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STUDY PROTOCOL

Development of a deep neural network derived from contours defined by consensus-based guidelines for automatic target segmentation in hepatocellular carcinoma radiotherapy: A study protocol [version 1; peer review: 1 approved, 1 approved with reservations]

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V1 First published: 01 Nov 2017, 6:1929
<https://doi.org/10.12688/f1000research.12892.1>

Latest published: 01 Nov 2017, 6:1929
<https://doi.org/10.12688/f1000research.12892.1>

Abstract

Hepatocellular carcinoma (HCC) is a leading cause of cancer death in China and around the world. Tumoricidal doses of modern radiation therapy (RT) can now be safely delivered with excellent local control and minimal toxicity. Delivering adequate doses of radiation to the primary tumor, while preserving adjacent healthy organs, depends on accurate target identification.

In recent years, different novel machine learning techniques, including artificial intelligence technology, have been exploited in RT with impressive results in automatic image segmentation. If the machine learning algorithms are trained on delineated contours, according to consensus contouring guidelines, it promises greatly reduced interobserver and intraobserver variability in target delineation, thus substantially improving the quality and efficiency of HCC radiotherapy.

This study protocol proposes to develop a fully-automated target structure contouring system, which is based on deep neural networks trained on contours delineated according to consensus contouring guidelines in HCC radiotherapy. In addition, the study will evaluate the contouring system's feasibility and performance during application in normal clinical operations. The study is ongoing (data analysis).

Keywords

hepatocellular carcinoma, radiation therapy, artificial intelligence, automatic target segmentation, deep neural network

Open Peer Review

Approval Status

	1	2
version 1
01 Nov 2017	view	view

1. **Laura A. Dawson**, University Health Network, Toronto, Canada
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Author roles: **Zhao J:** Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Wang J:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Software, Writing – Review & Editing; **Cheng M:** Conceptualization, Methodology, Project Administration, Resources, Software, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This study is funded by Shangfang Health Inc.

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How to cite this article: Zhao J, Wang J and Cheng M. **Development of a deep neural network derived from contours defined by consensus-based guidelines for automatic target segmentation in hepatocellular carcinoma radiotherapy: A study protocol [version 1; peer review: 1 approved, 1 approved with reservations]** F1000Research 2017, **6**:1929 <https://doi.org/10.12688/f1000research.12892.1>

First published: 01 Nov 2017, **6**:1929 <https://doi.org/10.12688/f1000research.12892.1>

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death in China (estimated 422,100 deaths in 2015) (Chen *et al.*, 2016), and the second leading cause of cancer-related death worldwide (approximately 745,000 deaths per year) (Siegel *et al.*, 2015), with China's deaths accounting for over 50% of cases. The incidence of HCC is on the rise due to viral hepatitis (hepatitis B and C virus), alcohol use, and nonalcoholic fatty liver disease (Hemming *et al.*, 2016).

Only a small group of HCC patients are eligible for liver transplant or resection, for the majority of HCC patients ineligible for surgery, radiation therapy (RT) has been playing an increasingly important role in achieving acceptable local control (Krishnan *et al.*, 2008; Ren *et al.*, 2011; Zhao *et al.*, 2008), especially with the recent advances in external beam RT technique, including 3-dimensional conformal RT, intensity modulated RT, stereotactic body RT, proton beam RT, and/or image-guided RT with respiratory motion management (Bujold *et al.*, 2013; Yeung *et al.*, 2017). Tumorcidal doses of modern RT can now be safely delivered with excellent local control and minimal toxicity. RT has thus become a recommended option in some international consensus and current clinical practice guidelines (Park *et al.*, 2016; Rim & Seong, 2016).

Accurate target delineation in HCC RT is essential to deliver adequate doses of radiation to the primary tumor, while preserving adjacent healthy organs. Target delineation is a complex part of RT planning, and manual segmentation is the most common way in clinical practice and research, but manual segmentation is tedious and time-consuming. Besides that, the interobserver variability in target delineation of HCC gross target volume (GTV) is noteworthy (Kim *et al.*, 2016).

Recently, a clear consensus on how to delineate GTV in radiotherapy for HCC was recommended by the Radiation Therapy Oncology Group (RTOG) (Hong *et al.*, 2014). For organs at risk (OARs) in the upper abdominal region, a contouring consensus was also proposed by RTOG, as well to improve the quality and consistency of contouring uniformity in radiation oncology (Jabbour *et al.*, 2014).

It is believed that, other than the use of guidelines, provision of autocontours shows promise to reduce the interobserver and intraobserver variability in target delineation, thus improving the quality of RT (Vinod *et al.*, 2016). Moreover, auto-segmentation also has the potential advantage to greatly reduce contouring time.

