RESEARCH ARTICLE

Manual Contouring Based Volumetric Evaluation for Colorectal Cancer with Liver Limited Metastases: A Comparison with RECIST

WJ Fang¹², KO Lam², SCY Ng², CW Choi³, DLW Kwong², SS Zheng¹*, VHF Lee²*

Abstract

Background: To compare response evaluation criteria in solid tumours (RECIST) and volumetric evaluation (VE) for colorectal cancer with liver-limited metastasis. Patients and Methods: VE of liver metastases was performed by manual contouring before and after chemotherapy on 45 pairs of computed tomography (CT) images in 36 patients who suffered from metastatic colorectal cancer (mCRC) with liver metastasis only. Cohen kappa was used to compare the agreement between VE and RECIST. Pearson correlation was performed for their comparison after cubic root transformation of the aggregate tumor volumes. Logistic regression was done to identify clinical and radiographic factors to account for the difference which may be predictive in overall response (OR). Results: There were 16 partial response (PR), 23 stable disease (SD) and 6 progressive disease (PD) cases with VE, and 14 PR, 23 SD and 8 PD with RECIST. VE demonstrated good agreement with RECIST (κ=0.779). Discordant objective responses were noted in 6 pairs of comparisons (13.3%). Pearson correlation also showed excellent correlation between VE and RECIST (r²=0.966, p<0.001). Subgroup analysis showed that VE was in slightly better agreement with RECIST for enlarging lesions than for shrinking lesions (r²=0.935 and r²=0.780 respectively). No factor was found predictive of the difference in OR between VE and RECIST. Conclusions: VE exhibited good agreement with RECIST. It might be more useful than RECIST in evaluation shrinking lesions in cases of numerous and conglomerate liver metastases.

Keywords: Manual contouring - volumetric evaluation - RECIST - liver metastases - colorectal cancer

Introduction

Colorectal cancer is one of the leading cancer causes of mortality in the world and liver is the predominant site of metastases in majorities of this disease (Shin et al., 2012). Evaluation of the metastatic liver nodules after treatment including chemotherapy is of crucial importance which can certainly lead us to earlier and more effective salvage treatment in an attempt to prolong survival. Response Evaluation Criteria in Solid Tumours (RECIST) has become the most frequently used response criteria for solid tumours (William et al., 2013). Nevertheless, there are shortcomings and criticism regarding its use in a number of clinical circumstances such as gastrointestinal stromal tumor (GIST) which has created inevitable inter-observer variability and non-reproducible judgments (Yankelevitz et al., 2000; Reeves et al., 2007; Heusser CP et al., 2007; Benjamin et al., 2007; Plathow et al., 2008; Mantatzis et al., 2009; Galizia et al., 2011). An important theoretical advantage of VE is that it offers more accurate measurement and reflection of overall tumor burden in an organ which is with less inter-observer variability and better than the mere measurement of the maximum diameters of up to five indicator lesions per organ (Prasad et al., 2002; Tran et al., 2004; Reiner et al., 2009). With regard to the similarities and potential discrepancies between these two assessment criteria, we carried out a retrospective study to evaluate their agreement and correlation, in an attempt to derive a more reliable assessment method of tumour response after systemic therapy for patients suffering from colorectal cancer with liver metastases only.
Materials and Methods

Study design and treatment schedule

Patients who had regular interval CT scans during treatment with 1st line chemotherapy +/- cetuximab as response assessment for their metastatic colorectal cancer (mCRC) with liver-limited disease were eligible for this study for tumour response using RECIST and VE. Unenhanced and dual-phase (arterial and porto-venous) contrast CT scans were performed by a 64 multidetector CT scanner (GE Medical Systems, Milwaukee, USA) at baseline and then after 3-4 cycles of chemotherapy +/- cetuximab. The CT images were then transferred to Eclipse Treatment Planning System version 8.0 (Varian Medical Systems, Palo Alto, CA, USA), a commercialized radiotherapy planning system for manual contouring. VE was performed by manual contouring of all liver metastases at baseline and after chemotherapy +/- cetuximab on every slice of image captured in porto-venous phase. The whole liver was also contoured in all patients as well. The contouring process was performed by two oncologists who had received prior training in radiology and radiation oncology. The volumes of the whole liver, all liver metastases and the residual normal liver (difference between the whole liver and liver metastases) were then obtained. The longest diameter of each target lesion (up to five lesions) on the liver was determined by electronic calipers and summed up for RECIST evaluation. VE criteria as well as RECIST were listed in Table 1 as described by previous literature (Therasse et al., 2000; Mantatzis et al., 2009). Logistic regression was performed to investigate for factors, including age, sex, use of cetuximab, location of primary tumour, number of liver metastasis, largest diameter of the liver metastasis and the ratio of liver metastases to the volume of whole liver, which may be predictive of difference in OR between VE and RECIST.

