Nasopharyngeal Cancer

8

Moses M. Tam, Nadeem Riaz, and Nancy Y. Lee

Keywords
Nasopharyngeal carcinoma • IMRT • Radiation therapy

8.1 Introduction

Nasopharyngeal carcinoma (NPC) is relatively uncommon in most parts of the world but is endemic to certain regions such as Southern China [1]. NPC is rare in the United States, with an incidence of less than 1/100,000 person-years compared with 27/100,000 person-years in Southern China.

NPC is unique histologically from other head and neck cancers. In the most recent World Health Organization classification in 2005, NPC comprises three main types, namely, keratinizing squamous cell carcinoma (type 1), non-keratinizing carcinoma (type 2), and basaloid squamous cell carcinoma [2]. Non-keratinizing carcinoma (type 2) is subdivided into differentiated (type 2a) and undifferentiated (type 2b). Type 2 is also strongly associated with Epstein-Barr virus (EBV) and is the most common histologic type found in endemic regions.

Intergroup 0099 established concurrent radiation therapy (RT) and chemotherapy as the standard of care for locally advanced NPC [3]. Although surgical resection is often an option for tumors at other head and neck sites, successful resection of NPC is nearly impossible given its location and frequent involvement of the

M.M. Tam, M.D.
New York University School of Medicine, New York, NY, USA

N. Riaz, M.D. • N.Y. Lee, M.D. (✉)
Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center,
1275 York Avenue, New York, NY 10065, USA
e-mail: leen2@mskcc.org

Y. Nishimura, R. Komaki (eds.), *Intensity-Modulated Radiation Therapy*,
DOI 10.1007/978-4-431-55486-8_8

lateral retropharyngeal lymph nodes. Thus, surgery is mostly limited to radical or selective neck dissections for persistent or recurrent disease after RT.

Toxicity is an issue with the use of conventional RT given the proximity of the nasopharynx to critical normal structures. Intensity-modulated radiation therapy (IMRT) offers advantages over conventional RT by optimizing the delivery of radiation to irregularly shaped volumes so as to spare organs at risk. Further, different doses can be delivered simultaneously to select regions by dose painting or a simultaneous integrated boost. These techniques allow increased sparing of nearby critical normal structures by simultaneously delivering higher radiation doses to gross disease and lower doses to regions suspected of harboring microscopic disease. In the next section, we evaluate the clinical evidence that has established IMRT as the standard of care for definitive RT in NPC.

8.2 Clinical Evidence for Intensity-Modulated Radiation Therapy

8.2.1 Dosimetry

Dosimetrically, IMRT improves coverage of disease while reducing the dose to the numerous critical adjacent structures relative to conventional RT (Fig. 8.1) [4, 5]. Dosimetric comparisons of IMRT versus two-dimensional (2D) RT and three-dimensional (3D) RT plans showed that IMRT led to lower doses to the spinal cord, mandible, temporal lobe, parotid glands, optic chiasm, and brainstem.

8.2.2 Salivary Function and Treatment Compliance

The most common complication of RT for NPC is a decline in salivary function, known as xerostomia, due to a damage of nearby salivary structures. The symptoms of xerostomia can significantly affect a patient's quality of life [6]. The severity of xerostomia depends mostly on the dose and volume of salivary gland within the radiation field. Dosimetric comparisons have revealed that a mean dose of 26 Gy or less to the parotid glands is necessary to preserve salivary function [7, 8].

The main benefit of IMRT over conventional RT for NPC is the ability to spare the parotid glands. Two phase III randomized controlled trials assigned patients to receive either 2D RT or IMRT with parotid-sparing techniques and evaluated outcomes at 1 year after treatment. The first trial found that IMRT was associated with superior quality of life outcomes [9]. The second study also found benefits in observer-rated xerostomia outcomes and preservation of parotid function (measured by parotid flow rate) with the use of IMRT [10], as well as a trend towards improvement in patient-reported xerostomia outcomes. The same study revealed the somewhat surprising finding that xerostomia quality of life scores only correlated weakly

