Role of dynamic contrast enhanced MR perfusion in differentiation between benign and malignant tumors

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KEYWORDS
Dynamic MRI; Head and neck tumors; Wash in rate

Abstract  Aim: Evaluation of diagnostic accuracy of dynamic contrast enhanced (DCE) MRI in differentiating benign from malignant head and neck tumors using both Quantitative and semi quantitative analysis.

Patients and methods: 55 patients with head and neck masses underwent DCEMRI at 1.5 T Philips Ingenia MR scanner. Their enhancement curve patterns, Time to peak, wash in and washout rates were analyzed and compared in benign and malignant tumors.

Results: 81.8% of benign tumors had gradual progressing and plateau curves, while 93.3% of malignant tumors had plateau and fast curves. TTP, wash in and wash out rates were significantly different between benign and malignant tumors. Using TTP cut off value of 83.3 s differentiated benign from malignant tumors with a sensitivity of 84.8% and specificity of 77.3%, while wash in rate at cut off value of 15.4 l/s provided a sensitivity of 87.9% and specificity of 90.9%, wash out rates provided at cut off value of 5.75 l/s, a sensitivity of 81.8% and specificity of 90.9%.

Conclusion: Dynamic contrast enhanced MRI is a promising method for differentiation between benign and malignant head and neck tumors, wash in rate is the most specific parameter used.

1. Introduction

Head and neck cancer is common in several regions of the world. Overall, head and neck cancer accounts for more than 550,000 cases annually worldwide (1).

Imaging has an important role in staging, planning treatment and post-treatment follow up of patients with head and neck cancer (2).
Magnetic resonance imaging (MRI) is effective for diagnosing tumors and has some advantages over other techniques, especially in detecting soft tissue lesions. However, conventional MRI is not able to differentiate normal highly vascular structures, e.g. intrinsic tongue muscles and pharyngeal mucosa from neoplasm, also not capable of determining whether a tumor is benign or malignant. It has been reported that dynamic contrast-enhanced MRI (DCE-MRI) is useful for differentiating normal highly vascular structures from neoplasm, allowing the investigator to determine the true extent of a lesion, also it is helpful in differentiating tumors, and many investigators have attempted to use it to identify differences between benign and malignant tumors, as well as to assess the malignancy of tumors (3).

So, head and neck imaging is shifting from the morphological to the functional techniques as these techniques are used to assess the complex interrelated processes in the cancer microenvironment, such as hypoxia and angiogenesis (4).

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is an important imaging technique used in oncology assessment as it is able to identify changes in tissue physiology.

A common approach in the analysis of DCE-MRI is drawing (ROI) in region of interest and observes how the average signal intensity of the ROI varies with time. It has been reported that the time versus signal intensity curve, is useful for differentiating head and neck tumors (5).

Although the semi quantitative evaluations have been widely applied, they do not provide information on the underlying pharmacokinetic nature in the tissue. Moreover, an analysis based on the signal intensity (SI) is predominantly affected by the scan parameters, and it is operator dependent (6).

So, there was also a need for a noninvasive quantitative method which enables the quantification of contrast agent exchange between the intravascular and the interstitial space (7).

Few researches studied the role of either quantitative or semi quantitative analysis in specific region in head and neck, e.g. sinonasal (6), palate (8).

The aim of our study was to present an overview of diagnostic accuracy of DCE-MRI in differentiation between benign and malignant head and neck tumors as a whole, and to compare specificity and sensitivity of both quantitative and semi quantitative analytical methods.

2. Patients and methods

2.1. Patients

This prospective study included Fifty seven patients (with a mean age of 44.84 ± 16.64 years); 38 males and 19 females who underwent DCE-MRI, these patients came to our hospital with head and neck masses between June 2012 and September 2014. They were referred from ENT, oncology center and radiotherapy departments of Mansoura University Hospitals.

All patients underwent DCE-MRI as a part of routine post contrast MRI study using Philips Ingenia 1.5 T. Two patients were excluded from this study whose lesions were too small to allow its signal intensity to be calculated. The final diagnosis of the masses was confirmed by histopathological examination as shown in Table 1. Thus, we finally evaluated 55 patients with head and neck tumors.

