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Pre-surgical Assessment of Mandibular Bone Invasion from Oral Cancer: Comparison Between Different Imaging Techniques and Relevance of Radiologist Expertise

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Pre-surgical Assessment of Mandibular Bone Invasion from Oral Cancer: Comparison Between Different Imaging Techniques and Relevance of Radiologist Expertise

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Abstract

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Materials and methods: Pre-surgical CT and MRI were reviewed independently by two radiologists with different expertise in head and neck oncology. A third radiologist reviewed CT and MRI simultaneously. Interobserver agreement was calculated by Cohen test. Association between radiological evidence of bone infiltration and histological reference were tested by Fisher's exact test or Chi-squared test, as appropriate. Receiving operator curve was calculated and area under the curve (AUC) was compared between CT, MRI, and both methods together.

Results: Interobserver agreement was moderate: the trainee under-reported periosteal reaction on CT, and inferior alveolar canal involvement on MRI. Imaging findings associated with histologic evidence of bone infiltration were: periosteal reaction and cortical erosion on CT; bone marrow involvement, contrast enhancement within bone, and inferior alveolar canal involvement on MRI. Sensitivity of MRI alone (74%) was higher than CT (52%). Simultaneous review of CT and MRI showed the highest specificity (91%), with increase of diagnostic performance in the subgroup of subjects with positive MRI (AUC=0.689; p=0.044).

Conclusion: Higher expertise allows pre-surgical detection of clinically relevant signs of bone infiltration Sensitivity of MRI alone is higher than CT for the detection of bone infiltration from oral cancer. In MRI positive cases, diagnostic integration with combined review of CT and MRI is suggested for optimal diagnostic performance.

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Introduction

The prevalence of mandibular bone invasion ranges from 12 to 56% in head and neck tumors [1, 2]. The diagnosis of mandibular invasion has paramount importance for the pre-operative planning because the surgical treatment is selected accordingly, with relevant influence on radical treatment as well as quality of life (from periosteal stripping to mandibulectomy) [3-6]. Pre-surgical assessment of mandibular invasion is obtained by diagnostic imaging. Therefore the best accuracy of imaging technique or algorithm is needed to tailor surgical approach with optimal balance between radical treatment and anatomical conservation.

Magnetic resonance imaging (MRI) and computed tomography (CT) are the imaging techniques with the best accuracy for description of local neoplastic invasion. MRI is more accurate than CT for description of soft tissue involvement [7, 8]. Conversely, there is debate about the optimal diagnostic accuracy for detection of bone invasion because MRI has high sensitivity but low specificity compared to CT [9]. To date, there is no definite indication to one or the other technique; indeed diagnostic protocols reported in the literature are extremely heterogeneous [2, 9-11].

The principal aim of this study was to compare diagnostic performance between CT and MRI for detection of bone infiltration, with histology as reference standard. Second, we sought to test inter-observer agreement between radiologists with different expertise and to describe its clinical relevance.

Materials and methods

Study population

The local Institutional Review Board approved this study; informed consent was waived for retrospective review of data. Subjects who undergone surgery for oral cancer between November 2008 to April 2014 were retrieved from the local archive of the Section of Maxillofacial Surgery of the University Hospital of Parma. Inclusion criteria were as follows: *a)* availability of both volumetric computed tomography (CT) with iodinated contrast agent and magnetic resonance (MR) with paramagnetic contrast agent within 4 weeks from surgery; *b)* pathological assessment of bone infiltration. Exclusion criteria were as follows: *a)* heavy beam hardening artifacts on CT with non-diagnostic image quality; *b)* motion artifacts on CT or MRI with non-diagnostic image quality. Exclusion criteria were assessed by a senior radiologist (G.C. with 18 years of experience in head and neck imaging).

Image acquisition

CT – Mutlidetector CT scanners were used for volumetric acquisition, either 64-row Sensation or 128×2-row Flash Definition (Siemens Medical Solution, Forchheim, Germany). Acquisition protocol was as follows: tube voltage 120 kV, tube current 150 mAs, 0.75 mm slice collimation, pitch 1, and rotation time 0.5 s. Scan volume was set from base of skull to origin of supra-aortic vessels. CT protocol included scans without contrast agent and 90 seconds after injection of 90 mL iodinated contrast agent Iomeprol at a concentration of 400 mg iodine/ml (Iomeron 400, Bracco, Italy), followed by 40 mL saline chaser; injection rate was 1.5 ml/sec by double-syringe electronic injector (Medrad Stellant, Bayer Ag, Germany). Reconstruction parameters were as follows: slice thickness 1.0-2.0 mm, slice increment 0.75-1.50 mm, kernel for soft and hard tissue (B30S and H70h, respectively), window level (WL) and width (WW) for soft tissue (WL = 50; WW = 250) and bone (WL = 400; WW = 4000).

