



Diagnostic and prognostic value of magnetic resonance imaging in the detection of tumor depth of invasion and bone invasion in patients with oral cavity cancer

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Abstract

Purpose To evaluate the accuracy of preoperative contrast-enhanced magnetic resonance imaging (MRI) in the assessment of radiological depth of invasion (rDOI) and bone invasion in patients with oral cavity cancer, and the prognostic value of preoperative rDOI.

Materials and methods This retrospective study included patients with surgically resected oral cavity cancer and preoperative MRI acquired within four weeks before surgery. Two readers evaluated the MRI to assess the superficial and deep bone invasion, preoperative T stage, and measured the rDOI. The rDOI was compared to the histopathological DOI (pDOI), used as reference standard. Prognostic value of preoperative features for the disease-specific survival was evaluated using the Kaplan–Meier curve and multivariable Cox proportional hazards analysis.

Results The final population included 80 patients (50 males, mean age 67.7 ± 13.6 years). There was a strong statistically significant correlation between the rDOI (median 10 mm) and the pDOI (median 9 mm) ($\rho: 0.978, p < 0.001$). The agreement between MRI and histopathological T stage was excellent ($k = 0.93, 95\% \text{ CI } 0.86, 0.99$). The sensitivity and specificity of preoperative MRI were 93.3% and 98.8% for deep bone invasion, while they were 75.0% and 95.8% for superficial bone invasion, respectively. The rDOI > 10 mm was associated with poorer disease-specific survival (log-rank $p = 0.016$). The rDOI remained the only independent preoperative predictor associated with poorer disease-specific survival at multivariable analysis (hazard ratio 5.5; 95% CI 1.14, 26.58; $p = 0.033$).

Conclusion Preoperative MRI is accurate for the assessment of DOI and bone invasion. The rDOI is an independent preoperative predictor of disease-specific survival in patients with oral cavity cancer.

Keywords Head and neck neoplasm · Oral cavity carcinoma · Oral cancer · Neoplasm invasiveness · Mandibular invasion · Magnetic resonance imaging

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Introduction

Oral cavity cancer is one of the most common malignancies, with growing incidence and high association with tobacco smoking and alcohol use [1]. Squamous cell carcinoma is the most common histologic type of oral cavity cancer accounting for up to 90% of all cancers [1]. Surgical resection is the treatment of choice, although patients often present in advanced stages with bone invasion or cervical lymph node metastases. Accurate tumor staging is crucial for patient management and indication for surgery. Currently, the tumor-node-metastasis (TNM) staging is the reference prognostic system in patients with oral cavity cancer. In the latest TNM staging system, released in the 8th edition of the Cancer Staging Manual of the American Joint Committee on Cancer tumor (AJCC), tumor size, depth of invasion (DOI), and invasion of adjacent structures are the most relevant factors for T stage [2, 3]. Particularly, DOI differs from the previously described maximum tumor thickness. The tumor thickness is measured from the tumor surface till the deepest point of invasion, whereas the DOI is measured perpendicularly from the line connecting the adjacent normal mucosal basement membrane to the deepest point of tumor invasion and it has been demonstrated to be a stronger predictive parameter compared to tumor thickness [3]. The cutoffs of histopathological DOI (pDOI) of ≤ 5 mm, > 5 mm but ≤ 10 mm, and > 10 mm were integrated in the 8th edition AJCC Cancer Staging Manual to define T1, T2, and T3 stages, respectively [2, 3].

Contrast-enhanced magnetic resonance imaging (MRI) has an upmost importance in the preoperative local tumor staging of oral cancers due to its excellent contrast resolution and high accuracy for preoperative locoregional staging [4]. Compared to the clinical assessment and other radiological imaging examinations (i.e., CT or cone-beam CT), MRI allows to evaluate the deep extension of the tumor, invasion of adjacent bone structures, and locoregional lymph node metastasis with high accuracy [4, 5]. Some recent studies evaluated the correlation between MRI-measured depth of invasion (rDOI) and the histopathological depth of invasion (pDOI) [6–14]. However, the impact of preoperative rDOI on patients' prognosis still needs to be determined.

