Physica Medica xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Original paper

Characterization of cervical lymph-nodes using a multi-parametric and multi-modal approach for an early prediction of tumor response to chemo-radiotherapy

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ARTICLE INFO

Article history:
Received 13 June 2016
Received in Revised form 4 August 2016
Accepted 6 September 2016
Available online xxxx

Keywords:
Head-and-neck lymph-nodes
Texture analysis
T2w-MRI
DW-MRI

ABSTRACT

Purpose: In the treatment of Head-and-Neck Squamous Cell Carcinoma (HNSCC), the early prediction of residual malignant lymph nodes (LNs) is currently required. Here, we investigated the potential of a multi-modal characterization (combination of CT, T2w-MRI and DW-MRI) at baseline and at mid-treatment, based on texture analysis (TA), for the early prediction of LNs response to chemo-radiotherapy (CRT).

Methods: 30 patients with pathologically confirmed HNSCC treated with CRT were considered. All patients underwent a planning CT and two serial MR examinations (including T2w and DW images), one before and one at mid-CRT. For each patient the largest malignant LN was selected and within each LN, morphological and textural features were estimated from T2w-MRI and CT, besides a quantification of the apparent diffusion coefficient (ADC) from DW-MRI. After a median follow-up time of 26.6 months, 19 LNs showed regional control, while 11 LNs showed regional failure at a median time of 4.6 months. Linear discriminant analysis was used to test the accuracy of the image-based features in predicting the final response.

Results: Pre-treatment features showed higher predictive power than mid-CRT features, the ADC having the highest accuracy (80%); CT-based indices were found not predictive. When ADC was combined with TA, the classification performance increased (accuracy = 82.8%). If only T2w-MRI features were considered, the best combination of pre-CRT indices and their variation reached an equivalent accuracy (81.8%).

Conclusion: Our results may suggest that TA on T2w-MRI and ADC can be combined together to obtain a more accurate prediction of response to CRT.

1. Introduction

Treatment of locally advanced Head-and-Neck Squamous Cell Carcinoma (HNSCC) is a challenging task, since it affects the overall quality of life of patients, and, despite chemo-radiotherapy (CRT) has been accepted as a standard management, the 5 year survival rate of these patients remains below 50% [1]. In this context, a timely identification of patients at risk of residual malignant lymph nodes (LNs) can help in choosing the best treatment [2]. However, the early prediction of treatment response presents many challenges and it is currently a hot topic in this research area, since reproducible and robust findings have not been established yet [3].

Recently, many studies have reported image-based criteria for treatment assessment, considering Computed Tomography (CT), morphological or functional Magnetic Resonance Imaging (MRI) [3–9]. The morphological criteria principally regard volume regression [5,7,9], the presence of focal abnormalities [3] and nodal density [8]. However, very heterogeneous results in the prediction performance using these criteria were reported in literature [10].

Great attention was given to Diffusion-weighted MRI (DW-MRI) [11] in the evaluation of diffusion properties of the primary tumor and malignant nodes, related to the treatment response [12]. In fact, it was reported that primary tumors and metastatic nodes characterized by lower pre-treatment values of apparent diffusion

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http://dx.doi.org/10.1016/j.ejmp.2016.09.003
1120-1797/

coefficient (ADC) can better respond to the CRT [13–15]. Moreover, ADC changes evaluated both during and early after CRT were found predictive of treatment response at the primary and nodal site [6,10,16].

Very few works [17,18] tried to perform a multi-parametric analysis, but they were limited to a combination of ADC and morphological features or ADC and PET findings. Moreover, morphological evaluations were performed using qualitative findings or very simple quantitative approaches, able to characterize nodes density or shape [3,9]. To our knowledge, there are no attempts to predict treatment response using advanced image analysis techniques, such as texture analysis, on anatomical images which can provide quantitative information about structural properties of the tissue, related to the spatial pattern. Only a very recent work proposed textural features applied on parametric maps derived on Dynamic Contrast Enhanced (DCE)-MRI for the prediction of tumor response [19].

Aim of this work was thus to investigate the potential of a multi-modal characterization descriptive of morphological, structural and functional properties at baseline and at mid-CRT, based on advanced image processing methods, for the early prediction of LNs response to CRT in patients with HNSCC. In particular, shape-related indices were calculated on T2w-MRI, textural features were extracted from T2w-MRI and planning CT, and ADC values from DW-MRI.

Table 1
Patient characteristics.

