MHz	Hockey stick
Songra	2005	UK	Prospective study	Ex-vivo	OSCC	14	Tongue 10; alveolar mucosa 1; lip 1; floor 1	T1: 7; T2: 5; T3: 0; T4: 1	Not indicated	Not indicated	Not indicated	HDI 5000 (Advanced Technologies Ltd., Seattle)	5–10 MHz	Small Parts probe
Takamura	2020	Japan	Retrospective study	In vivo	OSCC	Not indicated	Tongue	T1: 28; T2: 20	8 th Edition AJCC	28 M 20 W	Mean age 65.7	HI VISION Preirus (Hitachi, Tokyo, Japan)	7–13 MHz	Hockey stick
Tarabichi	2017	USA	Retrospective study	In vivo	OSCC	12	Not indicated	T1:11; T2: 1	Not indicated	6 M 6 W	Mean age 55	L15-7io	Not indicated	Hockey stick
Yamane	2006	Japan	Within-person study Prospective study	In vivo	OSCC	109	Tongue	T1: 41; T2:68	AJCC	77 M 32 W	Mean age 57	Aloka SSD-630 ultrasound system	10 MHz	Linear probe
Yesuratnam	2014	Australia	Prospective study	In vivo	OSCC	Not indicated	Tongue	T1-T2: 68; T3-T4:11	Not indicated	Not indicated	Not indicated	L15-7io	7–15 MHz	Hockey stick
Yoon	2020	USA	Prospective study	In vivo	OSCC	26	Tongue	Not indicated	Not indicated	Not indicated	Not indicated	L15-7io; Philips Healthcare	Not indicated	Linear probe

chances to develop nodal metastasis. Currently, this assessment is performed by histological evaluation on the bioptical sample and for the most clinical presentations, surgery is performed as primary treatment [9]. To prevent multiple surgeries, non-invasive preoperative approaches should be introduced into the clinical practice, with the aim to improve the pre-operative characterization of the lesion, thus improving decision-making in both bioptical sampling in terms of the area of the lesion to be taken and in primary curative surgery intervention [10]. A better pre-operative understanding of the microscopic pattern of the lesions might help surgeons in improving the surgical protocol, in terms of how extensive the surgery should be performed as well as a better understanding of histopathological characteristics, for example the DOI. This might help in managing and thus preventing locoregional relapse and minimal residual disease and to plan a more personalized treatment approach.

Various imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have been used in this aim. MRI provides better soft tissue resolution without the use of ionizing radiation. However, some limitations must be considered, such as the long waiting time for the patients, generally ranging from 65 to 105 days [11]; and the costs, being an expensive test, to be performed in specialized and equipped centers. Moreover, approximately 10 % of patients would not undergo this examination for reasons like foreign metal bodies, implants, and claustrophobia [12]. These limitations have limited the translational application of widespread pre-operative MRI examination of patients with suspect OSCC and OPMD characterization. In this scenario, ultrasounds (US) can offer a sensible alternative. US have been already used in various medical fields, due to the high resolution, which makes this technology particularly suitable for the investigation of superficial anatomy [13]. Different studies have highlighted how US can spot and characterize microscopical variability of the oral mucosa, for example the basal layer and, thus the DOI for pathological lesions. However, while several studies have been published correlating pre-operative US DOI measurement and its relative histopathological assessment, nowadays US are not routinely used in clinical practice. In the diagnosis of OSCC, recent studies have demonstrated that US can be useful in assessing both tumor thickness (TT) and DOI [14 15].

Besides its utility in diagnosis, US could potentially be applied for surgical procedures, as well. In fact, the challenge of achieving adequate margins in OSCC resections still remains, given the higher rate of positive surgical margins during the resections compared to other solid tumors [16]. Intraoperative US represents an advancing approach, offering several potential benefits, such as enabling surgeons to visualize the entire lesion, including its deepest extent, while being widely accessible and incurring in no additional capital expense for most of the institutions [16].

To bring US into clinical routine practice in the management of patients with OSCC and OPMD, the aim of this systematic review was to determine whether the accuracy of ultrasound is comparable to that of histology in the assessment of DOI and tumor thickness (TT). This comparison is essential to test whether ultrasound, as a minimally invasive, patient-acceptable, affordable, and easy-to-use method, can represent a useful tool in the management of both tumoral and potentially malignant oral lesions.

Review

The current systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards. The protocol was submitted and registered in the PROSPERO database: CRD42024536792.

Search strategy and database screening

An electronic search of the English language literature was performed up to February 2024 on the following database: PUBMED, SCOPUS, Web of science.

In addition, a direct search was also performed in the bibliographies of all reviewed articles.

The research process was carried out via a combination of mesh terms and free text words, combined using some Boolean operators (AND, OR). The following protocol was used for PUBMED: ((“mouth neoplasms”[MeSH] OR “oral neoplasm” OR “oral squamous cell carcinoma” OR “oral carcinoma” OR “oral cancer” OR “tongue squamous cell carcinoma”) OR (“oral premalignancy” OR “precancer” OR “oral precancerous lesion” OR “oral dysplasia” OR leukoplakia OR erythroplakia OR “oral lichen planus” OR OPMD OR “oral potentially malignant disorders”)) AND (“Ultrasonography”[MeSH] OR “Ultrasound” OR “Intraoral ultrasonography” OR “Intraoral Ultrasound”). Search strategies for each specific database are available in supplemental materials.