The aim of this study is to evaluate the diagnostic accuracy of preoperative contrast-enhanced magnetic resonance imaging in the assessment of radiological depth of invasion and bone invasion in patients with oral cavity cancer, and to determine the prognostic value of preoperative rDOI.

Materials and methods

This retrospective study was approved by the Ethical Committee of our University Hospital (approval No. 11/2021) with a waiver for informed consent due to its retrospective nature.

Population

A retrospective search was conducted in the institution database to select adult patients who underwent radical surgical resection of oral cavity cancers between 2014 and 2018. Inclusion criteria were: 1) surgical resection of oral cavity cancer; 2) available preoperative contrast-enhanced MRI with an imaging-to-surgery time interval of a maximum of four weeks; 3) histopathological examination performed at our institution. Patients with contrast-enhanced MRI outside the above defined interval or with severe imaging artifacts, as well as patients who underwent preoperative treatments with radio-chemotherapy or partial resections were excluded. The initial population consisted of 99 patients (61 males and 38 females, mean age 61.1 ± 14.1 years). Among them, patients with carcinoma in situ (Tis) were excluded from the study population ($n = 19$) due to the lack of detectable tumor on MRI.

The following data were collected for each patient: age at the time of surgery, sex, histopathological features including type of primary tumor, depth of invasion, bone invasion, and pathologic T stage.

MRI technique

All patients underwent preoperative MRI examination performed with the same clinical 1.5 T MRI system (Achieva, Philips, Amsterdam, The Netherlands) with a dedicated head and neck coil. The standard MRI protocol included axial and coronal T1 turbo spin-echo (TSE) sequences, axial and coronal T2 TSE sequences, axial short tau inversion recovery (STIR), diffusion weighted imaging (DWI). After the intravenous administration of contrast agent, the following sequences were acquired: axial three-dimensional T1 high-resolution isotropic volume examination (THRIVE; Philips Healthcare, Amsterdam, The Netherlands) sequence at 80 s after contrast injection followed by axial and coronal spectral presaturation with inversion recovery (SPIR) sequences, and axial T1 TSE sequence. All patients received a weight-based dose of 0.1 ml/Kg mmol/kg of Gadobenate Dimeglumine (MultiHance, Bracco Imaging Italia s.r.l., Milan, Italy) or Gadoteridol (Prohance, Bracco Imaging Italia s.r.l., Milan, Italy) injected at a rate of 1–2 mL/s, followed by 20-mL saline flush at the same injection rate, using an automatic

injector (Medrad® Spectris Solaris® EP, Bayer Healthcare, Berlin, Germany). Detailed acquisition parameters are provided in Supplementary Table 1.

MRI analysis

Preoperative MRI examinations were reviewed in consensus by two readers (A.L.C. a subspecialized head and neck radiologists with more than 30 years of experience and R.T. a senior radiology resident with 4 years of experience in head and neck imaging), blinded to the histopathological characteristics of the lesions. The readers evaluated the presence of superficial and deep bone invasion, preoperative T stage and measured the radiological depth of invasion (rDOI) in all lesions. Any disagreement was resolved by consensus reassessment.

MRI diagnostic criteria used for evaluation of bone invasion were: lack of typical hypointense signal of cortical bone on T1 and T2, replaced by adjacent tumor signal intensity (to assess cortical invasion); evidence of hyperintense signal of bone marrow adjacent to tumor on STIR and T1-enhanced sequences (to demonstrate marrow involvement).

According to the definition on the AJCC Cancer Staging System, 8th edition, the rDOI was measured by the two readers in consensus as the perpendicular deepest point of tumor invasion from the horizontal basal line passing by the junctions of the tumor and the adjacent normal mucosa [2, 3]. The rDOI was measured on T2 sequences and post-contrast THRIVE or SPIR sequences, and the average measurement was considered for the analysis [12]. Particularly, the rDOI was measured by drawing perpendicular lines from the reference line to the point of maximal tumor projection (Fig. 1), as described in prior studies [7, 9, 11, 13].

