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Radiation-induced nasopharyngeal ulcers after intensity modulated radiotherapy in primary nasopharyngeal carcinoma patients: A dose-volume-outcome analysis

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ABSTRACT

Objective: This is a retrospective dose-volume-outcome analysis of radiation-induced nasopharyngeal ulcers after intensity modulated radiotherapy in primary nasopharyngeal carcinoma (NPC) patients, with the aim to determine how the radiation doses to nasopharynx influence the occurence of radiation-induced nasopharyngeal ulcer (RINU) and predict the most serious complication of radiotherapy for NPC.

Methods: Data from 6023 consecutive and nonselected histologically proven primary NPC patients treated with definitive IMRT were collected and 25 patients were diagnosed with nasopharyngeal ulcer and met the diagnosis criteria of RINU. Predictive dosimetric factors were identified by using univariate and multivariate analysis.

Results: Paired samples t-tests showed all dosimetric factors were significantly correlated with the development of RINU, and these factors were associated with each other closely. ($P < 0.001$) Multivariate analysis revealed D3cc (dose to 3 mL of the nasopharynx) was an independent predictor for RINU ($P = 0.01$); the area under the ROC curve for D3cc was 0.87 ($P < 0.001$), and the cutoff point 73.67 Gy may be the dose tolerance of the nasopharynx. The primary tumor location, distribution of high dose regions and the location of RINU were consistent.

Conclusions: The study indicates that radiation-induced nasopharyngeal ulcer is consistent with primary tumor location and 'hottest spots' regions and we suggest a D3cc limit of 73.67 Gy for the nasopharynx. Physicians should be cautious of such 'hot spots' in the nasopharynxduring IMRT treatment plan optimization, review and approval to avoid the most serious complication of radiotherapy for NPC.

Introduction

Nasopharyngeal carcinoma (NPC) is a common malignancy in Southeast Asia and it is highly sensitive to radiotherapy (RT) [1]. Intensity-modulated radiation therapy (IMRT) has been widely applied in the field of radiation oncology over the last decade and is considered as a major breakthrough for nasopharyngeal carcinoma (NPC) due to its capability of delivering high radiation dose to the target while sparing the adjacent organs [2]. However, complications from radiation therapy can present in early and late phases. Early complications are related to acute mucosal injury radiation may cause both acute effects, which occur during radiation and in the immediate weeks and months following treatment, and late effects, which develop gradually over several months or years, result in poor quality of life and poor prognosis [3]. Radiation-induced nasopharyngeal ulcer (RINU) is ulcer of the surrounding and affiliated tissues of the nasopharynx, such as the mucosa, musculus longus capitis, parapharyngeal tissues, and skull base, which have been exposed to radiation months or years ago [4]. RINU becomes life threatening when the carotid sheath is involved, especially when internal carotid artery is eroded [5]. The diagnosis and treatment of RINU has not been discussed widely, mainly because of the lack of the dose constraints for particular structures that influence the occurrence of RINU in the IMRT era [6]. There is a critical need for more accurate information regarding dose limits to prevent RINU in primary NPC patients receiving IMRT.

This retrospective study is the first of its kind to analyze the clinical outcomes and dose-volume effect of radiation-induced nasopharyngeal ulcer after intensity modulated radiotherapy in primary nasopharyngeal carcinoma patients in a large cohort with extended follow-up, with the aim to determine how the radiation doses to nasopharynx influence the occurence of RINU and predict the most serious complication of radiotherapy for NPC.

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Materials and methods

Patient and pretreatment evaluations

Between January 2009 and December 2017, data from 6023 consecutive and nonselected histologically proven NPC patients were collected at Fudan University Shanghai Cancer Center and all patients underwent intensity-modulated radiotherapy (IMRT). Pretreatment evaluation consisted of a complete history and physical examination, indirect or fibre optic endoscopic examination, complete blood counts, determination of serum electrolytes, chest CT scan or X-ray, magnetic resonance imaging (MRI) scan of the head and neck, ultrasound of the liver and abdomen, and dental evaluation. Urinalysis, bone scan, and 18F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) were performed when clinically indicated.

Intensity-modulated radiotherapy

Immobilization and simulation

All patients were immobilized in the supine position with a thermoplastic mask, followed by conventional simulation and planning. Intravenous contrast-enhanced CT, using a slice thickness of 5 mm, was performed for planning. Image fusion of the T1 sequences with gadolinium enhanced MRI was performed with the CT simulation images for target delineation. The CT data were imported to treatment planning system (TPS) for treatment design.

Target delineation

The target volumes were defined in accordance with the International Commission on Radiation Units and Measurements Reports. The primary gross tumor volume (GTV_P) included all gross tumors and was determined by imaging, clinical, and endoscopic findings. The enlarged retropharyngeal nodes were outlined together with primary GTV on the IMRT plans.