Eligibility criteria

Inclusion criteria

No publication year restriction was applied to the mentioned search. Studies were screened based on the following inclusion criteria: (1) English language; (2) Cohort, case-control, observational retrospective or longitudinal studies; (3) Studies focusing on the role of US in the management of OSCC and OPMD; (4) and studies performed on humans.

Exclusion criteria

The exclusion criteria were as follows: (1) Systematic review and meta-analysis and studies not including information about the use of US in the OSCC and OPMD; (2) Studies not in English.

Focused PICO question and effect measure

(P) Participants: patients with a diagnosis of OSCC and/or OPMD.

(I) Intervention: assessment of TT and/or DOI with intraoral ultrasonography.

(C) Comparison: assessment of TT and/or DOI measurement on histology.

(O) Outcome: correlation between ultrasonographic TT and/or DOI and pathologic DOI; mean and standard deviation of TT and DOI both in ultrasound and histological assessment.

To be eligible for inclusion in the meta-analysis, the outcome had to be reported as TT histological mean, TT ultrasound mean, DOI histological mean, DOI ultrasound mean, Spearman correlation and Pearson correlation.

Studies screening and inclusion

Two authors (FE and VCAC) independently screened for the retrieved citations, by reading the title and abstract. After considering inclusion and exclusion criteria, the authors came up with a list to screen for full-text eligibility evaluation. The third author (LLR) was involved in making a final decision in case of disagreements.

Data extraction

Similarly, data extraction was undertaken by two reviewers (FE and VCAC), independently and results were compared and merged by using an ad hoc extraction sheet. In case of discrepancy, articles were rescreened in a joint meeting with the third reviewer (LLR). The extraction sheet in Excel format included the following fields: Author names, year of publication, country, study design, lesion type, number of lesions, site, staging, staging edition, clinical feature (number of participants of the study, gender, age), US feature (model, frequencies, feature) (Table 1).

