PET/CT target delineation

Multiple training interventions significantly improve reproducibility of PET/CT-based lung cancer radiotherapy target volume delineation using an IAEA study protocol

Tom Konert\(^{a,b}\), Wouter V. Vogel\(^{a,b}\), Sarah Everitt\(^{c}\), Michael P. MacManus\(^{c}\), Daniela Thorwarth\(^{d}\), Elena Fidarova\(^{e}\), Diana Paez\(^{e}\), Jan-Jakob Sonke\(^{b}\), Gerard G. Hanna\(^{f,*}\)

\(^{a}\)Nuclear Medicine Department; \(^{b}\)Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands; \(^{c}\)Division of Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne, Australia; \(^{d}\)Department of Radiation Oncology, University Hospital Tubingen, Germany; \(^{e}\)Department of Nuclear Sciences and Application, International Atomic Energy Agency, Vienna, Austria; and \(^{c}\)Centre for Cancer Research and Cell Biology, Queen’s University of Belfast, United Kingdom

A R T I C L E   I N F O

Article history:
Received 6 May 2016
Received in revised form 1 September 2016
Accepted 4 September 2016
Available online 20 September 2016

Keywords:
Lung cancer
PET/CT
Radiation treatment planning
Radiotherapy
Target volume delineation
Training interventions

A B S T R A C T

Background and purpose: To assess the impact of a standardized delineation protocol and training interventions on PET/CT-based target volume delineation (TVD) in NSCLC in a multicenter setting.

Material and methods: Over a one-year period, 11 pairs, comprised each of a radiation oncologist and nuclear medicine physician with limited experience in PET/CT-based TVD for NSCLC from nine different countries took part in a training program through an International Atomic Energy Agency (IAEA) study (NCT02247713). Teams delineated gross tumor volume of the primary tumor, during and after training interventions, according to a provided delineation protocol. In-house developed software recorded the performed delineations, to allow visual inspection of strategies and to assess delineation accuracy.

Results: Following the first training, overall concordance indices for 3 repetitive cases increased from 0.57 ± 0.07 to 0.66 ± 0.07. The overall mean surface distance between observer and expert contours decreased from −0.40 ± 0.03 cm to −0.01 ± 0.33 cm. After further training overall concordance indices for another 3 repetitive cases further increased from 0.64 ± 0.06 to 0.80 ± 0.05 (p = 0.01). Mean surface distances decreased from −0.34 ± 0.16 cm to −0.05 ± 0.20 cm (p = 0.01). Conclusion: Multiple training interventions improve PET/CT-based TVD delineation accuracy in NSCLC and reduce interobserver variation.

© 2016 The Authors. Published by Elsevier Ireland Ltd. Radiotherapy and Oncology 121 (2016) 39–45 This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Lung cancer is the most common cause of death from cancer worldwide, estimated to be responsible for nearly 17% of the total [1] and it is estimated that more than 80% of patients in low and middle income countries are diagnosed with lung cancer in an advanced stage (III and IV) [2,3]. The use of fused \(^{18}\)F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (FDG-PET/CT) imaging is now the standard method of acquiring FDG-PET images for the purpose of baseline staging and RT treatment preparation [4], since it has been shown to be superior to either PET or CT alone [5,6]. The number of PET/CT scanners has increased in low and middle income countries in the last decade [7] and additional training in the use of PET/CT in radiotherapy planning (RTP) is vital to ensure appropriate interpretation of PET/CT with the hope, that the use of PET/CT will improve outcomes for patients treated with radiotherapy.