Reference standard

One pathologist (with more than 30 years of experience) reviewed all the resection specimens assessing histologic tumor type, size, and location of the tumor. Pathologist measured pDOI on specimens from the basement membrane of adjacent normal epithelium to the deepest extent of the tumor with the image analysis system Leica QWin v.3.4.0 which includes a digital camera DFC480 (Leica Microsystems, Wetzlar, Germany) [2, 3]. Histologic sections were then analyzed for the absence or presence of superficial or deep bone invasion.

Statistical analysis

Categorical variables were reported as numbers, proportions, and percentages, while continuous variables as means $\pm$ standard deviations and ranges, or medians and interquartile ranges (IQR), after testing for normal

distribution by the Shapiro–Wilk test. The correlation between rDOI and pDOI was evaluated using the Spearman's rank correlation coefficient (Spearman's ρ). Bland–Altman analysis was performed to evaluate the magnitude of variation between radiological and pathological measurements. The averages of the differences and 95% limits of agreement were calculated. The Cohen's kappa (k) test was used to assess agreement between MRI and histopathological T stages. Agreement was categorized as poor ($k < 0.00$), slight ($k = 0.00–0.20$), fair ($k = 0.21–0.40$), moderate ($k = 0.41–0.60$), substantial ($k = 0.61–0.80$), or almost perfect ($k = 0.81–1.00$) [15].

Disease-specific survival was calculated from the date of surgery to the date of cancer-related death or the last follow-up. Survival analysis was conducted by using the Kaplan–Meier method, including the 10-mm cutoff reported in the 8th edition of TNM classification, deep bone invasion, and T stage [2, 3]. Curves were compared by using the log-rank test. Patients alive at the last available follow-up were censored. Multivariable Cox proportional hazards analysis with stepwise backward elimination was used to select preoperative features associated with disease-specific survival. Hazard ratio (HR) with its 95% confidence interval (95% CI) was calculated for statistically significant variable at multivariable analysis.

Statistical significance level was set at $p < 0.05$. Statistical analysis was performed by using IBM SPSS software version 26.0 (Armonk, NY, USA: IBM Corp.) and MedCalc Statistical Software (version 14.8 Ostend, Belgium).