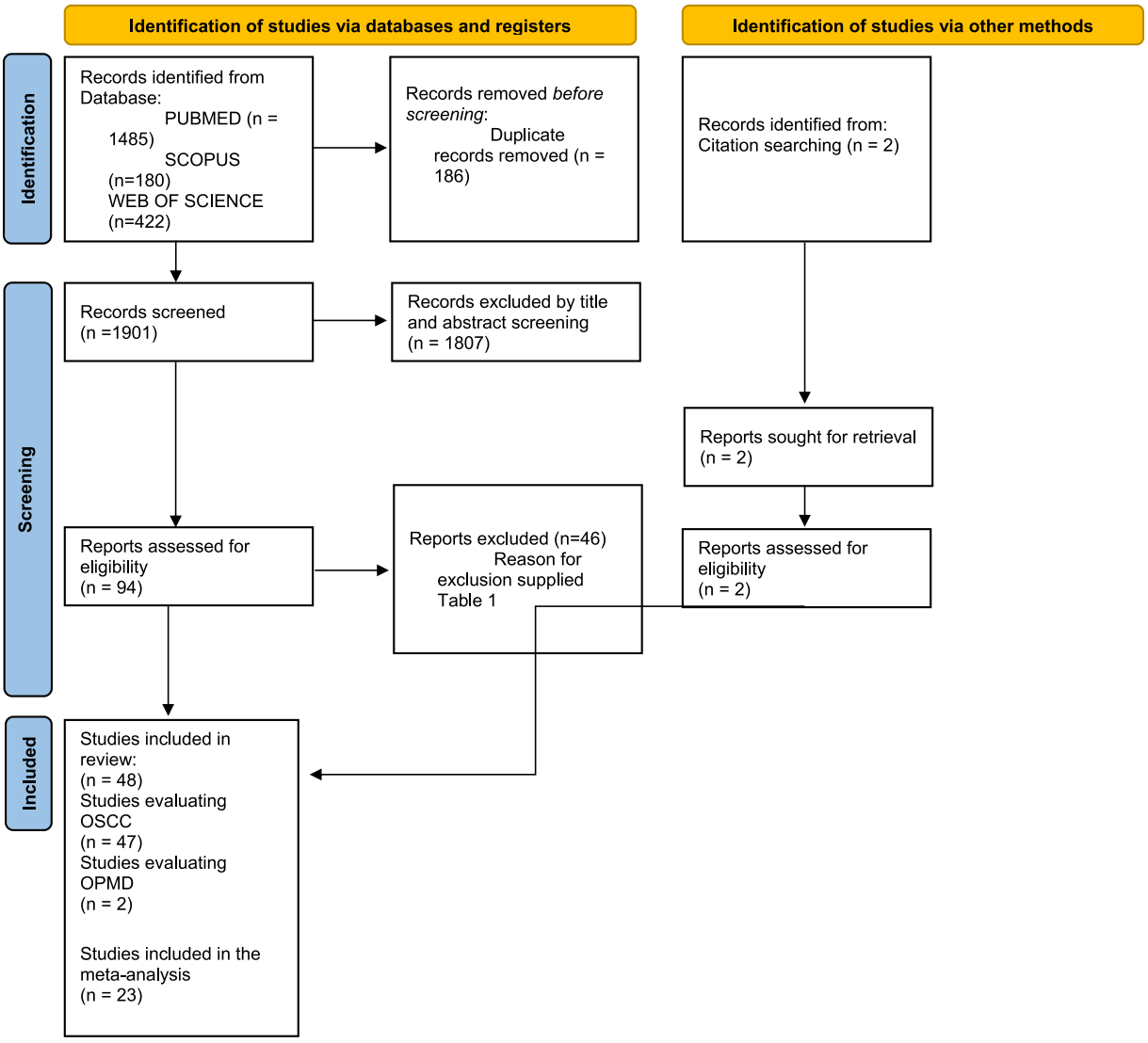

Fig. 1. Flowchart of studies' selection process.

Assessment of risk of bias

The quality assessment and the risk of bias of the included studies was performed following the criteria of the ROBINS-I tool (Risk of Bias In Non-randomized Studies of Interventions) evaluating selection, comparability, and outcome domains for each study. When the study was judged critically or seriously, it was thought to be highly biased [17].Two authors (FE and VCAC) independently performed such assessment and discrepancies were resolved in a joint meeting with the third reviewer (LLR).

Statistical analysis

Based on the information retrieved from the included studies, TT and DOI were recorded as: 1. mean values, standard deviations (SD), and sample size for the control group (histological assessment) versus the test group (ultrasound assessment); 2. the correlation value between the histological and ultrasound assessment as Pearson's or Spearman's correlation, using the "R" program, with the *meta* and *metafor* packages.

In the study of Izzetti et al [13] DOI and TT results were presented separately for exophytic and endophytic lesions. To be included in the meta-analysis, the means and SD of both groups were combined employed the formula from the Cochrane Handbook for Systematic Reviews of Interventions version 6.3 [18]. Spearman's correlation values [19–22] were converted to Pearson's correlation using the formula $2sin(\rho\pi/6)$ [23]. Resulting values were adjusted according to Rupinski et al. [24]. The study conducted by Iida [21] was not included in the meta-analysis because the standard deviation was missing.

The overall standardized mean difference (SMD) and corresponding relative 95 % confidence interval (95 % CI) were computed using Hedges'g weighted data. Forest plots were utilized for graphical representation in either a fixed or random effect model, depending on the observed heterogeneity. Cochran's Q test assessed heterogeneity among studies, with quantification provided by the I^2 index.

A random effects model was employed for I^2 values exceeding 50 %, while a fixed effect model was utilized for lower values.

Heterogeneity was furtherly evaluated by investigating differences among studies based on moderators, such as (1) risk of bias, (2) country, (3) frequency (MHertz) (4), and publication year.

To inspect the influence of individual studies on overall standardized mean difference, leaving one out method was employed [25]. In the final step, a funnel plot was created to visually represent the publication bias and was complemented by trim and fill analysis [26] and Egger's test [27].

Trial-sequential analysis (TSA) was conducted to assess the power of the meta-analysis result, with a predetermined acceptable risk of type

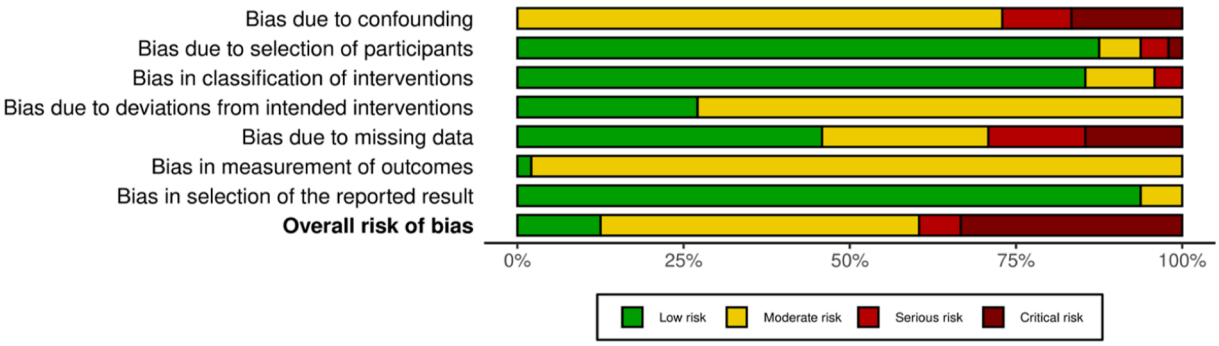

Fig. 2. Risk of bias assessment of the 48 articles included in the review. Plot generated with robvis tool [69].