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>No</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Benign</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
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</tr>
<tr>
<td>Inverted papilloma</td>
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<tr>
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<tr>
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<tr>
<td>Polyp</td>
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</tr>
<tr>
<td>Angiofibroma</td>
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<td>5.5</td>
</tr>
<tr>
<td>Dermoid cyst</td>
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<td>1.8</td>
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<tr>
<td>Chondroma</td>
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<td>3.6</td>
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<tr>
<td>Epidermoid</td>
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</tr>
<tr>
<td>Vocal cord papilloma</td>
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<td>1.8</td>
</tr>
<tr>
<td>Glomus vagale</td>
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<tr>
<td>Pleomorphic adenoma</td>
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<td>7.2</td>
</tr>
<tr>
<td>Warthin tumor</td>
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<td>3.6</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
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<td>5.5</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
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<td>7.3</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>Mucopeidermoid carcinoma</td>
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<td>1.8</td>
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<tr>
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<tr>
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<td>1.8</td>
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<tr>
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<tr>
<td>Fibrosarcoma</td>
<td>1</td>
<td>1.8</td>
</tr>
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</table>

2.2. MRI protocol

Our study was performed on Philips Ingenia 1.5 T MRI scanner in all of 55 cases, with the same scanning parameters. A precontrast reference scan was first performed through the region of interest (ROI), and this was followed by routine head and neck MR imaging protocol (axial 5 mm T2WI with fat suppression and axial T1WI parallel to hard palate from skull base to thoracic inlet, coronal and axial T1WI fat suppressed image), then intravenous administration of gadolinium (GD-DTPA).

T1-weighted image (600/20/2 [TR/TE/number of excitations]; field of view, 18 cm; matrix, 256 x 192; section thickness, 2 mm; section gap, 1 mm) and fast spin-echo (fat suppressed) T2-weighted image (4000/90/4; field of view, 18 cm; matrix, 256 x 256; section thickness, 2 mm; section gap, 1 mm) were obtained before the administration of contrast agent. A dynamic2D (axial T1WI fat suppressed) fast spoiled gradient recalled sequence (10.4/2.3/1; flip angle, 30°; field of view, 18 cm; matrix, 256 x 128; section thickness, 4 mm; section gap, 1 mm) with total acquisition time of 240 s during bolus injection (0.3 mmol/kg) of single dose contrast agent gadopentetate dimeglumine (Magnevist) with a maximum dose of 30 ml at a rate of 2.5 ml/S given intravenously via an automatic injector.

2.3. Image postprocessing

Multiphase dynamic images were analyzed using Philips extended work space (EWS) release 2.6 workstation. We placed a region of interest within an area of 10 mm² (the area...
in which the diameter of the tumor was greatest, cystic parts of the tumors were avoided and this area showed the greatest degree of early enhancement on the dynamic images). Time signal intensity curve (TIC) after an injection of Gd-DTPA in the ROI of each examination was plotted. The obtained TICs were classified into four types on the basis of TTP peak (the time to peak enhancement) into four types: type A (gradual enhancement), type B (rapid enhancement and low washout), type C (rapid enhancement and high washout), and type D (flat) (9).

Wash-in rate ($K_{\text{trans}}$) is defined as the rate of enhancement between 10% and 90% of the signal intensity difference between maximum signal intensity post-enhancement ($S_{\text{max}}$) and signal intensity prior to enhancement ($S_{\text{base}}$). It was derived from the first-pass phase of signal intensity enhancement according to the following equation (10):

$$W_{\text{in}} = \left\{ \frac{[S_{\text{max}} - S_{\text{base}}] \times 0.8}{[S_{\text{base}} \times (90\% - 10\%)]} \right\} \times 100$$

Wash-out rate ($K_{\text{ep}}$) is the rate of monoexponential decay of the enhancement signal in the tissue (i.e. vertebral body). It was derived from the enhancement signal decay phase according to the following equation:

$$y = \text{Span} \cdot \exp(-\lambda t) + \text{Plateau}$$

where $y$ refers to the MR signal ($Y$-axis values) and $t$ refers to time ($X$-axis values), Plateau refers to the MR signal value when the contrast-enhancement decays to a plateau (10).

### 2.4. Image interpretation

Based on the findings on T1-weighted, T2-weighted, and post contrast T1 fat suppressed images, dynamic contrast enhanced MRI images were evaluated by two experienced head and neck radiologists in consensus with 18 and 7 years of experience.

The region-of-interest (ROI) was placed in the solid part of the lesion to avoid bias of low perfusion of the necrotic part. The ROI was inserted using oval shaped function.

From this ROI, the time intensity curve and time to peak value were automatically generated.

Quantitative analysis of the DCE-MRI data was automatically performed using Philips extended work space (EWS) release 2.6 workstation giving color maps and values of wash in and wash out rates.

Semi quantitative and quantitative interpretations of the DCE-MRI were done. Semi quantitative interpretation was done using TIC and TTP.

Quantitative interpretation was done by measuring wash in and wash out rate values.