Results

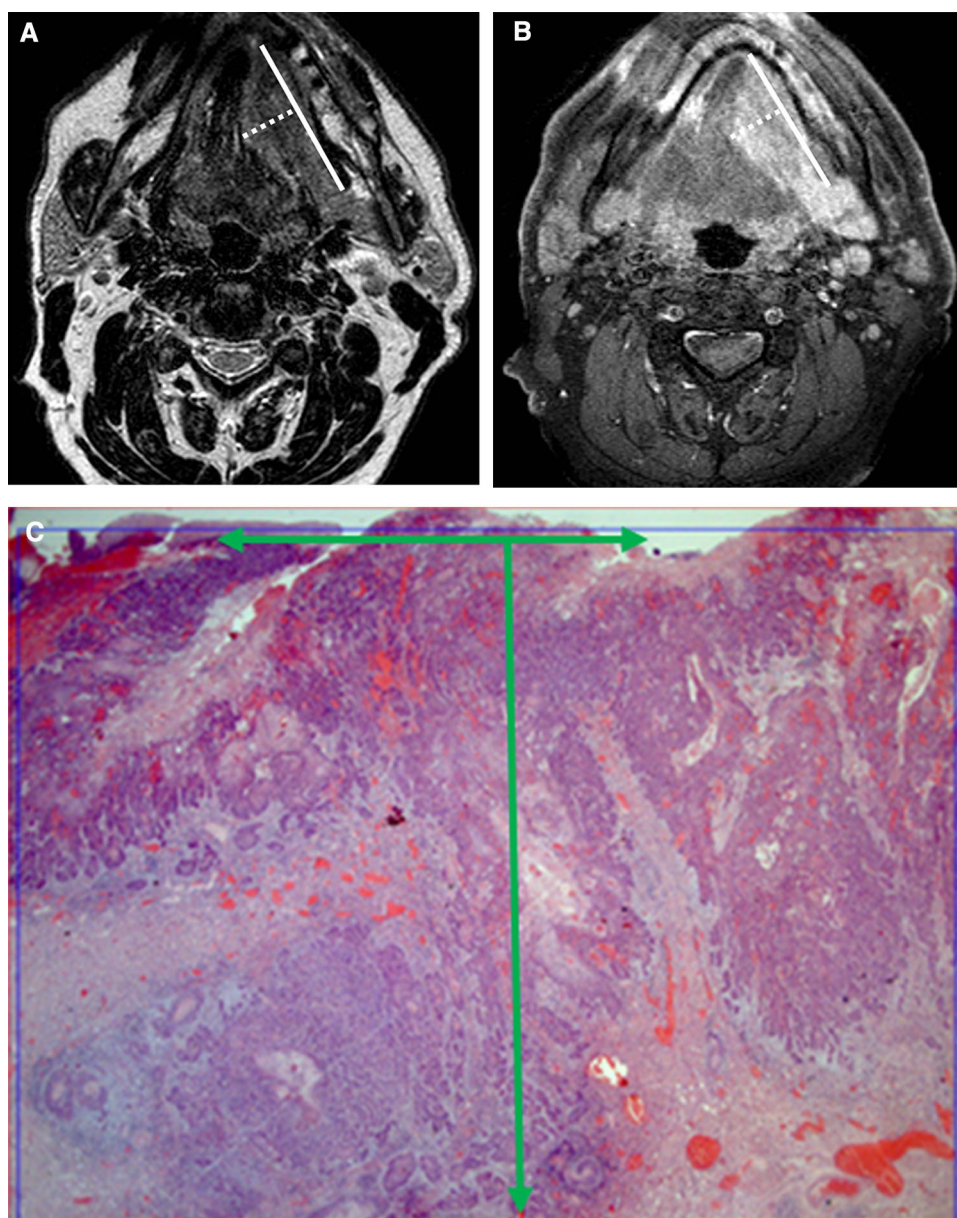
Population

Characteristics of the final population are summarized in Table 1. The final population included 80 patients (50 males, mean age 67.7 ± 13.6 years) with 80 surgically resected oral cavity cancers. The most common histopathological type was squamous cell carcinoma ($n = 76$, 95.0%), and oral cavity cancers most frequently involved the oral mucosa ($n = 34$, 42.5%), followed by anterior two-thirds of the tongue ($n = 29$, 36.3%).

MRI and histopathological staging

Median measured rDOI was 10 mm (IQR 5.5–16.5 mm, range, 0–47 mm), while median pDOI was 9 mm (IQR 6–15.5 mm, range, 2–47 mm). There was a statistically significant strong correlation (Fig. 2) between DOI measured at preoperative MRI and postoperative histopathological specimens ($\rho: 0.978$, $p < 0.001$). Bland–Altman plots (Fig. 3) showed that the mean difference between rDOI and pDOI

Fig. 1 MRI shows measurements of the radiological depth of invasion on axial T2 (A) and post-contrast SPIR (B) sequences in a 49-year-old man with squamous cell carcinoma of the left tongue. Histopathological image (C) shows pDOI measured perpendicularly from the line connecting the adjacent normal mucosal basement membrane to the deepest point of tumor invasion. The image analysis system Leica QWin v.3.4.0 with a digital camera DFC480 was used (Leica Microsystems, Wetzlar, Germany)



was 0.3 and the 95% limits of agreement were 3.0 and -2.3 . The pDOI was overestimated in a 32/80 (40.0%) patients by MRI with a mean increase of 17.4% in those patients.

Preoperative MRI revealed deep bone invasion in 15/80 (18.8%) tumors and superficial bone invasion in 9/80 (11.2%) lesions. Histopathological examinations confirmed superficial cortical bone erosion without deep invasion or deep bone invasion in 8/80 (10.0%) and 15/80 (18.8%) patients, respectively. The sensitivity and specificity of preoperative MRI were 93.3% and 98.8% for deep bone invasion, while they were 75.0% and 95.8% for superficial bone invasion, respectively.