In recent years, different novel machine learning techniques, including artificial intelligence technology, have been exploited in RT with impressive results in image segmentation. Machine learning may mimic labor intensive tasks, for example, target delineation via complex computational algorithms trained using the input from an expert radiation oncologist (Chu *et al.*, 2016; Trebeschi *et al.*, 2017).

Many algorithms have been proposed and explored for automatic normal organ segmentation in liver cancer RT, such as atlas-based method for liver auto-segmentation (Li *et al.*, 2017),

a random walker based framework segment for liver CT images (Moghbel *et al.*, 2016), and a deep fully convolutional neural networks for the segmentation of four organs (liver, spleen and both kidneys) (Hu *et al.*, 2017). As for liver tumors, a multi-channel fully convolutional network was developed to segment GTV from CT images (Sun *et al.*, 2017). However, those studies applied in a radiation oncology field need to be carefully implemented and validated before application in daily clinical practice. A set of recommendations regarding the ontology definition, performance evaluation tools and benchmark evaluation methods should be complied to meet the clinical standard (Valentini *et al.*, 2014).

A fully-automated target structure contouring system based on deep neural networks could automatically localize and segment GTV and OARs in RT. This study protocol proposes a study that aims to develop a contouring system derived from contours defined by consensus-based guidelines for automatic target segmentation in hepatocellular carcinoma radiotherapy.

Protocol Objectives

To develop a fully-automated target structure contouring system trained on contours delineated according to consensus contouring guidelines. In addition, to evaluate the contouring system's feasibility and performance during application in normal clinical operations.

Study dataset acquirement

Upper abdominal CT scans with or without contrast enhancement acquired from HCC patients who requested medical second opinion services from Shangfang Health Inc. between 1st October 2014 and 1st September 2017 will be retrospectively selected in this study. Patients in the supine position with arms extended overhead, and tumor stage meeting the liver-directed radiotherapy criteria (from the 5th Asia-Pacific primary liver cancer expert meeting) (Park *et al.*, 2016) will be eligible for inclusion.

CT datasets will be stored according to the digital imaging and communications in medicine (DICOM) standards of practice. The number of slices and the slice thickness in each CT series varies from 23 to 191 and 1.0 to 8.0 mm, respectively.

Targets delineation

CT image sets acquired from each patient will be loaded into a radiation treatment planning system (Pinnacle v9.0, Philips Healthcare, Madison, WI) or MIM Maestro software v6.7.5 (MIM Software Inc., OH) for manual delineation of targets. Following nomenclature for structure naming conventions in RT (Santanam *et al.*, 2012), liver tumors will be delineated as GTV. Thirteen abdominal OARs (liver, stomach, duodenum, spleen, left kidney, right kidney, small bowel, colon, gallbladder, esophagus, left lung, right lung and spinal cord) will be named liver, stomach, duodenum, spleen, kidney_L, kidney_R, smallbowel, colon, gallbladder, esophagus, lung_L, lung_R and spinalcord, respectively.

To ensure that a standardized approach to delineate OARs is used across radiation oncologists involved in the study, each participant will be provided with "upper abdominal normal organ contouring

guidelines and atlas: A RTOG consensus” (Jabbour *et al.*, 2014). As for the GTV delineation, it will be contoured according to the recommendation previously reported by RTOG - using the union of GTVs across all available phases of multiphasic imaging (Hong *et al.*, 2014).

Delineating OARs using the standard abdominal soft tissue window setting: window width (WW) of 350-400 Hounsfield unit (HU), window level (WL) of 35-50 HU; for GTV, using liver window setting: WW of 150 HU, WL of 50-100 HU.

Two well-trained residents in radiation oncology will be trained by the expert physician (JZ), making sure that they understand all the requirements. Subsequently, they will manually delineate all the targets and check each other’s targets and revise them when necessary. All contours will be reviewed by an attending physician independently to detect any other gross errors (e.g., missing slices) and revise any violations or deviations from the contouring guidelines, any gross errors and violations or deviations detected during the review process will be corrected. After the attending physician’s review and revise, the contours will be reviewed and finally approved by the expert physician. These contours are to be saved as DICOM-RT structure format and transferred to an in-house web based RT-PACS platform for the fully-automated target structure contouring system (deep neural network) development.

Automated target structure contouring system development

In order to develop the auto-contouring system, the following machine learning networks will be used, including supervised and semi-supervised convolutional neural networks, recurrent neural networks, unsupervised clustering, reinforcement learning, etc. The whole technique workflow is shown in Figure 1.

