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Review

Evolution of treatment for nasopharyngeal cancer – Success and setback in the intensity-modulated radiotherapy era

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ABSTRACT

Background and purpose: To assess the therapeutic gains and setbacks as we evolved from the 2-dimensional radiotherapy (2DRT) to conformal 3-dimensional (3DRT) and to intensity-modulated (IMRT) era.
Material and methods: 1593 consecutive patients from 1994 to 2010 were retrospectively analyzed. Evolving changes in the different era included advances in staging investigation, radiotherapy technique, dose escalation, and use of chemotherapy.
Results: The 3DRT era achieved significant improvement in local failure-free rate (L-FFR), disease-specific survival (DSS) and overall survival (OS). Neurological damage and bone/soft tissue necrosis were significantly reduced. However, the improvement in distant failure-free rate (D-FFR) was insignificant, and more hearing impairment occurred due to chemotherapy. Significantly higher D-FFR was achieved in the IMRT era, but L-FFR did not show further improvement. 5-Year DSS increased from 78% in the 2DRT, to 81% in the 3DRT, and 85% in the IMRT era, while the corresponding neurological toxicity rate decreased from 7.4% to 3.5% and 1.8%.
Conclusions: Significant improvement in survival and reduction of serious toxicity was achieved as we evolved from 2DRT to 3DRT and IMRT era; the therapeutic ratio for all T-categories improved with more conformal techniques. Improvements in tumor control were attributed not only to advances in RT technique, but also to better imaging and increasing use of potent chemotherapy. However, it should also be noted that hearing impairment significantly increased due to chemotherapy, L-FFR reached a plateau in the 3DRT era, and it is worrisome that the result for T4 remained unsatisfactory. Besides exploring for more potent chemotherapy and innovative methods, the guideline on dose constraint should be re-visited to optimize the therapeutic ratio.

Treatment of nasopharyngeal carcinoma (NPC) is one of the greatest challenges for oncologists. This cancer is notorious for its aggressive natural behavior with early lymphatic spread and high predilection for hematological dissemination. Majority of patients presented with advanced disease, and treatment is difficult due to anatomical location of the nasopharynx and proximity of critical structures.

The development of radiation therapy (RT) revolutionized the treatment of NPC. Moss et al. in 1965 showed 25% of patients were alive at 5 years, and established RT as the primary treatment modality [1]. The early series were mainly staged by X-ray and treated with 2-dimensional technique (2DRT); series from Queen Elizabeth Hospital (Hong Kong) and M. D. Anderson Cancer Center during 1954–1992 showed improvement of 5-year disease-specific survival (DSS) to 50% [2,3].

During the past decades, accumulation of knowledge on radiobiology and target volume delineation enabled us to evolve from 2DRT to 3-dimensional conformal technique (3DRT) and then intensity modulated technique (IMRT), leading to increasing conformity of tumor coverage with better sparing of normal structure. Incorporation of concurrent cisplatin-based chemotherapy leads to further improvement of tumor control for advanced disease.

As RT technique evolved, reports on clinical outcome show conflicting results. Studies on 3DRT boost showed no major benefit despite theoretical probability of improvement in uncomplicated tumor control [4,5]. The early reports using IMRT all showed excellent locoregional control. A randomized trial by Peng et al. comparing IMRT versus 2DRT showed significant improvement in OS [6]. However, a retrospective comparison by Lai et al. on 1276 patients showed no improvement in disease-free survival, and two other studies warned of unsatisfactory survival results for patients with advanced primary tumor [7–9].

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The objective of the study is to compare treatment outcome and toxicity among different radiotherapy techniques (2DRT, 3DRT, IMRT).

Materials and methods

Patient selection

Consecutive patients with non-disseminated NPC who were treated with radical intent were analyzed. They were divided into three groups according to the RT technique used: the 2DRT era from March 1994 to November 1998; 3DRT era from November 1998 to May 2005; and the IMRT era from May 2005 to December 2010.

Staging

Back in 1994, patients were staged by computed tomography (CT) only; metastatic work-up (by chest X-ray, ultrasonography of liver and isotope bone scan) was performed for those with stage IV disease. The facility to stage all patients (except those with contraindication) with magnetic resonance imaging (MRI) was first introduced in July 1997. Additional investigation by positron emission tomography with/without coupling with CT (PET ± CT) was not available until 2006.

Patients treated before 1997 were retrospectively staged using the 5th edition of the staging system jointly used by the American Joint Committee of Cancer and International Union Against Cancer (AJCC/UICC), so that all patients in this study were staged with the same set of criteria [10,11].

Primary treatment policies

All patients were treated with radical RT using 6 MV photons. The dose per fraction was 2 Gray (Gy) per fraction in all except 17 patients treated at commencement of IMRT. Conventional fractionation at 5 fractions per week was used for all patients with T1–2b tumor. Accelerated fractionation with 6 daily fractions per week was first introduced in 1996 for patients with T3–4 tumors [12]. Since 1999, patients were encouraged to participate in NPC-9902 Trial and NPC-0501 Trial for evaluating the therapeutic ratio of accelerated fractionation [13,14].

