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Role of Dynamic Contrast Enhanced MRIPerfusion in the Assessment of Vascular Permeability of Head and Neck Squamous Cell Carcinoma as a Predictor of Treatment Response

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Abstract:
Background: Cancers of squamous cell type are of growing incidence, especially those affecting the head and neck. Emerging non-invasive radiological tools can now aid in predicting and monitoring response of tumor tissue to treatment, hence improving the whole treatment plan. One of these emerging modalities is dynamic contrast enhanced magnetic resonance imaging (DCE-MRI), which is further investigated as regards its accuracy in predicting disease prognosis and monitoring changes in tumor characteristics with treatment. **Methods**: DCE-MRI perfusion was performed for 14 patients before and after receiving non-invasive treatment for different types of head and neck squamous cell carcinoma. Pharmakokinentic parameters were measures and compared before and after treatment including (Ktrans, Kep, Vp and iAUC). **Results**: 14 patients with a total of 40 lesions were included in the study. In all primary and nodal sites, Ktrans values were significantly lower in normal tissue compared to tumoral sites with a p value as low as 0. Pre-treatment values for Ktrans, Kep and iAuc showed statistically significant lower values in post-treatment scans compared to pre-treatment scans as regards Ktrans, Kep and iAUC values with p values of about 0. **Conclusion**: Ktrans, Kep and IAUC can be used as significant markers for assessment of tumor response in patients with HNSCC, Further studies are required to correlate the values between responders and non-responders.

Introduction:
Head and neck cancers are collectively ranked the seventh most common tumors worldwide (Ferlay et. al, 2012). More than 90% of them are of squamous cell type (Grégoire et al., 2010). Surgery and chemoradiotherapy (CRT) are the two main modalities of treatment with curative intent for patients with advanced stage HNSCC. Over the past decade the non-surgical approach has become more popular due to better organ preservation. But not all HNSCCs respond to CRT and approximately 25–30 % of patients will fail treatment at local or nodal sites in the head and neck (King and Thoeny,2016).
Dynamic contrast enhanced MRI (DCE-MRI) provides a promising non-invasive tool to evaluate the perfusion and permeability of these kinds of tumors in the head and neck, which is an important predictor of possible treatment resistance. Pre-treatment DCE-MRI, therefore, may be able to predict failure at primary and nodal SCC sites, while post-treatment DCE-MRI helps in distinguishing a favourable from an unfavourable treatment response (King et al.,2015).
This study is designed to assess the value of the quantitative parameters of DCE-MRI in predicting and monitoring response to treatment of HNSCC using K-trans as the primary end point, kep , (rate constant between the extracellular extravascular space and blood plasma), and Ve (volume of the extracellular extravascular space per unit volume of tissue) as secondary end-points.

Methodology:
A.DCE-MRI Data Acquisition:
MRI was performed on a 1.5T MRI scanner.
Baseline (pre-treatment) imaging:

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Before performing DCE-MRI, all enrolled patients underwent routine MRI head and neck protocol. The DCE-MRI sequence then was obtained using a short 3D T1-weighted spoiled gradient echo sequence in the axial plane covering the entire tumor .Contrast injection was given in the form of a bolus injection of gadopenetatedimeglumine at a concentration of 0.1 mmol/kg of body weight.

Following the DCE-MRI scan, post-contrast enhanced anatomical T1-weighted images was acquired as part of the routine examination.

Post treatment imaging:

For each patient the post-treatment scan was performed using the same MRI protocol mentioned above 6 -8 weeks following the end of treatment.

Image analysis:

Analysis of conventional MR images

T2-weighted, FLAIR and post contrast T1WI baseline images was used to identify the primary tumour site, and metastatic lymph nodes. For each patient the primary tumorwas measured by the largest dimension in the axial plane, while lymph nodes was measured by the maximum short axis diameter.