Due to advancements in radiotherapy techniques, accuracy in treatment delivery is improving and precise target volume definition has become more important, particularly in the era of dose escalation [8,9]. However, gross tumor volume (GTV) delineation is very sensitive to observer variation [10] and hence there is a potential risk of geographic miss of tumor [11]. PET has been shown to have a significant impact when used in the radiation treatment planning process and in particular when used for target volume delineation (TVD), where a significant reduction in interobserver variability (IOV) has been noted [11–15]. It is recommended that a radiation oncologist (RO) and a nuclear medicine physician (NMP)/PET radiologist should be both involved where PET is used for TVD [16,17]. Complex cases of GTV delineation in lung cancer patients should always be discussed in a multi-disciplinary quality control meeting. Most clinical studies have used a visual interpretation technique, while others have reported the use of a range of...
automated segmentation techniques to either guide or generate the relevant target volume [18–21]. There is no clear consensus on which method most closely approximates to the tumor position and tumor edge, and pathological correlation has proven difficult [22]. Preoperative PET imaging shows a remarkably good correlation with resected pathological specimens [23], although it is acknowledged that those specimens are affected by processing artifacts. Most recent guidance advises the use of visual interpretation of the PET signal when drawing the final contour, even in cases where auto-contouring is used to generate an initial draft for editing, if PET is to be used to inform the target volume [17].

Factors causing IOV in TVD are variable interpretation of guidelines, lack of differentiation between normal structures and tumor, incorrect interpretation of radiological images, lack of knowledge in cross sectional radiological anatomy, and suboptimal imaging techniques e.g. lack of IV contrast [24–26]. The use of a rigorous contouring protocol in which clinicians follow a detailed set of instructions and the use of a teaching intervention may help in minimizing IOV [21,31,32,34,35]. To ensure adequate and reproducible visual interpretation and application of PET images for RTP, this procedure should be standardized. A recent publication provided guidance on the use and role of PET/CT imaging for RTP in NSCLC patient [17]. This study evaluates the impact on the use of these practical guidelines through active teaching using multiple training interventions involving multiple centers with minimal experience in PET/CT-based TVD.

### Methods

#### Target volume delineation assignments

PET/CT-based TVD was assessed through the use of repeated delineation assignments. In all contouring assignments a team consisting of a RO and a NMP were asked to delineate tumor volumes of primary tumor (GTV). Before the training, participants were asked to delineate as per their local delineation protocol and then again after the first training intervention according to a standardized delineation protocol [17]. Fully anonymized patient cases were used, including three dimensional FDG-PET and CT image data sets acquired for the purpose of radiotherapy planning. No intravenous contrast agent was used. Comprehensive case specific medical reports were included in all assignments to avoid bias due to incorrect diagnosis. An overview of the patient cases used during this training program is given in Table 1. In each case two senior ROs and a senior NMP delineated one reference ‘expert’ contour (GTVexp) in agreement in the absence of a histopathologically proven gold standard.

### Participants

The participants in this study were from eleven medical centers from nine different countries (Brazil, Estonia, India, Jordan, Pakistan, Poland, Turkey, Uruguay, and Vietnam). Each center was represented by a RO and a NMP. Before the training program centers were asked if they already performed PET/CT-based RTP. Five out of eleven centers already had limited experience in TVD with PET/CT. Other centers used PET/CT imaging for diagnostic and staging purposes only. Participants were not able to see delineations of other centers.

#### Big Brother target volume delineation software

Software developed in the Netherlands Cancer Institute, called Big Brother, was used throughout this multicenter study as platform for image viewing and analysis, and TVD in FDG PET/CT imaging [10]. As soon as the observer starts the Big Brother software and initiates TVD, any interaction with the software is recorded such as mouse motion, window/level and use of delineation tools. This feature allows visual inspection of strategies and comparison with expert contours to assess delineation accuracy.

