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Ten-year survival outcomes for patients with nasopharyngeal carcinoma receiving intensity-modulated radiotherapy: An analysis of 614 patients from a single center

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ABSTRACT

Objectives: Intensity-modulated radiotherapy (IMRT) has been applied in nasopharyngeal carcinoma (NPC) for nearly twenty years, while little is known about the ten-year survival outcomes. This study aimed at evaluating the 10-year survival outcomes for patients with NPC receiving IMRT.

Materials and methods: Data on 614 patients with newly diagnosed, non-disseminated NPC treated by IMRT between 2004 and 2008 were retrospectively reviewed. Survival outcomes stratified by tumor stage were compared.

Results: The median follow-up duration was 112.7 months (range, 7.6–156.8 months) for the entire cohort. The 10-year local relapse-free survival rates for T1, T2 and T3 were 94.2%, 92.5% and 91.4% ($P > 0.05$), respectively, and significantly higher than that of T4 disease (79.3%, $P < 0.05$ for all rates). As N category increased from N0 to N3, the 10-year distant metastasis-free survival rates significantly decreased accordingly ($P < 0.01$ for all rates). Furthermore, the 10-year overall survival rates were 100%, 87.1%, 75.5% and 55.6% for stage I, II, III and IV, respectively ($P < 0.05$ except stage I and II). Multivariate analysis established tumor stage and age as independent prognostic factors. Late toxicities were assessable for 495 (80.6%) patients and most were Grade I/II damages. Xerostomia (387 of 489, 79.1%) and hearing impairment (212 of 495, 42.8%) remained the most troublesome.

Conclusion: IMRT could achieve satisfactory survival outcomes for NPC patients with acceptable late toxicities. However, distant control still remains poor, especially for patients with N3 disease.

Introduction

Nasopharyngeal carcinoma (NPC) is a rare cancer arising from the nasopharynx epithelium, and its geographical distribution is extremely unbalanced. In total, 86,500 cases of NPC were reported in 2012, and 71% of new cases were in the east and southeast parts of Asia, with south-central Asia, and north and east Africa accounting for the remainder [1]. Due to the anatomical constrains and highly radiosensitive nature of NPC, surgery is inappropriate and radiotherapy is the only curative treatment of choice for non-disseminated disease. Furthermore, NPC is also sensitive to chemotherapy and concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy has been established as the main treatment for advanced disease [2–4] as numerous studies have proven that a combined strategy of radiotherapy and chemotherapy could achieve better survival outcomes than radiotherapy alone [5–12].

In the era of two-dimensional radiotherapy (2DRT), a large cohort study consisting of 5037 NPC patients by Lee et al. [13] showed the ten-year overall and failure-free survival rates were 43% and 34%, respectively. The available data of this study add to the body of knowledge on long-term therapeutic outcomes of NPC patients receiving 2DRT. As the radiotherapy technique advances rapidly, intensity-modulated radiotherapy (IMRT) has replaced conventional two or three dimensional radiotherapy (2D/3DRT) to become the main treatment modality over the last decade, and numerous studies revealed a significant benefit of local control by using IMRT [14–17]. However, only 5-year survival outcomes with an overall survival of 79.6–87.4% [16–18] were reported in the IMRT era, and we still lack the 10-year data. Given

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the truth that the management of NPC patients has revolutionized after the adoption of IMRT and combined chemotherapy-RT strategies, it is therefore worth re-evaluating the 10-year survival outcomes for patients treated by IMRT. However, to the best of our knowledge, no study to date has been carried out to address this issue. Based on this premise, we conducted this retrospective study to comprehensively evaluate the 10-year outcomes for patients with NPC receiving IMRT from a non-epidemic region.

Materials and methods

Study patient

Between April 2004 and December 2008, data on 614 consecutive patients with newly diagnosed, biopsy-proven non-disseminated NPC treated at Nanjing Medical University Affiliated Cancer Hospital of China were retrospectively reviewed. All the patients included in this study had no malignant tumor history and did not receive radiotherapy previously. Complete medical records and follow-up data were well collected. This study was approved by the Research Ethics Committee of Jiangsu Cancer Hospital. Written informed consent was obtained from all the patients before treatment.

Pre-treatment workup

Initial workup included clinical and laboratory examinations, hematologic and biochemistry profiles, fiberoptic endoscope examination of the nasopharynx, magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) of the head and neck to evaluate the extent of the primary tumor and regional lymph nodes. Bone scintigraphy, chest radiography or contrast-CT, and ultrasonography of the abdominal region were performed to exclude distant metastasis. 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)-CT would also be performed if clinically indicated. Finally, 607 (98.9%) patients received MRI and 7 (1.1%) patients received CT as staging workup. Additionally, PET-CT was performed to 116 (18.8%) patients. All patients were restaged according to the 7th edition of the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) system [19].

Radiotherapy

All the patients received radical IMRT using simultaneous integrated boost (SIB) with 6 MV X-rays in our center as reported previously [20]. Briefly, gross tumor volume (GTVnx) included the primary tumor and metastatic retropharyngeal lymph nodes based on the MRI findings. Metastatic cervical lymph nodes were defined as GTVnd. The high-risk region was defined as clinical target volume (CTV1) which included the whole nasopharyngeal cavity, GTVnx, GTVnd with a margin of 5–15 mm, and levels II and III cervical lymphatic drainage region. Low risk area was defined as CTV2 which encompassed CTV1 with a margin of 3–5 mm, the lower neck, and the supraclavicular lymphatic drainage region. A total prescribed doses of 66–75 Gy/31–35 fractions to the planning target volume (PTV) of GTVnx, 65–75 Gy/32–35 fractions to the PTV of GTVnd, 56–60 Gy/30 fractions to the PTV of CTV1 and 50 Gy/30 fractions to the PTV of CTV2 were delivered with first 30 fractions to CTV1/CTV2 and then a boost to PTV of GTVnx and GTVnd for patients with locally or regionally residual tumor after prescribed dose. All patients were irradiated with 1 fraction daily, 5 days per week.

Chemotherapy

Prior to treatment, we recommended radiotherapy alone for stage I disease, radiotherapy with or without concurrent chemotherapy for stage II disease. Whenever possible, concurrent chemotherapy was provided for patients with stage III-IVB and induction or adjuvant chemotherapy would also be considered. Normally, induction chemotherapy is rigorously scheduled for patients with advanced N category to reduced micro-metastasis or shrink tumor volume. Occasionally, induction chemotherapy would also be delivered just for radiotherapy waiting time.

Platinum-based chemotherapy regimens, including 5-fluorouracil (1000 mg/m^2/d d1–d5) with cisplatin (80 mg/m^2 d1–3) (PF), docetaxel (75 mg/m^2 d1) with cisplatin (80 mg/m^2 d1-3) (TP) or triplet of docetaxel (60 mg/m^2 d1) and cisplatin (80 mg/m^2 d1–3) plus 5-fluorouracil (1000 mg/m^2/d d1–d5) (TPF), were administered before or after radiotherapy every three weeks. Concurrent chemotherapy regimens mainly consisted of cisplatin (80 mg/m^2 d1-3) plus fluorouracil (400 mg/m^2/d d1–d4) [11] or single agent of cisplatin (80–100 mg/m^2 d1) at 3-week interval for two or three cycles. The chemotherapy during the whole treatment period was limited to no more than six cycles in total.

Follow-up

Follow-up was measured from first day of therapy to last examination or death. Each follow-up visit included a clinical physical examination, nasopharyngoscopy, ultrasonography of the abdomen and chest X-ray. A CT scan or MRI of the head and neck region was conducted every 3 months during the first 2 years, then every 6 to 12 months thereafter (or until death). The Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring criteria [21] and Common Terminology Criteria for Adverse Events (Version 3.0) were used to assess the late toxicities of radiotherapy at patients' every visit. Only patients with regular follow-up were included in the analysis of late toxicities. For patients with evidence of local-regional recurrence or distant metastasis, additional examination or imaging modalities were performed to confirm or exclude disease progression at the discretion of the treating physician.

Statistical analysis

The Stata Statistical Package 12 (StataCorp LP, College Station, TX, USA) was used for all analyses. Kaplan–Meier method was adopted to calculate the local relapse-free survival (LRFS), regional relapse-free survival (RRFS), distant metastasis-free survival (DMFS) and overall survival (OS) rates, and the difference was compared using log-rank test. Multivariate Cox proportional hazards model using backward elimination method was undertaken to estimate hazard ratios (HRs) and 95% confidence intervals (CIs); age [22], gender [23], karnofsky performance score (KPS), radiation dose, T category, N category, overall stage and chemotherapy were included as variables. All statistical tests were two-sided, and $P < 0.05$ was considered as statistically significant.

Results

Baseline characteristics

For the entire cohort, the male (n = 444)-to-female (n = 170) ratio was 2.6:1, and the median age was 46 (range, 9–85 years) years old. The baseline characteristics of the 614 consecutive NPC patients were summarized in Table 1. The percentages of patients grouped as stage I, II, III and IVA-B were 2.8%, 21.8%, 44.1% and