MR – A 1.5 T system (Achieva 1.5T, Philips, Best, The Netherlands) was used for acquisition of MR images with a head-neck coil, before and after injection of 0,2 mmol/kg of gadoteric acid (Dotarem, Guebert, France); injection rate was 1.5 ml/sec by double-syringe electronic injector (Tennessee, Ulrich, Germany). Acquisition protocol was as follows: *1)* 3-plane survey; *2)* pre-contrast T1-weighted spin-echo images (TR 564 ms TE 1o ms) on axial and coronal plane; *3)* T2-weighted spin-echo images (TR 4431 ms TE 80 ms) on axial plane; *4)* short-tau inversion-recovery (STIR) sequences T2-weighted images (TR 2280 ms TE 55 ms) on axial and sagittal plane; *5)* post-contrast T1 weighted spin-echo images (TR 597 ms TE 10 ms) with fat saturation (SPIR) on axial, coronal, and sagittal plane. Scan volume was set from skull base to origin of supra-aortic vessels, slice thickness varied 3-5 mm. Visual assessment of images was performed during exam acquisition for quality assessment. In case of low quality image, clinically relevant sequences were repeated up to 3 times to achieve diagnostic quality.

Image scoring

All images were independently reviewed by one radiologist with 18-year expertise in head and neck oncologic imaging (GC) and a trainee in radiology with specific experience in head and neck imaging (EIZ, 3 years of training). CT and MRI were visually evaluated 4 weeks apart with the aim of describing bone infiltration by each imaging method, as follows.

CT – Post-contrast images were reviewed according to a scoring system adapted from Lenz et al [12]: *a) periosteal reaction*, described as focal thickening of bone surface; *b) cortical erosion,* described as focal tapering or complete interruption of cortical bone adjacent to the primary tumor; *c) abnormal attenuation of bone marrow,* described as reduction or absence of trabecular bony structure and/or focal obvious contrast enhancement within spongy bone [13]; *d) pathological fractures,* described as bone fractures without major traumatic event.

MR – The images were reviewed according to a scoring system adapted from Imaizumi et al [14], as follows: *a) mandibular cortical invasion on T1-weighted images,* defined as loss of hypointense signal of the cortical bone adjacent to the tumor mass; *b) bone marrow involvement*, hyperintense T2-weighted signal in bone marrow contiguous to the primary tumor; *c) contrast enhancement within bone*, evaluated on T1-weighted images and in relation to tumor-bone contiguity; *d)* inferior *alveolar canal involvement*, bone marrow involvement reaching the inferior alveolar canal with contrast enhancement of the nerve on T1-weighted images.

A third radiologist with 10-year expertise in head and neck oncologic imaging (IM) reviewed CT and MR simultaneously according to the aforementioned scoring system, with the aim of describing bone infiltration by the combination of the two different imaging methods.

Pathologic reference

Pre-surgical biopsies and surgical specimens were evaluated by a pathologist with 5-year experience (ET). All specimens were rated according to a binary score for presence of bone infiltration and used as reference standard for assessment of diagnostic accuracy of imaging descriptors.

Statistical analysis

The radiologic scores were compared between the experienced radiologist and trainee in radiology by Cohen test to assess the differences related to expertise in reading bone infiltration by CT or MRI. Cases with different scoring between the two readers were resolved in consensus. Cumulative scores were created including all CT findings ($SCORE_{CT}$), MRI findings ($SCORE_{MRI}$), and by combined CT and MRI findings ($SCORE_{Comb}$), to grant a simulation of different clinical scenarios, as the actual practice is based on heterogeneous imaging protocols, namely: *a)* CT only for pre-surgical staging; *b)* MRI only for pre-surgical staging; *c)* combined CT and MRI for pre-surgical staging. The Fisher's exact test or the Chi-squared test were used as appropriate to assess association between histological evidence of bone infiltration and: *a)* each consensus imaging finding; *b)* cumulative number of imaging findings. Furthermore, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated according to histological reference for each consensus imaging finding and for the 3 scores. Receiver operating characteristics (ROC) curve were calculated for each score, and area under the curve (AUC) was compared between the three scores. Furthermore, ROC curve was calculated for $SCORE_{Comb}$ in subjects with any sign of bone infiltration at MR. Statistical analysis was performed by MedCalc (Version 15.8, Ostend, Belgium).

