Oral Oncology 85 (2018) 8–14

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Temporal lobe injury patterns following intensity modulated radiotherapy in a large cohort of nasopharyngeal carcinoma patients

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ARTICLE INFO

Keywords:
Dose-volume-histogram
Intensity modulated radiation therapy
Nasopharyngeal carcinoma
Temporal lobe injury

ABSTRACT

Objectives: To analyze the correlation between dose-volume-histograms (DVHs) with three patterns (edema, enhancement, and necrosis) of temporal lobe injury (TLI) in patients receiving intensity modulated radiation therapy (IMRT) for nasopharyngeal carcinoma (NPC) and to determine optimal thresholds to predict the incidence of each TLI pattern, with particular emphasis on the relationship between edema volume and the risk of enhancement and necrosis.

Materials and methods: A cohort of 4186 NPC patients treated with IMRT was retrospectively reviewed with TLI presenting in 188 patients. The atlases of complication incidence (ACI) for each pattern were constructed using DVH curves of temporal lobes. Optimal threshold for predicting incidence of each pattern was determined using the point closest to top-left of the plot. The accuracy of using edema volume to predict enhancement and necrosis incidence was evaluated via area under curve (AUC) of receiver operator characteristics (ROC).

Results: All DVH parameters, D_{mean}, D_{max}, $D_{0.25cc}$, $D_{0.5cc}$, D_{1cc}, D_{3cc}, D_{6cc}, V_{20Gy}, V_{30Gy}, V_{40Gy}, V_{50Gy}, V_{60Gy}, and V_{70Gy}, except D_{min} showed statistically significant differences between subgroups of each pattern ($p < 0.05$). For predicting incidence of each pattern, optimal DVH thresholds over the range of $D_{0.25}$-D_{1cc}, D_{mean} and V_{20}-V_{70} were derived. The optimal thresholds of edema volume for predicting enhancement were 0.96 and 2.2cc and for predicting necrosis were 0.94 and 11.5cc.

Conclusion: Optimal DVH thresholds were generated for limiting risk of each injury pattern. Edema volume was a strong predictor for risk of enhancement and necrosis, which could potentially be reduced by lowering edema volume below threshold.

Introduction

Intensity modulated radiation therapy (IMRT) has been shown to increase local control rate for patients with nasopharyngeal carcinoma (NPC) [1–5]. However, even with IMRT, dose spills to surrounding temporal lobe (TL) are still significant and late-effect toxicity remains one of the greatest concerns for these patients [1,6]. Temporal lobe injury (TLI) is a common late complication of radiotherapy in NPC [7–9]. The incidence of TLI among patients receiving IMRT ranged from 2.27% to 8.30% [6,10–14].

As IMRT often exploits fluence modulation, inhomogeneous dose distribution [was observed within TL and such dose distribution was hard to summarize using 1-D conventional dose-volume-histogram (DVH) analyses [15–17]. Without accounting for DVH shape, there can be no adequate analysis of DVH data from IMRT planning that are 3-D in nature [11,12,14,18,19]. The dose-volume atlas of complication

Abbreviations: AUC, area under curve; ACI, atlas of complication incidence; CRT, chemotherapy and radiation therapy; DVH, dose-volume-histogram; IMRT, intensity modulated radiation therapy; MRI, magnetic resonance imaging; NPC, nasopharyngeal carcinoma; OARs, organs at risk; SIB, simultaneous integrated boost; TL, temporal lobe; TLI, temporal lobe injury

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https://doi.org/10.1016/j.oraloncology.2018.07.020
Received 25 March 2018; Received in revised form 24 July 2018; Accepted 29 July 2018

incidence (ACI) is essentially a summary of 3-D DVHs of a cohort for a specific organ and a specific complication, in terms of incidence at each DVH endpoint. The advantage of ACI is that the entire DVHs of all treated patients can be included and summarized, which enable comparison with treatment protocols for toxicity incidence [20,21].

When analyzing the association between dosimetric endpoints and incidence of injuries, it is important to differentiate coherent injury patterns [16,22]. Magnetic resonance imaging (MRI) provides a non-invasive method for identifying radiation-induced injury [14,23,24]. Three patterns of TLI assessed at MRI, white matter edema (edema), contrast enhanced lesions (enhancement), and necrosis or cysts (necrosis), are the most common [14,24,25]. It is still unknown if all injury patterns are equally associated with dosimetric endpoints. To answer this question and better understand the correlation, we defined endpoints of toxicity based on patterns of TLI.

Wang et al. [25] performed a retrospective study of 62 NPC patients with TLI to demonstrate the chronological changes of injury patterns in follow-up MRIs. In their results, edema was the most detected pattern and occurred first, followed by enhancement, and necrosis. Their study provided a valuable insight into the relationship among the three injury patterns. However, volumes of injury lesions could not be obtained in that study. Furthermore, we intend to perform volumetric analysis and propose limiting edema volume to control severe injury incidences, which may compromise cognitive function and quality of life [26].

In this study, we use ACI to analyze the DVH of TL with three patterns of TLI in patients treated with IMRT. We determine optimal thresholds to predict risk of TLI, with particular emphasis on the relationship between edema volume and risk of enhancement and necrosis.

