Proposal for an MRI-based score to differentiate pleomorphic adenoma and Warthin tumor in patients with benign parotid neoplasms

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Aims and objectives

The accuracy of MRI in the differential diagnosis between malignant and benign tumours is already proved; on the other hand, the role of MR in the differential diagnosis of common benign parotid masses is controversial. A few authors tried to differentiate pleomorphic adenomas and Warthin tumors (representing together more than 90% of benign parotid lesions), evaluating several MR features, as hyperintensity level on T2-weighted sequences [1], contrast enhancement patterns [2] or ADC values on DWI sequences [3]. To our knowledge, almost all these previous authors evaluated indipendently the different MR features of these benign tumours.

The purpose of our study was to evaluate the diagnostic efficacy of a complex diagnostic score based on several MRI features, in order to differentiate pleomorphic adenomas and Warthin tumors in patients with parotid benign neoplasms.
Methods and materials

Patients selection

After obtaining institutional ethic review board approval and informed consent, 20 patients were prospectively enrolled in the study through the Departments of Maxillofacial Surgery and Otolaryngology. Patients ranged in age from 35 to 87 years (average age 65.3 years); 10 patients were men and 10 were women. Diagnostic studies were performed over a 7-month period (from September 2013 to March 2014). For inclusion in this study, all patients referred the lesion had appeared at least three months before; none of the lesions had shown any growth subjectively perceived by the patients. All patients had one or more US examinations performed in the department of radiology of our Institution, by a radiologist experienced in salivary gland imaging. None of the patients had undergone previous surgery in the neck region. Final diagnosis was based on pathologic proof obtained after US-guided fine-needle aspiration cytology (FNAC) or surgical resection (superficial or total parotidectomy).

Study protocol

Before surgery, all patients underwent an MR examination with a 3 Tesla unit (Discovery MR750, GE Healthcare, Milwaukee, Wisconsin) with a dedicated eight-channel neurovascular phased array coil. Field of view was adjusted to include the area from the Frankfurt plane to the level of the aortic arch. All patients were imaged using a dedicated MRI protocol composed of a three-plane localizer and T1 and T2 weighted sequences on multiple planes, with the following protocol: coronal T2-weighted FSE sequence, axial T2-IDEAL FSE sequence, diffusion weighted sequence, axial T1-weighted FSE sequence, multiple T1-weighted sequences after administration of contrast media (acquired with an effective temporal resolution of 18 s each for an overall scan time of almost 300 seconds) and a final T1-weighted IDEAL LAVA FLEX five minutes after contrast media administration. A total of 0.1 mL/kg of a gadolinium-based contrast (Gadobenic acid, Multihance BRACCO, Milan, Italy) was administered at 2 ml per second followed by a 20-ml saline flush at the same rate. Imaging parameters are summarized in Table 1.

Image Review

Two radiologists with 8 and 7 years of experience in head and neck imaging and a fifth year radiology resident reviewed the MRI examinations by simultaneous consensus. They were naturally blinded to the surgical and pathology results since imaging was always performed before FNAC and surgery. Once the lesion was identified, the three radiologists evaluated several features: hyperintensity on T2 weighted sequences, ADC
values, enhancement pattern, bilateral or multiple location. The evaluation was performed as follows:

- Hyperintensity: The radiologists were asked to subjectively describe the signal intensity of the lesion in comparison with the parotid gland parenchyma on T2 FSE sequences, as highly hyperintense, mildly hyperintense or not hyperintense.

- ADC values: The radiologists drew three regions of interest (ROIs) in the solid part of the tumour, avoiding vessels and cystic components. The mean ADC value was calculated.

- Enhancement pattern: The radiologists drew a region of interest (ROIs) in the solid part of the tumour, trying to reproduce the one used in the DWI analysis and avoiding vessels and cystic components. The same ROI was automatically reproduced in all post-contrast sequences and a time to signal intensity curve (TIC) was generated for each tumor.

- Bilateral or multiple lesions.

**Data Analysis**

A score based on the evaluated features was proposed and applied to a total amount of 24 lesions. The score was applied by the three radiologists in consensus as follows:

- Hyperintensity: 0 points were assigned to highly hyperintense lesions; 1 point to mildly hyperintense lesions; 2 points to not hyperintense lesions.

- ADC values: 0 points were assigned to lesions with ADC value >1.4x10-3 mm2/sec; 1 point to lesions with ADC value between 1.0 and 1.4x10-3 mm2/sec; 2 points to lesions with ADC value <1.0x10-3 mm2/sec.