Results

Inter-observer agreement

Seventy-seven patients underwent both CT and MRI with overall moderate agreement between the two readers. Moderate to good interobserver agreement was observed for contrast enhancement within bone on MRI (k = 0.581), better than any other MRI and CT imaging finding (Table 1). In particular, periosteal reaction on CT and inferior alveolar canal involvement on MRI were under-rated by the trainee.

Comparison between imaging and histology

Pathologic specimen was available in 58/77 (75.3%) patients, with histologic evidence of bone infiltration in 23/58 (39.7%) patients. The comparison between imaging findings and histologic reference is reported in Table 2. CT findings associated with histologic evidence of bone infiltration were: periosteal reaction and cortical erosion. MRI findings associated with histologic evidence of bone infiltration were: bone marrow involvement, contrast enhancement within bone, and inferior alveolar canal involvement.

The highest sensitivity was observed for signs of cortical invasion on both CT and MRI (e.g. cortical erosion on CT and mandibular cortical invasion on T1-weighted MRI images). Cortical erosion on CT showed better specificity (0.71) and PPV (0.62) than cortical invasion on T1-weighted MRI (specificity 0.51; PPV 0.47), and slightly higher diagnostic accuracy (0.71 and 0.59, respectively). Periosteal reaction on CT showed extremely high specificity (0.97) with good NPV (0.74) and diagnostic accuracy (0.74). This sign could be referred to in case of positive MRI, because the high NPV of periosteal reaction could improve diagnostic accuracy of the majority of MRI findings, which are characterized by low PPV (Table 3). On MRI, inferior alveolar canal involvement showed perfect specificity (1.00) and PPV (1.00), however sensitivity was extremely low (0.26). Of note, the consensus score of both periosteal reaction on CT and inferior alveolar canal involvement on MRI was in complete accordance with experienced radiologist score, suggesting that the clinical applicability of such high-specificity signs is strongly related to radiologist expertise. Pathological fractures on CT showed perfect specificity (1.00), but extremely low sensitivity (0.05), which makes this sign not suitable for accurate pre-surgical assessment.

There was association between histological evidence of bone infiltration and the cumulative number of positive imaging findings in both CT and MRI (Table 4), suggesting that presence of more than one finding increased the likelihood of actual bone infiltration.

Sensitivity, specificity, PPV, NPV, and diagnostic accuracy of $SCORE_{CT}$, $SCORE_{MRI}$, and $SCORE_{Comb}$, the three scores are reported in Table 5. ROC curve for $SCORE_{Comb}$ showed the highest area under the curve (AUC = 0.827), compared to $SCORE_{CT}$ (AUC = 0.60) and $SCORE_{Comb}$ (AUC = 0.717), with statistically significant difference between the 3 scores (p = 0.0012; Figure 1). The diagnostic performance of $SCORE_{CT}$ and $SCORE_{Comb}$ was also tested in the subset of MRI positive subjects (Figure 2), with evidence of potential for increase of diagnostic performance both with CT (AUC = 0.656; p = 0.049) or combined image reading (AUC = 0.689; p = 0.044).

Discussion

The detection of bone infiltration is of paramount importance for pre-surgical planning of oral cancer treatment. This study showed that the interobserver agreement in rating CT and MRI imaging for bone infiltration is low between radiologists with different expertise. Notably, the test performance was higher for the more experienced radiologist. The comparison between different techniques showed the complementary value of CT and MRI, namely, suggesting that CT could play a role in case of positive finding at MRI, especially when CT and MRI images are read simultaneously.