Analysis of dynamic data

DCE-MRI data was exported to the workstation for post processing using a specialized software which generated the DCE-MRI pharmacokinetic parameter maps using the extracted arterial input function based on the Tofts model. Whole-lesion regions of interest (ROI) of each pre-treatment SCC site (primary site or metastatic nodal site) and any residual masses at these SCC sites on the post treatment scan was outlined on the T1W dynamic images using the T2-weighted and T1-weighted post-contrast axial images for guidance. Ktrans, kep, vewill then be generated.

Statistical Analysis

IBM SPSS statistics (V. 26.0, IBM Corp., USA, 2019) was used for data analysis. Date were expressed as median and percentiles for quantitative non-parametric measures in addition to both number and percentage for categorized data.Comparison between two independent groups for non-parametric data using Wilcoxon Rank Sum test was done.Results were considered statistically significant at p value of ≤ 0.05.

Results

14 patients were included in this study. 35.7% of them were females (5) and 64.3% were males (9). Mean age was 53.6 $\pm$17.7 years old. Pre-treatment DCE-MRI was performed on 40 lesions of (15 primary sites and 25 nodal). Ktrans, Kep, and Vp and AUC values were obtained and recorded at baseline pre-treatment scan for future correlation with post-treatment values.

Post-treatment DCE-MRI was performed for 26 lesions(10 primary sites and 16 nodal). Follow up was lost for 5/40 lesions; an MRI was not performed (1), renal impairment prevented the administration of contrast (2), or the MRI was delayed (2). Quantitative data were obtained and recorded same way as in the pre-treatment scan.

Table-1 shows the correlation between the median values of pre-treatment DCE-MRI parameters and normal tissue in the same patient. In all primary and nodal sites, Ktrans values were significantly lower in normal tissue compared to tumoral sites (0.148 in lesional sites compared to 0.017 at normal surrounding tissue) with a *p* value as low as 0. Kep and iAuc values in pre-treatment lesions measured 0.991 and 0.133 respectively compared to 0.497 and 0.024 at normal surrounding tissue respectively with a significantly lower values recorded at normal sites compared to lesional sites. However Ve values in pre-treatment lesional sites measured 0.1515, which was insignificantly correlated to the measured value in surrounding normal tissue (0.107)

Table 1 Correlation between Pre-treatment quantitative parameters of DCE-MRI and the normal tissue

		n	Median	p
K.trans	Normal	11	0.017	
	Pre	40	0.148	0
Kep	Normal	11	0.497	
	Pre	40	0.991	0.001
Ve	Normal	11	0.107	
	Pre	40	0.1515	0.551
iAuc	Normal	11	0.024	
	Pre	40	0.133	0.001

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Table 2 represented the correlation between post treatment values of Ktrans, Kep, Ve and iAuc in lesional sites to the values recorded at the surrounding normal tissue.

Table 2 Representing correlation between post-treatment value of quantitative DCE-MRI parameters to the surrounding normal tissue.

		n	Median	p
K.trans	Normal	11	0.017	
	Post	26	0.039	0.067
Kep	Normal	11	0.497	
	Post	26	0.642	0.485
Ve	Normal	11	0.107	
	Post	26	0.069	0.894
iAuc	Normal	11	0.024	
	Post	26	0.056	0.139

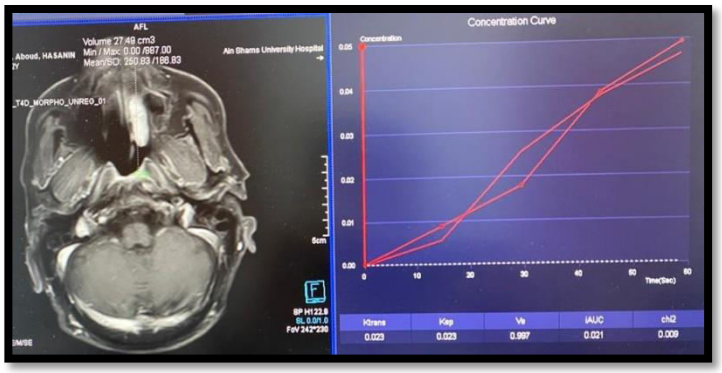
In post treatment lesional sites, K-trans measures about 0.039 compared to 0.017 in the normal tissue, Kep measured 0.642 compared to 0.497 in the surrounding normal tissue, Ve measured 0.069 compared to 0.107 in the normal tissue and iAUC measured 0.056 compared to 0.024 in the normal tissue. These measurements were insignificanty correlated to the measurements taken at the normal surrounding tissue in the same patient with *p* values of about 0.067, 0.485, 0.894 and 0.139 respectively.