- Enhancement pattern: TICs were evaluated with reference to Yabuuchi et al, considering time to peak (superior or inferior to 120 seconds) and wash-out ratio (as [(maximum intensity signal - 5 minutes signal intensity/ (maximum intensity signal - initial signal intensity)) x 100 (%). TICs were classified as: pattern A (time to peak >120 sec, persistent pattern); pattern B (time to peak <120 sec and Wash-out ratio>30%, wash-out pattern); pattern C (time to peak <120 sec and wash-out ratio <30%, plateau pattern); pattern D, no significant enhancement (flat pattern).

0 points were then assigned by the radiologists to lesions with type A or C enhancement pattern; 1 point to lesions with type D enhancement pattern; 2 points to lesions with type B enhancement pattern.

- One additional point was assigned to bilateral or multiple parotid lesions.

A total score of three or less was thus considered as suggestive of pleomorphic adenoma, whereas a score higher than three was considered as suggestive of Warthin tumor.
### Table 1: MR protocol

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<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR (msec)</th>
<th>TE (msec)</th>
<th>FOV</th>
<th>Matrix</th>
<th>Thickness (mm)</th>
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<tr>
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<td>124</td>
<td>290x290</td>
<td>320x224</td>
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<tr>
<td>Ax T1 FSE</td>
<td>320</td>
<td>9</td>
<td>260x260</td>
<td>320x224</td>
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<tr>
<td>Ax T2 FSE-IDEAL</td>
<td>2723</td>
<td>112</td>
<td>260x260</td>
<td>320x224</td>
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</tr>
<tr>
<td>DWI</td>
<td>2400</td>
<td>79</td>
<td>260x260</td>
<td>126x224</td>
<td>5</td>
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<tr>
<td>Ax T1 perf.</td>
<td>4</td>
<td>2</td>
<td>270x300</td>
<td>320x224</td>
<td>4</td>
</tr>
<tr>
<td>Ax T1 LAVA</td>
<td>4</td>
<td>2</td>
<td>300x300</td>
<td>320x224</td>
<td>4</td>
</tr>
</tbody>
</table>
Results

Twenty patients underwent complete MR examinations, for a total amount of 24 lesions. Three patients were excluded from the study because of MR features suggesting less common histotypes (respectively lipoma, sialolipoma, haemangioma). The remaining 21 lesions were evaluated by three radiologists in consensus, the proposed score was applied to all of them. Final diagnosis after FNAC/surgery revealed 6 pleomorphic adenomas, 13 Warthin tumors, 1 oncocytoma, 1 granulomatous lymph node. Radiologists correctly identified 6 out 6 pleomorphic adenomas and 13 out of 13 Warthin tumors; the remaining two lesions, defined as pleomorphic adenomas by radiologists, revealed to be respectively an oncocytoma and a granulomatous lymph node after surgical resection. The application of the score to all lesions is shown in Tab. 2.
<table>
<thead>
<tr>
<th>SCORE</th>
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<th>RM diagnosis</th>
<th>Final diagnosis</th>
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<td>0</td>
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<td>2 Pleomorphic adenoma</td>
<td>2 Pleomorphic adenomas</td>
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<tr>
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<td>3</td>
<td>3 Pleomorphic adenoma</td>
<td>3 Pleomorphic adenomas</td>
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<tr>
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<td>1 Pleomorphic adenoma</td>
<td>1 Pleomorphic adenoma</td>
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<tr>
<td>3</td>
<td>2</td>
<td>2 Pleomorphic adenomas</td>
<td>Ioncocytoma, Hymph node</td>
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<tr>
<td>4</td>
<td>3</td>
<td>3 Warthin tumors</td>
<td>3 Warthin tumors</td>
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<td>3</td>
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<tr>
<td>7</td>
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</table>

**Table 2:** Score application and results

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Conclusion

The management and preoperative planning of patients with parotid benign neoplasm may differ depending on the histological type of tumor. In fact, pleomorphic adenoma requires more aggressive surgical approach, because of its higher tax of malignant degeneration and post surgical recurrence; on the other hand, the possibility to follow up the lesion instead of performing surgical resection may be considered in patients with Warthin tumor, especially in poor candidates for surgery or in elderly patients (4,5). In addition, the surgical plan also slightly differs depending on whether the tumor is a pleomorphic adenoma or a Warthin tumor. Superficial parotidectomy with preservation of the facial nerve or partial superficial parotidectomy is recommended in patients with pleomorphic adenoma, with a sufficient margin including the tumor capsule, in order to reduce the odds of local recurrence (6); on the other hand, enucleation or superficial parotidectomy with preservation of the facial nerve is adapted for patients with a Warthin tumor (5).