In the literature, the diagnostic accuracy of CT and MRI for the detection of mandibular invasion varies between different researchers (Table 6) [4, 8, 11, 14-21]. A number of authors reported high specificity for CT in detecting mandibular bone involvement [8, 15, 17, 18, 20]. This observation is in line with the technical basis of this imaging method: *a)* good contrast resolution for high-density structures; *b)* spatial resolution up to 0.6 mm. Indeed, the high density of normal mandibular bone is an intrinsic CT feature that allows confident detection of pathological infiltration by soft tissue (e.g. focal low-density notch on cortical bone). This is also reflected by the excellent positive predictive value of CT [14, 15, 18, 20]. A meta-analysis from Li et al reported that the diagnostic accuracy of CT is similar between scans with and without contrast agent [13]. This pooled observation highlights CT potentiality in the assessment of bony structure and suggests that optimization of CT protocol could be sought with significant control of radiation exposure along with avoidance of iodinated contrast agent. Conversely, iodinated contrast agent is indicated for assessment of soft tissue, because tumor and normal soft tissue frequently show similar density despite different structure (e.g. vascular texture, necrosis). However, the accuracy of contrast enhanced CT for assessment of soft tissue is lower than MRI [8]. Therefore, MRI should be considered the reference standard for pre-surgical imaging and local tumor staging, in the diagnostic algorithm of oral cancer. Nevertheless, characterization of bone infiltration remains a critical issue between the two imaging techniques because MRI specificity appears to be low compared to CT. Technical explanations for variable accuracy of MRI in bone infiltration have been proposed (e.g. slice thickness, chemical shift artifacts) [14]. Moreover, intrinsic false positive is well known from bony edema, which cannot be definitely differentiated from neoplastic infiltration. For this reason, MRI is overall more sensitive than CT, but less specific in the assessment of bony structures. The very topic of bone infiltration is therefore to be evaluated to foster consensus in optimal imaging protocol for pre-surgical assessment of oral cancer [22]. Rajesh et al reported that MRI should be a sort of stand-alone imaging because implementation of CT or single photon emission CT (SPECT) does not provide significant increase in accuracy [16]. Our data are show different perspective of the two imaging techniques, namely, we showed that MRI alone has higher sensitivity than CT. On the other hand, we also reported that CT imaging alone can improve diagnostic performance in case of MRI positive findings. Moreover, combined reading of CT and MRI simultaneously appears to be the most accurate algorithm to perform pre-surgical assessment of bone infiltration from oral cancer.. The underlying hypothesis is that false positive cases from MRI could be ruled out by CT, which has higher specificity. Such complementary application of CT in the subset of positive MRI is supported by evidence from the literature [19]. Indeed, we found 5 false negative MRI over 23 cases of histologically confirmed bone infiltration. Among these 5 cases, 4 were false negative CT as well, confirming that CT does not significantly contribute to reduce MRI false negative. Conversely, CT should be performed in subjects with positive findings at MRI with the aim of increasing specificity as well as positive predictive value. Therefore we suggest MRI as first imaging method for pre-surgical assessment of oral cancer, and its integration with plain CT only in case of MRI signs of bone infiltration. Moreover, we highlight the need for specific expertise in head and neck imaging, to reduce the number of false negative, notably in the detection of inferior alveolar canal.

This study has several limitations, first the comparison between two radiologists with such different expertise might not reflect the clinical scenario, future studies might consider assessing the imaging rating between experienced radiologist and maxillofacial surgeon. Second, the population might have been under proportionated to the relatively high number of radiological features. Larger studies are granted to confirm these data. Third, there was high proportion of cancer of the tongue, which has a lower rate of mandibular invasion in early stages, compared to other oral tumors of the oral cavity, even in advanced TNM stage. This specific histology might have increased the proportion of minimal bone invasion in our population, with consequent worse diagnostic performance compared to other studies with different primary site of cancer, such as alveolar ridge [19].

In conclusion, detection of bone infiltration in oral cancer by diagnostic imaging is directly related to radiologist experience. MRI has higher sensitivity and NPV than CT, thus a negative MRI result can confidently exclude bone infiltration. Conversely, CT has higher specificity and PPV than MRI, therefore optimal surgical planning of patients with positive MRI should encompass integration with CT imaging to rule out false positive findings and gain the best balance between radical and conservative surgery.

Compliance with Ethical Standards

Ethical approval: 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.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figure legend

Figure 1: ROC curves of $SCORE_{MRI}$, $SCORE_{CT}$, and $SCORE_{Comb}$. $SCORE_{Comb}$ shows the highest AUC with statistically significant difference between the three AUC (p = 0.0012).

Figure 2: ROC curve of $SCORE_{CT}$ (2a) and $SCORE_{Comb}$ (2b) in the subset of patients with any positive MRI finding shows potential for improving diagnostic performance by CT alone (AUC = 0.656; p = 0.049) or by combined image reading (AUC = 0.689; p = 0.044).

table 1

Table 1: Interobserver agreement by Cohen's *k* test.

Imaging finding	**Cohen's *k***
CT	
– periosteal reaction	0.381
– cortical erosion	0.487
– abnormal attenuation of bone marrow	0.471
– pathological fractures	0.486
MRI	
– mandibular cortical invasion on T1-weighted images	0.434
– bone marrow involvement	0.494
– contrast enhancement within bone	0.581
– inferior alveolar canal involvement	0.000*

* No subject was rated with involvement of inferior alveolar canal by the trainee.

table 2

Table 2: Association between histologic evidence of bone infiltration and consensus imaging findings according to Fisher's exact test.

Imaging finding	**Histologic evidence of bone infiltration** No (n = 35)	Yes (n = 23)	*P*
CT			
– periosteal reaction	1	9	0.001
– cortical erosion	10	16	0.005
– abnormal attenuation of bone marrow	12	14	0.085
– pathological fractures	0	1	0.831
MRI			
– mandibular cortical invasion on T1-weighted images	17	16	0.191
– bone marrow involvement	10	14	0.030
– contrast enhancement within bone	7	13	0.010
– inferior alveolar canal involvement	0	6	0.006

table 3

Table 3: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of each consensus imaging finding are reported.

Imaging finding	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
CT					
– periosteal reaction	0.39	0.97	0.90	0.74	0.74
– cortical erosion	0.70	0.71	0.62	0.78	0.71
– abnormal attenuation of bone marrow	0.61	0.66	0.54	0.72	0.64
– pathological fractures	0.05	1.00	1.00	0.61	0.62
MRI					
– mandibular cortical invasion on T1-weighted images	0.70	0.51	0.47	0.72	0.59
– bone marrow involvement	0.61	0.71	0.34	0.74	0.67
– contrast enhancement within bone	0.57	0.80	0.58	0.64	0.71
– inferior alveolar canal involvement	0.26	1.00	1.00	0.67	0.71

table 4

Table 4: Association between histologic evidence of bone infiltration and cumulative number of positive imaging findings according to Chi-squared test.

Imaging findings		**Histologic evidence of bone infiltration** No (n = 35)	Yes (n = 23)	*P (trend)*
Cumulative number of positive CT findings				
	0	17	5	0.002 (0.0003)
	1	13	6	
	2	5	3	
	3	0	8	
	4	0	1	
Cumulative number of positive MRI findings				
	0	15	5	0.009 (0.001)
	1	9	3	
	2	8	4	
	3	3	6	
	4	0	5	

table 5

Table 5: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of each score are reported.