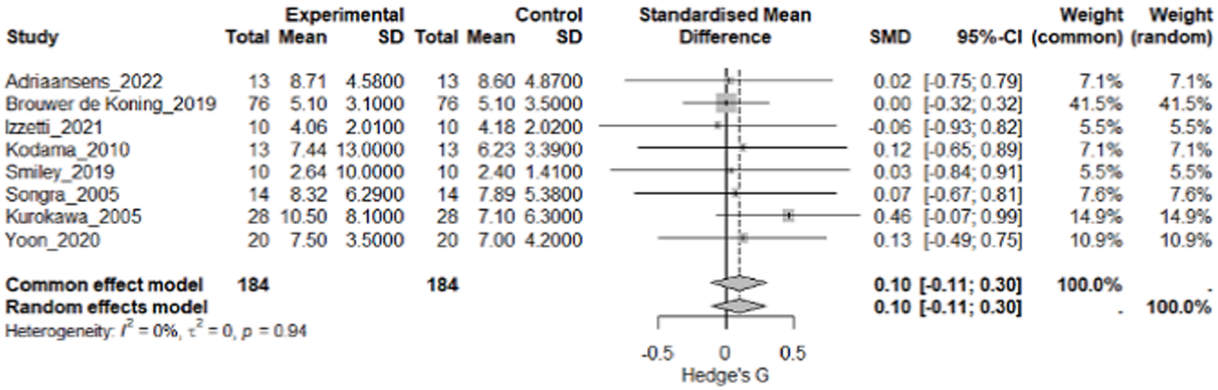

Fig. 3. Forest plot depicting overall standardized mean difference estimation for meta- analysis comparing US vs histological TT assessment. SMD: Standardized mean difference, 95 % CI: 95 % Confidence Interval.

one errors (α) set at 5 % and a power of 80 %. This analysis involved continuous data. TSA process produced graphical representations illustrating the cumulative sample size alongside trial sequential monitoring boundaries. These boundaries indicated the points at which statistical significance or futility could be determined, considering one or two error values. Additionally, the required information size (RIS) was calculated based on the provided values in the intervention (ultrasound) and control arms (histological).

The mean difference for generating the RIS was user-defined. In the case of TT meta-analysis, the mean difference was set to "2"; in the case of DOI meta-analysis, this was set to "1". The values were set by evaluating the 8th edition of AJCC, for which a difference of +/- 2 and 1, respectively of TT and DOI would lead to an over- or underestimation of the tumor staging classification [8].The variance was based on an empirical model. The study also applied a model variance-based approach to correct for heterogeneity and used a graphical evaluation to determine if the cumulative Z-curve met defined thresholds.

Results

Study selection

The electronic search retrieved a total of 2087 articles from the electronic database search and 2 articles from the hand search published up to May 2024. After the removal of duplicates (186), title and abstract analysis was performed on 1901 articles, of which 1807 were excluded after the screening of titles and abstracts. Full text analysis was performed on the remaining 94 articles, and 46 articles were further excluded (Supplemental materials). The final review included 48 articles (46 studies included patients with OSCC[9,13,19–22,28–34,16,36–66]1 study included both patients with OSCC and OPMD[67,68] (Fig. 1.). Of these, 23 reported enough data to be included in the meta-analysis [13,19–22,28,31,33,16,36,44,46,47,49,51,55,59–62,64–66].(See Fig. 2).

Risk of bias assessment

Nineteen studies [13,19–22,28,31,33,16,36,44,46,47,49,51,55,59–62,64–66]showed a high risk of bias.

These studies did not provide detailed information on the number of samples examined, the stage of the lesions, type of probe and site of lesions which makes it impossible to assess their reliability.

Study characteristics

The eligible studies (Table 1) were conducted from 1985 to 2023, in various countries around the world, including: Australia [65], Austria [41], Brazil [36], Canada [30], France [34], 3 Germany [42,43,70], 5 India [39,48,50–52], 9 Italy [9,13,19,20,29,35,40,67,68], Korea [31], 12 Japan [21,22,44–47,55,57–60,64], 7 Netherlands [28,32,33,37,38,49,56], 2 Sweden [53,54], UK [62],4 USA [16,61,63,66].

A total of 1615 lesions were identified, with 1302 located on the tongue.

Information for the staging system was available for 27 studies [13,20,22,29,31,32,34,35–38,40,41,46–48,51,53,56–58,60–65,70]; in particular, only 1 study used the 1997 classification [47], 13 used the 8th edition of the AJCC [9,20–22,28,32,16,37,40,48,50,53,54], and 3 used the International Union Against Cancer Staging system (UICC) [44,57,70 60].

The study population consisted of 1416 patients, with a mean age of 62.35 years. Information on gender distribution was available for 35 out of 48 articles [9,13,19–22,28,29,31,32,34,36–40,44,46–49,51,53,55–61,63,64,67,68,70], with 853 males and 563 females.

In 44 studies, information on the type of frequencies employed was available: above 16 MHz in 9 studies [13,19,29,35,40,53,54,67,68],