FNAC currently represents the gold standard in the preoperative characterization of parotid neoplasms, even though its results are not always conclusive due to insufficient specimens obtained from a small sample size or because of the deep location of the tumor (up to 10% of cases) (7,8). Other disadvantages are those intrinsic to the technique, as the impossibility to provide information about the entire tumour and the operator-dependency; we must consider also that the sample site is arbitrarily established by the operator and could be chosen depending on its accessibility, thus it does not always represent the larger or the more solid component of the neoplasm.

All patients were submitted to FNAC and/or surgery, revealing 13 Warthin tumors and 6 pleomorphic adenomas. The high prevalence of Warthin tumors in our series is probably due to the number of male patients included in the study; in fact, even if parotid neoplasms are slightly more frequent in females, Warthin tumors are largely observed in males (M:F=8:1).

In our series, three patients were excluded from the study, because their MR examinations showed features suggesting histotypes different from pleomorphic adenoma or Warthin tumor. One lesion was entirely composed by fat tissue and thus identified as lipoma. One lesion was mainly composed by adipose tissue, containing a few gland-like islets, then it was classified as sialolipoma. One lesion showed lobulated margins, strong hyperintense signal with multicystic appearance on T2 weighted sequences, and slow centripet enhancement after contrast media administration, and it was defined as haemangioma. All these three diagnostic hypothesis were lately confirmed after surgical resection. So our results confirmed that MR could be very helpful in depicting features suggesting less common histology, as previously reported by a few authors [9, 10].
In the remaining patients we explored the use of a complex score based on several MR features. Both pleomorphic adenomas and Warthin tumors could be hyperintense on T2 weighted sequences, but previous authors, using heavily T2 weighted sequences, demonstrated that the solid portions of most of the pleomorphic adenomas displayed a higher signal intensity, in comparison with Warthin and malignant tumors [1]. In our series pleomorphic adenomas were classified as highly hyperintense in 3 cases and mildly hyperintense in 3 cases, without any not significantly hyperintense lesion; among Warthin tumors, there were no cases of highly hyperintense lesion, 3 were considered as mildly hyperintense and 10 as slightly/not hyperintense. Our observations are in substantial agreement with those of Sakamoto et al [1].

Regarding contrast enhancement patterns, our results confirmed what previously reported by Yabuuchi et al, who categorized the salivary gland tumours into four time-signal intensity curves (TIC) types, according to time to peak of 120 seconds and wash out ratio of 30% (a persistent pattern, B wash out pattern, C plateau pattern, D flat pattern) and observed some recurrent patterns in the two different histotypes [2, 3]. Also in our study, Warthin tumors usually showed wash-out or flat patterns after contrast media injection, being not so well visible on post-contrast sequences, while pleomorphic adenomas showed strong and persistent enhancement, often well visualized also in the last post-contrast sequences. More in detail, in our study, three pleomorphic adenomas presented A pattern, two C pattern and one D pattern, whereas Warthin tumors presented B pattern in nine cases, D pattern in three cases and C pattern in one case.

In our series, three pleomorphic adenomas presented ADC>1.4x10-3 mm2/sec, three showed values between 1.0x10-3 mm2/sec and 1.4x10-3 mm2/sec, without any lesion showing ADC values<1.0x10-3 mm2/sec; on the other side, six Warthin tumors showed values<1.0x10-3 mm2/sec and seven presented intermediate ADC values without any lesion showing values >1.4x10-3 mm2/sec. We can therefore affirm that Warthin tumors effectively showed significantly lower ADC values if compared with pleomorphic adenomas also in our series, in line with the previous observations of Yabuuchi et al [3]. This feature could be due to group of epithelial elements which represent foci of restricted diffusion in Warthin tumors, probably corresponding to areas of lower hyperintensity on T2 sequences [1].

In our score, an additional point was given to bilateral/multicentric lesions; this choice was based on previous evidences that Warthin tumors can be bilateral in up to 20% of cases but even more on the fact that the final diagnosis is Warthin tumor in up to 80% of patients with bilateral/multicentric tumors (5).

The use of our score led to correct diagnosis in 90% of cases. Only two lesions, originally defined by radiologists as pleomorphic adenomas, lately revealed to be an oncocytoma and a granulomatous lymph node. The first lesion was slightly hyperintense on T2 sequence (1 point), with D-flat pattern after contrast media administration (1 point) and ADC value of 1.1x10-3 mm2/sec (1 point); so the lesion was classified as pleomorphic adenoma with a total score of 3. The lesion did not show the typical behaviour of an
oncocitoma, which is usually well-visualized on T1 weighted sequences and not on T2 weighted and post-contrast T1 weighted sequences (also known in literature as "the vanishing mass"). This is one of the larger limit of this kind of score: lesions with atypical behaviour or mimicking that of other tumors could be misinterpreted; however, pleomorphic adenomas and Warthin tumors are so largely diffused in comparison with other histotypes, that this evenience could be rare. However, the proposed score has to be employed in larger samples of lesions in order to assess its real accuracy in recognizing hystotypes other than pleomorphic adenomas or Warthin tumors.

