A traffic light protocol workflow for image-guided adaptive radiotherapy in lung cancer patients

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Abstract

Background and purpose: Image-guided radiotherapy using cone beam-CT (CBCT) images is used to evaluate patient anatomy and positioning before radiotherapy. In this study, we analyzed and optimized a traffic light protocol (TLP) used in lung cancer patients to identify patients requiring treatment adaptation.

Materials and methods: First, CBCT review requests of 243 lung cancer patients were retrospectively analyzed and divided into 6 pre-defined categories. Frequencies and follow-up actions were scored. Based on these results, the TLP was optimized and evaluated in the same way on 230 patients treated in 2018.

Results: In the retrospective study, a total of 543 CBCT review requests were created during treatment in 193/243 patients due to changed anatomy of lung (24%), change of tumor volume (24%), review of match (18%), shift of the mediastinum (15%), shift of tumor (15%) and other (4%). The majority of requests (474, 87%) did not require further action. In 6% an adjustment of the match criteria sufficed; in 7% treatment plan adaptation was required. Plan adaptation was frequently seen in the categories changed anatomy of lung, change of tumor volume and shift of tumor outside the PTV. Shift of mediastinum outside PRV and shift of GTV outside CTV (but inside PTV) never required plan adaptation and were omitted to optimize the TLP, which reduced the CBCT review requests by 23%.

Conclusions: The original TLP selected patients that required a treatment adaptation, but with a high false positive rate. The optimized TLP reduced the amount of CBCT review requests, while still correctly identifying patients requiring adaptation.

Image-guided radiotherapy (IGRT) using cone-beam CT (CBCT) imaging allows for precise patient set-up procedures to assure correct alignment of the patient on the linear accelerator [1,2]. CBCT imaging may also detect anatomical changes that could lead to a clinically relevant over-dosage to an organ at risk (OAR) or under-dosage of the planning target volume (PTV) that requires treatment adaptation, i.e. adaptive radiotherapy [3].

Anatomical changes observed during the course of radiotherapy treatment of lung cancer, such as changes in tumor volume, changes in anatomy of the lung (e.g., atelectasis, pleural effusion), or a shift of the tumor, have been analyzed in previous studies [4–9]. Since predicting which patients will exhibit these changes is difficult, regular imaging to monitor patient anatomy is performed during treatment.

The identification of patients with anatomical changes that require adaptation is not always straightforward. Action level-based decision support systems, like traffic light protocols (TLPs), could guide radiotherapy technicians (RTTs) in their response to observed anatomical changes. A limited number of studies have demonstrated the use of TLPs to select lung cancer patients for adaptive re-planning during radiotherapy in clinical practice [10,11]. However, these TLPs have not been optimized for efficiency or prospectively evaluated.

A TLP for lung cancer patients was implemented in our clinic in 2015. The aim of this study was to investigate the efficiency of this protocol by quantifying frequency and reasons for adaptation. Opportunities to optimize the protocol were investigated and evaluated prospectively.

Materials and methods

Patient, treatment and imaging characteristics

Lung cancer patients treated between July 2016 and June 2017 (n = 243) were included in this study. Fractionation schedules for non-small cell lung cancer (NSCLC) were 60–66 Gy in 30–33 fractions for concurrent chemoradiotherapy, 55–66 Gy in 20–24 frac-
tions for sequential chemo-radiotherapy and 45 Gy in 30 twice daily fractions for small cell lung cancer (SCLC). The imaging procedure for online patient set-up consisted of a daily 3DCBCT (Varian TrueBeam, Varian Medical Systems, Palo Alto, CA) that was registered with the planning-CT scan based on the match instruction indicated by the radiation oncologist. This match instruction depended on the location and expanse of the primary planning target volume (PTVp) and/or nodal planning target volume (PTVn) and could be to align based on the bony anatomy (extensive or multiple target volumes), the primary tumor (only PTVp), the carina (only PTVn, or both PTVp and PTVn), or the spinal canal (target volume close to the spinal cord). See Supplementary Table 1 for more detailed planning and treatment characteristics [12–14].

Fig. 1. The adaptation protocol. The online TLP generates CBCT review requests that are reviewed offline to determine the correct follow-up action. TLP: traffic light protocol, CBCT: cone beam-CT, EPR: Electronic Patient Record, DGRT: Dose guided radiotherapy.

