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Review

Staging of nasopharyngeal carcinoma – The past, the present and the future

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SUMMARY

This article reviews the evolution of the International Union Against Cancer/American Joint Committee on Cancer staging system for nasopharyngeal carcinoma. With the increasing availability of newer imaging methods, more sophisticated radiotherapy techniques and rapidly evolving molecular assays, we also examine newer clinical features that might have impact on staging. A new version of the staging system taking into account of some of these factors is also proposed.

Introduction

The current International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) TNM Classification for nasopharyngeal carcinoma (NPC) is a staging system based purely on the anatomical extent of the disease. Its primary purpose is to help the physician estimate the disease prognosis and design management plan. The year of 1997 is the most significant milestone in its development as diverse classifications were used prior to it. It was until in its 5th edition that international experts were able to reach consensus on a unified NPC staging classification [1]. Compared with other head & neck cancer staging, this 5th edition has a unique N classification with the definition of supraclavicular fossa (SCF) as first described by Ho [2].

During the past 15 years, there have been some slow but significant refinements in the TNM classification system. Coupled with these changes, there were also significant advancements in imaging technology, radiotherapy (RT) delivery and integration of systemic chemotherapy for loco-regional advanced disease. New biomarkers and functional imaging have also been introduced. This article describes in details the evolution of TNM classification from the 5th to 7th edition [1,3,4], as well as the stage migration due to the increasing availability of computerized tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). We will also discuss some of the unsettled anatomical issues due to better soft tissue resolution of MRI and the way forward. Finally we will review some tumor and host factors that have important bearings in the treatment outcomes of this disease.

The 7th edition TNM – what's new? (Table 1)

One of the revisions in the current edition is the adjustment in T1, T2a and T2b categories within the previous edition [3,4]. A consistent finding is the absence of difference in treatment outcome between T1 and T2a diseases, leading to the reclassification of patients with oropharynx and/or nasal fossa involvement to T1 category [5–7]. Also, analysis of the T2b disease indicated that it remained a distinct unfavorable group as compared to the proposed T1 category, exhibiting a significantly higher hazard of local and distant failure with consequent impact on cancer-specific death, justifying that this subcategory continued independently as a T2 category within the TNM classification. The second revision is the inclusion of retropharyngeal lymph node (RPLN) involvement into the TNM classification. RPLN involvement is very common in NPC. However, because of limited diagnostic capability prior to the era of MRI imaging, consistent principles of designation of RPLN could not be identified in the previous TNM classifications. Evidence from retrospective studies indicated that patients with RPLNs alone have a risk of distant metastasis (DM) similar to N1 disease regardless of its laterality [8,9]. The third revision is the inclusion of medial and lateral pterygoid muscle into the definition of masticator space. This is one of the controversial areas that we will address in the subsequent section.

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Stage migration

Significant stage migration has been observed with the increasing use of advanced imaging technology. PET or PET-computed tomography (PET-CT) has been shown to be more sensitive and specific than conventional imaging in detecting DM [10–13]. In one of the studies, PET modified the M staging in 7.2% of the patients and was more accurate than MRI for determining cervical nodal metastasis [11]. In an Australian series, PET-CT was valuable for detecting occult metastases and defining the extent of neck nodal disease, impacting management in 33% (8% major impact in detecting M1 disease and 25% medium impact by upstaging the N category, or showing the exact lymph node extent) of the patients [14]. On the other hand, retrospective study by Liao et al. showed that MRI was more sensitive than CT in detecting local disease extension especially parapharyngeal tumor extension, oropharyngeal extension and ethmoid sinus spread [15]. These resulted in changes in 49.8% of T category (32% upstaging), 10.7% of N category (5.2% upstaging, 5.5% downstaging), and 38.6% of group stage (two-third upstaging). The changes in T category were due to the superiority of MRI in diagnosing soft tissue and bone marrow extension. In total, 9.3% benefited from an adjustment in treatment strategy with the use of MRI.

Unsettled anatomic issues and possibility of sub-classification

Due to the increasing use of MRI and PET-CT as a diagnostic and staging tool, apart from its effects on stage migration, various sub-classifications have been proposed based on new information made available with these imaging findings.