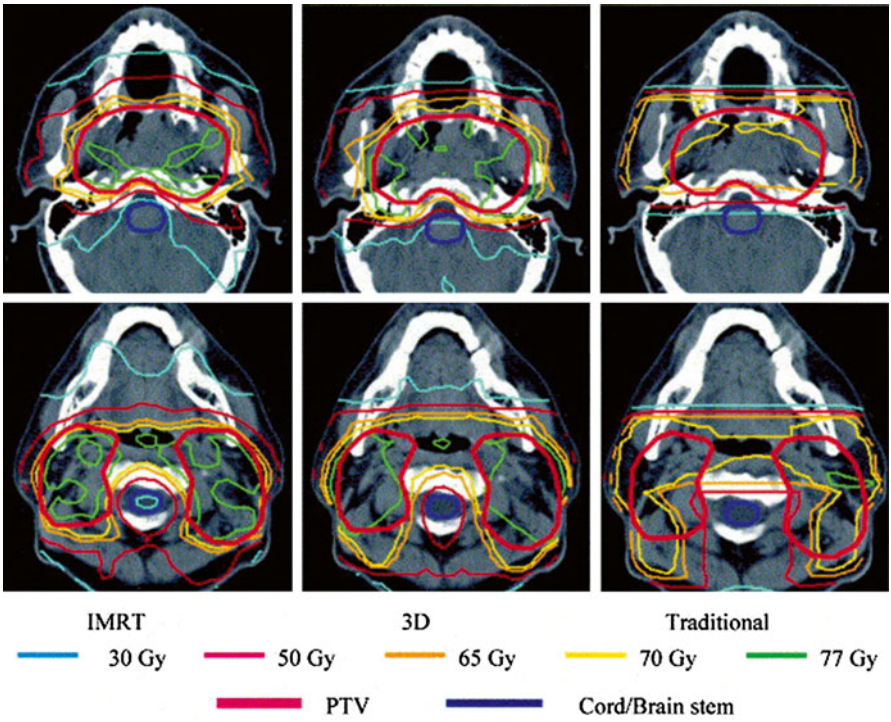

Fig. 8.1 Dosimetric comparison of treatment plans for intensity-modulated radiation therapy (IMRT) vs. 3D-conformal RT vs. traditional RT. Axial dose distributions through the center of the nasopharynx and neck for IMRT (*left*), 3D-conformal RT (*middle*), and traditional treatment plans (*right*). Note the relatively poor coverage of the skull base and medial nodal regions in the traditional plan and the improved dose conformality of the IMRT plan (From: Hunt et al. [4], with permission from Elsevier)

with both salivary flow rates and observer-rated xerostomia outcomes. Therefore, evaluation of both patient-reported and physician-reported outcomes remains important. Regardless, both phase III studies showed improved xerostomia outcomes with the use of IMRT compared with conventional 2D RT.

The lesser toxicity associated with IMRT may also improve treatment compliance or the ability of patients to tolerate the prescribed therapy. A multi-institutional trial of IMRT by the Radiation Therapy Oncology Group, RTOG 0225, showed that 90 % of patients were able to receive the full 70-Gy prescribed dose and that 88 % of the patients with T2b or higher or N+ disease were able to receive the full three cycles of concurrent cisplatin [11]. These findings compare favorably to previous studies that used conventional RT techniques, for example, chemotherapy compliance rates were 63 % in the Intergroup 0099 trial, 71 % in a Singapore randomized trial, and 52 % in the Hong Kong NPC-9901 trial [3, 12, 13].

8.2.3 Disease Control

In addition to improving toxicity outcomes, excellent disease control outcomes have been reported by several institutions. Lee et al. reported findings from an initial series of patients with NPC treated with IMRT, with an incredible 4-year local control rate of 97 %, despite 70 % of patients in that study having locally advanced disease [14]. Kwong et al. reported the first prospective series, with 3-year outcomes of 100 % local control (LC), 92.3 % regional control, and 100 % overall survival (OS) rates [15]. These excellent outcomes are supported by additional published series from many individual institutions, comprehensively reviewed by Wong et al. (Table 8.1) [16]. The RTOG 0225 trial further demonstrated the feasibility of implementing IMRT techniques across the multiple US institutions [11]. That phase II study reported excellent 2-year outcomes of 93 % LC, 89 % local-regional control (LRC), and 80 % OS rates (Table 8.1).

Notably, other factors may contribute to improvements in LRC associated with IMRT, including the use of chemotherapy, better supportive care, and technologic advances in imaging that provide better tumor delineation. Other limitations associated with historical comparisons include changes in the criteria for disease staging over time as well as improved staging with the use of magnetic resonance imaging (MRI) and positron emission tomography (PET) [17]. For example, because MRI is more sensitive than computed tomography (CT) for detecting minimal skull base involvement or intracranial extension, the T category tends to be upstaged when MRI is used rather than CT.