To consider the 3D structure of the CT image, 5 CT image slices were simultaneously input into the network. To increase model training efficiency, a two phases training process was implemented. In phase 1, we only identify whether this slice has an organ or GTV, which is the classification task. Then a segmentation task follows with adapted weight in last phase. Both phases were trained 200 epochs. A recurrent neural structure, such as LSTM, will be tested in research if available. After initial training, the results will be reviewed by physician, the correction information will be recorded and feed back to automatic contouring network as the input of a reinforcement learning.

Sample size

Approximately 400 retrospective CT data sets from patient cases will be used to establish the automatic contouring system for OARs, and an additional 200 CT data sets will be needed for GTV delineation. Another 50 CT data sets will be used as an external validation data set. The sample size is informed by the existing literature (Chu *et al.*, 2016; Hu *et al.*, 2017; Sun *et al.*, 2017) and by our previous work on knowledge-based radiotherapy treatment planning prediction (Fan *et al.*, 2017).

Data analysis and statistical plan

For external validation patients, all the contours will be manually delineated by expert teams following the same process mentioned previously (in *Targets delineation*) and used as ground truth. In order to evaluate the performance of auto-segmentation of the deep neural network, segmentation results will be compared with the ground truth for those patients. Analysis and comparison with four methods (HD, MDA, Dice and Jaccard) will be utilized to detect the common areas of disagreement. The explanation of these indices is as follows: HD = Hausdorff Distance, the maximum distance across

Figure 1. The whole technique workflow of development of the deep neural network.

all points on a surface and their closest point on another surface; MDA = Mean Distance to Agreement, which is similar but using the mean; Dice = $2 * (\text{volume of intersection of A and B}) / (\text{volume of A} + \text{volume of B})$; Jaccard = $(\text{volume of intersection of A and B}) / (\text{volume of union of A and B})$.

Ethical considerations

This research is not a clinical trial, and doesn't involve any direct patient contact. The CT images were acquired with permission from Shangfang Health Inc., who own the data. Shangfang Health Inc. has already obtained written informed consent from the patients, who allowed their anonymized CT data to be used for scientific research purposes. Since the data were acquired during standard procedures, with patient consent for use in research, and were anonymized, this study doesn't need any approval from a Human Research Ethics Committee.

Dissemination

The results of our research will be disseminated through presentations at conferences, such as radiation oncologist and medical physicist education and radiation oncology conferences, regionally and nationally, and through articles published in

peer-reviewed journals related to the treatment of cancer using radiation.

Conclusion

We propose a machine learning proof of concept system to develop a fully-automated target structure contouring system aiming to utilize in HCC radiotherapy. The study is ongoing (data analysis). It will be of help to improve the quality and efficiency of RT. The progress made here can be subsequently applied to other tumor sites in clinical settings.

Competing interests

No competing interests were disclosed.

Grant information

This study is funded by Shangfang Health Inc.

Acknowledgments

The authors thank the residents and the attending physician for their works on target delineation. Ying Zhao is responsible for the data protection and security in this research protocol.

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Current Peer Review Status:

Version 1

Reviewer Report 09 August 2018

<https://doi.org/10.5256/f1000research.13974.r36679>

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Sergio Casciaro

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The authors present a study protocol to develop a fully-automated contouring system based on deep learning neural network to identify target delineation of Hepatocellular carcinoma (HCC) gross target volume (GTV) in liver CT images.

The protocol of the study clearly describes the data selection and the manual contouring procedure. However, the level of details provided to develop the auto-contouring system based on neural network should be improved. For example, the authors should provide more details about the architecture of the chosen neural network and additional information about the neural network input data that they are expecting to use.

The content of the paper is an acceptable scientific standard and therefore it is suitable for publication. Authors should provide more details about the automatic data analysis workflow.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 07 December 2017

<https://doi.org/10.5256/f1000research.13974.r28784>

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Laura A. Dawson

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There is rationale for investigating how to standardize contouring. Hepatocellular carcinoma is an excellent site to investigate neural networks, since there is variability in contouring, and sometimes, the full extent of HCC is challenging to delineate. However, normal tissues and OAR atlases already exist, so there is less rationale to include some OARs where automated segmentation is already in the clinic.

Design of the research is reasonable, with one exception. Training two residents to contour is likely to be associated with inaccuracies in contours. It would be better to have experienced faculty radiation oncologists contour, and a radiologist to provide input, especially for challenging cases

Datasets are described, but more details are needed. E.g. what exact cases are to be used? Early stage HCC, or HCC with vascular invasion. Snapshots of the exact cases in an appendix may be helpful.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Partly

Competing Interests: No competing interests were disclosed.

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