Controversy in T3 and T4 categories

There are two studies that suggest classifying patients with different extent of skull base involvement into different T3 sub-categories [16] or even upstaging those with most extensive involvement as a T4 disease [17], and one study that suggest classifying patients with different extent of intracranial extension involvement into different T4 sub-categories [18], but more than 80% of patients in these studies were treated by two-dimensional RT (2DRT), the relevance in intensity modulated RT (IMRT) era was uncertain, and it is quite unlikely that such sub-categorization could offer substantial help in guiding treatment decision.

Definition of masticator space

The most ambiguous term among the defining criteria is 'masticatory space'. This was introduced in the 6th edition as a synonym of infra-temporal fossa [3], defined as extension beyond the anterior surface of the lateral pterygoid muscle or beyond the posterolateral wall of the maxillary antrum and/or the pterygo-maxillary fissure. Unfortunately, this differs from the definition used in classical radiological textbooks as "primarily the muscles of mastication (the medial and lateral pterygoid, masseter and temporalis) enclosed by the superficial layer of the deep cervical fascia", and this description was adopted in the 7th edition [4]. While this is anatomically correct, the most important issue is whether this truly reflects the clinical prognosis. The study by Tang et al. supported this definition for T4 classification due to its significant impact on survival, even it posted no effect on local failure [8]. They stated that comparison of the 265 patients with medial and lateral pterygoid muscles involvement versus the 9 patients with temporalis muscles invasion showed no significant differences. However, over 80% of the series were treated by 2DRT, and the sample of patients with extensive infiltration was too small for evaluation. Base on a more recent study from the same institute on patients with T4 disease treated by IMRT, they advocated sub-classifying the 47 patients with mastication muscles involvement as T4a because their survival (5-year overall survival (OS): 83% versus 63%) and distant control were significantly better than those with other T4 criteria [19]. As these patients actually have survival rate similar to that with T2 disease, it may not be appropriate to classify these patients to T4a based on mastication muscles involvement (without temporalis muscle invasion) alone.

Prognostic significance of prevertebral space involvement

Several retrospective studies have shown that prevertebral space involvement (PSI) is an independent prognostic factor for treatment outcomes [20–22]. For patients with primary treatment using 2DRT, PSI carried a poor prognosis on local and distant control [20]. In another retrospective series, distant metastasis free survival was increased from 72% to 100% by adjuvant chemotherapy in the patients with PSI, but this effect was not observed in the group without PSI [21]. The only contemporary study in the IMRT era indicated that PSI was an independent prognostic factor for both OS and distant metastasis free survival [22]. However, this had no significant impact on local failure. Classifying disease with prevertebral space involvement as T4 had been suggested but there were no data whether these patients had treatment outcome similar to that of T4.

Synchronous or metachronous solitary metastasis as M1a

DM has been recognized to be a major cause of treatment failure in patients with NPC. The Hong Kong NPC Study Group [23] conducted a retrospective review on 2915 patients and DM was found to be the most common mode of failure, with a 5-year actuarial rate of 14.9%. In particular, patients with lung metastasis alone had a median OS of 3.9 years, which was significantly longer than the median OS for other sites of pure DM. With the increasing use of systemic and local ablative therapy, it was also found that selected groups of patients with solitary metastasis could benefit from aggressive therapy and some are even cured [24–27]. Studies also showed that liver metastasis is an adverse prognostic factor for survival in metastatic NPC when compared with lung or bone metastases [23,24,28,29]. It was proposed to categorize patients with pulmonary metastasis and/or solitary lesions as M1a whereas those with multiple metastasis located in any other anatomic site as M1b as the former group of patients was expected to benefit from more aggressive treatment [30].

New proposal – the "8th" edition

Despite the known limitations, TNM classification remains the most important system for guiding treatment decision. The importance of maximizing its prognostic accuracy cannot be overemphasized. The changes introduced in the current edition [4] was based on studies in which the majority of the patients were staged with CT, and/or irradiated by 2DRT technique, without the addition of concurrent chemotherapy for advanced diseases [5–8]. However, multiple studies have shown that IMRT is able to achieve excellent loco-regional control ($\geqslant$90%) especially for early stage NPC [31–33]. In one of the recent studies, multivariate analyses of 305 patients undergoing IMRT revealed that T-classification had no predictive value for local control and survival, whereas only N-classification was a significant prognostic factor for OS [34]. Therefore, evaluation of the current edition for suitability in the modern IMRT era is needed.