Oral Oncology 75 (2017) 120–126

Contents lists available at ScienceDirect

Oral Oncology

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

Delayed clinical complete response to intensity-modulated radiotherapy in nasopharyngeal carcinoma

Wen-Fei Li[a,1], Yuan Zhang[a,1], Xu Liu[a], Ling-Long Tang[a], Li Tian[b], Rui Guo[a], Li-Zhi Liu[b], Ying Sun[a], Jun Ma[a,*]

[a] Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, 651 Dongfeng Road East, Guangzhou 510060, Guangdong, People's Republic of China
[b] Imaging Diagnosis and Interventional Center, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, 651 Dongfeng Road East, Guangzhou 510060, Guangdong, People's Republic of China

ARTICLE INFO

Keywords:
Nasopharyngeal carcinoma
Clinical complete response
Prognosis
Intensity-modulated radiotherapy

ABSTRACT

Objective: Twelve weeks after radiotherapy is the recommended time-point for assessing tumor response in nasopharyngeal carcinoma (NPC); however, regression after 12 weeks remains unclear. We explored NPC regression and the prognosis of patients with delayed clinical complete response (cCR).

Materials and methods: MRI images of 556 NPC patients treated with intensity-modulated radiotherapy (IMRT) between 2009 and 2012 were retrospectively reviewed. Clinical tumor response was assessed at 3–4 (assessment 1) and 6–9 months (assessment 2) after IMRT, and survival rates were compared.

Results: Of the 556 patients, 463 (83.3%) had cCR at assessment 1 (early cCR). Of the 93 patients with partial response at assessment 1, 45 (48.4%) achieved cCR at assessment 2 (delayed cCR), and 48 did not have cCR at assessment 2 (non-cCR). Locoregional failure rate was lower in patients with a cCR than those without a cCR at assessment 1 (7.1% vs. 26.9%, $P < .001$) and assessment 2 (7.1% vs. 45.8%, $P < .001$). Multivariate analysis showed cCR was a favorable prognostic factor for locoregional failure-free survival (LRFFS), failure-free survival (FFS), and overall survival (OS). Early and delayed cCR groups had better 5-year LRFFS (92.6% vs. 93.3% vs. 54.2%), FFS (83.8% vs. 84.4% vs. 48.5%) and OS (92.1% vs. 90.6% vs. 65.4%) than the non-cCR group (all $P < .001$).

Conclusions: Nearly half of the patients with partial response at 3–4 months achieve cCR by 6–9 months; delayed cCR is not a poor prognosticator. We suggest later assessment of cCR at 6–9 months after IMRT is acceptable in responding NPC.

Introduction

Nasopharyngeal carcinoma (NPC) is a common head and neck cancer in China, especially the southern regions, with 60,600 new cases reported in 2015 [1]. Unlike other head and neck cancers, radiotherapy (RT) is the primary treatment modality for non-disseminated NPC due to its anatomical location and sensitivity to radiation. The optimal time-point for assessing the tumor response to RT is very important in NPC, as it determines whether the patient has residual or persistent disease and whether salvage treatment should be initiated [2–4]. Studies have shown a histologic response takes approximately 12 weeks to occur after RT, and additional treatment is unnecessary unless positive biopsy samples are obtained at 10–12 weeks after RT [2,4]. Thus, 12 weeks after RT is recommended as the optimal time-point for assessment of tumor response in NPC.

However, the optimal time-point and method for assessing tumor response after RT need further evaluation in light of recent advances in detection and treatment. Firstly, routine biopsies are controversial in the context of monitoring response to treatment because of its invasive nature. In clinical practice, magnetic resonance imaging (MRI) is often used to evaluate the tumor response to RT or chemoradiotherapy [5]; this high resolution imaging technique is non-invasive and has the ability to determine the extent of disease [6,7], so biopsy is only necessary if a suspicious lesion is detected by imaging. Secondly, previous studies only assessed tumor response up to 12 weeks after RT [2,4], and whether tumors may continue to respond after this time-point remains

* Corresponding author at: Department of Radiation Oncology, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, Guangdong, People's Republic of China.
E-mail address: majun2@mail.sysu.edu.cn (J. Ma).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.oraloncology.2017.10.020
Received 9 July 2017; Received in revised form 11 October 2017; Accepted 23 October 2017

unknown. Thirdly, previous studies were based on patients treated with two-dimensional conventional radiotherapy (2DCRT) [2,4]. Intensity-modulated radiation therapy (IMRT) has become the primary RT technique for NPC as it significantly improves survival and reduces toxicity [8,9], while the pattern of tumor regression and timing of maximum response in patients with NPC treated with IMRT remain unclear.

Therefore, we conducted a retrospective study to investigate the pattern of regression after IMRT and explore the associations between achieving a clinical complete response (cCR) at different time-points up to 6–9 months after IMRT and prognosis. The aim of this study was to identify the optimal time-point for assessing tumor response after IMRT in NPC.

Patients and methods

Patients

Medical records for 1811 patients with newly-diagnosed, non-distant metastatic, histologically proven NPC treated with IMRT at Sun Yat-sen University Cancer Center between November 2009 and February 2012 were retrospectively analyzed. All patients underwent a physical examination, endoscopy and conventional imaging scans before treatment, and were restaged according to the 7th edition of the Union for International Cancer Control and American Joint Committee on Cancer (UICC/AJCC) staging system [10]. The 556 patients who underwent nasopharyngeal and neck MRI before treatment, 3–4 months after RT, and 6–9 months after RT were included in this study. This study was approved by the institutional review board at Sun Yat-sen University Cancer Center. Informed consent was obtained from all the patients.