On preoperative MRI 25/80 (31.2%) lesions were classified as T1, 17/80 (21.3%) were T2, 23/80 (28.7%) were T3,

and 15/80 (18.8%) were reported as T4. Final histopathological staging included 27/80 (33.7%) T1 stage, 15/80 (18.8%) T2, 23/80 (28.7%) T3, and 15/80 (18.8%) T4 oral cavity cancers (Table 2). MRI and histopathological T stages were concordant in 76/80 (95.0%) patients. MRI underestimated final stage in 3/80 (3.8%) patients, while the histopathological stage was overestimated in 1/80 (1.3%) patient. The overall agreement between MRI and histopathological T stage was excellent ($k=0.93$, 95% CI 0.86, 0.99).

Survival analyses

During a mean follow-up time of 28.3 ± 16.3 months (range 5–64 months), death due to tumor recurrence or

Table 1 Characteristics of the final population

Characteristic	Number (%)
Sex	
Males	50 (62.5)
Females	30 (37.5)
Age (years)	
Mean $\pm$ standard deviation	67.7 $\pm$ 13.6
Range	29–95
Histopathological tumor type	
Squamous cell carcinoma	76 (95.0)
Oral salivary gland carcinoma	2 (2.5)
Spindle cell carcinoma	1 (1.3)
Polymorphous low-grade adenocarcinoma	1 (1.3)
Anatomical location	
Oral mucosa	34 (42.5)
Tongue (anterior two-thirds)	29 (36.3)
Floor of the mouth	2 (2.5)
Hard palate	2 (2.5)
Soft palate	2 (2.5)
Retromolar trigone	1 (1.3)
Lips	1 (1.3)
Overlapping of multiple sites	9 (11.3)

Continuous variable (age) is expressed as mean and standard deviation; categorical variables are expressed as numbers and percentages in parenthesis

distant metastases was observed in 9/80 (11.3%) patients. Kaplan–Meier curves according to the preoperative MRI staging are presented in Fig. 4. Pairwise curves comparisons showed significantly poorer disease-specific survival

in patients with rDOI > 10 mm compared to rDOI $\leq$ 10 mm (log-rank $p=0.016$). The 6-months, 1-year, and 2-years estimated disease-specific survival rates were 97.8%, 95.4%, and 95.4% for rDOI $\leq$ 10 mm, and 93.3%, 82.2%, and 67.8% for rDOI > 10 mm. There was no difference in Kaplan–Meier curves according to deep bone invasions (log-rank $p=0.514$) and radiological T stage (log-rank $p=0.082$) on preoperative MRI.

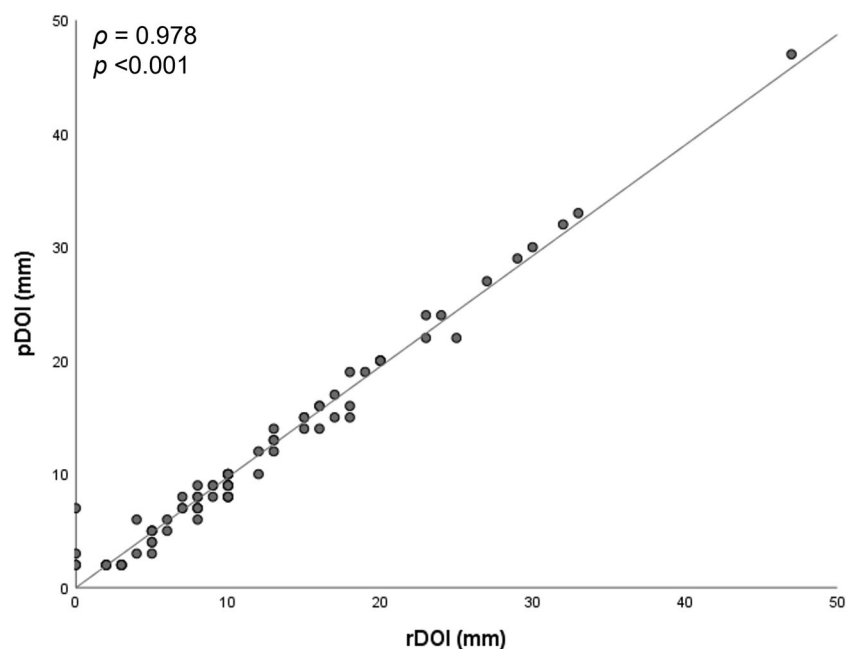
Multivariable analysis of preoperative variables associated with disease-specific survival is reported in Table 3. The rDOI remained the only independent preoperative variable associated with poorer survival at multivariable analysis (HR 5.5; 95% CI 1.14, 26.58; $p=0.033$).

Discussion

Correct pretreatment tumor staging is crucial for patient management and surgical planning. The need for neoadjuvant treatment, surgical technique (segmental mandibulectomy with reconstruction and/or prophylactic lymph node resection), and prognosis of patients with oral cavity cancer are affected by the local tumor stage and invasion of the adjacent bone in clinical practice. MRI demonstrated an excellent performance for the preoperative evaluation of oral cavity cancer in the present study, there was, in fact, a significant strong correlation between rDOI and pDOI, a good-to-excellent diagnostic performance for the prediction of bone invasion, and an almost perfect agreement between radiological and histopathological T staging.

Few prior studies evaluated the correlation between radiological and pathological measurements of DOI, reporting

Fig. 2 Correlation between radiological (rDOI) and histopathological (pDOI) measurements of the depth of invasion



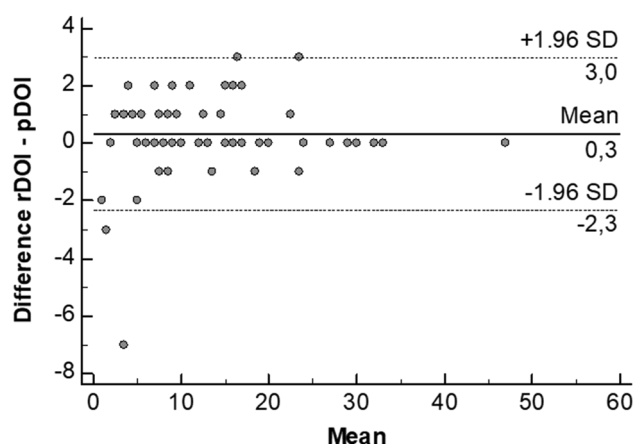


Fig. 3 Bland–Altman plot comparing radiological (rDOI) and histopathological (pDOI) measurements of the depth of invasion

a strong correlation between rDOI and pDOI [6–14]. Furthermore, Xu et al. [10] and Fu et al. [11] observed a higher frequency of cervical lymph node metastases by using the cutoff of rDOI greater than 7.5 mm and 10.5 mm, respectively. The results of the current study provided a strong positive correlation between preoperative MRI-measured DOI and histopathological DOI, which is consistent with prior investigations [9, 11, 13, 14]. It should be noted that MRI can overestimate the pDOI by an increase of 5–15%, especially in thin superficial tumors, regardless of the sequence in which the rDOI is measured [11, 13, 16]. In the present study the preoperative assessment overestimated the pDOI in 40% of patients. Nevertheless, the mean increase in measured DOI was only 17.4% compared with the histopathological assessment. A possible explanation of the discrepancy between rDOI and pDOI is the shrinkage and distortion of the tumors during surgical procedure and the processing of histopathological specimens with formalin fixation [8, 13]. Also, peritumoral edema and inflammation can affect the rDOI measurement, especially on T2 images [11]. Despite differences in measured DOI, there was an

excellent agreement between the MRI and pathological T staging, being concordant in 95.0% of patients. The T stage was overestimated in one patient and underestimated in three patients by MRI in the present study.

