



The importance of quality and consistent target volume definition in the treatment of locally advanced non-small cell lung cancer

Shahed N. Badiyan, Michael C. Roach, Gregory Vlacich, Cliff G. Robinson, Jeffrey D. Bradley

Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO, USA

Correspondence to: Shahed N. Badiyan, MD. 4921 Parkview Place CAM LL, St. Louis, MO 63110, USA. Email: sbadiyan@wustl.edu.

Comment on: Nestle U, De Ruyscher D, Ricardi U, *et al.* ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer. *Radiother Oncol* 2018;127:1-5.

Received: 07 August 2018; Accepted: 17 August 2018; Published: 04 September 2018.

doi: 10.21037/tro.2018.08.05

View this article at: <http://dx.doi.org/10.21037/tro.2018.08.05>

Introduction

The Advisory Committee on Radiation Oncology Practice (ACROP) of the European Society for Radiotherapy and Oncology (ESTRO) has developed a number of high quality radiation oncology practice guidelines since its inception in 2012 (1-6). Recently, the committee published an excellent set of guidelines focused on target volume definition in the treatment of locally advanced non-small cell lung cancer (NSCLC), an area in which there is considerable variability in practice (7). This article aims to comment on data behind the key elements of this guideline and the future direction of radiation therapy (RT) treatment planning for locally-advanced NSCLC.

RT guidelines such as those published by the ESTRO ACROP committee are vital publications in the field of radiation oncology as they guide those in practice to apply quality, consistent, evidence-based procedures to improve patient outcomes. A number of studies have been published in recent years highlighting the importance of consistent quality of RT and its relation to patient outcomes. Ohri *et al.* performed a secondary analysis of eight RT clinical trials in which quality assurance (QA) deviations and disease control and survival outcomes were measured. They found that RT QA deviations were common, occurring from 8% to 71% (median 32%) of prescribed treatments, and were associated with a significant decrease in overall survival (HR =1.74, 95% CI: 1.28 to 2.35; P<0.001) and treatment failure (HR =1.79, 95% CI: 1.15 to 2.78; P=0.009) (8). An analysis of the Radiation Therapy Oncology Group (RTOG) 0617 phase III trial investigating radiation dose escalation for locally advanced NSCLC found that patients

treated at high-volume centers (those enrolling 4 to 18 patients to the trial) had significantly longer overall survival compared to patients treated at low-volume centers (1-3 enrolled patients) (median 26.2 *vs.* 19.8 months; P=0.002). In addition, patients treated at high-volume centers were more likely to receive intensity modulated radiation therapy (IMRT) and had significantly lower mean esophageal doses and heart V5 and V50. There were trends for fewer grade 5 adverse events and RT terminations due to adverse events in patients treated at high-volume centers. On multivariable analysis, treatment at a high-volume center remained significantly associated with overall survival (9). These studies are evidence that the quality of the RT plan and the experience of the cancer center impact clinical outcomes.

Evidence-based guidelines such as the ESTRO ACROP guideline for locally advanced NSCLC are important tools to improve RT quality. The ESTRO ACROP committee made a number of consensus recommendations for treatment planning and delivery. We will briefly discuss these recommendations as they pertain to imaging, target volume delineation, and motion management.

Imaging

Similar to ongoing clinical trials, the committee mandates a diagnostic positron emission tomography/computed tomography (PET-CT) for staging purposes. Interestingly, the committee recommends a specific planning-PET-CT in the RT planning position and recommend that imaging studies not obtained in the planning position not be co-registered with the planning CT due to concerns for

misregistration. Although misregistration is a possibility, software solutions have greatly improved in recent years and can perform high quality deformable or non-deformable image registrations with excellent reliability (10). In addition, in some countries such as the United States, the cost of a repeat PET-CT for the purpose of RT planning is not typically reimbursed by insurance companies, reducing the likelihood that they can be performed. The guidelines also leave optional the use of a 4D PET-CT which is not yet widely utilized in most practices but can potentially help to distinguish between tumor and adjacent soft tissues or atelectasis.

Target volume delineation

The delineation of target volumes for locally advanced lung cancer have been refined significantly over the last three decades as improved understanding of patterns of failure and technological improvements have become adopted. PET-CTs have greatly improved staging (11), elective lymph node irradiation is no longer recommended due to increased toxicity risk and marginal tumoricidal benefits (12,13). Technologies such as image-guided radiation therapy (IGRT), IMRT, and particle therapy have allowed for an increase in dose conformality and a shrinking in target volumes (14). Nevertheless, there is still variability in the creation of target volumes amongst radiation oncologists and cooperative groups. In the ongoing cooperative group phase III clinical trial for locally advanced NSCLC, RTOG 1308, enlarged (≥ 1 cm) or smaller but clinically suspicious PET-negative lymph nodes are to be included in the gross tumor volume (GTV). Within the ESTRO ACROP guidelines, the committee goes into more detail regarding suspicious lymph nodes recommending that, although it is not mandatory to include enlarged PET-negative lymph nodes in the GTV, physicians should err on the side of over-including lymph nodes when there is uncertainty. For example, the committee recommends that PET positive lymph nodes should always be included unless definitive biopsy results via mediastinoscopy (but not endobronchial ultrasound due to its high false negative rate) show evidence of lack of malignancy in the lymph node (15).