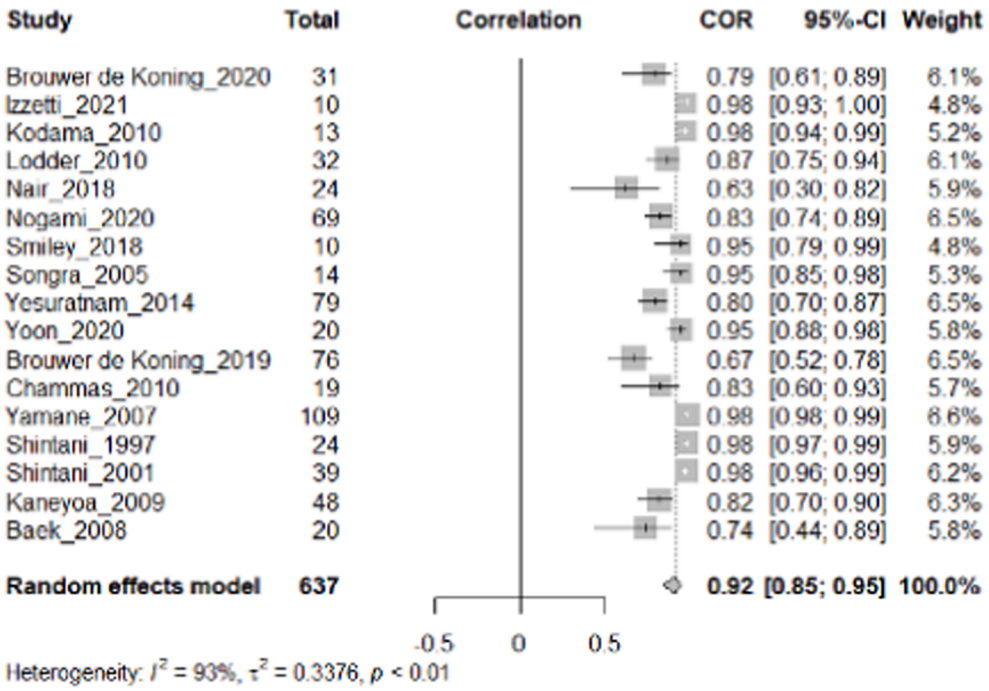

Fig. 4. Forest plot depicting overall standardized Pearson Correlation estimation for meta- analysis comparing US Tumor Thickness vs Histological Tumor Thickness 95 % CI: 95 % Confidence Interval.

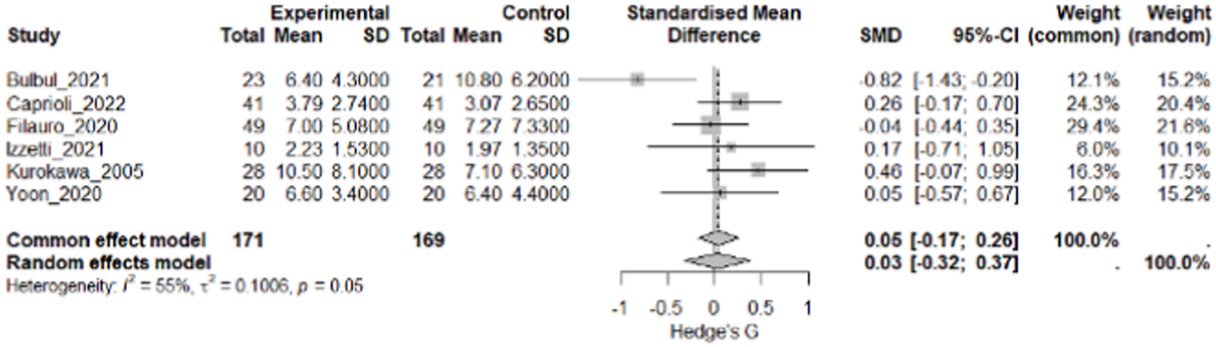

Fig. 5. Forest plot depicting overall standardized mean difference estimation for meta- analysis comparing US Depth of Invasion vs Histological Depth of Invasion SMD: Standardized mean difference, 95 % CI: 95 % Confidence Interval.

while below 16 MHz in 35 studies [9,20–22,28,31–34,36–39,41–52,55–62,64,65].

Information on the type of probe used was available for 38 studies, with 15 using a hockey stick probe [9,19,20,22,28,32,35,37,38,48,50,56,61,63,65]; 19 using a linear probe [13,21,29,31,16,40,45,46,49,51–54,57,60,64,66–68,70], one Picker fingertip [42], one sector probe [47], one small Parts probe [62] and one T-shaped [36].

Meta-analysis

Tumor thickness mean difference

Heterogeneity results showed low heterogeneity among studies (I^2 = 0.00 %) (Fig. 3). Heterogeneity among studies was furtherly investigated by leave-one-out method (Supplemental materials) which did not show differences in SMD estimation.

The overall was 0,10, C.I 95 % of −0,11;0,30 and p value of 0,353.

Tumor thickness correlation

Heterogeneity results showed high heterogeneity among studies (I^2 = 93 %). (Fig. 4.) Heterogeneity among studies was furtherly investigated by leave-one-out method (Supplemental materials), which did not show different SMD after elimination of studies included into the analysis.

Depth of invasion mean difference

Heterogeneity results showed average heterogeneity among studies (I^2 = 55 %) (Fig. 5). Heterogeneity among studies was furtherly investigated by leave-one-out method (Supplemental materials) which did not show different SMD after elimination of studies included into the study.

The overall was 0,03; C.I 95 % of −0,32;0,37 and p value of 0,881.

Depth of invasion correlation

Heterogeneity results showed average heterogeneity among studies (I^2 = 62 %). (Fig. 6) Heterogeneity among studies was furtherly investigated by leave-one-out method (Supplemental materials) which did not show different SMD after elimination of studies included into the study.