### 2.5. Statistical analysis

Data are expressed as mean value ± SD for quantitative data and as frequency (number-%) for qualitative data. Comparisons were carried out by unpaired $t$ test for parametric data. Inter-group comparison of categorical data was performed by using chi square test ($X^2$-value). The sensitivity, specificity, positive
Fig. 2  Left maxillary squamous cell carcinoma in 44 years old male. (A) Axial T1 fat suppressed post contrast spin echo weighted image shows intense enhancement. (B) TIC shows type C curve (gradual wash out). (C) TTP, wash in and wash out rates measures. (D) Wash in rate. (E) Wash out rate.
Fig. 3  Left sided sphenopalatine nasopharyngeal angiofibroma in a male patient aged 16 years. (A) Axial T1 fat suppressed post contrast spin echo weighted image shows intensely enhancing mass. (B) TIC shows type A curve. (C) TTP, wash in and wash out rates measures. (D) Wash in rate. (E) Wash out rate.
Fig. 4  Warthin tumor of the left parotid gland of male patient aged 45 years. (A) Axial T1 spin echo fat suppressed post contrast weighted image shows homogenous enhancement. (B) TIC shows type C curve (rapid wash out). (C) TTP, wash in and wash out rates measures. (D) Wash in rate. (E) Wash out rate.
Fig. 5  Melanoma of the right side of the nasal cavity of female patient aged 58 years. (A) Axial T1 spin echo fat suppressed post contrast weighted image shows intense homogenous enhancement. (B) TIC shows type C curve (rapid wash out). (C) TTP, wash in and wash out rates measures. (D) Wash in rate. (E) Wash out rate.
Fig. 6 Malignant fibrous histiocytoma in a male patient aged 12 years. (A) Axial T1 spin echo fat suppressed post contrast weighted image shows small intramuscular lesion of intense homogenous enhancement. (B) TIC shows type C curve (rapid wash out). (C) TTP, wash in and wash out rates measures. (D) Wash in rate. (E) Wash out rate.
Fig. 7  Right vocal cord papilloma in a female patient aged 32 years. (A) Axial T1 fat suppressed post contrast spin echo weighted image shows faintly enhancing mass. (B) TIC shows type A curve (gradual progressing curve). (C) TTP, wash in and wash out rates measures. (D) Wash in rate. (E) Wash out rate.
There was significant difference in wash in and wash out rates between benign and malignant tumors \((p < 0.001)\) (Table 3). The results of ROC analysis of wash in rate at cut off value of 15.4 \(1/s\) provided a sensitivity of 87.9\% and specificity of 90.9\% with (AUC) of 0.94, those for wash out rates provided at cut off value of 5.75 with (AUC) of 0.91, a sensitivity of 81.8\% and specificity of 90.9\% for differentiation of benign and malignant tumors (Table 4).

Warthin tumor shows type C curve and rapid wash out rates than malignant tumors (Fig. 4).

4. Discussion

Conventional MRI helps in diagnosing head and neck tumors, but differentiating benign from malignant moreover is still difficult in many situations; hence, the physiologic properties of lesions can be estimated by kinetic studies after contrast-medium injection, we report in this study the utility of DCE-MRI by two different analytical methods (semiquantitative and quantitative) in differentiating benign and malignant tumors. We firstly applied semi quantitative analysis by plotting SI response against time. The use of the TIC is the most conventional method of assessing a DCE-MR study.

Sasaki et al. (11) used visual analysis and classification of TIC to differentiate between benign and malignant tumors as in our study. While Ziech et al. (12) used it to investigate the activity of inflammatory processes, while Lavini et al. (13) used it to assess the effect of drugs.

The majority of the studies were done in the musculoskeletal system investigating bone, soft tissue tumors and inflammatory processes (14,14,15).

Takashima et al. (16) classified the TIC of 79 head and neck lesions into five groups according to the time at which they displayed peak enhancement: type A, the curve peaked at 0–30 s after the administration of contrast medium; type B, the curve peaked at 30–60 s after the administration of contrast medium; type C, the curve peaked at 60–210 s after the administration of contrast medium; type D, the curve displayed a gradual upward slope; and type E, the curve was flat.

Eida et al. (9) in agreement with us classified TIC into four types: type A (gradual enhancement), type B (rapid enhancement and low washout), type C (rapid enhancement and high washout), and type D (flat). In our study 81.8\% of benign tumors had types A and B curves (31.8\% and 50\% respectively), while 93.9\% of malignant tumors had types B and C curves (24.2\% and 69.7\% respectively).

Study made by Sasaki et al. (17) on 44 patients with head and neck tumors revealed that benign lesions present flat, gradual progressing and fast curves types (D, A and C) in disagreement with our study, while malignant tumors contain fast and plateau curves types (C and B) in agreement with the present study.