Two clinical target volumes (CTVs) were defined in our radiotherapy: CTV1 and CTV2. All received elective neck irradiation to levels II, III, and VA, and one CTV was defined in our radiotherapy: CTV1. The CTV1 was defined as the high-risk region that included GTV_P plus a 5- to 10-mm margin. CTV1 should also encompass the entire nasopharynx, skull base, parapharyngeal space, retropharyngeal lymph nodal regions, inferior sphenoid sinus, pterygoid fossae, clivus, the posterior third of the nasal cavity and maxillary sinuses, and any high risk nodal regions, including the bilateral upper deep jugular nodes. The low-risk CTV (CTV2) referred to levels IV and Vb without metastatic cervical lymph nodes. There were two corresponding planning target volumes of high-risk region (PTV-Cs) in our radiotherapy: PTV_C1 (CTV1 + 3 mm) and PTV_C2 (CTV2 + 3 mm). The PTV_Cs would encompass the corresponding CTV with a 3-mm margin in all directions. However, when the CTV was near critical organs, such as the brainstem, spinal cord, PTV_C was generated as small as 1 mm.

The organs at risk (OAR) include the spinal cord, brain stem, optic chiasm, optic nerves, eyeballs, lens, temporal lobes, parotid glands, oral mucosa, larynx and temporomandibular joints. A 5-mm margin was added to the spinal cord and brainstem during optimization to form the planning organ-at-risk volume (PRV).

Treatment planning and delivery

All patients were treated with external-beam radiation therapy using 6-MV photons, 7–9 radiation fields. The treatment technique used was the simultaneous integrated boost (SIB) technique. The prescribed dose was 66 Gy in 30 fractions to planning target volume of primary tumor (PTV_G) for T1-2 and 70.4 Gy in 32 fractions for T3-4. The dose delivered to PTV_C1 and PTV_C2 was 60 Gy and 54 Gy, respectively in 30–32 fractions. All patients were treated with one fraction per day for 5 days per week. The number of patients receiving a PTV volume of < 95% of the prescription dose was not to exceed 1%. No patients were to receive more than 110% of the prescription dose into or out of the PTV. The dose distribution was also examined slice by slice on the CT images.

Chemotherapy

Chemotherapy, including neoadjuvant chemotherapy, concurrent chemotherapy and adjuvant chemotherapy, was given to patients when clinically indicated. The most common regimen of neoadjuvant and adjuvant chemotherapy included two to three cycles of TP (docetaxel 75 mg/m^2/day, day 1, cisplatin 25 mg/m^2/day, days 1–3), TPF (docetaxel 75 mg/m^2/day, day 1, cisplatin 25 mg/m^2/day, days 1–3, and 5-fluorouracil 0.5 g/m^2/day, days 1–3), or GP (gemcitabine 1 g/m^2/day, day1, day 8, cisplatin 25 mg/m^2/day, days 1–3) regimen. Induction chemotherapy was given every 3 weeks. Four weeks after the completion of RT, the adjuvant chemotherapy was administered every 3 weeks. Concurrent chemotherapy consisted of 80 mg/m^2 of cisplatin every 3 weeks for 2–3 cycles.

Patient evaluation

All patients were evaluated weekly for treatment response and toxicities during radiation therapy. After IMRT, patients were clinically evaluated every 3 months in the first 2 years, every 6 months from the third year to the fifth year, and annually thereafter. Each follow-up included examination of the nasopharynx and palpation of neck nodes, MRI of the nasopharynx, chest CT scan, and ultrasound of the abdomen after the completion of IMRT. Additional tests were ordered when indicated to evaluate local or distant relapse. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria [7].

Diagnosis criteria of RINU

RINU was diagnosed according to patients' characteristics, clinical manifestations, specific MRI features, endoscopic findings, and pathologic findings. The criteria for diagnosing RINU at MRI imaging were discontinuous nasopharyngeal mucosa line and/or a focal area of low signal intensity on contrast-enhanced T1-weighted images. MRI scans show defects in the nasopharyngeal wall and when pathologic changes deteriorate, MRI shows obvious defects in the carotid sheath and internal carotid artery (ICA) exposure (Fig 1). All MRI scans were re-valuated separately by two radiologists specializing in head-and-neck cancers according to the criteria. Any disagreement was resolved by consensus. 25 patients were diagnosed with nasopharyngeal ulcer and met the diagnosis criteria of RINU. All patients were evaluated clinically at the time of diagnosis and follow-up MRI study. RINU accompanied with recurrence were excluded [8].

Dosimetric parameters

For patients with RINU, the location and extent of RINU were transferred to the pretreatment planning computed tomography (CT) for dosimetric analysis. Original IMRT plans for patients were restored to TPS and MR images with the first RINU lesions during follow-up were fused with planning CT images based on bony landmarks. DVH curves were exported from the original treatment plans on the Pinnacle (Pinnacle 3; Philips Corp, Fitchburg, WI) TPS. Dose parameters including the volume of the RINU, maximum dose (Dmax), minimum dose (Dmin), mean dose (Dmean), absolute volume receiving n Gy (Vn), dose covering n volume (Dncc), and dose of n percentage volume (Dn) were derived from the exported DVH curves.

Treatment of RINU and follow-up data

The treatment of RINU has not been discussed widely, mainly because of the lack of understanding and effective treatment approaches for this complication. Most of patients received conservative treatment included daily nasopharyngeal irrigation with 2% aqueous hydrogen dioxide (5–10 mL each time) or saline (50–100 mL each time),