Results

There were 45 pairs of CT images for comparison in total (Table 2). 23 out of 36 patients received cetuximab in addition to systemic chemotherapy due to the absence of KRAS mutation (De Gramont et al., 2000; Oxnard et al., 2006; Cassidy et al., 2008; Bokemeyer et al., 2009; Van et al., 2009). Seven patients had 4 CT scans and one had 6 CT scans in total for further evaluation of tumor response after additional chemotherapy +/- cetuximab while the rest of 28 patients had only 2 sets (baseline and after treatment)

### Table 1. Category of Objective Response Determined by RECIST and VE

<table>
<thead>
<tr>
<th>Category</th>
<th>RECIST</th>
<th>VE</th>
</tr>
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<tbody>
<tr>
<td>Complete response (CR)</td>
<td>Tumor disappearance</td>
<td>Tumor disappearance</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>≥30% reduction in sum of maximal diameters</td>
<td>≥65% reduction in total volume of all metastatic lesions</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Between that for partial response and stable disease</td>
<td>Between that for partial response and stable disease</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>≥20% increase in sum of maximal diameters</td>
<td>≥73% increase in total volume of all metastatic lesions</td>
</tr>
</tbody>
</table>

### Table 2. Patient Characteristics (n=36)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Male 22 (61.1); Female 14 (38.9)</td>
</tr>
<tr>
<td>Location of primary tumor</td>
<td>Colon 21 (58.3); Rectum 13 (36.1); Colon+Rectum 2 (5.6)</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>FOLFOX4 5 (13.9); XELOX 8 (22.2); FOLFOX4 + cetuximab 9 (25.0); XELOX + cetuximab 13 (36.1); FOLFIRI + cetuximab 1 (2.8)</td>
</tr>
</tbody>
</table>

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of data in VE, Pearson correlation displayed an excellent correlation between VE and RECIST ($r^2=0.966$, $p<0.001$). Logistic regression failed to identify any predictive factor to account for the difference in OR between VE and RECIST.

**Subgroup analysis**

As mentioned, there were altogether 39 pairs of comparisons in which the effect evaluation of liver metastases is the same in both RECIST and VE. Interestingly, for the enlarging lesions confirmed including 6 pairs of PD and 4 pairs of SD, VE showed better correlation with RECIST ($r^2=0.935$, $p=0.001$) while the correlation was weaker (though still strong) for shrinking lesions including 13 pairs of PR and 16 pairs of SD ($r^2=0.780$, $p<0.001$).

**Discussion**

There have been various previous studies comparing volumetric measurements against uni-dimensional measurements with contrasting results (Prasad et al., 2002; Tran et al., 2004; Heussel et al., 2007; Mantatzis et al., 2009). The study conducted by Tran et al and Heussel et al demonstrated good agreement (discordance rate 3.3% and 13% respectively) while Prasad et al revealed fair agreement only (discordance rate 31.6%) (Prasad et al., 2002; Tran et al., 2004; Heussel et al., 2007). Our study result was in accord with that published by Mantatzis et al (Mantatzis et al., 2009). In his study, magnetic resonance imaging (MRI) was used to evaluate tumour response in 57 patients with liver metastases from colorectal cancer. RECIST and VE were in good agreement when comparing patients’ overall response and individual lesions ($\kappa=0.735$ and $\kappa=0.741$ respectively compared with $\kappa=0.779$ in our study). However, our discordance rate was 13.3% which was better than that in his study. One of the major differences between our study and Mantatzis’ study was that we performed cubic root transformation of the data in VE before performing correlation analysis with RECIST. It was because VE is a three-dimensional measurement in which its data should be cubic-root transformed in order to allow meaningful comparisons with the uni-dimensional data in RECIST. In fact, we demonstrated excellent correlation between VE and RECIST after transformation was conducted. And we also produced highly comparable results by using multidetector CT scanner taking less than 20 seconds for a scan, obviating the need of at least 30 minutes for a MRI scan (Maughan et al., 2011).

Though manually demanding and time-consuming taking at least 15 minutes to clearly differentiate tumours from adjacent structures like bile ducts, portal vein and inferior vena cava and complete volumetric contouring for one set of images, volumetric measurement should be praised for its superiority of accuracy and reliability over RECIST, as found to be especially practicable and reproducible in our patients with liver metastases only. Evolution of novel medical imaging tools may soon overcome this tedious and cumbersome manual task (Gavrielides et al., 2009). Additional manual modifications of the contours of the target lesions are still necessary.

**Table 3. Comparison of OR Between RECIST and VE**

<table>
<thead>
<tr>
<th>Methods and OR</th>
<th>VE</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>SD</td>
<td>3</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>23</td>
<td>6</td>
<td>8</td>
<td>45</td>
</tr>
</tbody>
</table>

Cohen Kappa = 0.779 (good agreement)
despite this novel auto-segmentation technique.

As VE reflects the actual change in size of the lesions and it has good agreement with RECIST shown in our study and previous literature, it makes us feel comfortable and confident to use the simpler method RECIST in daily clinical practice. However, our subgroup analysis offered us some new information. Of note, it was found that VE had better agreement with RECIST for enlarging lesions than for shrinking lesions. This interesting finding may imply that VE may be more useful in evaluating shrinking lesions of liver metastasis because RECIST was less sensitive as compared with VE. Of course, the number of patients in these subgroups was relatively small, which was one of the limitations of our study. Further studies are warranted to confirm this finding.

In conclusion, manual contouring based VE showed good agreement with RECIST for evaluation of tumour response of liver metastases in mCRC. Of note, it might be more sensitive especially in monitoring numerous, conglomerate and shrinking lesions in liver metastases, if the time of radiologists and oncologists is not a concern.

Acknowledgements

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References