8.3 Techniques

8.3.1 Diagnostic Work-Up for Target Volume Delineation

Disease staging should include both CT and MRI of the head and neck. CT is important for assessing cortical bone involvement; MRI provides superior visualization of skull base involvement and tumor invasion into soft tissue structures compared with CT [18]. Infiltration of disease into the bone marrow is best seen as hypodense regions relative to normal marrow on T1-weighted non-contrast MRI scans. Fusion of the skull base portion of the CT scan with the MRI scan should aid in delineating the gross tumor volume (GTV). MRI also allows retropharyngeal lymph nodes to be distinguished from primary tumor, whereas CT may not.

Enlarged retropharyngeal lymph nodes should be considered a gross disease. Involvement of other lymph node regions is suggested by the presence of central necrosis, extracapsular spread, or nodal diameters of 1 cm or more. PET/CT may help to clarify involvement of borderline lymph nodes. Generally, because NPC has a high likelihood of nodal spread, any nodes suspected of harboring disease should be considered a gross disease.

Table 8.1 Published studies of IMRT for nasopharyngeal cancer

Reference	Stage	No. of patients	Median follow-up time, mo	Time point, y	Local control rate, %	Regional control rate, %	Freedom from DM rate, %	Overall survival rate, %
Lee et al. (2002) (UCSF) [14]	All	67	31	4	97	98	66	88
Kwong et al. (2004) (Hong Kong) [15]	T1 N0–1	33	24	3	100	92	100	100
Kam et al. (2004) (Hong Kong) [22]	All	63	29	3	92	98	79	90
Wolden et al. (2006) (MSKCC) [24]	All	74	35	3	91	93	78	83
Kwong et al. (2006) (Hong Kong) [23]	III–IVB	50	25	2	96	NA	94	92
Lee et al. (2009) (RTOG 0225) [11]	All	68	31	2	93	91	85	80
Lin et al. (2010) (China) [25]	IIB–IVB	370	31	3	95	97	86	89
Lee et al. (2012) (RTOG 0615) [19]	IIB–IVB	42	30	2	NA	NA	91	91

Abbreviations: *DM* distant metastasis, *UCSF* University of California, San Francisco, *RTOG* Radiation Therapy Oncology Group

8.3.2 Simulation and Daily Localization

The patient should be set up for treatment simulation supine, with the neck extended. The immobilization device to be used should include at least the head and neck; if possible, shoulders should also be immobilized to ensure the reproducibility of patient setup from day to day, especially when an extended-field IMRT plan is to be used. A bite block can be placed during treatment simulation and throughout treatment to move the tongue away from the high-dose regions in the nasopharynx.

CT-based treatment simulation should involve 3-mm-thick scan slices with intravenous contrast to help delineate the GTV, particularly the lymph nodes. The isocenter is typically placed immediately above the arytenoids. Image registration and fusion applications with MRI and PET should be used to help delineate target volumes, especially regions of interest that encompass the GTV, skull base, brainstem, and optic chiasm.

8.3.3 Target Volume Delineation and Treatment Planning

Several IMRT dose-fractionation regimens have been used for NPC (Table 8.2). Excellent LRC rates in excess of 90 % have been reported with the use of these regimens.

Several acceptable definitions of target volumes, including the GTV, the clinical target volume (CTV), and planning target volume (PTV), have been used at different institutions, as reviewed by Wong et al. [16]. The RTOG established a guideline for target volume delineation with RTOG 0225, which was successfully implemented in that multi-institutional study [11]. Suggested target volumes for the GTV and high-risk CTV are described in the following sections (Tables 8.3 and 8.4 and Figs. 8.2, 8.3, and 8.4). In a recent RTOG 0615 trial, the lower-than-expected 2-year LRC rate of 84 % was attributed to an increased incidence of major deviations in

Table 8.2 IMRT dose and fractionation schemes

Dose and fractionation	Study institution and reference			
	RTOG [19]	Fujan [20]	SKL [43]	PWH [22]
Gross disease, Gy	69.96	66.0–69.75	68	6,674
Gross disease, Gy/fraction	2.12	2.2–2.25	2.27	2
High-risk region, