



Proposal for a new risk classification system for nasopharyngeal carcinoma patients with post-radiation nasopharyngeal necrosis



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ABSTRACT

Purpose: To analyze the clinical outcomes of nasopharyngeal carcinoma (NPC) patients with post-radiation nasopharyngeal necrosis (PRNN) and construct a new risk classification system for predicting survival of PRNN.

Methods: A total of 276 patients with PRNN were consecutively enrolled. Complete magnetic resonance (MR) images of the nasopharynx and neck were available for all patients and were used to assess nasopharyngeal necrosis status. After 2010, patients with PRNN were initially treated by radical endoscopic necrectomy followed by reconstruction with nasal flap (ENNF).

Results: The 1-year and 2-year overall survival (OS) was 65.0% and 51.6%, respectively. Three variables affected survival: osteoradionecrosis, re-irradiation, and internal carotid artery (ICA) exposure, and only two variables were found to be independent prognostic factors: re-irradiation (hazard ratio [HR] 1.75, $P = 0.001$) and internal carotid artery (ICA) exposure (hazard ratio [HR] 1.80, $P = 0.001$). These two variables were combined to create a new risk classification system for PRNN. 131 (47.5%), 110 (39.9%), and 35 (12.7%) patients were classified into low-, intermediate- and high-risk group, with the 2-year OS rates of 64.8%, 45.1%, and 22.5%, respectively ($P < 0.001$). ENNF was associated with a better OS in these three group patients compared with conservative management with statistical or marginal statistical significance (2-year OS low-risk group, 90.9% vs 61.1%, $p = 0.081$; intermediate-risk group: 100% vs 37.8%, $P = 0.001$; and high-risk group, 57.1% vs 20.8%, $p = 0.066$).

Conclusion: The new risk classification system provides accurate estimates of prognosis. ENNF surgery may lead to better survival outcome than conservative management in PRNN patients.

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Introduction

Radiotherapy (RT) is the mainstay treatment for nasopharyngeal carcinoma (NPC). Recent developments in RT technique have resulted in improved survival rates even among locoregionally advanced NPC patients, with a 3-year overall survival (OS) rate from 71.0% to 94.3% [1,2]. Nevertheless, complications of the irradiation fields are inevitable and the quality of life among NPC survivors is often compromised [3–6].

Post-radiation nasopharyngeal necrosis (PRNN) is one of the most serious complications of radiotherapy for NPC. Patients with PRNN usually present with severe headache, foul odor, and epistaxis [5,6]. Severe and even fatal complications of PRNN, including massive hemorrhage, infection, and cachexia, have occasionally been seen [5,6]. The mortality may reach 72.7% when internal carotid artery (ICA) is exposed to necrotic lesions. [6].

Management of PRNN remains challenging due to poor understanding of its irreversibility and etiology. Various treatment strategies such as hyperbaric oxygen, daily nasopharyngeal irrigation, intravenous nutrition, and systematic antibiotic therapy have clinically been tested but the outcomes are disappointing. Although repeated endoscopic debridement is commonly used as an effective approach to relieve symptoms, the effect may fall away once the treatment is discontinued [5,6]. In 2010, a novel surgical

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treatment for PRNN patients, radical endoscopic necrectomy followed by reconstruction with nasal flap (ENNF) was initiated. The surgical treatment has recently acquired promising results with the advantage of minimal invasion (data unpublished).

To date, all reports regarding optimal treatments and survival outcomes of PRNN have been largely in the form of case series, while studies with large sample sizes are lacking. Therefore, we retrospectively analyzed 276 NPC patients with PRNN with the aim of proposing a new staging system of PRNN for predicting survival and guiding treatment.

Materials and methods

Patient selection

Between April 2005 and March 2016, a total of 24,886 NPC patients received nasopharyngeal examinations with nasopharyngoscopy during their treatment or follow-up in our department. Within this cohort, 276 patients with histologically or radiologically confirmed nasopharyngeal necrosis who received definitive radiotherapy initially before necrosis were enrolled in this study. Complete magnetic resonance (MR) images of the nasopharynx and neck were available for all patients and were used to assess nasopharyngeal necrosis status. This study was approved by the ethical committee of Sun Yat-Sen University Cancer Centre. Written informed consent was obtained from all the patients.

Diagnosis of PRNN

PRNN was confirmed by nasopharyngeal endoscopy followed by biopsy for most of the patients. Endoscopy showed foul necrotic secretion or granulation in nasopharynx, and exposed bone or sequestra could be seen after removal of the secretion (Fig. 1). Those patients without pathologic results were diagnosed radiologically according to specific magnetic resonance image (MRI) features. The criteria for diagnosing PRNN at MR imaging were discontinuous nasopharyngeal mucosa line and/or a focal area of

low signal intensity on contrast-enhanced T1-weighted images (Fig. 1). Skull base osteoradionecrosis and ICA exposure were found in 138 and 81 cases respectively.

