Assessment of the influence of preoperative chemotherapy in patients with osteosarcoma by dynamic contrast-enhanced MRI using pharmacokinetic modeling

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Abstract. A novel method is introduced for predicting the effect of preoperative chemotherapy in patients with osteosarcoma. The method is based on the histogram of wash-in rates as estimated by fitting a pharmacokinetic model to each voxel within a region of interest. The 80-percentile of this histogram is the best predictor for the effect of chemotherapy; among 7 good and 13 poor responders solely 4 were predicted wrongly. The kappa measure is 0.560, and is significantly different from zero with a p-value smaller than, $p<0.01$. Our gold standard is the pathologic specimen from which the response to chemotherapy is assessed, above/below 10% viable remnant tumor.

1 Introduction

The effect of preoperative (neoadjuvant) chemotherapy on high-grade bone tumors is an important prognostic indicator for the expected survival rate of patients. Patients for whom the preoperative chemotherapy resulted in less than 10% viable tumor – so-called *good responders* – have significantly better prospects for five-year survival than patients with more than 10% viable remnant tumor.

An earlier study indicated a high correspondence between the presence of viable remnant bone tumor and a fast up-take of paramagnetic tracer (Gd-DTPA) in patients with Ewing's sarcoma [1]. This is caused by the disposition of Ewing's sarcoma to form isolated islands (remnants), which can clearly be distinguished on a macroscopic level in histologic specimen of the postoperative tumor due to their intense basophilic properties. Osteosarcoma, on the other hand, exhibits a different reaction to preoperative chemotherapy resulting in microscopic nests with viable remnant tumor that interwove areas with necrosis, granulation tissue and normal bone cortex. It is hard to assess quantitatively the amount of viable remnant tumor in preoperative MR-images of patients with osteosarcoma because of this intermingling pattern of viable and necrotic areas. To circumvent this problem, we introduce different aggregate measures for the effect of preoperative chemotherapy in patients with osteosarcoma.

In the sequel, we introduce a novel statistic for predicting whether more or less than 10% viable tumor remains after patients with osteosarcoma have been treated with preoperative chemotherapy. The nonparametric statistic is based on two pharmacokinetic parameters estimated for each voxel in a region of interest (ROI). The statistic combines the estimated wash-in rate (k_1) and the maximal enhancement (a) per voxel in the ROI. It is demonstrated that the absolute character of the wash-in rate – virtually an acceleration term – makes it suited as an absolute estimator for the response to chemotherapy. The usefulness of the approach is illustrated for twenty patients with osteosarcoma who obtained preoperative chemotherapy.

2 Materials and methods

2.1 Subjects

In total 20 patients with osteosarcoma, verified by biopsy, were included in our study. All patients had received preoperative chemotherapy according to an EORTC protocol. Among the 20 patients, seven responded well to chemotherapy resulting in less than 10% viable remnant tumor as estimated from the histologic section of the post-chemotherapy resected specimen. The tumors in the remaining 13 patients showed a poor response to chemotherapy.

2.2 MR imaging

Subsequent to preoperative chemotherapy, MR examination was performed on 0.5 T super-conductive Gyroscan (Philips, Best, The Netherlands) by means of a surface coil. Besides the static T_1-weighted and T_2-weighted MR-images, one, two or three sections were selected for T_1-weighted dynamic contrast-enhanced imaging using a magnetization prepared imaging gradient recalled echo technique. The dynamic MR images were acquired with a repetition time (TR) of 12 ms (independent of the number of sections), an echo time (TE) of 5.7 ms, and a prepulse delay of 741 ms. The flip angle was set to 30 degrees. The field-of-view varied per patient depending on the size of the tumor. All MR-images were acquired with a matrix size of 256×256 voxels, a slice thickness of 8 mm and a slice gap of 12 mm. The dynamic contrast-enhanced MR images were acquired while an intravenous bolus injection of Gd-DTPA (Magnevist®) was given followed by a saline flush. For each MR section, 47 to 60 dynamic MR images were acquired with a temporal resolution of 3.3 sec.

2.3 Pharmacokinetic analysis

In an earlier study, we investigated the possibility of locating (macroscopic) remnants with viable tumor in postchemotherapy patients with Ewing's sarcoma [1]. This approach cannot be used to assess the effect of preoperative chemotherapy in patients with osteosarcoma because relevant staining differences cannot be recog-

nized at the macroscopic level. However, it can be expected that the average density of capillaries will be higher in a tumor of a poor responder than in a patient with a very good response to chemotherapy. We propose to perform aggregated pharmacokinetic analysis of patients with osteosarcoma after completion of preoperative chemotherapy to assess their response.

The pharmacokinetic analysis is based on the two-compartment model introduced in [1]. The model characterizes the exchange of tracer between the arterial and the extracellular compartments. It models the infusion of the contrast tracer in the arterial compartment as a Dirac pulse. The following differential equations capture the exchange of tracer between the arterial compartment

$$\frac{dC_b}{dt} = -\frac{k_1}{V_b}(C_b - C_e) - \frac{k_2}{V_b}C_b \tag{1}$$

and the extracellular compartment

$$\frac{dC_e}{dt} = \frac{k_1}{V_e}(C_b - C_e) \tag{2}$$

with C_b the concentration and V_b the volume of tracer in the arterial blood. C_e is the concentration of tracer in extracellular water, k_1 and k_2 the (half-life) transfer rates from the blood to the extracellular space and from the blood to the kidneys, respectively. Solving these equation results in a bi-exponential equation [1]

$$C_e(t) = \frac{1}{1+e^{-g(t-t_0)}} a(e^{-m_2(t-t_0)} - e^{-m_1(t-t_0)}) + \varepsilon(x,y,z,t) \tag{3}$$

The dynamic MR image sequence can be used to analyze the pharmacokinetic properties of a tumor. Define the dynamic MR signal by f(x,y,z,t), a function of the three spatial coordinates (x,y,z) and the time t. The parameters of Eq. (3) are estimated for each voxel (x,y,z) within a region of interest, (x,y,z) $\in \Omega$, as a function of time t. The fit is obtained by minimizing the residual sum per voxel (x,y,z), Σ_t ε(x,y,z,t), which is performed by the Levenberg Marquart algorithm [2].

The fit procedure results in a vector with pharmacokinetic parameters for each voxel within the region of interest Ω, $\boldsymbol{r}(x,y,z)=(a(x,y,z),m_1(x,y,z),m_2(x,y,z),t_0(x,y,z))^{\mathrm{T}}$. These parameters can be visualized in the form of parametric images where each image indicates areas with a high and a low amplitude (a), wash-in rate (m_1), wash-out rate (m_2) and local arrival time (t_0), respectively. Like Bonnerot *et al.* [3], we define a set of nonparametric statistics based on the distribution of wash-in rates within the conditional region of interest $\Omega(a)$. Define the i'th percentile, P_i, of the distribution of wash-in rates by

$$P_i = m_1(x,y,z), \left\{\mathrm{card}(m_1(x',y',z') < m_1(x,y,z)) / \mathrm{card}(m_1(x,y,z))\right\} = i, \quad (x',y',z'),(x,y,z) \in \Omega(a) \tag{4}$$

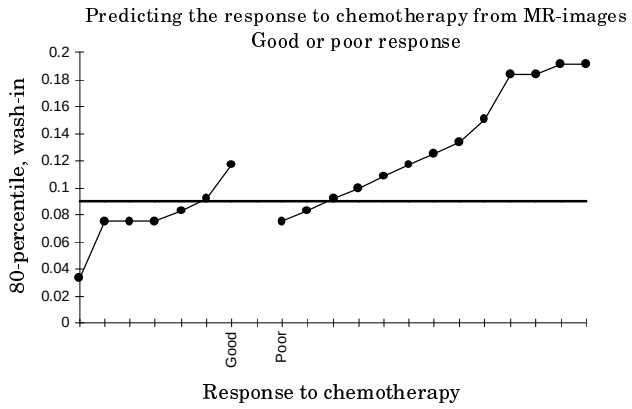

Figure 1. Twenty patients ranked according to the 80-percentile of the wash-in rate inside the region of interest. The study contained 7 good and 13 poor responders to preoperative chemotherapy. The vertical line, 0.09, indicates the best discrimination between the good and the poor responding patients.

with card(●) denoting the number of elements in a set and the conditional region of interest being $\Omega(a)=\{(x,y,z)\in\Omega \mid a(x,y,z)>a_{\min}\}$. The pharmacokinetic analysis is restricted to the subset of voxels in Ω for which the signal enhancement exceeds $a_{\min}$, because the wash-in rate, $m_1(x,y,z)$, cannot be estimated with confidence when the signal enhancement is at the same order of magnitude as the noise present in the dynamic MR-signal.

3 Results

The prediction by our statistic – the 80-percentile of the histogram of wash-in rates – into good and poor responders is illustrated in Figure 1. It is clear that the good responders have a much smaller amount of highly perfused voxels than the poor responders. In total 4 patients, 2 good and 2 poor responders, are predicted wrongly, see Table 1. Consequently, 80% of the patients were predicted correctly. The kappa value is 0.560, which is significantly different from zero for $p<0.01$. The high significance level obtained for a sample of 20 patients shows that our absolute measure for the effect of preoperative chemotherapy has a high predictive power.

Table 1
Contingency table showing the correspondence between the assessment from analysis of the MR-images and the gold standard obtained from pathology.

		Pathology	
		Good	Poor res.
MR	Good	5	2
	Poor res.	2	11

In the histograms used to compute the statistic in Figure 1, the minimal amplitude was set to $a_{\min}=10$. We recomputed the wash-in statistic for other values, $a_{\min} \in$

{0,5,10,20,50}, but the 80-percentile resulted in the same four patients being misclassified.

Also other percentiles from the histogram were investigated, the 50-percentile (median), the 90- and the 95-percentiles. Moreover, the predictive power of the mean wash-in rate was investigated. However, all these statistics gave a poorer discrimination between the two groups of responders than did the 80-percentile.

4 Discussion

We have introduced a novel statistic based on the histogram of the wash-in parametric image to predict the response to chemotherapy in patients with high-grade osteosarcoma according to a generic criterion, above/below 10% viable remnant tumor. Although the MR-signal expresses a *relative* measure for the relaxivity of the tissue under study, the wash-in rate defined in our pharmacokinetic model is an absolute (acceleration) term, which does not directly depend on the absolute value of the MR-signal. However, because the wash-in rate cannot be estimated with high confidence when the signal enhancement is small compared to the noise present in the MR-signal, it is necessary to remove unreliable wash-in rates from the histogram before the derived statistics are computed.

The fact that the other statistics we computed resulted in poorer predictions of the effect of chemotherapy, is ascribed to insensitivity and over sensitivity. The median and mean of the histogram are too insensitive to a small number of scatted voxels with a high wash-in rate. The 90- and 95-percentiles, on the other hand, are too sensitive to noise and outliers in the histogram. We believe that the 80-percentile gives the best trade-off between sensitivity to highly perfused voxels and robustness to noise and outliers.

5 References

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