In table 3, correlation between pre-treatment and post-treatment values for K-trans, Kep, Ve and iAuc are demonstrated.

Table 3shows the correlation between DCE-MRI parameters in pre-treatment and post-treatment scans.

		n	Median	p	Sig.
K.trans	Pre	40	0.148		
	Post	26	0.039	0	HS
Kep	Pre	40	0.991		
	Post	26	0.642	0	HS
Ve	Pre	40	0.1515		
	Post	26	0.069	0.733	NS
iAuc	Pre	40	0.133		
	Post	26	0.056	0	HS

Pre-treatment values for Ktrans, Kep, Ve and iAuc measured 0.148, 0.991, 0.1515 and 0.133 respectively. While post-treatment values measured 0.039, 0.642, 0.069 and 0.056 respectively showing statistically significant lower values in post-treatment scans compared to pre-treatment scans as regards Ktrans, Kep and iAUC values with *p* values of about 0. While correlation between pre- and post treatment values for Ve were statistically insignificant with a *p* value of about 0.733.



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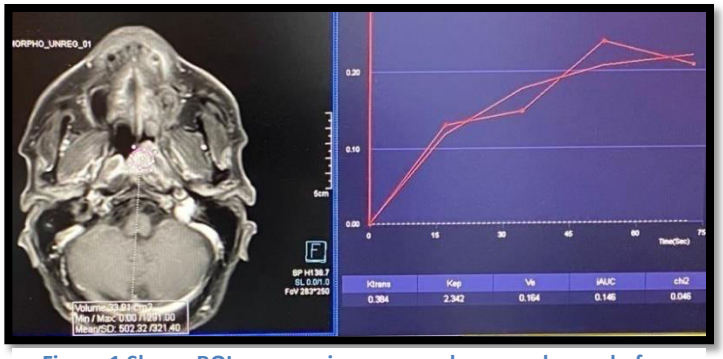
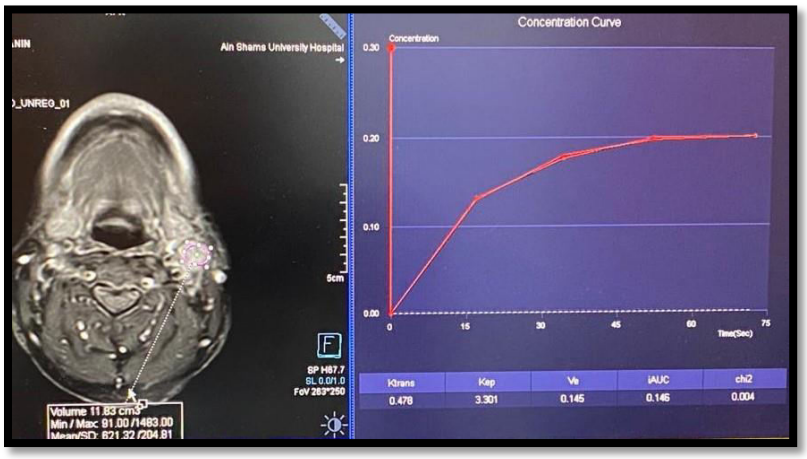


Figure 1 Shows ROI over a primary nasopharyngeal mass before (below image) and after (above image) treatment with the DCE-MRI parameters obtained in both settings.