In the 2DRT era, the total RT dose used was 66 Gy, a supplementary parapharyngeal boost of 10 Gy was given to patients with bulky parapharyngeal extension to minimize marginal miss. The total dose was increased to 70 Gy since commencement of 3DRT; an adjuvant boost of 5 Gy (in 2 fractions) was given to stage I–IIB patients: high dose-rate brachytherapy was used for T1–T2a and stereotactic RT for T2b tumors. No dose escalation was attempted for patients treated by IMRT. Throughout the study period, patients with residual tumor at 8 weeks after completion of the primary course would be given an additional median dose of 20 Gy.

All stage I–IIB patients (except one patient with very bulky disease) were treated with RT alone. Addition of cisplatin-based chemotherapy was recommended to medically fit patients with stage III–IVB disease, but the sequence varied with evolving knowledge. Before 1996, the departmental policy was to use induction chemotherapy for patients with T4 disease and adjuvant chemotherapy for N3. With the first report of survival benefit by the Intergroup-0099 Study, the Intergroup concurrent-adjuvant regimen was increasingly used in patients with $T \geqslant 3$ or $N \geqslant 2$ [15]. From 1999 to 2004, patients were encouraged to participate in NPC-9901 and NPC-9902 Trials comparing concurrent-adjuvant CRT versus RT alone [13,16]. With increasing data about the promising result of induction-concurrent chemotherapy since 2000, patients with stage IV disease abutting/infiltrating neurological structures were accrued into phase II studies [17,18]. Starting in 2006, patients with stage III–IVB disease were encouraged to participate in NPC-0501 Trial comparing induction-concurrent CRT versus concurrent-adjuvant CRT [14].

Radiotherapy technique

Details of RT technique have been described in previous publications [12,19,20]. The 2DRT technique composed of 3 phases [12]. Phase I consisted of lateral-opposed facial-cervical fields for the primary tumor and enlarged neck nodes, and a lower anterior cervical field for the lower cervical lymphatics. Phase II was used after 40 Gy to avoid the spinal cord. This consisted of 3-fields (lateral-opposed plus anterior facial fields) for the nasopharyngeal region and an anterior cervical field for the whole neck. Phase III was the final cone-down after 50–60 Gy (depending on the T-stage) to avoid the brainstem, optic chiasma, and to protect as much temporal lobes as possible. Supplementary treatment for patients with bulky parapharyngeal extension was delivered via a postero-lateral field.

The 3DRT technique was described in the previous publication [19]. The gross tumor volume (GTV) was based on the tumor extent delineated by imaging and endoscopic findings at presentation. The clinical target volume (CTV1) for 70 Gy included the whole nasopharynx and the GTV with a 2–5 mm margin. The CTV2 aimed at 60 Gy covered high-risk local structures (including the parapharyngeal spaces, posterior third of nasal cavities and maxillary sinuses, pterygoid processes, base of skull, lower half of sphenoid sinus, anterior half of the clivus, and petrous tips), bilateral retropharyngeal nodes, and upper lymphatic (Levels II, III, and VA). The CTV3 aimed at 50 Gy covered the remaining potential sites of local infiltration up to the roof of the sphenoid sinus and bilateral lower lymphatics (Levels IV and VB). The cervical region was treated with anterior-posterior opposed fields with a 2–3 cm shield to minimize doses to the larynx and esophagus.

The IMRT technique used 9 coplanar beams to cover the entire region [20]. Same principle as 3DRT was used for delineating clinical target volume. The standard prescription was 70 Gy to CTV1 and 61.25 Gy to CTV2 in 35 fractions, 52.5 Gy to CTV3 in 30 fractions. The specification of dose constraints for inverse planning basically followed the protocol of Radiation Therapy Oncology Group (RTOG) Trial 0225 [21]. Top priority is given to critical neurological structures, followed by tumor targets, organs with intermediate importance, and finally those with lesser importance.

Statistical analyses

The endpoints for tumor control include actuarial rates of local failure-free rate (L-FFR: persistence/recurrence in the nasopharyngeal region), nodal failure-free rate (R-FFR: persistence/recurrence in the cervical region), distant failure-free rate (D-FFR: hematogenous metastasis), disease-specific survival (DSS: death due to NPC), and overall survival (OS: death due to any cause). The endpoints for major late toxicities include actuarial rates of potentially serious toxicities (temporal lobe necrosis, cranial neuropathy, damages to brainstem, spinal cord or optic chiasm) of all grades, deafness, soft tissue and bone necrosis of grade 3 or above. The scoring criteria of the RTOG were initially used before 2006, and the grading was retrospectively converted to that in accordance with Common Terminology Criteria for Adverse Events version 3.0 [CTCAE-v3] for easy reference with contemporary series [22,23]. All events were measured from the date of diagnosis. The actuarial rates were calculated by Kaplan Meier method, and the differences were compared by the log-rank test. Multivariate analyses of significant factors were conducted using the Cox proportional hazard model. The χ^2 test was used for comparing categorical variables, and