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Original article

Is replacement of the supraclavicular fossa with the lower level classification based on magnetic resonance imaging beneficial in nasopharyngeal carcinoma?

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ABSTRACT

Purpose and objectives: To investigate the pattern of lymph node metastasis and treatment outcome after intensity-modulated radiotherapy (IMRT) in nasopharyngeal carcinoma (NPC), and assess the possibility of replacing Ho's supraclavicular fossa (SCF) with the lower level (LL; cervical extension below caudal edge of cricoid cartilage) based on magnetic resonance imaging (MRI) as a criterion for N3 disease.

Methods and materials: We retrospectively reviewed 749 patients with biopsy-proven non-metastatic NPC treated with IMRT. Lymph node metastasis was mapped using the 2013 International Consensus Guidelines.

Results: Cervical lymph node (CLN) laterality, CLN greatest dimension (>60 vs. ⩽60 mm) and Ho's SCF were independent prognostic factors for disease-free survival (DFS) and distant metastasis-free survival (DMFS; $P < 0.01$) in multivariate analysis. Replacing Ho's SCF with the LL was also predictive for DFS and DMFS ($P < 0.01$). Compared to the 7th UICC/AJCC, N-categories based on the LL provided more satisfactory distinction between hazard ratios for distant and disease failure for each N-category. N3a and N3b as defined by the 7th UICC/AJCC had similar DMFS ($P = 0.31$) and DFS ($P = 0.21$).

Conclusions: Replacing Ho's SCF with the LL is simple and practical. The N-category staging system could be further simplified by merging N3 subcategories.

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The tumor-node-metastasis (TNM) staging system for nasopharyngeal carcinoma (NPC) is crucial for accurately estimating prognosis and guiding treatment strategies for different risk groups, and also for evaluating and comparing different treatments and facilitating information exchange between treatment centers [1].

The supraclavicular fossa (SCF) was originally described by Ho [2] in the mid-seventies, before computed tomography (CT) cross-sectional imaging was widely employed for N-categorization in NPC. The SCF, an anatomical boundary primarily assessed by clinical examination, is the triangular region defined by the superior margin of the sternal end of the clavicle, the superior margin of the lateral end of the clavicle, and the point where the neck meets the shoulder. Previous studies have consistently shown that patients with extensive lymphatic spread to Ho's SCF have the poorest prognosis [3,4]. However, definition of Ho's SCF is primarily based on landmarks determined by clinical examination, which can lead to inconsistent assessment between clinicians and a low accuracy of estimation.

With the implementation of intensity-modulated radiation therapy (IMRT), a more reliable method to define the delineation of target volumes in cross-sectional imaging is required. Previous studies applied the recommendations for the radiological boundaries of the neck node levels (based on cross-sectional imaging) for N-categorization in NPC, and found that N-category staging systems based on these recommendations were highly predictive and may provide a more objective method for staging NPC [5–8]. Ng et al. [6] used the radiological nodal levels IV and Vb (Som's classification) [9] to replace Ho's SCF, and found this substitution was predictive for both distant control and overall survival. In support of these observations, Li et al. [8] reported that the involvement of levels IV and Vb and the SCF as defined by the International Consensus Guidelines [10,11] was an independent prognostic factor for distant failure and disease failure. Although these studies adopted a variety of different definitions of the neck node levels

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based on cross-sectional imaging, they all suggested that the cervical region below the cricoid cartilage should be used to replace Ho' SFC. The cricoid cartilage is an anatomical landmark that can be reliably defined by physical examination and also accurately located in cross-sectional images. Therefore, replacing Ho's SCF with extension below the caudal edge of the cricoid cartilage, termed the lower level (LL) [12], may be a simple and practicable approach.

Therefore, in this study we retrospectively reviewed data on 749 patients with NPC from an endemic area who were treated with IMRT, and explored the feasibility of replacing Ho's SCF with the LL as one component of defining the N3 category, in order to provide evidence for future improvements to the N-category staging system for NPC.

Methods and materials

Patient characteristics

A total of 749 patients with newly diagnosed, biopsy-proven, non-metastatic NPC treated at Sun Yat-sen University Cancer Center using IMRT between January 2003 and December 2007 were retrospectively reviewed. The cohort included 580 males and 169 females, with a male:female ratio of 3.43:1 and median age of 43 years (range, 13–78 years). Histologically, 99.3% (744/749) of patients had WHO type II or III disease, and 0.7% (5/749) had WHO type I disease. All patients completed a pre-treatment evaluation including a complete physical examination, fiber optic examination, chest X-ray, abdominal ultrasound, MRI imaging studies and single photon emission computed tomography (SPECT) whole body bone scan. Additionally, 21.6% (162/749) of patients underwent positron emission tomography-computed tomography (PET-CT). The 6th edition of the UICC/AJCC Staging System was used for initial staging and treatment decisions.

