Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Contouring of prostate tumors on multiparametric MRI: Evaluation of clinical delineations in a multicenter radiotherapy trial

Marcel A. van Schie [a], Cuong V. Dinh [a], Petra J. van Houdt [a], Floris J. Pos [a], Stijn W.T.J.P. Heijmink [b], Linda G.W. Kerkmeijer [c], Alexis N.T.J. Kotte [c], Raymond Oyen [d], Karin Haustermans [e], Uulke A. van der Heide [a,*]

[a] Department of Radiation Oncology, The Netherlands Cancer Institute; [b] Department of Radiology, The Netherlands Cancer Institute, Amsterdam; [c] Department of Radiation Oncology, University Medical Center, Utrecht, The Netherlands; [d] Department of Radiology; and [e] Department of Radiation Oncology, University Hospitals, Leuven, Belgium

ARTICLE INFO

Article history:
Received 18 December 2017
Received in revised form 26 March 2018
Accepted 11 April 2018
Available online xxxx

Keywords:
Multiparametric MRI
Prostate cancer
Tumor delineation
FLAME
Multicenter trial

ABSTRACT

Purpose: To date no guidelines are available for contouring prostate cancer inside the gland, as visible on multiparametric (mp-) MRI. We assessed inter-institutional differences in interpretation of mp-MRI in the multicenter phase III FLAME trial.

Methods: We analyzed clinical delineations on mp-MRI and clinical characteristics from 260 patients across three institutes. We performed a logistic regression analysis to examine each institute's weighting of T2w, ADC and K^{trans} intensity maps in the delineation of the cancer. As reviewing of all delineations by an expert panel is not feasible, we made a selection based on discrepancies between a published tumor probability (TP) model and each institute's clinical delineations using Areas Under the ROC Curve (AUC) analysis.

Results: Regression coefficients for the three institutes were −0.07, −0.27 and −0.11 for T2w, −1.96, −0.53 and −0.65 for ADC and 0.15, 0.20 and 0.62 for K^{trans}, with significant differences between institutes for ADC and K^{trans}. AUC analysis showed median AUC values of 0.92, 0.80 and 0.79. Five patients with lowest AUC values were reviewed by a uroradiologist.

Conclusion: Regression coefficients revealed considerably different interpretations of mp-MRI in tumor contouring between institutes and demonstrated the need for contouring guidelines. Based on AUC values outlying delineations could efficiently be identified for review.

Radiotherapy is one of the standard treatment options for prostate cancer. Although it has been shown that tumor foci are non-uniformly distributed over the prostate [1], the prostate is usually irradiated with a more or less homogeneous dose distribution. Local recurrence of the disease has been observed at the original location of the tumor, suggesting an insufficient radiation dose at that location [2,3]. As dose escalation to the entire gland would likely increase treatment-related toxicity, a focal dose escalation was proposed [4]. Recently, accrual of patients in the FLAME trial (clinicaltrials.gov identifier NTC01168479) was ended. This large multi-center single-blinded randomized controlled phase III trial aimed to investigate the clinical benefit of focal escalation of the radiation dose to the visible cancer to 95 Gy. This required delineation of the tumor as visible on multiparametric (mp-) MRI, consisting of a T2-weighted (T2w) scan, a diffusion-weighted MRI (DWI) and a dynamic contrast-enhanced (DCE) MRI.

Guidelines on detection, localization, characterization and risk stratification of suspected prostate cancer using recommended mp-MRI were published in the Prostate Imaging – Reporting And Data System (PI-RADS) in 2012, and updated to PI-RADS v2 in 2015 [5,6,7]. These guidelines were however not available when the majority of patients were included in the FLAME trial. Moreover, guidelines on contouring of prostate tumors based on mp-MRI are not available to date. Steenbergen et al. showed the large inter-observer variability that exists in a prostate tumor delineation study using mp-MRI [8]. Such variability can also be expected in the FLAME trial. In the absence of guidelines, institutional differences in contouring practice caused by differences in interpretation and weighting of the various sequences in mp-MRI scans may have occurred as well.

In this work we investigated the contours of prostate tumors in the FLAME trial, focusing on the weighting of the individual mp-MRI sequences within three institutes. We combined mp-MRI data

* Corresponding author at: Dept. of Radiation Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
E-mail address: u.vd.heide@nki.nl (U.A. van der Heide).

https://doi.org/10.1016/j.radonc.2018.04.015
0167-8140/

with the actual clinical delineations to assess the relative contribution of each MRI sequence to the tumor contouring decision. As revision of all contours by a panel of experts is not feasible, we applied a pathology validated model for prostate tumor localization in order to identify cases that showed discrepancies between clinical delineations and MRI data. We selected the patients with the highest inconsistency between predicted tumor location and delineation and reviewed these retrospectively.

