Original Article

CT perfusion in evaluation of post therapy cervical lymphoma

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Abstract

Objective: Compare CT perfusion between responders and non-responders in patients with residual cervical nodes after lymphoma treatment.

Subjects and methods: Twenty-seven patients with treated pathologically proved lymphoma were included in this prospective study, divided into two groups: responders (n. 15) and non-responders to treatment (n. 12). Blood flow (BF), blood volume (BV), mean transit time (MTT) and permeability (PS) were determined using CT perfusion. Lymph nodes sizes were measured (short axis).

Results: BF, BV and PS were significantly higher in non-responders group [93.3 (65.3–111) ml/min/100 g, 6.3 (5.2–8) ml/100 g and 18.9 (14.5–25.1) ml/min/100 g respectively] as compared to responders group [54 (43.8–77.5) ml/min/100 g, 4.1 (2.2–4.8) ml/100 g and 9.4 (7.5–14.5) ml/min/100 g respectively], [p 0.019, 0.004 and 0.004 respectively]. MTT had a trend to be low in non-responders group, but did not reach statistical significance (p 0.305). Cutoff value for BF, BV and PS was 59.5 ml/min/100 g, 3.6 ml/100 g and 11.1 ml/min/100 g respectively, 92% sensitivity for the three parameters and specificity 67%, 47% and 73% respectively. Lymph node sizes had no relation to the perfusion parameter values.

Conclusion: CT perfusion is a functional imaging tool with promising results in differentiating between responders and non-responders in treated lymphoma patients, using BF, BV and PS.

Keywords: CT perfusion, Lymphoma, Cervical lymphadenopathy

1. Introduction

Computed tomography (CT) is still the most commonly used imaging tool for initial staging and follow up of lymphoma. However, CT has low accuracy in the diagnosis of relapse, identification of viable tumor masses is usually not possible by CT. The presence of residual mass after treatment occurs in 64–88% of cases in both lymphoma subtypes [1–5]. A functional imaging tool to monitor the activity of any residual tissue is favored in lymphoma [4–6].

Fluorodeoxyglucose positron emission tomography (F-FDG PET) has advanced to a state-of-the-art imaging technique in staging and monitoring the response to treatment of lymphoma, due to its high sensitivity for assessment of tumor vitality [7–9]. The main disadvantage of F-FDG PET is its high false positive results caused by reactive tracer uptake, e.g. thymus hyperplasia, sarcoidosis or inflammation [5,6,10–12].

Non-invasive measurements of tumor related angiogenesis represent an alternative approach to the characterization of residual lymphoma masses. Vascular characteristics, such as vessel wall permeability and
perfusion could be assessed by CT perfusion which can be combined with the routine conventional CT [5,6,12].

CT perfusion is suitable for this purpose due to its widespread availability, plus that CT is already used for lymphoma staging and follow up of all patients. A key advantage of CT perfusion is the linear relation between iodine concentration and tissue density changes which means direct calculations in a more simple way than Magnetic resonance imaging (MRI). In addition, the routine availability of commercial software for CT perfusion for tumor diagnosis [13].

The data on the usefulness of CT perfusion in lymphoma patients are limited [4,13]. The chief reason for this is the idea that angiogenesis is not a predominant feature of lymphoma as compared to other types of malignancies [13].

However, results of previous studies demonstrated that active lymphoma revealed an increase in perfusion values as compared to inactive lymphoma [12]. Moreover, the degree of residual lymphoma perfusion at end of treatment helps to identify patients likely to remain in remission 1 year after completion of therapy [5].

The aim of this study was to evaluate the role of CT perfusion in the differentiation between responders and non-responders after treatment of lymphoma patients.

2. Materials and methods

Institutional review board (IRB) approval was obtained for this prospective study.

2.1. Subjects

Our study included 27 patients (12 males, 15 females), their ages ranged between 18 and 70 years with median age 47 years. General inclusion criteria were; pathologically proved lymphoma, treated for more than 3 months or after finishing at least one cycle of chemotherapy, follow up post contrast CT showed residual cervical lymph nodes more than 1 cm in its short axis (fine needle aspiration cytology FNAC revealed 19 cases of NHL, 14 of them were diffuse large B cell type Diffuse large B cell lymphoma (DLBCL), and 8 cases of Hodgkin lymphoma (HL)).

Patients were divided into two groups; group 1, responders to treatment (partial remission PR or stable disease SD) and group 2, progressive disease PD. Inclusion criteria for group 1 were; final clinical assessment suggests PR or SD, and comparison with previous pretreatment CT showed same or decrease in cervical nodal size. Inclusion criteria for group 2 were; final clinical assessment suggests PD, and comparison with previous pretreatment CT showed increase in cervical nodal size. Exclusion criteria were general contraindications of post contrast CT; Pregnancy, hyperthyroidism, renal impairment (creatinine level >1.5), history of hypersensitivity for iodinated contrast media, heart failure.

2.2. CT perfusion technique

Dynamic CT acquisitions were performed on a 64-MDCT scanner (Brilliance 64 CT scanner, Philips Healthcare, Best Netherlands). First, a non-contrast CT scan was performed which served as a localizer to determine the desired scanned region to be included in the dynamic study. Low tube peak kilovoltage and low tube current were used for the localizer scan (80 kVp and 150 mAs) as well as slice thickness (5 mm).

The dynamic study consisted of eight contiguous slices, of 5 mm thickness each. The dynamic acquisition was performed using low tube voltage 80 kVp and tube current 200 mAs. The scan duration was 50 s to cover the first pass of contrast and allow for calculation of permeability surface area product as well. The temporal resolution was one image per two seconds, with total 25 images for each of the eight slices. Imaging was initiated 6 s after the injection of contrast. The total dose of contrast was 50 ml of non-ionic iodinated contrast agent (Optiray 350 mg/ml Mallinkrodt Medical, Pmc, Mallinckrodt, Inc.). The rate of injection was 5 ml/s. This was followed by 20 ml saline flush with the same rate of injection to keep the injection bolus tight and prevent its retention in venous line. An automated power injector and a 16-G antecubital cannula were used. Patients were instructed to breathe quietly and to avoid deglutition.

Temporal resolution of one image per two seconds was used to lower the radiation dose in all patients [14].

2.3. Post processing

For all cases post-processing was done using separate workstation (Advantage Windows 4.2; GE Medical Systems, Mil.) running the perfusion software (Body perfusion 3 Perfusion 3; GE Medical Systems). All the dynamic CT images were reviewed in the cine-mode to ensure the absence of significant motion artifacts.

An arterial input ROI was manually inserted using a standardized circular ROI. The resultant arterial time attenuation curve was reviewed to ensure the presence of a rapid rise to a high peak, followed by rapid descent of attenuation. Identification of the start and the end of first pass of contrast was then done manually.

The software automatically generates the following perfusion parametric maps: BF (ml/min/100 g), BV (ml/100 g), MTT (seconds), and PS (ml/min/100 g). Every pixel of the images obtained is attributed a color which represents a numeric value of the perfusion parameter calculated for that pixel.

The dynamic CT section showing maximum nodal diameter was selected from the available 8 sections and a free-hand ROI was traced around tumor boundaries to encompass as much nodal tissue as possible avoiding large vessels, areas of necrosis and peri-nodal tissue. The software calculated numeric values for each ROI which corresponds to the average BF, BV, MTT and PS in this ROI. The perfusion values for the lymph node were recorded for every patient.

2.4. Statistical analysis

Test of normality was done to the data, which was found to be non-parametric. Statistics were done using SPSS 16, and the median (interquartile range) of the four
perfusion parameters (BF, BV, MTT and PS) of patients in the two groups was calculated. The results were compared using man-whitney test, p values less than 0.05 were considered significant.

When statistical significance was found, ROC curve analysis was performed to define cut off values between the two groups.

Pearson's correlation coefficient was used to test for correlation between the lymph node size and different perfusion parameters.

3. Results

Responders group (1) were 15 patients (9 males and 6 females), and non-responders group (2) were 12 patients (3 males and 9 females).

No significant difference was noted between both groups as regarding the mean age and gender, as shown in Table 1, both p-values were non-significant.

Median, interquartile range and results of comparison between BF, BV, MTT and PS are summarized in Table 2, Fig. 1. There was significant difference between the BF, BV and PS of the responders group and the non-responders group (Figs. 3 and 4), p-value was (0.019, 0.004, and 0.004 respectively). On the other hand, there was no significant difference between MTT of both groups (p-value was 0.305).

The receiver operating characteristic curve (ROC curve) was done for the three significant parameters. ROC curve analysis results for BF, BV and PS are demonstrated in Table 3. Results revealed a cutoff value for BF, BV and PS (59.5 ml/min/100 g, 3.6 ml/100 g and 11.1 ml/min/100 g respectively) (Fig. 2).

When testing for correlation between the size of the selected lymph node of all cases and different perfusion parameters, there was no significant correlation (all p-values were >0.05).

The radiation dose recorded with our CT perfusion technique was (computed tomography dose index CTDI vol = 46.9 mGy and dose length product DLP = 187.6 mGycm).

4. Discussion

In our study, we discovered significant difference between the values of BF, BV and PS between responders and non-responders to treatment groups, using CT perfusion parameters quantitative values.

CT perfusion is a unique CT technology that enables functional imaging by both qualitative and quantitative assessment of tissue vascularity [15].

The data on the role of CT perfusion in lymphoma patients are limited [4,13]. The chief reason for this is the idea that angiogenesis is not a predominant feature of lymphoma as compared to other types of malignancies [13].

In this study, blood flow (BF) was significantly higher in non responders than in responders, and this can be used in the differentiation between responders and non-responders to treatment (p-value 0.019). That was in agreement with Dugdale et al. [4], who investigated 39 patients with proved lymphoma in their study, the median perfusion values were higher in active disease than in non-active disease (0.55 vs. 0.37 ml/min/100 g). Our results were also in agreement with Syha et al. [5] who compared perfusion parameters before and after treatment in 26 patients, and found significant reduction of BF in lymphoma patients at end of treatment (P<0.001).