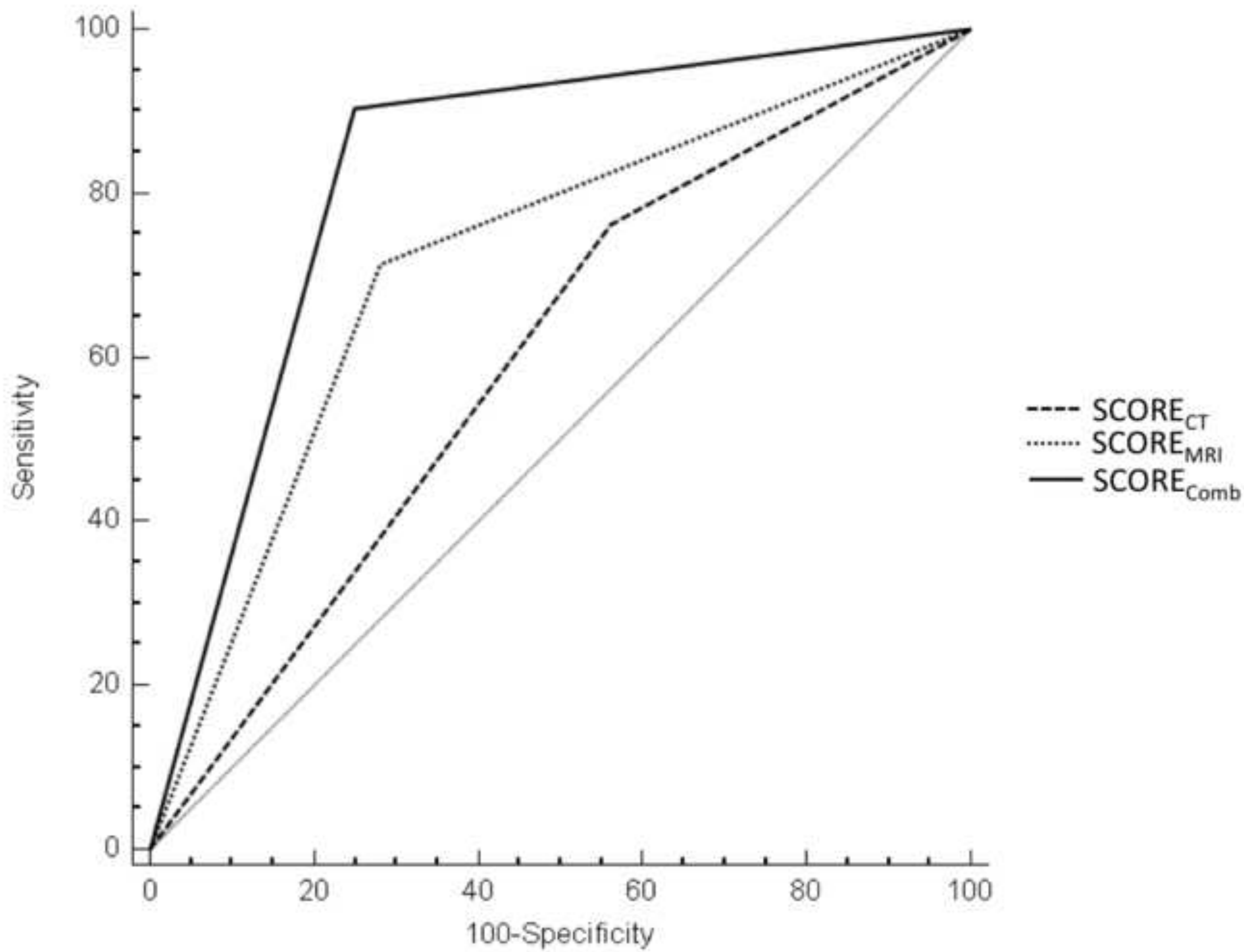
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
$SCORE_{CT}$	52%	79%	70%	63%	68%
$SCORE_{MRI}$	74%	73%	65%	80%	73%
$SCORE_{Comb}$	91%	74%	68%	93%	80%