Image assessment and criteria for lymph node metastasis

All patients underwent MRI using a 1.5-T system to examine the region from the suprasellar cistern to the inferior margin at the sternal end of the clavicle with a head-and-neck combined coil. Two experienced radiologists evaluated the MRI images separately. Any disagreements were resolved by consensus. The diagnostic criteria for metastatic lymphadenopathy included: (a) any individual lateral retropharyngeal lymph node (RLN) with a minimal axial diameter (MID) in the largest plane of at least 5 mm or any node seen in the median retropharyngeal (RP) group, lymph nodes with a MID of at least 11 mm in the jugulodigastric region or 10 mm for all other cervical nodes except the RP group; (b) lymph nodes of any size with central necrosis or a contrast-enhanced rim; (c) nodal grouping, the presence of three or more contiguous and confluent lymph nodes (each of which should have a MID of 8–10 mm); and (d) lymph nodes of any size with extracapsular spread, the presence of indistinct nodal margins, irregular nodal capsular enhancement or infiltration into the adjacent fat or muscle [13,14].

The locations of the lymph nodes were defined according to the 2013 International Consensus Guidelines [10,11,15]; the following 16 nodal groups were assessed: level Ia, Ib, IIa, IIb, III, IVa, IVb, Va, Vb, Vc, VI, VIIa, VIIb and VIII–X.

Treatment

All patients underwent radical radiotherapy, and the tumor volumes of the nasopharynx and upper neck were treated using IMRT for the entire treatment course. The lower neck was treated using a conventional anterior or anteroposterior opposing cervical technique. Further details of the IMRT techniques have been reported previously [16]. The prescribed radiation dose was: total dose of 68–70 Gy in 30–33 fractions at 2.13–2.27 Gy/fraction to the planning target volume (PTV) of the GTV-P, 60–68 Gy to the nodal gross tumor volume PTV (GTV-N), 60 Gy to the PTV of CTV-1 (high-risk regions), and 54 Gy to the PTV of CTV-2 (low-risk regions and neck nodal regions). All patients were treated with one fraction daily 5 days per week. During the study period, our institutional guidelines recommended no chemotherapy in stage I–IIA, concurrent chemoradiotherapy in stage IIB, and concurrent chemoradiotherapy with or without induction/adjuvant chemotherapy for stage III–IVA-B, as defined by the 6th edition of the UICC/AJCC Staging System. In total, 71.4% (535/749) of the patients were given platinum-based chemotherapy. The sequence used was concurrent in 33.5% (233/749), induction-concurrent 32.8% (246/749), and concurrent-adjuvant 6.1% (46/949). 86.2% (424/492) of patients with stage III–IV disease received chemotherapy. When possible, salvage treatments such as intracavitary brachytherapy, surgery and chemotherapy were provided in documented relapse or persistent disease.

Clinical staging methods

Medical records and imaging studies were retrospectively analyzed, and all patients were restaged according to the 7th edition of the UICC/AJCC Staging System (Table 1). Using the radiological definition of the LL (levels IVa, IVb, Vb and Vc) based on MRI as the demarcating criterion for N3 disease, a modified 'Level' system of N-category classification was applied, as follows: N0: no regional lymph node metastasis; N1: unilateral cervical or retropharyngeal nodes (irrespective of laterality) $\leqslant$6 cm above the LL; N2: bilateral cervical nodes $\leqslant$6 cm above the LL; N3a: any node >6 cm; N3b: involvement of the LL.

Follow-up and statistical analysis

Follow-up was calculated from the first day of therapy to the day of death or last examination. Patients were examined at least every 3 months during the first 2 years, and every 6 months thereafter for 3 years or until death. SPSS version 16.0 (SPSS) was used for statistical analysis. The following endpoints (measured from the start of treatment to the first defining event) were estimated: local relapse-free survival (LRFS), nodal relapse-free survival (NRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS) and overall survival (OS). Diagnosis of failure was based on signs of progressive disease in clinical and/or radiological examinations. Actuarial rates were calculated using the Kaplan–Meier method [17] and compared using the log rank test [18]. Multivariate analyses with the Cox proportional hazards model [19] were used to test for independent significance by backward elimination of insignificant explanatory variables. The Cox proportional hazards model was used to calculate hazard ratios (HR). Host factors (age and gender) therapeutic intervention (chemotherapy), and tumor factors (WHO type, T classification, nodal level, laterality, and size) were included as covariates in all tests. Two-tailed P-values <0.05 were considered statistically significant.

Results

Tumor control

The median follow-up period was 81.4 months (range, 3.1–126.5 months). In total, 129 (17.2%) patients developed distant metastases, 56 (7.5%) experienced local-regional failure and 149 (19.9%) died. The 5-year OS rate for all patients was 83.9%, with a DFS rate of 75.9%, DMFS rate of 83.1%, LRFS rate of 94.7%, and NRFS rate of 97.1%.

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