#### Target volume delineation training program

The training program consisted of four contouring assignments, two training events and three additional clinical cases for practice (see Fig. 1). Contouring assignments 1 and 2 were performed before the first training event without the use of a standardized delineation protocol and were used as a baseline measurement. The first training event was face-to-face over a three-day period and included various lectures about relevant topics in nuclear medicine and radiation oncology and a delineation workshop on the use of PET/CT for RTP in NSCLC. The delineation workshop contained three more clinical cases which were again performed without the IAEA delineation protocol. The delineation protocol as described in the IAEA consensus document was introduced during the workshop [17]. The differences between the results and the IAEA protocol constituted the basis for a teaching discussion, consequently clarifying protocol ambiguities. More contouring assignments followed after this training to evaluate its impact on delineation accuracy and IOV. Contouring assignment 3 was performed three months after contouring assignment 2 and contained the same clinical cases. To allow the participants to practice more with the delineation protocol three additional clinical cases were added.

After results were obtained from the above described assignments, an interim analysis was performed with the aim of identifying difficult areas in TVD and to ensure delineation occurred

---

**Table 1** Sequence of events and characteristics of the included patients. Abbreviations: T = Primary tumor, N = Regional Lymph Nodes according to the 7th edition TNM classification.

<table>
<thead>
<tr>
<th>Case number</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Stage</th>
<th>Lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contouring Assignment 1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>IIB</td>
</tr>
<tr>
<td>Contouring Assignment 2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>IIIA</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>IIB</td>
</tr>
<tr>
<td>Training 1</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>IIIA</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>IIIB</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>IIIA</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>IIIB</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>IIIA</td>
</tr>
<tr>
<td>Contouring Assignment 3</td>
<td>Consisting of cases 3, 4 and 5 (repeat assignment)</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Practice</td>
<td></td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Training 2</td>
<td>Webinar/feedback reports</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Contouring Assignment 4</td>
<td>Consisting of cases 1, 6 and 7 (repeat assignment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
following the standardized approach. Detailed personal feedback reports were written with the aim of correcting misinterpretations of the delineation protocol and to advise on specific areas prone to deviation from the IAEA expert contour. This served as a preliminary to the webinar which was held as a second training event. An update on PET/CT-based TVD in RTP and general feedback was given in the webinar. Afterward the content was discussed with the group. As a final step participants performed contouring assignment 4 with three clinical cases, which they had performed earlier during the training program, eight months after the first training event.

Data analysis

To examine the impact of the training interventions the contours from the participants were analyzed. Various parameters such as the GTV size, miss of GTV\textsubscript{exp}, Concordance Index (CI) and surface mean distance were calculated, and also volumetric and 3-dimensional analysis was performed as described by Deurloo et al. [27]. The CI is defined as the intersection of two delineated volumes divided by their union:

\[
CI = \frac{(A \cap B)}{A \cup B}
\]

The CI can vary between 0 and 1 where 0 means there is a complete disagreement between the observers and a CI of 1 indicates a perfect agreement [28]. It was calculated for measuring the delineation accuracy relative to the expert contour (CI\textsubscript{expert}). Intragroup agreement (CI\textsubscript{group}) was also calculated using the surface median as a reference. The surface median was obtained as described by Rasch et al. [29]. The mean (absolute) surface distance between the observers’ GTV and expert GTV and the distance between each observers’ GTV and surface median were both calculated. For all parameters, the mean ± SD is reported unless stated otherwise. Wilcoxon’s signed rank tests were used to estimate the significance of any differences after the training events and p-values of 0.05 or less were considered significant.

Results

In all contouring assignments, teams were asked to delineate GTV of the primary tumor as per study protocol. One of the pairs with a RO, who was not board certified at the time of the training, was excluded from the analysis. After the first training event the overall CI\textsubscript{expert} slightly increased from 0.57 ± 0.07 to 0.66 ± 0.07. The mean CI\textsubscript{expert} and CI\textsubscript{group} per case are given in Fig. 2. Observer volumes were larger after the training and miss of GTV\textsubscript{exp} was significantly reduced from 127.32 ± 42.43 cc to 59.94 ± 48.94 cc. A detailed summary with p-values is given in Table 2. The overall mean surface distance and mean absolute surface distance compared to the reference contour decreased from -0.40 ± 0.03 cm to -0.01 ± 0.33 cm and from 0.47 ± 0.08 cm to 0.45 ± 0.17 cm respectively. The overall CI\textsubscript{group} decreased from 0.81 ± 0.07 to 0.75 ± 0.10.