Materials and methods

Patient characteristics

We analyzed 260 prostate cancer patients who were included in the FLAME trial and randomized in the escalated dose arm. These patients had biopsy-proven prostate cancer, clinically localized intermediate or high-risk disease and no evidence of metastatic disease, according to Ash et al. [9]. Institutional review board approval was obtained and all patients provided written informed consent. The patients were treated in three institutes: 160 patients in the University Medical Center Utrecht (UMCU), 54 patients in the Netherlands Cancer Institute (NKI), and 46 patients in the University Hospitals in Leuven (UZL). Thirty-five patients were excluded because they had missing MRI data (15), missing biopsy reports (3), missing delineations (10), registration artifacts (2) or they did not receive the escalated dose (5), which led to analysis of 140, 33 and 52 patients from UMCU, UZL and NKI respectively.

MRI data

All patients received an mp-MRI exam consisting of a T2w, DWI and DCE sequence. Specifications of the scanner type and sequences for each of the institutes are listed in Table 1. An apparent diffusion coefficient (ADC) map was derived from the b-values of the DWI using a mono-exponential fit. We determined the volume transfer constant (K^{trans}) values with the Tofts model using a population-based arterial input function [10,11]. Within each institute a radiation oncologist in consultation with a radiologist had prospectively delineated the prostate and all tumors visible on mp-MRI.

Image processing

We processed the MRI data according to the method of Dinh et al. [12]. To minimize the impact of differences between acquisition protocols among the participating institutes, this method applies a normalization of T2w and K^{trans} to the median signal intensity in the peripheral zone (PZ). Since no PZ delineations were made in our cohort, we assumed that 75% of the prostate volume was PZ tissue and 25% central gland [7]. The T2w signal in the central gland tends to be lower than in the PZ, while the K^{trans} is higher [13]. Considering the upper and lower 75% of the T2w and K^{trans} signal intensity histograms as belonging to the PZ, we normalized the signal to the upper and lower 37.5% respectively.

The data set per patient consisted of normalized T2w and K^{trans} images, ADC, biopsy map and tumor prevalence map, plus the clinically delineated tumor and prostate. From the delineations a labeling mask was derived that contained labels for healthy and tumor tissue within the prostate. The data sets were resampled to an in-plane resolution of 0.49 mm, equal to the resolution of the image data used by Dinh et al. [12], and a slice thickness of 1.0 mm.

Institutional interpretation

We evaluated the institutional differences on interpretation of the mp-MRI with a logistic regression analysis on voxel level of three intensity features, i.e. the T2w, ADC and K^{trans} intensity images. A transformation of each feature i to zero mean and unit variance was applied to allow comparison between features. The logistic regression function is:

$$F(x) = \frac{1}{1 + e^{-(\beta_0 + \sum \beta_i x_i)}}, \quad (1)$$

where $F(x)$ is the probability that voxel x is included in the tumor delineation, x_i is the intensity value of feature i, β_i is the regression coefficient of feature i and represents weight factor, and β_0 is the offset.

Probability model

For the automatic evaluation of the manual delineations we used a published tumor probability (TP) model [12], which is a logistic regression model trained on mp-MRI and biopsy data and validated on histology data from 40 patients in two institutes. The coefficients of the TP model are found in Table 2. We combined 29 features from the normalized mp-MRI with biopsy and prevalence information, and applied the TP model to calculate a TP per voxel within the prostate.

For each calculated TP map and labeling mask we derived the Area Under the receiver operating characteristic Curve (AUC). We selected the patients that had a large disagreement between calculated TP map and labeling mask with AUC values below 0.50 and reviewed the clinical delineations. For each of the review cases

Table 1
mp-MRI parameters per institute.

MRI parameters	I-1	I-2	I-3
Scanner type	Siemens 1.5 T	Philips 3.0 T	Philips 3.0 T
Scanner Sequence			
tT2w			
Pixel size/slice thickness (mm)	0.78/4.0	0.40/3.0	0.49–1.0/2.5–4.0
TR/TE (ms)	11,250/124	3126–3828/120	2698–6717/110–130
ADC			
Pixel size/slice thickness (mm)	2.73/4.0	1.07–1.11/3.0–3.7	1.17–2.38/2.5–4.0
TR/TE (ms)	7110–9900/67	2712–3500/58–73	3119–10036/59–94
b-Values (s/mm^2)	0, 50, 100, 500, 750, 1000	0, 188, 375, 563, 750 or 200, 400, 600, 800[a]	0, 300, 500, 1000 or 0, 300, 1000[a]
Ktrans			
Pixel size/slice thickness (mm)	1.37–1.68/4.0	1.02–1.36/3.0	0.94–2.5/2.5–7.0
TR/TE (ms)	4–5/1.5	4–5/1.9	4/1.0–1.7
Dynamic scan time (s)	4.4	2.5	2.5

[a] b = 0 s/mm^2 was acquired but not used for ADC map calculation.

Please cite this article in press as: van Schie MA et al. Contouring of prostate tumors on multiparametric MRI: Evaluation of clinical delineations in a multicenter radiotherapy trial. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.04.015