Table 1
Criteria of the three classifications (Green, Orange and Red) in the online traffic light protocol for the original TLP and the optimized TLP. Date in brackets indicate the time period of each TLP. Selection is based on visual evaluation by the RTT at the treatment machine. PRV: planning risk volume, CTV: clinical target volume, PTV: planning target volume, TLP: Traffic Light Protocol.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria to evaluate the CBCT</th>
<th>Original TLP (1-9-2015 to 31-12-2017)</th>
<th>Optimized TLP (1-1-2018 to 31-12-2020)</th>
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<tbody>
<tr>
<td>Code Green</td>
<td>Deviation of bony anatomy of less than 5 mm around the target volume, the visible tumor is within the CTV, no change of anatomy of the lung (e.g., no change in atelectasis or pleural effusion), no change in tumor volume, mediastinum (near tumor/nodes) inside PRV (i.e., mediastinum expanded by 5 mm). Depending on registration method.</td>
<td>Deviation of bony anatomy of less than 5 mm around the target volume, the visible tumor is within the PTV, no change of anatomy of the lung (e.g., no change in atelectasis or pleural effusion), no change in tumor volume, Depending on registration method. carina inside PRV (carina expanded by 2 mm), spinal cord is located outside the critical isodose structure (54 Gy).</td>
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<tr>
<td>Code Orange</td>
<td>Deviation of bony anatomy of more than 5 mm around the target volume. Partly changed anatomy of lung (e.g., atelectasis or pleural effusion), changed tumor volume, shift of tumor outside CTV but inside PTV, shift of mediastinum (near tumor/nodes) outside the PRV (mediastinum +5 mm). Depending on registration method. carina outside PRV (carina expanded by 2 mm).</td>
<td>Deviation of bony anatomy of more than 5 mm around the target volume. Partly changed anatomy of lung (e.g., atelectasis or pleural effusion), changed tumor volume, Depending on registration method. carina outside PRV (carina expanded by 2 mm).</td>
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<tr>
<td>Code Red</td>
<td>Shift of tumor outside the PTV, tumor not visible, complete regression, complete change of anatomy of the lungs (e.g., atelectasis, pleural effusion). Depending on registration method. spinal cord is located inside the critical isodose structure (54 Gy)</td>
<td>Shift of tumor outside the PTV, tumor not visible, complete regression, complete change of anatomy of the lungs (e.g., atelectasis, pleural effusion). Depending on registration method. spinal cord is located inside the critical isodose structure (54 Gy)</td>
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is a code red or for other situations not indicated in the TLP (e.g., review of match, patient specific problems etc.).

CBCT review requests were evaluated offline by a radiation oncologist, RTT and/or medical physicist specialized in lung cancer treatment before the next fraction of the patient’s treatment. The CBCT images were registered with the corresponding planning-CT during treatment and could be re-evaluated in dedicated software (Offline review v11.0–15.1, Varian Medical Systems). A dose recalculation in Eclipse on the CBCT (calibrated for accurate CT number and dose calculation) allowed for visual evaluation of potential under- and over-dosage of the PTV and OAR, respectively [15]. For this, the treatment plan and the corresponding structure set were copied to the CBCT using the rigid registration between planning-CT and CBCT (Supplementary Fig. 1). Dose recalculation was performed for a worst-case scenario (all fractions on this CBCT) and was evaluated at the discretion of the radiation oncologist. Dose recalculations were not performed systematically but estimated by the radiation oncologist.

A radiation oncologist determined how to proceed with the treatment, combining visual and dosimetric data, also taking into account the time of occurrence within the treatment. For severe changes in plan quality, e.g., exceeding of the maximum dose in serial OAR structures, e.g., the spinal cord (>54 Gy), the mediastinal envelope (>66 Gy or >76 Gy), the brachial plexus (>76 Gy) and/or loss of target volume coverage (<93% for the CTV) a plan adaptation was necessary to ensure an adequate dose distribution for the remaining fractions of the radiotherapy course. A new 4D planning-CT scan was acquired and a new treatment plan was made. Meanwhile, the patient could continue treatment on the current treatment plan or the treatment was temporarily paused until the new treatment plan was ready, this was decided by the radiation oncologist. When plan adaptation was required, patients could start within 1 or 2 days after they were selected by the TLP.

To ensure the quality of the TLP a sample test was done every quarter. For a selection of patients all rigid registrations and TLP outcomes (green, orange, red) of the entire treatment were retro-
spectively checked. Feedback was given to the RTTs working on the treatment machine regarding the results and points of improvement.