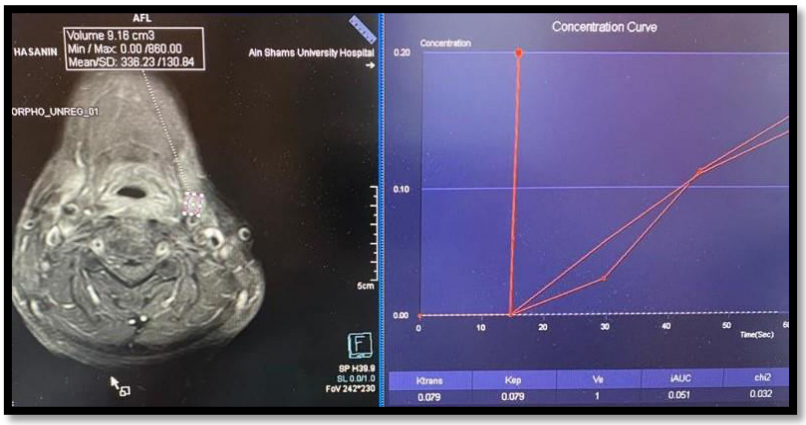


Figure 2Shows ROI over a nodal site of metastatic SCC before (upper image) and after (lower image) treatment with the DCE-MRI parameters obtained in both settings.

Discussion

In this study, three out of four DCE-MRI parameters reported in pre-treatment sites of SCC in the head and neck were significantly correlated to treatment response, namely (Ktrans, Kep and iAUC). Meaning that, the values of

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Ktrans, Kep, and iAuc were all lower compared to pre-treatment corresponding sites' measurements in patients whose clinical assessment showed regressive course of the disease.

Another important finding reported during this study was that the values of DCE-MRI parameters reported in post-treatment sites of patients who achieved clinical and radiological regressive course were very close to the values measured at normal tissue adjacent to these sites in the same patient.

However, no significant correlation could be reported between the measurement of extra-cellular extra-vascular space (Ve) and treatment response. Meaning that; Ve values in pre-treatment and post-treatment measured sites didn't indicate any significant difference to be a useful tool for assessment or prediction of treatment response.

These findings were contrary to those reported in the majority of studies performed for the same aim as our study. The most recent of which is a study performed by King, et. Al, where they clearly stated that none of the pre-treatment parameters of DCE-MRI in patients of head and neck SCC were colcluded to be significant predictors for treatment response. This could be-in part-due to different study design.While our study exclusively selected patients who showed favourable treatment outcomes and compared the pre- and post-treatment values to see if they can tell before-hand the predicted post-treatment behaviour of the tumor, King's study included patients with both favourable and un-favourable post treatment responses and correlated the post-treatment measurements between both groups as well as in pre- and post-treatment setting.

While Kings et. Al couldn't find significant difference in DCE-MRI parameters between site control and site failure patients, the values of Ktrans, Kep, Ve and AUC where significantly different between pre- and post treatment measured sites. This comes-in part-in alignment with our study results.

Another study whose conduction was so close to our current study was performed by Chikuiet. Al. That study performed DCE-MRI after non-surgical treatment and correlated the results with pathology reports of primary oral SCCs. A significant increase in Ve, AUGC, and Ktrans, as well as significantly higher post-treatment ve and AUGC were found in responders compared to non responders. However, our results also showed a significant decrease in Ktrans, Kep and iAUC in post-treatment measurements of patients with favourable response compared to their original pre-treatment value, with an insignificant decrease in Ve values.

Not all patients had a residual tumortissue and even when a mass was present it was too small or too necrotic for our analysis. besides, selecting a residual abnormality in post-treatment sites can be more difficult than selecting the pre-treatment tumor because of the complex treatment induced signal abnormalities in the adjacent normal tissue. Our study design was limited to the patients whose post-treatment clinical and radiological assessment was favourable (responders), so even though the sample size was sufficient to show difference between pre- and post treatment values, it wasn't enough to compare between responders and non-responders.

Conclusion

Ktrans, Kep and IAUC can be used as significant markers for assessment of tumor response in patients with HNSCC as they show significantly reduced values in patients with favourable treatment response. Ve - on the other hand-couldn't be considered as a marker of significance when it comes to the difference between its pre- and post-treatment values. Further studies are required to correlate the values between responders and non-responders.

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