Perfusion characteristics of radiation-induced parotitis: quantitative evaluation with dynamic contrast-enhanced MRI

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Introduction:

Parotid glands are highly radiosensitive and are often injured by head and neck radiotherapy, leading to clinical symptom of xerostomia [1]. Conventional MR imaging usually discloses strong enhancement after intravenous injection of gadolinium, suggesting that the radiotherapy might either damage the blood vessels and increase their permeability or cause glandular death and consequently increase the interstitial spaces that collecting more amount of contrast agent [2]. However, the true reason of post-radiation glandular enhancement remains puzzlingly for decades. By using compartment models, dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is capable of quantitatively investigating the tracer kinetics between the blood vessels and the glandular tissues [3]. In this study, the perfusion characteristics of the irradiated parotid glands were quantified by DCE-MRI so that the phenomenon of post-radiation parotid enhancement could be better understood.

Materials and Methods:

Subjects and radiation dosage: The study enrolled 41 subjects, including a radiotherapy group, which consisted of 19 patients (M:F = 16:3, 53.2 ± 14.9 years), and a control group, which comprised of 22 subjects (M:F = 13;9, 47.5 ± 15.9 years). The estimated dose exposed to the parotid glands of 38.1 ± 14.5 Gy. The total of 38 irradiated parotid glands were further categorized into two subgroups according to the estimated radiation dose to the parotid glands. The low-dose subgroup consisted of 13 glands with the estimated radiation dose equal to or lower than 35 Gy, whereas the high-dose subgroup consisted of 25 glands with the estimated radiation dose higher than 35 Gy. **Imaging acquisition:** Axial dynamic contrast-enhanced perfusion-weighted MR images were obtained on a 1.5 Tesla MR system (ECLIPSE, Philips Medical System, Cleveland, Ohio, U.S.A.) using a multi-slice 2D T1-weighted fast spin-echo sequence with a field-of-view of 230 mm, matrix of 256 × 256, slice thickness of 5 mm, slice number of 6, and TR/TE of 372/12. A total of 20 dynamic phases at an interval of 10.4 seconds were acquired with a total scan time of 208 seconds. **Data analysis:** The MR image data were digitally transferred to a personal computer from the MR operating console and then processed by software developed in-house using Matlab (MathWorks, Natick, MA, U.S.A). The concentration time data were fitted, by means of a non-linear least square curve fitting algorithm, to the Brix pharmacokinetic model [3] as Eq. (1).Goodness-of-fit was assessed by R^2 values used in nonlinear curve fitting. **Error assessment:** Possible error due to the finite temporal resolution of 10.4 seconds in the estimation of perfusion parameters was assessed using Monte Carlo simulation at different levels of additive noise. **Statistical analysis:** Student t test was used for statistical analysis to examine the difference in perfusion parameters between the radiotherapy and the control groups, as well as between parotid glands receiving high dose and low dose of radiation.

$$C_t = \frac{A}{k_{21} - K_{el}}\left(e^{-K_{el}\cdot t} - e^{-k_{21}\cdot t}\right) \quad ..(1)$$

Results:

Good curve fitting of the concentration-time data was achieved in all subjects. The R^2 values were 0.952 ± 0.052 in the radiotherapy group and 0.953 ± 0.046 in the control group, respectively, suggesting that the use of the Brix model is appropriate in parotid perfusion. For the image acquisition protocol used in our study, SNR was at the level of about 30 in all subjects, corresponding to imprecision of -0.93 ± 7.84%, -1.25 ± 9.44% and 5.14 ± 29.16% for A, K_{el}, and k_{21}, respectively. The peak enhanced T1-weighted images and percent signal enhancement of the irradiated and controlled parotid glands were demonstrated (Fig. 1). The results of perfusion parameters and the derived indices for the irradiated and non-irradiated parotid glands were shown (Fig. 2). The radiotherapy group had relatively marginally lower k_{21} ($P < 0.05$) and significantly lower K_{el} (P value <0.0005) than the control group, but the amplitude scaling constant A was unchanged ($P = 0.26$). Alterations in these perfusion parameters resulted into significantly higher values for the peak enhancement ($P < 0.0005$) and time-to-peak ($P < 0.0005$) consistent with the common observation of increased signal enhancement with contrast administration, with insignificant changes in the wash-in slope ($P = 0.45$). When taking into account the estimated radiation dosage to the parotid glands, the difference from the control group became more prominent for the high-dose group. For the low-dose group, on the other hand, only K_{el} showed marginally significantly lower value than the control group ($P < 0.05$).