Analysis

The aim of the TLP was to identify patients that require an adaptation of the treatment plan (true positives), however, the TLP also selected some patients which did not need an adjustment (false positives). To evaluate the effectiveness of the adaptive protocol the classifications and frequencies of the CBCT review requests and their follow-up actions were determined. All available CBCT review requests were classified in the categories: shift of the mediastinum outside its planning risk volume (PRV, the mediastinum with a 5 mm expansion), shift of tumor outside the clinical target volume (CTV, inside PTV or outside PTV), changed anatomy of the lungs (e.g., atelectasis, pleural effusion), change of tumor volume (tumor regression, tumor progression), review of match (e.g., match criteria was adjusted and the RTT wants to be sure the match was executed correctly, other things RTTs want to have checked) and other (positioning issues, poor tumor visibility). For every CBCT review request, the follow-up action was determined. Follow-up actions were classified as: no action required, review after N fractions (typically 5 fractions), adjustment of match criteria, or plan adaptation.

Optimization and evaluation

In January 2018, the TLP was optimized based on the results of the previous period by eliminating criteria that did not identify patients for plan adaptations. This optimized TLP was evaluated in the same manner on all patients treated in our institute in 2018 with identical inclusion criteria (n = 230). Statistical significance was tested with a Chi Square test (IBM SPSS Statistics for Windows, version 26, IBM Corp., Armonk, NY, USA).

Results

In the retrospective analysis, a total of 243 lung cancer patients were included and 6369 treatment fractions were evaluated using the daily CBCT acquired on the treatment machine. Of these patients, 21% (50/243) did not receive a CBCT review request during the entire treatment (all CBCTs were coded green). For the other 79% (193/243) of the patients, a CBCT review request was created at least once during treatment, resulting in a total of 543 reviewed treatment fractions. The total amount of CBCT review requests per patient ranged from 0 to 12, and was on average 2 (Supplementary Fig. 2). The majority of the CBCT review requests, 97% (525/543), was classified as code orange, and a minority, 3% (18/543), was classified as code red. The distribution of CBCT review requests during the course of treatment showed that most requests were generated in the beginning of the treatment. Ten percent (55/543) of the CBCT review requests was created at the first fraction of the treatment. While most categories decreased during treatment, change of tumor volume occurred more often in the middle of the treatment (Fig. 2).

Table 2 gives an overview of the different categories, follow-up actions and dose recalculations. CBCT review requests were mostly caused by changed anatomy of lung (24%, 133/543), change of tumor volume (24%, 131/543), and review of match (18%, 96/543). For the majority of the CBCT review requests, a visual inspection of the image registration and anatomical changes by a radiation oncologist was sufficient. In 30% (161/543) a dose recalculation was requested to gain additional insight of the effect of the visible change on the dose distribution. Dose recalculations were required predominantly for cases of tumor regression (42%, 68/161) and changed anatomy of lung (39%, 62/161).

The majority of the CBCT review requests was classified as not clinically relevant by the treating radiation oncologist (68%, 370/543). Anatomical deviations were negligible, not located near the target volume or not expected to cause a change in the dose distribution, therefore no further action was required.
For 19% (104/543), the reported anatomical changes were substantial (tumor shifts, partly changed atelectasis, change of tumor volume). No immediate action was needed but patients were re-evaluated after a certain number of fractions (i.e., amount of fractions determined by the treating radiation oncologist). Typically, the patient’s anatomy was re-evaluated after five fractions. In the meantime, RTTs at the treatment machine would accept the visible change and send a new CBCT review request at the specified fraction unless it would progress to a code red. This follow-up action was mostly seen in the categories changed anatomy of lung (40/104) and changed tumor volume (35/104).

An adjustment of the patient online positioning criteria was applied in 6% (30/543) of the CBCT review requests and was mostly seen in the categories shift of tumor and review of match. The adjustment consisted mostly of a transfer from a carina match to bony anatomy match or a mediation between two criteria indicating matching problems when dealing with multiple target volumes.

Plan adaptation was required in 7% (39/543) of the CBCT review requests. The plan adaptation could either be a new treatment plan (34/39), a reduction of the total number of fractions by omitting the final fraction (4/39) or other (1/39). Five patients had their plan adapted twice during treatment. The majority of plan adaptations was due to a change in tumor volume (12/39, 2/12 tumor progression, 10/12 tumor regression) or changed anatomy of lung (14/39). The category shift of tumor outside the PTV was very efficient at selecting patients that required adaptation. Due to involved node stations these patients were matched on bony anatomy or the carina to ensure good coverage for both nodes and primary tumor. Plan adaptation was required in 80% (8/10) of the CBCT review requests in this category. The majority of CBCT review orders classified as a code red (18/543) required a plan adaptation (13/18). An overview of the plan adaptations during treatment is given in Fig. 2.