Radiotherapy

All patients received definitive external-beam radiotherapy with either 60Co or megavoltage linear accelerators before diagnosis of PRNN. The radiotherapy techniques employed in this study include the conventional radiotherapy (CRT), three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and brachytherapy (BT), in accordance with the treatment policy adopted by each center. The detailed radiotherapy techniques have been previously reported [7,8]. When it comes to the primary radiotherapy technique, 53.3% of the total patients were given conventional two-dimensional radiotherapy, 1.1% received 3D-CRT and 45.7% received IMRT. Nineteen (6.9%) patients received brachytherapy to the NP. Fifteen of these patients received brachytherapy for persistent disease at 6 weeks after the first course of radiotherapy. Three patients received brachytherapy as part of the re-irradiation treatment. One patient received brachytherapy for both indications. The cumulative radiation doses were 60–80 Gy to the primary tumor and 50–70 Gy to the involved neck area. By the time PRNN was diagnosed, 99 patients received re-irradiation for their local recurrence.

Treatment of PRNN

Conservative management

Conservative treatment included daily nasopharyngeal irrigation with 2% aqueous hydrogen dioxide (5–10 mL each time) or saline (50–100 mL each time), intravenous nutrition, and systematic antibiotic therapy. Endoscopic debridement and excision of the necrotic tissues were also considered to be conservative and they were usually performed every 2 or 4 weeks until their clinical symptoms, such as foul odor, headache, and hemorrhage, were alleviated.

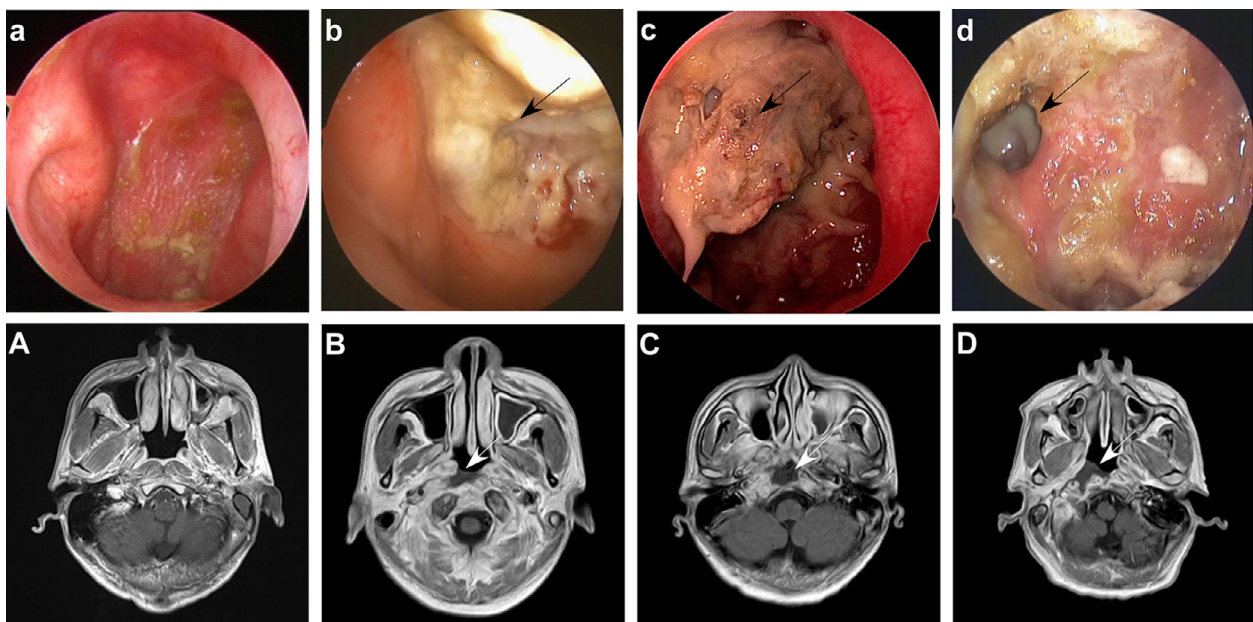


Fig. 1. Endoscopic images and magnetic resonance images (MRIs) of four patients with NPC after radiotherapy. (a) Endoscopic image and (A) transverse, contrast enhanced T1 weighted MRI of a 36-year-old man show the regular nasopharynx after radiotherapy. (b) Endoscopic image and (B) transverse, contrast enhanced T1 weighted MRI of a 41-year-old man show the necrosis in the nasopharyngeal posterior wall (arrow). (c) Endoscopic image and (C) transverse, contrast enhanced T1 weighted MRI of a 37-year-old man show the necrosis with osteoradionecrosis (arrow). (d) Endoscopic image and (D) transverse, contrast enhanced T1 weighted MRI of a 42-year-old man show the necrosis in the right nasopharyngeal lateral recess and the exposed internal carotid artery (arrow).

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