Treatment

All patients received radical IMRT to treat the nasopharyngeal and neck tumor volumes for the entire treatment course [11]. All patients were immobilized in the supine position using a head, neck and shoulder thermoplastic mask. Intravenous contrast-enhanced CT simulation was performed at 3 mm intervals from the head to 2 cm below the sternoclavicular joint using a CT simulator. Target volumes were delineated slice-by-slice on treatment planning CT scans according to the locoregional extension pattern of NPC [12], in accordance with International Commission on Radiation Units and Measurements reports 50 and 62. Prescribed doses were 66–72 Gy at 2.12–2.43 Gy/fraction to the planning target volume (PTV) of primary gross tumor volume (GTVnx), 64–70 Gy to the PTV of the GTV of the lymph nodes (GTVnd), 60–63 Gy to the PTV of high-risk clinical target volume (CTV1), and 54–56 Gy to the PTV of low-risk clinical target volume (CTV2). All targets were treated simultaneously using the simultaneous integrated boost technique.

Institutional guidelines recommended only IMRT for stage I NPC and concurrent chemoradiotherapy with or without neoadjuvant and/or adjuvant chemotherapy for stage II to IVB. Neoadjuvant or adjuvant chemotherapy consisted of cisplatin with 5-fluorouracil, cisplatin with taxels (docetaxel or paclitaxel) or a triplet of cisplatin and 5-fluorouracil plus taxels every three weeks for two or three cycles. Concurrent chemotherapy consisted of weekly cisplatin (30–40 mg/m^2) or three-weekly cisplatin (80–100 mg/m^2) on weeks 1, 4 and 7 of RT.

Imaging protocol

The region from the suprasellar cistern to the inferior margin at the sternal end of the clavicle was examined in each patient by MRI using a 1.5-T system (Signa CV/i; General Electric Healthcare, Chalfont St. Giles, United Kingdom) with a head-and-neck combined coil. Axial, coronal and sagittal T1-weighted fast spin-echo images (repetition time 500–600 ms, echo time 10–20 ms, 22 cm field of view) and axial T2-weighted fast spin-echo MR images (repetition time 4000–6000 ms, echo time 95–110 ms, 22 cm field of view) were obtained before intravenous injection of contrast material (0.1 mmol/kg gadopentetate dimeglumine; Magnevist, Schering, Berlin, Germany), then spin-echo T1-weighted axial and sagittal and spin-echo T1-weighted fat-suppressed coronal sequences (section thickness 5 mm, matrix size 512 × 512) were sequentially acquired using the same parameters.

Image assessment

All MRI scans were retrospectively reviewed independently by two radiologists with more than 10 years' experience in head-and-neck cancer MRI; disagreements were resolved by consensus. Treatment responses were assessed according to the Response Evaluation Criteria in Solid Tumors (version 1·1) [13]. A cCR was defined as no evidence of residual tumor or nodal disease, i.e. no unequivocal soft tissue mass in the local region base on MRI and flexible nasopharyngoscopy [14] and all retropharyngeal lymph nodes (RLNs) and cervical lymph nodes (CLNs) considered negative based on diagnostic criteria for nodal metastases [15,16]. An overall cCR referred to the simultaneous cCR of the primary tumor, RLN(s), and CLN(s).

Follow-up and assessments

Examinations were recommended at least every 3 months during the first 2 years after IMRT, and every 6 months thereafter (or until death). Routine follow-up included physical examination, plasma Epstein-Barr virus (EBV) DNA assay, nasopharyngeal fiberoptic endoscopy, nasopharyngeal and neck MRI, chest X-ray or CT, liver scan and whole-body bone scan. Locoregional recurrence or distant metastasis were recommended to be confirmed by fine needle aspiration or biopsy. For recurrences or metastasis at inaccessible sites, clinical diagnosis was accepted if classical changes were observed on at least two imaging methods with or without clinical symptoms, including (18) F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)-CT, MRI, CT, abdominal sonography and/or a whole-body bone scan. To increase diagnostic accuracy, diagnoses of tumor recurrence were retrospectively confirmed by two experienced doctors based on abnormal imaging findings, progressive disease and/or response to treatment.

Follow-up period was measured from the end of RT to day of last examination or death. Overall survival (OS) was calculated from end of RT to date of last follow-up or death; failure-free survival (FFS), to locoregional failure; distant failure, or death from any cause, whichever occurred first; distant failure-free survival (DFFS), to distant failure; and locoregional failure-free survival (LRFFS), to first locoregional failure.

Statistical analysis

Statistical analyses were performed using SPSS v13.0 (SPSS Inc, Chicago, IL, USA). Categorical variables were compared using the Chi-square test (or Fisher's exact test, if expected number was $<$ five in at least one cell). Survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses with the Cox proportional hazards model [17] were used to calculate hazard ratios (HR), 95% confidence intervals (CI) and test the independent significance of different factors by backward elimination of insignificant variables. Two-tailed P-values < 0.05 were considered significant.

Results

Treatment outcomes

The clinical characteristics of the 556 patients are shown in Table 1.