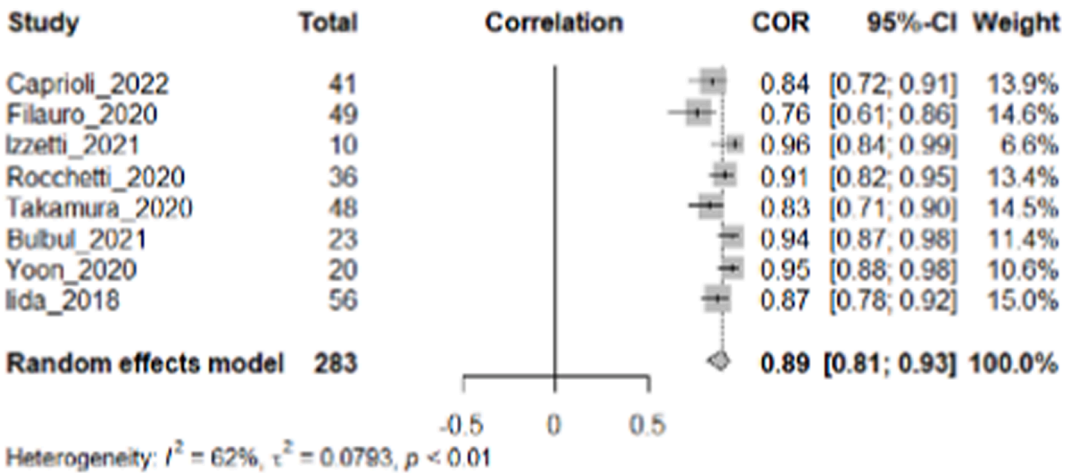

Fig. 6. Forest plot depicting overall standardized Pearson Correlation estimation for meta- analysis comparing US Depth of Invasion vs Histological Depth of Invasion 95 % CI: 95 % Confidence Interval.

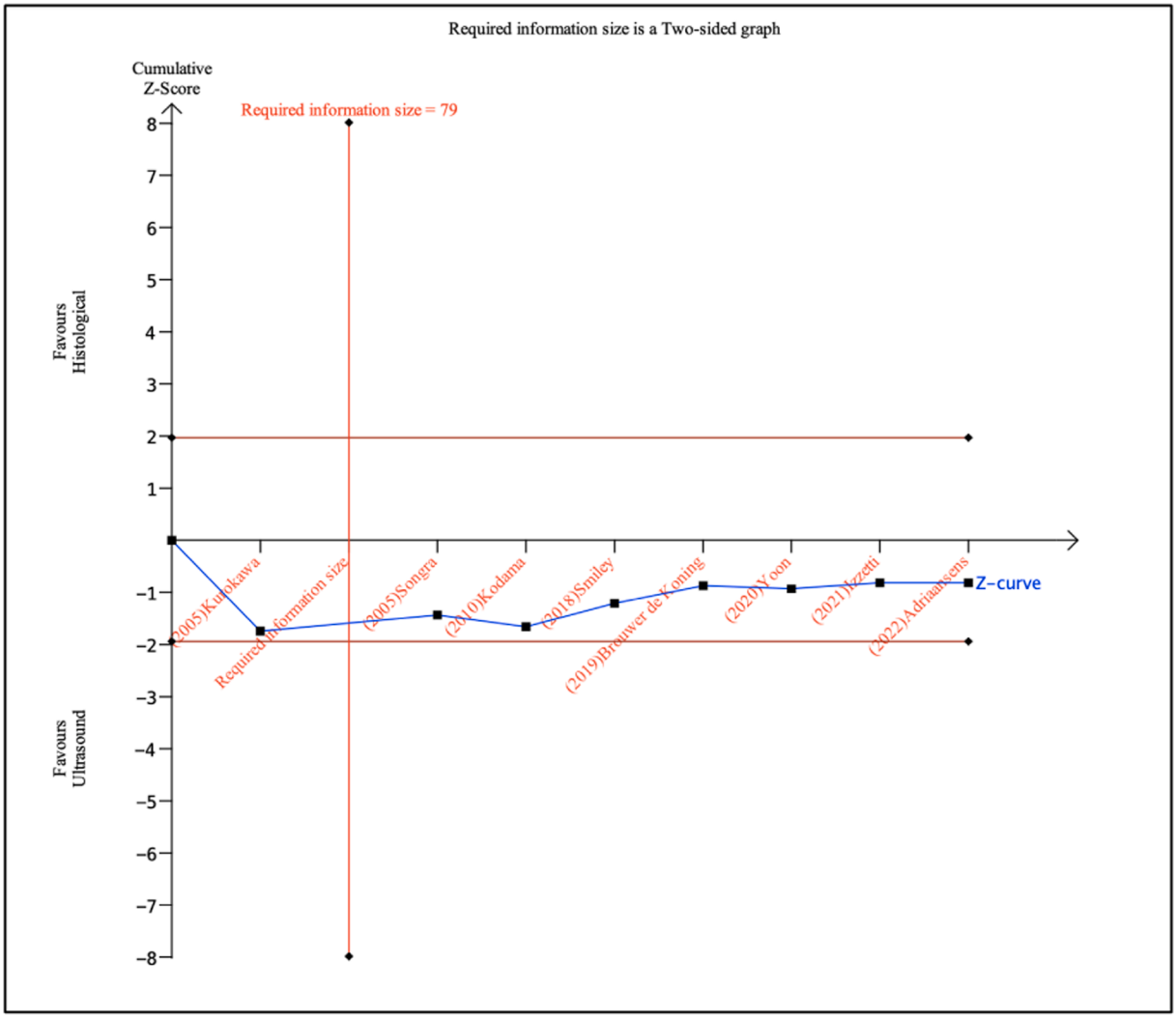

Fig. 7. TSA TT.