After the second teaching event overall CI\textsubscript{expert} for another 3 repetitive cases increased from 0.64 ± 0.06 to 0.80 ± 0.05 (see Fig. 3 for more details). A reduction of GTV\textsubscript{exp} miss from

![Fig. 1. Schematic view of the training program. Over a one year period, 11 pairs of a radiation oncologist and a nuclear medicine physician performed four contouring assignments and three more cases for practice, and also attended two training events. Assessment 1, 2 and cases in Training 1 functioned as baseline measurements. Assessment 2 and 3 contained the same cases and results were compared to assess the impact of the first training event. Assessment 4 contained one case from Assessment 1 and two from Training 1 and the results were compared to assess the impact of the complete training.](image-url)

![Fig. 2. Delineation accuracy relative to expert versus intragroup with 95%-CI before and after Training 1 using a standardized delineation protocol. CI\textsubscript{group} = median concordance index between the observers’ GTV and the median surface contour. CI\textsubscript{expert} = median concordance index between the observers’ GTV and expert GTV.](image-url)
78.89 ± 22.95 cc to 42.86 ± 25.01 cc was observed, next to an increase in observer volume. Overall mean surface distances between observers and the expert contour decreased from 0.34 ± 0.16 cm to 0.05 ± 0.20 cm in overall mean absolute surface distance was observed. The overall CI_group increased from 0.80 ± 0.08 to 0.85 ± 0.08. Examples of improvement in IOV and delineation accuracy before and after the training program are given in Fig. 4 and in supplementary Fig. 1.

Discussion

Many studies have reported on the effect of guidelines or protocols and testing of the effect of specific teaching and measured contouring variability before and after an intervention [30]. This study is the first to report on the impact of a training program about the use of the recently published IAEA guidelines for PET/CT based radiotherapy planning in lung cancer patients in an international multicenter trial. To the best of our knowledge this
is the first study about the use of multiple teaching interventions using not only face-to-face training, but also providing an online learning platform in the form of a webinar which showed to play an effective role in harmonizing the delineation process globally. In terms of practicalities of delivering this type of training, the use of innovative technology such as the delivery of live webinars may significantly reduce cost without significantly reducing educational quality. Any economic assessment regarding the cost benefit ratio undertaking repeated tests of training exceeded the scope of this study.

Before any training was given, centers delineated their GTV based on local delineation protocols and thus a variety of approaches were observed. Results after the first training suggest that the use of a delineation protocol increased delineation accuracy, however a significant reduction in IOV and better adherence of the outlining protocol were only achieved through additional extended training.

A major contribution in reducing IOV may have been feedback participants received from the interim analysis that was performed before the second training intervention. While it is acknowledged that the cases selected for the practice case (see Table 1) may have been more challenging to delineate than the test cases, the use of these helped identify several areas that caused difficulty in TVD for the participants. These areas of variation included atelectasis, PET window level settings, nearby normal structures (e.g. pulmonary veins or arteries) that were seen as tumor, and/or suspicious areas on CT showing low FDG uptake. These areas of variation were documented in the individual feedback reports, and were also included in the general feedback and discussed during the webinar. This may have contributed to the significant impact on delineation accuracy seen in the last assignment. This emphasizes the importance of additional training events to correct errors in delineation still occurring after the first training. Schimek-Jasch et al. found out that the use of a dummy-run and study group meetings as part of Quality Assurance (QA) in multicenter clinical trials helps to identify misinterpretations of a standardized delineation method which helped in reducing IOV [32]. However, the outcome of that study did not show a significant effect which may underline the take-home message of our study that changing behavior requires multiple and multi-faceted interventions. Lack of other studies investigating the impact of multiple training interventions in TVD makes comparison of outcomes difficult. Further studies with more observers would be needed to validate the results in this study. Currently the IAEA conducts a multicenter international study investigating the impact of blended distance learning (with additional training interventions) in the field of RT contouring on quality of delineation (CRP E33040).