The phase III LungART trial evaluating the benefit of post-operative RT for completely resected NSCLC with mediastinal nodal involvement mandates inclusion of the tumor bed, bronchial stump, ipsilateral hilar and level 4 as well as the level 7 lymph node stations in the clinical target volume (CTV). They also recommend inclusion of one

lymph node station above and below each of the involved mediastinal lymph node stations and every station lying in between the involved stations. The ESTRO ACROP committee recommends a slightly simplified version consisting of a CTV that includes the resected involved anatomical mediastinal lymph node stations, the bronchial stump, the ipsilateral hilum and nodal stations 4 and 7.

Motion management

The guidelines also provide valuable direction on the creation of a planning target volume (PTV). They provide three strategies for the motion-related uncertainties of the PTV. The first is to create an internal target volume (ITV) by including all CTV positions during the breathing cycle on a 4D-CT per International Commission on Radiation Units & Measurements (ICRU) 62. However, since it is not possible to visualize motion of microscopic disease encompassed by the CTV, pragmatic deviations from the ICRU 62 definition have been used. For example, RTOG 0617 planning guidelines instead defined the ITV as an envelope that encompasses the GTV motion for a complete respiratory cycle, then expanded the ITV by 0.5 to 1 cm to form a CTV. The ongoing trial RTOG 1308 redefines the classic ITV structure as iGTV then expands by 8 mm (without extending into uninvolved organs such as the esophagus, heart, or bone) to create a CTV.

The ESTRO ACROP guideline's second strategy is to use a mid-ventilation or mid-position approach that then integrates tumor motion from a 4D-CT into the van Herk statistical PTV margin (16). Their third strategy is application of respiratory-synchronized techniques such as gating or tracking, with use of system-specific PTV margins according to departmental definition. Gating on conventional linear accelerators based on external or internal surrogates (17) and gating with continuous MRI tracking of the tumor itself (18,19) both potentially allow for smaller volumes of normal lung to be treated at the cost of extending the duration of each treatment.

In addition to the respiratory motion uncertainties of the PTV margin, the guidelines recommend that each individual department should quantify residual set-up positioning errors based upon department specific positioning and image guidance policy. RTOG 0617 was more specific stating that if an ITV approach is used for planning, the PTV margin could be reduced to 0.5 cm if daily imaging is used to align the vertebral bodies. If daily imaging is not done with an ITV approach, RTOG 0617

stated that the PTV margin should not be less than 1 cm. It should be noted that regardless of the strategy, these guidelines recommend against manual editing of the PTV contour.

The future of RT treatment planning for NSCLC may be largely shaped by advances in planning software. The introduction of artificial intelligence learning algorithms, such as knowledge-based treatment planning, into the plan generation process has the potential to improve RT treatment planning for complex target volumes such as locally advanced NSCLC by consistently creating superior radiation plans more efficiently than manually generated plans. Consistent contouring of target volumes is essential for the implementation of these next-generation planning solutions to allow for more efficient automation and quality control of individual treatment plans. Knowledge-based RT planning is a novel method that has been shown to create IMRT plans for locally-advanced NSCLC that on-average have improved target coverage (PTV V100, PTV max dose) and reduced doses to organs at risk (decreased cord max and esophagus mean dose) compared to manually developed treatment plans (20), and may potentially help to select patients more likely to benefit from advanced technologies such as particle therapies (21).

Conclusions

The quality of radiation planning has been shown to be associated with clinical outcomes. Treatment planning guidelines such as the ESTRO ACROP target volume guideline for locally advanced NSCLC are important and useful tools to improve the consistency and quality of RT treatment planning and may better allow for the implementation of more automated treatment planning processes to further enhance RT treatment plans.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Chun-Ru Chien (Department of Radiation Oncology, China Medical University Hospital, China Medical University, Taiwan).

Conflicts of Interest: The authors have no conflicts of interest

to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/tro.2018.08.05

Cite this article as: Badiyan SN, Roach MC, Vlacich G, Robinson CG, Bradley JD. The importance of quality and consistent target volume definition in the treatment of locally advanced non-small cell lung cancer. *Ther Radiol Oncol* 2018;2:35.