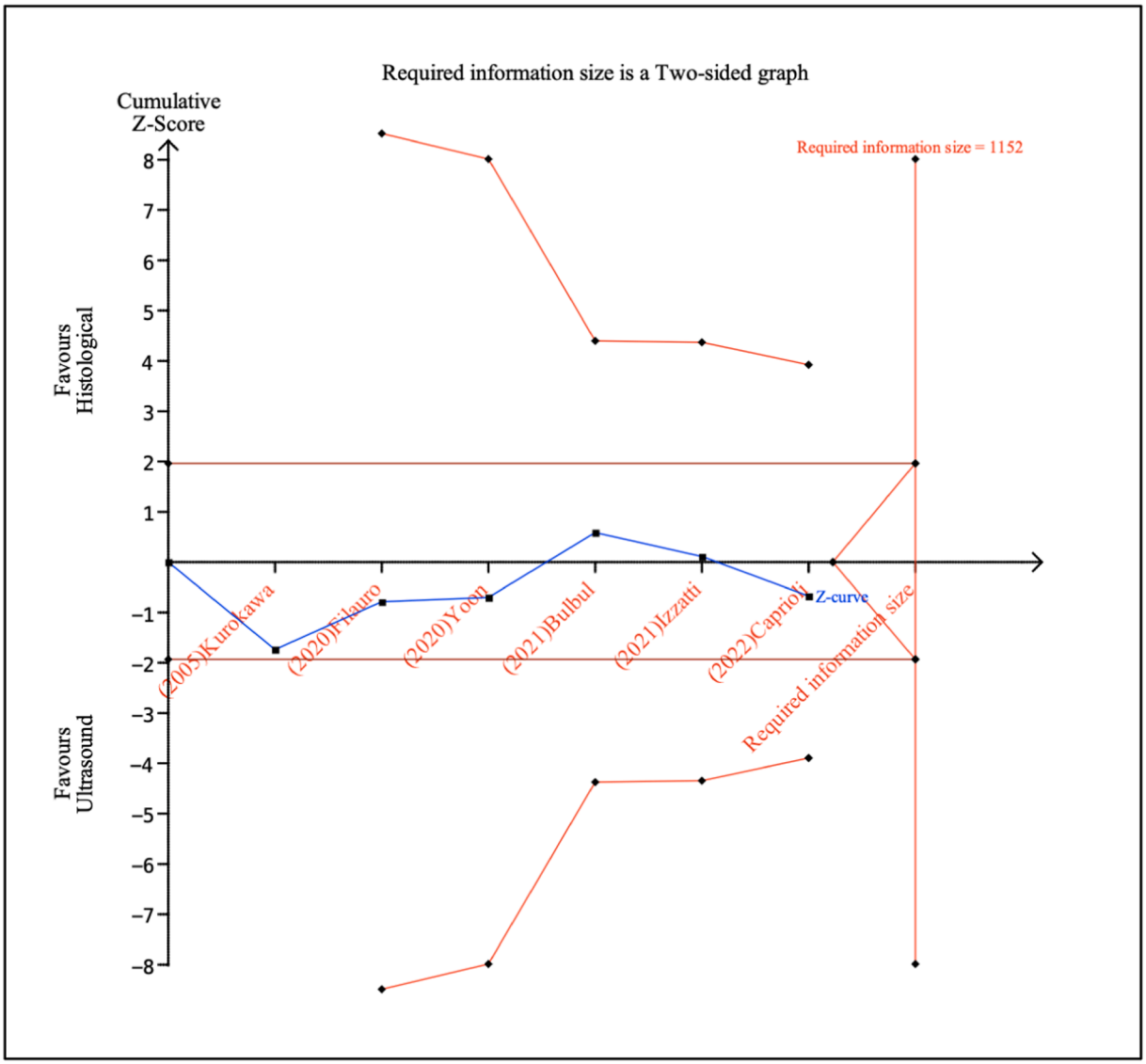

Fig. 8. TSA DOI.

Trial sequential analysis (TSA)

TSA TT

Results from this meta-analysis were confirmed by the TSA. Fig. 7 (Fig.7.) shows that the cumulative Z curve crossed the trial sequential significance boundary and reached required meta-analysis sample size.

TSA DOI

The fig. 8 (Fig.8) shows that the cumulative Z curve did not cross the conventional significance boundary and trial sequential significance boundary. The sample size was 340, which did not exceed the required meta-analysis sample size (1152),so additional studies are required in order to reach the RIS.