Oral cavity cancers are associated with high rate of bone invasion due to the close anatomical relationship, with a reported prevalence of 26–43% of all resected cancers [17–19]. The presence of bone invasion requires bone resection and reconstruction to allow a curative surgical treatment with potential functional consequences. Prior investigations comparing the performance of CT and MRI for the preoperative detection of bone invasion provided discordant results [17, 19–21]. Suzuki et al. [20] reported lower specificity of MRI compared to CT (78% vs 89%), while DeAngelis et al. [19] reported a higher sensitivity and specificity of MRI (87.1% and 80.5%, respectively) over CT (69.0% and 79.6%) in the detection of bone invasion. Furthermore, a systematic review found no superiority of CT or MRI over the other for the detection of bone invasion [22]. Oftentimes both examinations are acquired during preoperative staging for the local tumor assessment. In the present study preoperative MRI demonstrated a good performance for diagnosis of superficial bone erosion without deep bone invasion with a sensitivity of 75.0% and a specificity of 95.8%, while there was an excellent performance in the assessment of deep bone invasion, with a sensitivity of 93.3% and a specificity of 98.8%. These results could support the use of MRI in clinical practice for the locoregional staging in patients with oral cavity cancer as a single preoperative examination providing accurate information on both DOI and adjacent bone invasion due to its intrinsic high contrast resolution for the assessment of both soft tissue and bone structures.

Our study provides further advances in knowledge regarding the role of rDOI for the preoperative prediction of patient survival. Indeed, patient prognosis was affected by the preoperative rDOI, being significantly worse in patients with rDOI > 10 mm. The 10-mm DOI measured on a histopathological specimen has been related to the disease-specific survival, and it has been integrated into

Table 2 Correlation between MRI and final histopathological T stage

	Pathological stage					<i>k</i> value (95% CI)
	T1	T2	T3	T4	Total	
MRI stage						
T1	25 (31.2)	2 (2.5)	0 (0)	0 (0)	27 (33.7)	
T2	0 (0)	15 (18.8)	0 (0)	0 (0)	15 (18.8)	
T3	0 (0)	0 (0)	22 (27.5)	1 (1.3)	23 (28.7)	
T4	0 (0)	0 (0)	1 (1.3)	14 (17.5)	15 (18.8)	
Total	25 (31.2)	17 (21.3)	23 (28.7)	15 (18.8)	80 (100)	0.93 (0.86, 0.99)

Categorical variables are expressed as numbers and percentages in parenthesis. Agreement between preoperative MRI and postoperative histopathological staging was assessed using the Cohen's kappa (*k*) test with its 95% confidence interval (95% CI)