Material and methods

Patients

Between January 2010 and November 2013, 4186 new NPC patients, without previous radiotherapy or chemotherapy, were treated with IMRT at Sun Yat-sen University Cancer Center. The treatment data from these patients was retrospectively reviewed with the approval from the Institutional Ethics Board and written patient informed consents. In the follow-up MRI scans, TLIs were found in 217 patients. Among these patients, twenty-nine patients were excluded due to unavailable planning data, age $\geq$70 yr, or inability to differentiate TLI with recurrent tumor at nasopharynx. The remaining 188 patients with TLI were included.

Pretreatment assessment included routine physical examination, especially examination of the head, neck, and nasopharynx. All patients received MRI plain and enhanced scan of the head and neck. The pathological type followed WHO classification standard. All patients were restaged according to the 8th UICC/AJCC staging system [27].

Targets and organs at risk delineation

Contouring of targets was performed in accordance with the institutional protocols previously reported [1,2] under the planning system (Eclipse 11.o, Varian or Monaco 5.01, Elekta). The contouring was in the fusion images of CT with MRI or PET/CT. Gross tumor volume (GTV) included primary nasopharyngeal tumor (GTVnx) and metastatic neck lymph nodes (GTVnd). Two clinical target volumes (CTV) were delineated: (1) CTV1, the high-risk CTV of primary/nodal tumor, was defined as GTVnx and GTVnd plus a 5–10 mm margin (2–3 mm margin posteriorly) to encompass the high-risk sites of microscopic extension and the whole nasopharynx; (2) CTV2 for primary/nodal tumor was defined as the CTV1 plus a 5–10 mm margin (2–3 mm margin posteriorly) to encompass the intermediate to low-risk sites of microscopic extension and the elective neck area. The temporal lobe (TL) organs at risk (OARs) were contoured according to the previously reported recommendation [28]. The planning systems allow overlapping structures. Therefore, the DVH include entire volume of TL. To improve the contouring consistency, all TL OARs were retrospectively contoured by two primary radiation oncologists in a few sittings.

Treatment

All patients received full-course IMRT with Varian Clinic 600 C/D and Electa Synergy system using a simultaneous integrated boost (SIB) technique. According to the institutional treatment protocol [1,2], the prescribed dose for PTV were: 68–70 Gy (fraction dose: 2.27–2.33 Gy) for GTV of nasopharynx; 60–68 Gy (fraction dose: 2–2.20 Gy) for GTV of lymph nodes; and 54 Gy (fraction dose 1.8 Gy) for prophylactic risk region including cervical lymphatic area. Doses of organs at risk (OARs) were constrained and radiation treatment plans were approved by 3–4 senior head and neck radiation oncologists. Except for three patients with T2 and N0 diseases, all patients received chemotherapy and radiation therapy (CRT). The CRT regimens included concurrent chemotherapy (cisplatin weekly or on days 1 and 29) or 2–3 cycles induction chemotherapy (cisplatin and 5-fluorouracil with/without docetaxel) followed by concurrent chemotherapy.

Follow-up

Patients were followed clinically every three months in the first three years and every six months thereafter. Contrast-enhanced MR of the head and neck was a routine element of the assessment at every visit. MRI scan (GE Signa CV/I and HDx Echo speed, 1.5 T) covered from the parietal bone to the lower neck. The T1-weighted, fast spin-echo images in the axial, coronal and sagittal planes (repetition time, 500–600 ms; echo time, 10–20 ms; field of view, 256 × 256 cm; matrix, 512 × 512) and T2-weighted, fast spin-echo images in the axial plane (repetition time, 4000–6000 ms; echo time, 95–110 ms; field of view, 256 × 256 cm; matrix, 512 × 512) were obtained before contrast injection. The section thickness was 5–6 mm, with a 1-mm inter-slice width. After intravenous injection of gadopentetated imeglumine (0.1 mm/lkg; Magnevist), T1-weighted, spin-echo axial, sagittal and fat-suppressed coronal sequences were sequentially performed using the same parameters as the unenhanced T1-weighted sequence.

Toxicity endpoints

MRI-assessed TLI was used as a surrogate marker for TLI. MRI was independently reviewed by three radiologists and disagreements were resolved by consensus. Three patterns of TLI based on MRI characteristics were used as toxicity endpoints. Each pattern was individually contoured with the peak lesions on follow-up MRI and was transferred to the planning system (Fig. 1).

- Edema pattern: areas of finger-like lesions of increased signal intensity on T2-weighted images.
- Enhancement pattern: lesions on post-contrast T1-weighted images with heterogeneous signal abnormalities on T2-weighted images.
- Necrosis pattern: round or oval well-defined lesions of very high signal intensity on T2-weighted images with a thin or imperceptible wall.

Based on each toxicity endpoint, three subgroups were defined: edema/edema-free; enhancement/enhancement-free; and necrosis/necrosis-free.

Atlas of complication incidence (ACI)

The DVHs were exported from IMRT planning system to compose the Atlas. The ACI was constructed using DVH curves of TL, with y-axis being the percentage of volume with 10% bins, and x-axis being the