<table>
<thead>
<tr>
<th>Area under the curve (95% CI)</th>
<th>Cutoff value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak (s)</td>
<td>0.84(0.71–0.96)</td>
<td>83.3 &gt;</td>
<td>84.8</td>
<td>77.3</td>
<td>84.8</td>
<td>77.3</td>
</tr>
<tr>
<td>Wash in rate (1/s)</td>
<td>0.94(0.87–1.00)</td>
<td>15.4 &lt;</td>
<td>87.9</td>
<td>90.9</td>
<td>93.5</td>
<td>83.3</td>
</tr>
<tr>
<td>Wash out rate (1/s)</td>
<td>0.91(0.82–1.00)</td>
<td>5.75 &lt;</td>
<td>81.8</td>
<td>90.9</td>
<td>93.1</td>
<td>76.9</td>
</tr>
</tbody>
</table>

2. Results

Twenty-two patients had benign tumors, while remaining 33 had malignant tumors.

Of benign tumors 81.8\% had types A (Figs. 3 and 7) and B curves (31.8\% and 50\% respectively), while 93.9\% of malignant tumors had types B and C (Figs. 2 and 4–6) curves (24.2\% and 69.7\%) with significant difference for curves A and C for differentiation of benign and malignant tumors \((p = 0.01 \text{ and } p = 0.004)\), no significant difference for curves B and D between benign and malignant tumors \((p = 0.2 \text{ and } p = 0.6)\) (Table 2).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Benign</th>
<th>Malignant</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Type of curve</td>
<td>A</td>
<td>7</td>
<td>31.8</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>11</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>2</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>2</td>
<td>9.1</td>
</tr>
</tbody>
</table>

There was significant difference in TTP between benign and malignant tumors (Table 3). The results of ROC analysis of TTP provided at cut off value of 83.3 s a sensitivity of 84.8\% and specificity of 77.3\% with an area under curve (AUC) of 0.84 (Table 4).
The differences in types of curves happened between our study and Sasaki et al. study could be explained by large number of warthin tumors contained in their study which gave type C curve.

TTP in our study showed significant difference between benign and malignant tumors, giving mean value of 101.19 s for benign tumors and 74.83 s for malignant tumors with cut off value of 83.3 s at (AUC of 0.84) giving specificity of 77.3% and sensitivity of 84.8%. These results were consistent with Yabuuchi et al. (18) who studied TTP in 29 patients with salivary gland tumors and concluded that TTP of 120 s enabled the differentiation of pleomorphic adenomas from malignant tumors.

However the TIC shape analysis does not provide absolute measures. It is dependent, affected by the length of the scan, and the scan parameters (TR/flip angle), all these factors can influence the final shape, resulting in the same tissue possibly being classified differently when using different parameters (19).

In contrast to semi-quantitative techniques, intrinsic physiologic information of tissue microcirculation can be provided by quantitative techniques which depend on contrast concentration curves over time to observe the extravasation of contrast agent from the vascular space to the interstitial space (20).

Pharmacokinetic modeling of the DCE-MRI signal is used to calculate the kinetic parameters such as wash in and wash out rates describing tumor and tissue permeability that are hallmarks of the angiogenic phenotype associated with most cancers (21).

In the current study, we found significant difference ($p < 0.001$) as regards wash in and wash out rates between benign and malignant tumors in agreement with Junfang et al. (20), and the present study demonstrated mean value of wash in rate was 9.98 l/s for benign tumors and 18.95 l/s for malignant tumors, while mean value of wash out rate was 2.11 l/s for benign tumors and 9.47 l/s for malignant tumors.

Different studies on malignant tumors of the breast, prostate, cervix, liver, lung, rectum, brain, and head and neck reported that malignant tumors had higher wash in rate ($K_{trans}$) and washout rates ($K_{ep}$) (20,22,23).

Although DCE-MRI is safe, non invasive, can be repeated and performed on conventional MRI examination (19); however, there is some limitations to the routine clinical use of DCE-MRI which is lack of standardized and optimized perfusion MRI protocols, lacking of simple and standardized perfusion postprocessing software and apparent complexity of perfusion MRI for nonexpert radiologists (24).

5. Conclusion

We concluded that DCE-MRI plays a superior role to the conventional MRI in differentiating benign from malignant head and neck tumors.

Quantitative parameters improve the accuracy of DCE-MRI by studying the tissue pharmacokinetics and tissue properties, and wash in rate was the best parameter used for differentiation between benign and malignant tumors with cut off value 15.4 l/s giving a sensitivity of 87.9% and specificity of 90.9% with (AUC) of 0.94.

6. Conflict of Interest

There is no conflict of interest to declare.

References


725