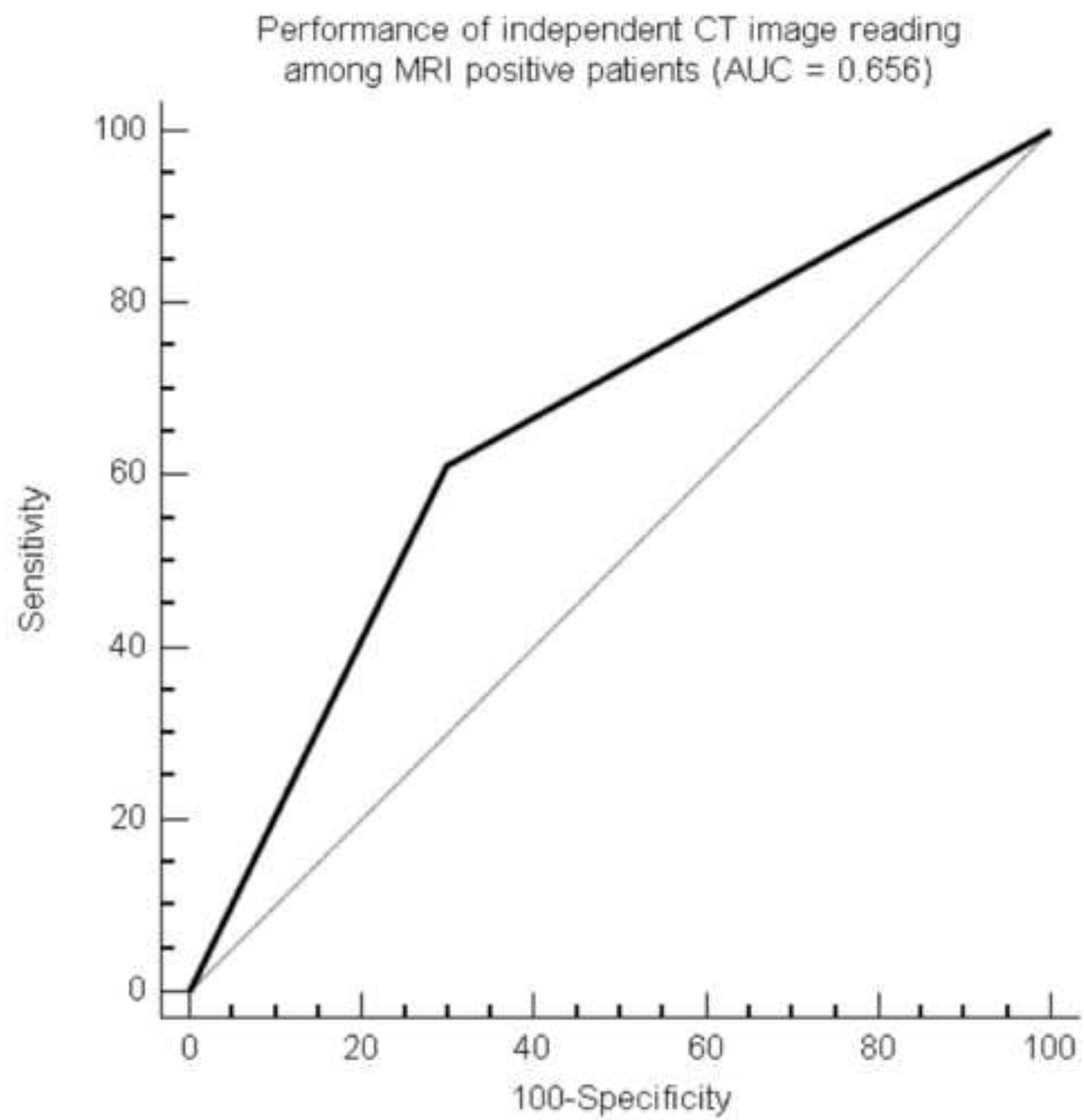
table 6

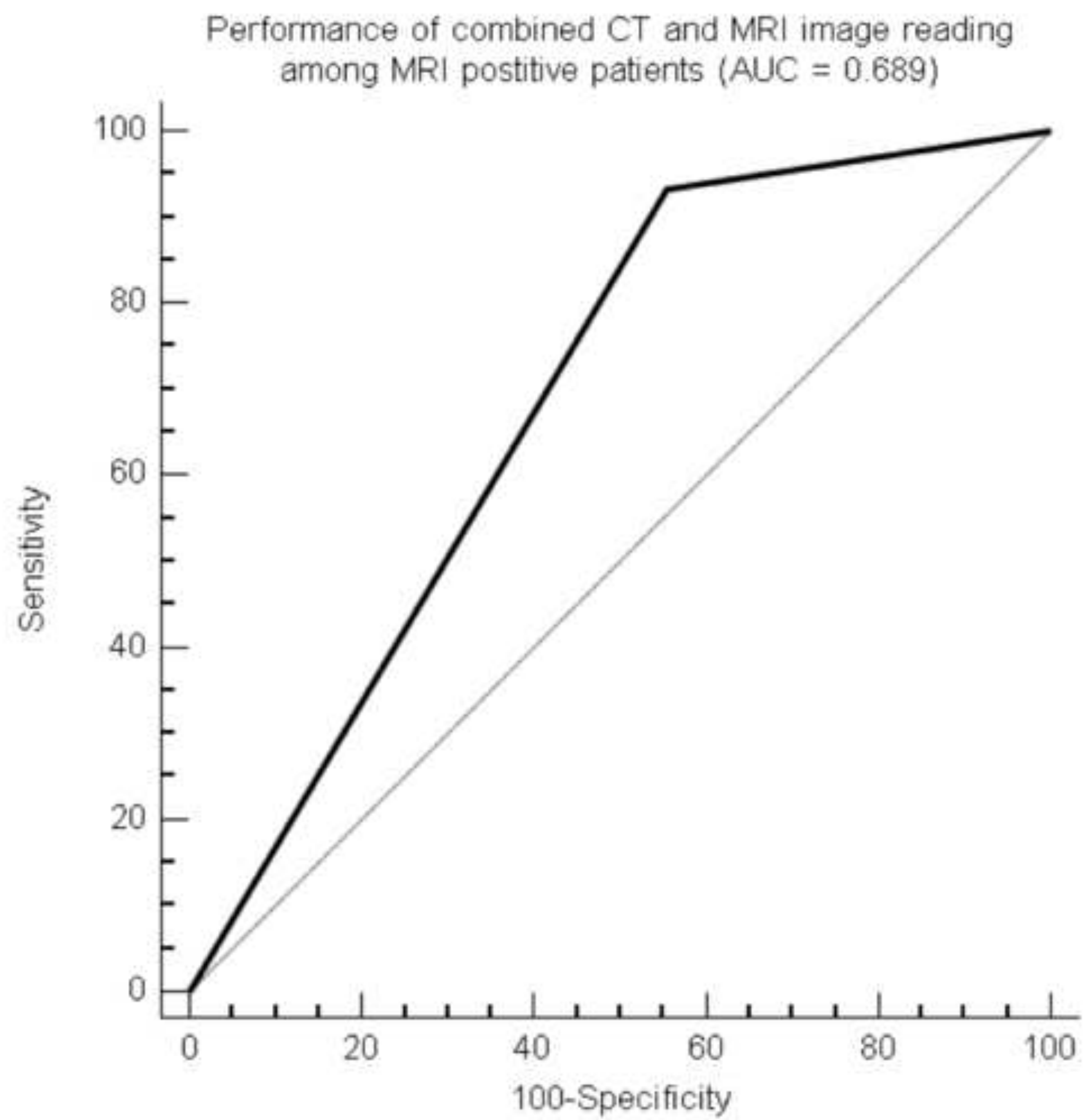
Table 6: Imaging accuracy in the recent literature

Author *Year* (rate of positive histology)	**Imaging method**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
Bolzoni A *2004* [11] (15/43)	MRI	93%	93%	88%	96%	93%
Goerres GW *2006* [15] (12/34)	CT	92%	100%	100%	96%	97%
Imaizumi A *2006* [14] (25/51)	CT	100%	88%	100%	89%	94%
	MRI	96%	54%	93%	67%	74%
Rajesh A *2008* [16] (19/23)	MRI	100%	75%	95%	100%	96%
Hendrikx AWF *2010* [18] (11/23)	MRI	82%	67%	69%	80%	74%
	CBCT	91%	100%	100%	92%	96%
Gu DH *2010* [17] (12/46)	CT	42%	100%	NA	NA	85%
	MRI	58%	97%	NA	NA	87%
Vidiri A *2010* [4] (14/36)	CT	79%	82%	73%	86%	81%
	MRI	93%	82%	76%	95%	86%
Abd El-Hafez YG *2011* [19] (37/114)	MRI	97%	61%	55%	98%	73%
Dreiseidler T *2011* [20] (46/77)	CT	80%	100%	100%	75%	NA
	CBCT	92%	97%	98%	88%	NA
Huang SH *2011* [8] (5/17)	CT	60%	100%	67%	85%	NA
	MRI	100%	91%	83%	100%	NA
Handschel J *2012* [21] (46/107)	CT	83%	87%	83%	87%	NA
Current study (23/58)	CT	52%	79%	70%	63%	68%
	MRI	74%	73%	65%	80%	73%
	MRI&CT	91%	74%	68%	93%	80%

Legend: PPV = positive predictive value; NPV = negative predictive value; CBCT = cone beam CT.


100
80
60
40
20
0
Sensitivity
0
20
40
60
80
100
100-Specificity
SCORE$_{CT}$
SCORE$_{MRI}$
SCORE$_{Comb}$


Performance of independent CT image reading
among MRI positive patients (AUC = 0.656)
Sensitivity
100
80
60
40
20
0
0
20
40
60
80
100
100-Specificity


Performance of combined CT and MRI image reading
among MRI postitive patients (AUC = 0.689)
Sensitivity
100
80
60
40
20
0
0
20
40
60
80
100
100-Specificity