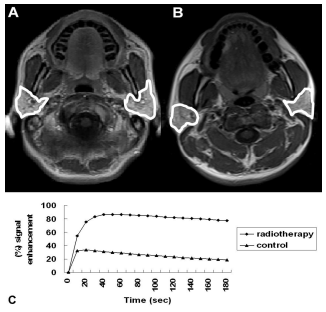

Fig. 1. Peak-enhanced T1-weighted images of irradiated (A) and control (B) parotid glands and their corresponding signal enhancement-time curves (C).

Discussion:

Slow-exchange behavior of irradiated parotid glands: The results from our dynamic MR imaging study show that the increased peak enhancement following contrast administration is predominantly determined by the prominent alterations of K_{el} and k_{21}. The statistically significant decreases in the transfer constants showed a coincided perfusion behavior in slow-exchange tissues rather than in tissues with increase vascular permeability. When the delivery of the contrast medium between the plasma and the EES is inefficient, a slower elimination of contrast medium occurs. **Effect of radiation dosage:** Sub-group comparison shows no statistically significant changes of the perfusion characteristics compared with the control group when the radiation dose is lower than 35 Gy. At a radiation dose higher than 35 Gy, on the other hand, the irradiated parotid glands differ substantially from the non-irradiated glands in K_{el} (<0.0005), which can readily be observed in the original dynamic imaging series from a higher peak enhancement (<0.0005) and a longer time-to-peak (<0.0005). **Quantified perfusion:** The unique feature of our study is the quantification of parotid perfusion parameters which, to the best of our knowledge, has not been investigated before. A quantitative investigation using curve fitting to an appropriate model provides the important advantage that the underlying changes can be examined physiologically (such as EES as opposed to vascular permeability), and that the influence of noise or finite sampling interval could be minimized. **Conclusion:** quantitative analysis of DCE-MRI with the Brix model is an effective tool investigating the perfusion characteristics of the parotid glands after radiotherapy. The dose-dependent change of perfusion characteristics suggests that the persistent accumulation and delayed wash-out of the contrast agent at late stage of radiation injury reflects the slow-exchange nature of irradiated parotid glands rather than increase of vascular permeability.

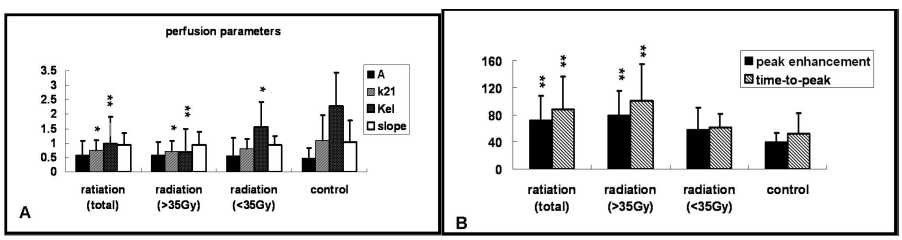

Fig. 2. Perfusion parameters of irradiated and non-irradiated parotid glands. The scales and units on the vertical axes are: $\times 10^{-1}$ for A, $\times 10^{-1}$ sec^{-1} for k_{21}, $\times 10^{-3}$ sec^{-1} for K_{el} (the above for 5A), and $\times 1$ % . sec^{-1} for slope, % for peak enhancement, sec for time-to-peak (the above for 5B), respectively. Data are presented as mean + SD with P value < 0.05 (*) and P value < 0.0005 (**) being statistically significantly different as compared to the control group.

References:

1. Jen YM, et al. *Radiother Oncol* 2005;75:204
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3. Brix G, et al. *JCAT* 1991; 15:621