In our work, blood volume (BV) and permeability (PS) were significantly higher in non-responders than in responders, and this can be used in the differentiation between responders and non-responders to treatment (same p-value 0.004 for both). There was a trend for MTT to be lower in non-responders than in responders to treatment, but did not reach statistical significance. Miles & Kelley [16] were not in agreement with our study, they found no difference between treated and untreated patients in mean value of BV. Our results were in agreement with Syha et al. [5], who found significant reduction of BV in lymphoma patients at end of treatment (P<0.001). Syha et al.'s [5] results match the hypothesis that assumes that the vascularity of lymphoma decreases after successful treatment. Miles & Kelley [16] were not in agreement with our study, they found no difference between treated and

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<tr>
<th>Table 1</th>
<th>Age and gender comparison between group 1 and group 2.</th>
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<tr>
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<td>Group 1 (responders to treatment)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>15</td>
</tr>
<tr>
<td>Mean of age ± SD</td>
<td>45.47 ± 17.89</td>
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<tr>
<td>Gender</td>
<td>9 males, 6 females</td>
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<th>Table 2</th>
<th>Perfusion parameters of responders to treatment (partial remission PR or stable disease SD) and non-responders to treatment: Progressive disease PD/or Relapsed disease.</th>
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<tr>
<td>Parameter</td>
<td>Responders median (interquartile range)</td>
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<tr>
<td>Blood flow (ml/min/100 g)</td>
<td>54 (43.8–77.5)</td>
</tr>
<tr>
<td>Blood volume (ml/100 g)</td>
<td>4.1 (2.2–4.8)</td>
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<tr>
<td>Mean transit time (s)</td>
<td>6.9 (4.6–8.8)</td>
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<tr>
<td>Permeability surface area product (ml/min/100 g)</td>
<td>9.4 (7.5–14.5)</td>
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* p-Value is considered significant if <0.05.
untreated patients in mean value of capillary permeability. Also Dugdale et al. [4], found that median values of permeability were slightly different between active and inactive disease. Syha et al. [5] were in agreement with our work, they found that reduction in k-trans was significant for patients who underwent VPCT at both baseline and end of treatment.

The cutoff value proposed by our results for BF was (59.5 ml/min/100 g, sensitivity was 91% and specificity was 66%). That was not in agreement with Dugdale et al. [4], who found that Perfusion below 0.2 ml/min/100 g means inactive disease (p < 0.03), which is much lower than our cutoff value. Their use of an indirect semi-quantitative method to calculate the perfusion parameters might be the cause. Our work was also not in agreement with Syha et al. [5] did CT perfusion at end of treatment of lymphoma, BF > 18.51 ml/min/100 g meant they are non-responders (sensitivity 92.86%, specificity 72.73%, accuracy 84%). The cause of such disagreement might be that our high grade lymphoma cases are more than those in Syha et al’s [5] study. Cutoff values for BV & PS were 3.6 ml/100 g and 11.1 ml/min/100 g respectively, with 92% sensitivity for the two parameters and specificity 47% and 73% respectively.
In our work, we tested the correlation between the size of the selected lymph node of all cases and the different perfusion parameters, there was no significant correlation (all p-values were >0.05). This proved that the vascularity inside the lymph node had no relation to its size, which contradicts the assumed hypothesis, that correlate the size
with the activity of the tumor. That result might help in a better assessment of recurrence.

One of the limitations of the routine use of CT perfusion is the exposure to relatively higher radiation dose than the conventional CT. Increasing the sampling interval to two seconds (instead of the routinely used 1 s in most of CT perfusion studies for head and neck tumors), the radiation dose was nearly half the common radiation dose in CT perfusion studies for head and neck tumors [14]. We tried to decrease the radiation dose in our study by using the same technique with low radiation (CTDI vol = 46.9 mGy and dose length product DLP = 187.6 mGycm).

Limitations of the study were; small sample size, different pathological types of NHL and HL in an unequal distribution (most of the patient were DLBCL), which eliminated the possibility of using the pathology results in statistics. Also we had no gold standard to measure the vascularity in the pathology results, as mean vascular density (MVD), to be compared with CT perfusion parameters. MVD requires tissue excision and special pathological work, which was not part of our protocol. Lymphoma is considered a systemic disease that affects different body parts, not only the neck. Our work on CT neck only is considered a limitation of the study, but our aim was testing the ability of CT perfusion to detect the activity of lymphoma in a residual lesion, which can be applied on any residual tumor mass in other body parts in the future studies.

5. Conclusion

CT perfusion could be useful in the assessment of residual or recurrent lymphoma masses by measuring the vascularity inside the mass which reflects its activity. BF, BV and PS were the useful perfusion parameters for this differentiation, we defined a cutoff value for all of the three significant parameters (59.5 ml/min/100 g, 3.6 ml/100 g and 11.1 ml/min/100 g respectively) above which the patient is considered a non-responder to treatment. We recommend future studies with larger number of patients, for further proof of our results.

Conflict of interest

We have no conflict of interest to declare.
References