The categories mediastinum outside PRV and shift of tumor outside CTV but within the PTV accounted for 15% (79/543) and 13% (73/543) of all CBCT review requests, respectively, but they did not select any patients that required a plan adaptation (Fig. 3). The majority of reported shifts of the mediastinum was evaluated as minor and clinically not relevant according to the radiation oncologist (97%, 77/79). The same applied to shifts of the tumor outside of CTV but inside PTV (subgroup shift of tumor) where in 89% (65/73) no action was taken. Evaluation of these shifts was mostly based on visual inspection by a radiation oncologist since a dose recalculation was only performed six times in each category indicating that the perceived shift was evaluated as minor and not relevant. Omitting these two categories from the TLP could lead to a reduction of CBCT review requests of 28% (152/543).

The results of this study lead to the optimization of the original TLP. Criteria that did not identify patients for plan adaptation were removed, i.e., the mediastinum outside PRV and shift of tumor outside CTV but within the PTV. The optimized TLP (Table 1) was clinically implemented in January 2018 and re-evaluated after 12 months. Evaluation of the optimized group showed a reduction of CBCT review requests of 23% (Table 3). The fraction of plan adaptations and adjustment of match criteria per patients treated remained similar (32/230 versus 39/244). A significant increase of 10% was seen in the category Review of match. Within this category CBCT orders for mediastinum outside PRV and shift of tumor outside CTV were reported 2 and 16 times respectively, but did not lead to a plan adaptation.

**Fig. 3.** Distribution of follow-up actions. Relative number of follow-up actions per CBCT review request category and distribution of CBCT review requests follow-up actions over the course of treatment. CBCT: cone beam-CT, GTV: gross tumor volume, CTV: clinical target volume, PTV: planning target volume, PRV: planning risk volume.
Discussion

Our analysis showed that a TLP can serve as a selection tool to identify patients that might require a plan adaptation. In the original TLP, the false positive rate turned out high since only a subgroup of the CBCT review requests selected by the TLP led to a re-planning (7%) or adjustment of the match criteria (6%). Only 14% of the patients (34/243) had their treatment plan adapted. This indicates that the currently used PTV margins ($\geq$8 mm) ensure robust treatment plans that account for the majority of changes that occur during treatment. Decreased PTV margins could potentially lead to lower toxicities but are expected to require a higher treatment plan adaptation rate [16]. Plan adaptation was mostly required in patients with severe changes in lung anatomy (atelectasis, pleural effusion) or shifts of the tumor outside the PTV that induced too much loss of tumor coverage. In patients with tumor regression, plan adaptation was mostly necessary to limit the maximum dose in a serial OAR.

The criteria in the original TLP were very extensive to ensure that all possible anatomical deviations were covered. Therefore, the false negative rate of the TLP was anticipated to be low. This led to a high workload of CBCT review requests that needed offline review. By omitting the criteria that did not select patients requiring adaptation (mediastinum outside PRV, shift of tumor outside CTV but inside PTV), the number of CBCT review requests decreased by 23%, decreasing the workload both online (creating CTV but inside PTV), the number of CBCT review requests needed for re-planning. By omitting the criteria that did not select patients requiring plan adaptation, the false negative rate of the TLP was anticipated to be low. This indicates that the currently used PTV margins ($\geq$8 mm) ensure robust treatment plans that account for the majority of changes that occur during treatment. Decreased PTV margins could potentially lead to lower toxicities but are expected to require a higher treatment plan adaptation rate [16].