Several studies concluded that the use of a standardized delineation protocol helps in decreasing IOV [31,32,34] and our results concur with that. There was a non-significant increase in IOV seen after the first training event, however a decrease was noted after the complete training program. In spite of the first training, visual inspection with Big Brother showed that some observers misinter-

![Fig. 4. Results from contouring the GTV in case 6 before (top images) and after (bottom images) the complete training. From left to right an image slice in the axial plane from CT, PET, and a 3D model of the expert contour with mean surface distance errors projected (from blue to red, corresponding with a mean absolute surface distance of 0 to > 1 cm). The bold red line represents the GTVexp.](image-url)
repeated assignments. Not all cases in Training 1 were suitable for inclusion in Assessment 4 due to the small tumor size in case 8 and therefore one case of the first assignment (case 1) had to be included. It is acknowledged that observers were less familiar with the software in the beginning than later in the training program, however the delineation software is similar to any other delineation tool used in clinic and it is hypothesized that if there is any learning effect present, this only has an impact on the delineation speed. Above that, a similar increase is seen in all cases after the complete training suggesting that the learning effect of the delineation software was negligible (see Fig. 3).

Spoelstra et al. had seen that a significant IOV in contouring confounded interpretation of post-operative radiotherapy and concluded that Quality Assurance (QA) procedures would need to be incorporated to tackle this problem [34]. A German multicenter PET study also covered a similar interesting topic i.e. harmonization of diagnostic viewing and reporting and also outlined the importance of QA [35]. They concluded that a structured interventional harmonization process significantly improved the IOV in their expert panel. However, no focus had been given on target volume delineation. In our study, additional training led to an increased delineation accuracy and decreased the IOV. In clinic, the IOV should also be assessed in order to see if it is necessary to provide more training in order to achieve reproducible results among ROs. Therefore it is recommended that assessment of IOV should be performed frequently next to having multi-disciplinary quality control meetings as part of the QA on TVD.

A study examining the influence of experience and qualification in PET based TVD concluded that IOV may be dependent on qualification, but not on years of experience [16]. It is known that some centers already had minimal experience in PET/CT-based TVD and that there were centers with no experience in this field. However, no significant difference in performance was seen after comparison of inexperienced versus minimal experienced participants.

Conventional 3-dimensional PET/CT imaging was chosen as the modality for TVD, since not all participants in the study had experience in PET/CT-based radiotherapy planning in NSCLC patients. The impact of 4-dimensional PET/CT has not been investigated and may be of interest to further increase accuracy. Furthermore, if a PET/CT acquired for diagnostic or staging purposes is used to inform the TVD process, care must be taken when registering a diagnostic PET/CT with a planning CT. Guidance regarding this has been described in the IAEA study protocol [17].

Conclusion

ROs and NMPs with limited experience in PET/CT-based TVD for lung cancer benefit significantly from receiving multiple training interventions with a standardized delineation protocol. Future research within a larger population should validate the results in this study to provide more evidence on the impact of multiple training interventions about PET/CT-based TVD for NSCLC.

Conflict of interest

None to declare.

Acknowledgements

The authors would like to thank Heloisa Carvalho and Paolo Duarte (Instituto do Câncer do Estado de São Paulo), Camilla Mosci and Carlos Zuliani (Hospital das Clínicas UNICAMP), Darja Altuhhova and Liina Karusoo (North Estonia Medical Center), Rakesh Kapoor and Ashwani Sood (Postgraduate Institute of Medical Education and Research), Jamal Khader and Akram Al-Ibraheem (King Hussein Cancer Center), Shahid Abubaker and Muhammad Numair
Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2016.09.002.

References