Other studies not included into the meta-anlysis

Out of the 25 remaining studies [9,29,30,32,34,35,37–43,45,48,50,52–54,56–58,63,67,68]none were included in the meta-analysis due to the lack of suitable statistical data for analysis. Nevertheless, these papers were considered relevant as they met the inclusion criteria for this systematic review.

In manies studies, Ultrasound was able to differentiate between alterations of the oral mucosa and healthy mucosa [9,29,30,35,38,40–43,45,48,54,57,63,67,68]. The potential role of ultrasound in preoperative assessment was explored in the works by Brouwer de Koning et al. [32], de Koning et al. [38], Noorlag et al. [56], and Nilsson et al. [54] which highlighted insufficient deep resection margins.

On the other hand, Shinozaki et al. [58]noted limitations in the use of ultrasound, including an overestimation of measurements compared to histology. Additionally, several studies observed limited effectiveness for detecting small lesions [39,52] and for lesions located in specific areas, such as the posterior third of the tongue [34,50].

Discussion

In this systematic review and meta-analysis we reviewed all the articles that used US in the assessment of OSCC and OPMD.

Although ultrasound is gaining popularity for diagnosing OSCC in the oral cavity, its application in the early valuation of OPMD seems to be limited. Only two investigations [67,68], both conducted by the same researchers, have explored the potential utility of ultrasound in diagnosing these lesions, demonstrating that US was able to differentiate superficial alterations of the oral mucosa with a 97 % specificity [67 68].

Initially, the use of ultrasound in oral cancer assessment was limited to fine needle aspiration biopsy (FNAB), as demonstrated by Au in 1997

(30); then, the high-resolution diagnostic intraoral ultrasound has been shown to work excellently for real-time examinations of soft tissues [47].

Indeed, the ultrasound measurements showed a high degree of reliability with histological measurements for tumor thickness [62 51], with a consistency ratio of 91.4 % to 98.2 % [31].

Furthermore, it appears to be more accurate than Computer Tomography (CT) or MRI when used for preoperative assessment, particularly for tongue cancer [44 58]; According to Smiley et al, US has the capacity to accurately detect lesions that are undetectable by MRI because of dental artifact [61]. This is also confirmed by more recent studies conducted by [20] and Nogami et al [55].Ultrasonography finds indication in the presence of small tumors, which are not detectable through other diagnostic imaging techniques such as computed tomography and magnetic resonance [71 22 34].

In addition to TT, this systematic review also examined the role of ultrasound in diagnosing DOI. This consideration is particularly relevant since, starting from 2017 with the eighth edition of the AJCC staging manual, DOI has emerged as a crucial parameter in the prognosis of oral OSCC [72].

Iida and colleagues [21] compared usDOI with MRI-measured DOI (mriDOI) and found a stronger correlation between mriDOI and pDOI than that between usDOI and pDOI. Rocchetti and colleagues [9] and Caprioli et all [35] observed a robust correlation between usDOI and pDOI.

According to Nilsson et al [53], ultrasound better determines the DOI in T1 lesions, in line [19] and Noorlag et al [56].

In accordance with the latter's studies, in tumors with a DOI up to 10 mm (pT1-2 tumors in the 8th TNM classification), intraoral ultrasound is more accurate than MRI and should be the preferred imaging technique since MRI tends to overestimate DOI [56].

One of the limitations of this study pertains to the difficulty of using ultrasound to diagnose retromolar tumors, which may be challenging to assess with currently available probes. This challenge is further exacerbated by poor patient compliance, as noted by Angelelli et al. and Manchanda et al., and supported by Ota et al [29,50,57]. MRI remains the most accurate method for T3 lesions, as highlighted by Nilsson [53].

Another relevant aspect that needs to be further investigated is the possibility of using US in the assessment of tumor-free margins; in 2017 Tarabichi [63] showed the possible use of this tool to evaluate clear deep margins. nonetheless, Adriaansens et al. showed that US had the tendency to overestimate tumor-free margins [28]; thus, additional studies are required.

As regards to examine variables for which meta-analysis was carried out: (1) TT mean difference, (2) TT correlation, (3) DOI mean difference, and (4) DOI correlation,no statistically significant differences between the results obtained with histology and ultrasound were found.

This information was further validated by TSA. In particular, regarding TT, the RIS was reached and exceeded. This provides confidence that the use of ultrasound in the assessment of oral cancer will not lead to overestimates or underestimates of +/- 2, which would lead to different diagnoses in staging.

Instead, further studies are needed to evaluate the use of US in the assessment of DOI.

Conclusion

This systematic review with meta-analysis shows that there were no statistically significant differences between the results of ultrasound and histological examination; nonetheless the clinical use of this device requires further confirmation. In fact, a difference of 1 mm in DOI could lead to over- or under-staging of the tumor. Further studies are therefore needed to ensure the clinical reliability of ultrasound.

CRediT authorship contribution statement

Esperouz Fariba: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Caponio Vito Carlo Alberto:** Data curation, Formal analysis, Writing – review & editing. **Santarelli Andrea:** Validation. **Ballini Andrea:** Data curation, Formal analysis. **Lorenzo Lo Muzio:** Conceptualization, Data curation. **Domenico Ciavarella:** Data curation. **Lo Russo Lucio:** Conceptualization, Supervision, Validation, Visualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2024.107104.

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