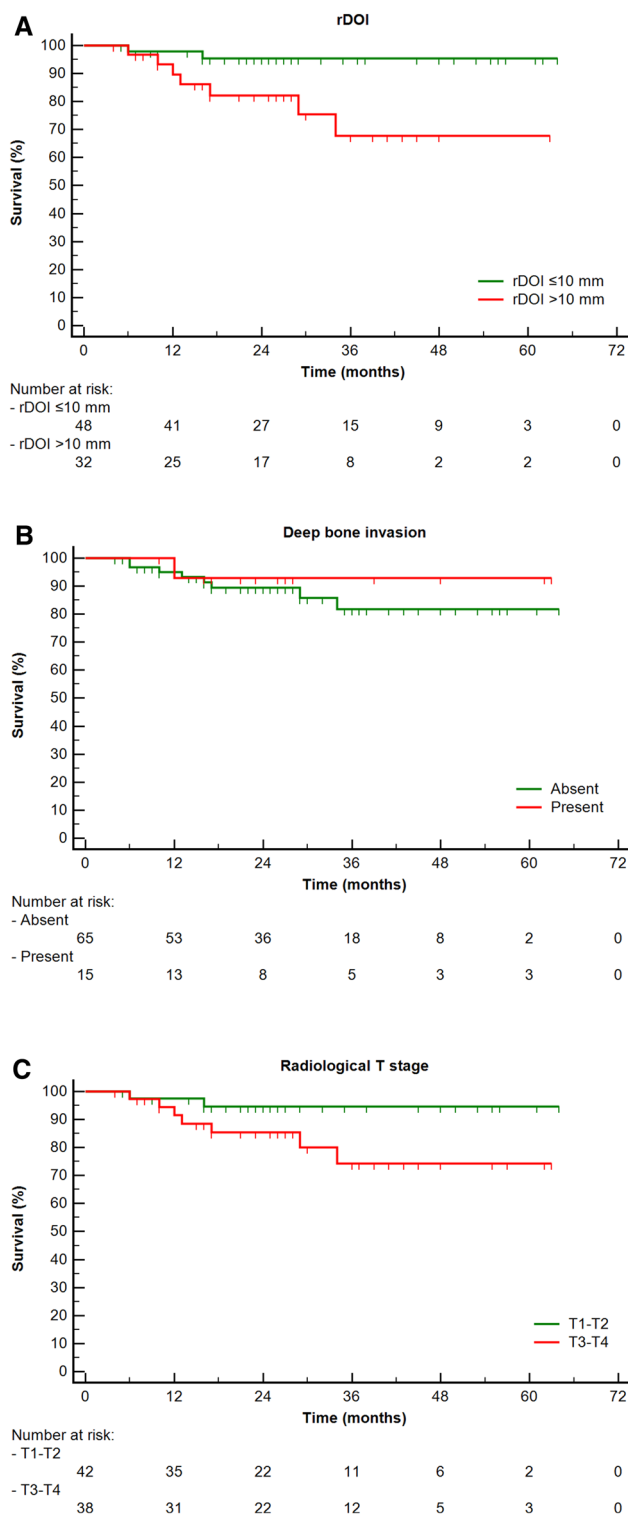


Fig. 4 Kaplan–Meier curves for disease-specific survival according to **A** the radiological depth of invasion (rDOI), **B** radiological deep bone invasion, and **C** radiological T stage

Table 3 Multivariable Cox proportional hazards analysis using step-wise selection with backward elimination for the prediction of disease-specific survival according to preoperative tumor characteristics

Variables	HR	95% CI	p value
Age			0.367
Male sex			0.928
Radiological depth of invasion > 10 mm	5.52	1.14, 26.58	0.033
Deep bone invasion			0.149
Preoperative T stage			0.210

Statistically significant ($p < 0.05$) variable is highlighted in bold

CI confidence interval, HR hazard ratio

the 8th edition of the AJCC Cancer Staging [3, 23]. The measurement of the rDOI can offer the advantages to stratify patient risk before surgical resection [10]. In a study of 49 patients with buccal squamous cell carcinoma, Wang et al. [14] observed a significantly poorer overall survival in patients with rDOI > 8.5 mm. Mao et al. [7] provided a rDOI cutoff of 11 mm as the best discriminator of disease-specific survival. Importantly, in the current study the rDOI was the only preoperative independent predictor associated with disease-specific survival, as demonstrated by multivariable analysis. If supported by larger multicentric studies, the rDOI could represent a relevant noninvasive marker to select patients in which a more aggressive perioperative management is needed.

This study is limited by the retrospective patient selection from a single institution. The inclusion of only patients with resected oral cavity cancer could introduce a selection bias as a large number of advanced oral cavity cancers are not suitable for surgical excision due to the extensive local invasion or metastatic disease. However, histopathological analysis of resection specimen remains a necessary reference standard for the definitive assessment of pDOI. Secondly, the diagnostic performance of MRI was not compared with other imaging techniques such as intraoral ultrasound, conventional CT, or cone-beam CT, as this has been largely assessed in prior investigations [8, 18, 21, 24]. Finally, this study did not evaluate the differences in rDOI measurements according to the MRI sequences. A standardization of rDOI measurement on MRI is currently lacking, and differences among MRI sequences were rarely reported [25]. Future studies should focus on the differences in rDOI measurements according to the acquired MRI sequences and scan planes.

In conclusion, preoperative MRI provides accurate measurements of tumor depth of invasion and high sensitivity and specificity for the detection of bone invasion. The rDOI is an independent preoperative predictor of disease-specific survival in patients with oral cavity cancer.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11547-022-01565-7>.

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Author contributions All authors contributed to the study conception and design. A.L.C., R.C., R.T., M.A. performed data curation and formal analysis; A.C., D.M., G.C., G.R., V.R. contributed to resources; A.L.C. supervised and validated the study; A.L.C., R.C. wrote the original draft; all authors helped in writing—review & editing. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors declare that they have no conflict of interests.

Ethical standards This retrospective study was approved by the Ethical Committee of our University Hospital (approval No. 11/2021) with a waiver for informed consent due to its retrospective nature. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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