Characteristic	No.
Patient number	30
Age (years)	
Median (range)	58 (28–82)
Sex (M/F)	27/3
Primary tumor site	
Oropharynx	12 (40.0%)
Nasopharynx	11 (36.7%)
Hypopharynx	5 (16.7%)
Larynx	1 (3.3%)
Unknown	1 (3.3%)
T stage	
T1	6 (20%)
T2	11 (36.7%)
T3	5 (16.7%)
T4	7 (23.3%)
T0	1 (3.3%)
N stage	
N1	6 (20%)
N2a	4 (13.3%)
N2b	6 (20%)
N2c	8 (26.6%)
N3	6 (20%)
LN volume (cm^3)	
Median (range)	4 (0.8–44)

2. Materials and methods

2.1. Patient population

From October 2011 to March 2014, a total of 30 patients with histologically proven HNSCC were included retrospectively in the present study. This retrospective analysis was performed on an existing data-set of a prospective study conducted at Regina Elena National Cancer Institute and previously approved by the ethics committee of the hospital. The primary end point of the study, currently closed, was to investigate the ability of DWI to predict the treatment response of HNSCC patients after CRT.

All patients underwent a planning CT and two serial MRI examinations, before RT and at mid-RT (at the 16th or 17th fraction of RT), and they were staged according to the AJCC Cancer Staging Manual (7th edition) [20].

All patients received intensity modulated radiation therapy and concomitant chemotherapy (cisplatinum 100 mg/m^2 for three cycles every 21 days). A seven-field simultaneous integrated boost technique was used to deliver 70 Gy in 33 fractions to the macroscopic disease (primary tumor and affected LNs), 60 Gy to the regions at high risk of microscopic disease and 54 Gy to the regions at low risk of microscopic disease. Patient characteristics are shown in Table 1.

2.1.1. Follow-up criteria

Follow-up consisted of clinical assessments and imaging examinations. The first MR scan was performed 8 weeks after the end of CRT and every 6 months during the first two years after conclusion of CRT, and afterwards once year. PET-CT was performed 12 weeks after conclusion of CRT and then once a year. Local regional control (RC) was defined as the complete disappearance of LN on both physical examination and imaging, absence of any new mass, or a static and/or decreasing existing residual mass based on a minimum six-month follow-up. Local regional failure (RF) was defined as a positive histological examination by biopsy or surgical resection, development of a new mass, or serial increase in size of residual mass during follow-up.

2.2. Imaging procedure

2.2.1. Image studies

The image-based analysis used in this work was performed on the planning CT and on T2w-MRI and DW-MRI acquired before CRT (MRI1) and at mid-treatment (MRI2). MRI2 examination was not performed in three patients because of lack of patient compliance, while two patients had missing mid-treatment values due to poor image quality.

Planning CT images were acquired for each patient by using a 16-slice CT scanner (LightSpeed Pro 16, GE HealthCare, Milwaukee, Wisconsin, USA), with acquisition matrix 512 × 512, field of view 50 cm, voxel size 0.98 × 0.98 mm, slice thickness 2.5 mm.

MRI was performed on a 1.5-T system (Optima MR 450w, GE Health-care, Milwaukee, WI, USA) with dedicated 16-channel receive-only radiofrequency coils: a head coil, a surface neck coil and a spine coil. All MRI exams included fast spin-eco (FSE) T2w-MRI and DW-MRI. FSE T2w-MRI images on the coronal plane were first obtained, followed by axial FSE T2w-MRI images (acquisition matrix 256 × 256, field of view 26–28 cm, TR/TE = 2260 ms/119 ms; slice thickness 4 mm, spacing between slices 5 mm), acquired from the level of the skull base to the thoracic inlet. DW-MRI were obtained by single-shot spin-echo echo-planar imaging with acquisition matrix, 128 × 128; field of view, 26–28 cm; TR/TE = 4500 ms/77 ms; slice thickness 4 mm; spacing between slices 5 mm. Three different b values (b = 0, 500 and 800 s/mm^2) were used, with all diffusion-sensitizing gradients applied in three orthogonal directions to obtain trace-weighted images.

2.2.2. Tumor delineation

In patients with several lymph node metastases, the largest LN in the neck was selected for the analyses. In case of regional recurrence in a different LN, the exact nodal site of the recurrence was identified on MRI1 and MRI2 and analyzed.

Three contiguous sections of LNs, covering the largest cross-sectional areas of the lesion, were identified on DW-MRI with

Please cite this article in press as: Scalco E et al. Characterization of cervical lymph-nodes using a multi-parametric and multi-modal approach for an early prediction of tumor response to chemo-radiotherapy. Phys. Med. (2016), http://dx.doi.org/10.1016/j.ejmp.2016.09.003