Table 3

| Table 3 | Number of patients treated, CBCT review requests and plan adaptations before and after TLP optimization. P-values show significance between Original TLP and Optimized TLP (1-1-2018 to 31-12-2018). Note that plan adaptations can occur multiple times within a single patient. TLP: traffic light protocol, CBCT: cone beam-CT. |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | Original TLP (1-7-2016 to 30-6-2017) | Adjustment of match/Adaptation | Optimized TLP (1-1-2018 to 31-12-2018) | Adjustment of match/Adaptation | p-value | Optimized TLP (1-1-2019 to 31-12-2019) | Adjustment of match/Adaptation | Optimized TLP (1-1-2020 to 31-12-2020) | Adjustment of match/Adaptation |
| Total patients treated | 243 | 230 | 261 | 0.077 | 314 (67%) | 228 (71%) | 471 | 318 |
| Total CBCT review requests | 543 | 418 | 471 | 0.205 | 96 (20%) | 60 (19%) | 11 (4%) |
| No action required | 370 (68%) | 262 (63%) | 314 (67%) | 0.077 | 314 (67%) | 228 (71%) | 471 | 318 |
| Review after N fractions | 104 (19%) | 94 (22%) | 96 (20%) | 0.205 | 96 (20%) | 60 (19%) | 11 (4%) |
| Adjustment of match criteria | 30 (6%) | 30 (7%) | 22 (5%) | 0.294 | 22 (5%) | 11 (4%) |
| Plan adaptation | 39 (7%) | 32 (8%) | 39 (8%) | 0.781 | 39 (8%) | 19 (6%) |
| Changed anatomy of lung | 133 (24%) | 170 (41%) | 184 (39%) | 0.000 | 184 (39%) | 115 (36%) | 2/19 | 115 (36%) | 19 (6%) |
| Changed tumor volume | 131 (24%) | 1/2 | 100 (24%) | 1/2 | 4/7 | 136 (29%) | 3/6 | 98 (31%) | 1/5 |
| Shift of tumor outside CTV | 73 (13%) | 8/0 | – | – | – | – | – | – | – |
| Shift of tumor outside PTV | 10 (2%) | 1/8 | 9 (2%) | 1/8 | 4/5 | 13 (3%) | 3/6 | 12 (4%) | 6/4 |
| Mediastinum outside PRV | 79 (15%) | 2/0 | – | – | – | – | – | – | – |
| Review of match | 96 (18%) | 14/2 | 116 (28%) | 14/2 | 105 (22%) | 10/4 | 83 (26%) | 3/1 |
| Other | 21 (4%) | 1/3 | 23 (6%) | 4/2 | 0.229 | 33 (7%) | 4/4 | 10 (3%) | 0/0 |

*In 2020 the total number of patients treated was smaller compared to the other years, this was due to the introduction of proton therapy at our clinic and these patients followed a different adaptive protocol. In 2020 69 lung cancer patients were treated with protons and were not included in this study.*
action levels selected by their TLP in clinical practice. Only a small subgroup (13%) required a plan adaptation, which was similar to the number of patients requiring an adaptive plan in our analysis. In the prospective study of Müller et al. [10], the number of patients requiring re-planning was 27%. They used different match procedures and other margins, which could have an influence on the adaptation rate in the individual populations.

Currently, a limited set of (objective) tools is available to decide the correct follow-up action. CBCT dose recalculations are a step in the right direction, but decisions are still very much depending on visual interpretations and the experience of the treating radiation oncologist. There are no strict criteria (e.g., in which situation a dose calculation is required, what the acceptance limit is for dose deviation, the relevance in relation to the point of time during treatment) that help specialists in determining the correct follow-up action and do this in a uniform manner. More research on the clinical relevance of anatomical changes should be performed to investigate when treatment adaptation is indicated. More accurate information of the actual dose delivered for a given fraction could help establish better decision making criteria in clinical practice. Developments in the field of automatic contouring, deformable registration, synthetic CT, dose summation and automatic planning play a role in simplifying and improving this decision making process by providing quicker and more accurate information about the dose distribution [19–23].

Conclusion

The criteria used in the TLP are able to select patients that require treatment plan adaptation. However, the number of false positives is high and this leads to a high workload. Changes in anatomy of lung, tumor regression and a shift of the GTV outside of the PTV are the predominant causes that require plan adaptation. The criteria mediastinum outside PRV and GTV outside CTV of the PTV are the predominant causes that require plan adaptation. However, the number of false positive interpretations and the experience of the treating radiation oncologist. There are no strict criteria (e.g., in which situation a dose calculation is required, what the acceptance limit is for dose deviation, the relevance in relation to the point of time during treatment) that help specialists in determining the correct follow-up action and do this in a uniform manner. More research on the clinical relevance of anatomical changes should be performed to investigate when treatment adaptation is indicated. More accurate information of the actual dose delivered for a given fraction could help establish better decision making criteria in clinical practice. Developments in the field of automatic contouring, deformable registration, synthetic CT, dose summation and automatic planning play a role in simplifying and improving this decision making process by providing quicker and more accurate information about the dose distribution [19–23].

Conflict of interests

Authors did not report any conflict of interests.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.08.030.

References