In our series, a granulomatous lymph node was also erroneously defined as pleomorphic adenoma. Our selection criteria probably allow to exclude acute inflammatory lymph nodes, which may rarely appear as indolent long-standing masses, but they probably lead to the erroneous inclusion of chronically inflamed lymph nodes. Larger studies are required to investigate the effective incidence of these findings and their role in compromising the potential use of scores like the one we presented in this paper. In no case the score led to an erroneous diagnosis of pleomorphic adenoma in case of Warthin tumor or viceversa, demonstrating a good diagnostic accuracy, even though in a preliminary study performed in a small patient sample. In addition, the score scale demonstrated an accuracy of 100% for scores 0-2 and 4-6 (leading to diagnosis of pleomorphic adenomas and Warthin tumors respectively), since both diagnostic errors corresponded to lesions with a final score of 3.

In our opinion, a better knowledge of the MR features of parotid lesions and the use of score scales, as the one we explored in this study, may represent the first steps towards the use of MR in the characterization of salivary gland lesions. We do not trust that MR could never completely substitute FNAC, but we expect it might have a more important role in the definition of specific tumor hystotipes, rather than only defining their anatomical extension or only suggesting benign vs malignant nature. MR may be used as a reliable adjuvant technique to FNAC, first of all in case of not conclusive results; then it may provide information about tumor components not included in the bioptic samples, which could be interesting in case of heterogeneous lesions. Furthermore, MR could suggest the most appropriate site for FNAC, indicating the more hypercellular portion; that might be extremely useful if we consider that all pleomorphic adenomas may virtually contain carcinomatous foci.

The major limitations of this study were the small patient sample and the subjective assessment of the T2-hyperintensity, although this second issue may be partially overlooked due to the image review method, consisting in three expert radiologists performing the image analysis in consensus. However, larger studies are required in order to confirm our observation and to consolidate reliable and reproducible diagnostic scores. The strength of our study was represented by its prospective nature, leading to homogeneous MR protocol and comparable examinations.
In conclusion, our score, combining the evaluation of several MR features, proved to be useful in the characterization of parotid benign lesions, although used in a small sample of patients. We expect that in the next future MR may have a larger role in the preoperative management of these patients, due to its potential capability to suggest tumor histology both in common and uncommon histotypes, to provide information over the entire neoplasms, to indicate the most common site for FNAC and to validate its results in case of uncertain cytologic diagnosis.
Fig. 1: 54-year old female. (A) Axial fat-suppressed T2-weighted images showing an hyperintense lesion located in the superficial lobe of the right parotid gland. (B) DWI sequence showing hyperintensity of the lesion, only due to shine through effect and corresponding to high values in the ADC map (C); (D) (E) (F) Axial T1-weighted perfusion sequences showing gradual and persistent enhancement of the lesions, well-visualized even in the last post-contrast fat-suppressed T1-weighted sequence performed 5 minutes after contrast media administration (A pattern) (G). With a final score of 0, the lesion was defined as pleomorphic adenoma by both radiologists; final diagnosis after right total parotidectomy was pleomorphic adenoma.

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Fig. 2: 49-year old male. (A) Axial fat-suppressed T2-weighted images showing an isointense lesion mainly located in the superficial lobe of the right parotid gland, extending also in the deep lobe (white arrow). Another smaller lesion was noted in the left parotid gland (blue arrow). (B) DWI sequence showing water restricted diffusion of both lesions, corresponding to intermediate values in the ADC map (C). (D) (E) (F) Axial T1-weighted perfusion sequences showing early enhancement and rapid wash-out of both lesions (B pattern). One additional point was given to both lesions because of bilateral location. With a final score of 6, both lesions were defined as Warthin tumors by the radiologists. Final diagnosis after total parotidectomy of the right gland confirmed the diagnosis of Warthin tumor.
Fig. 3: 66-year old male. (A) Axial fat-suppressed T2-weighted images showing an isointense lesion mainly located in the superficial lobe of the right parotid gland, extending also in the deep lobe. (B) DWI sequence showing water restricted diffusion of the lesion, corresponding to low values in the ADC map (C). (D) (E) (F) Axial T1-weighted perfusion sequences showing early enhancement and rapid wash-out of the lesion (B pattern). With a final score of 6, the lesion was defined as Warthin tumor by the radiologists. Final diagnosis after total parotidectomy of the right gland confirmed the diagnosis of Warthin tumor.

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References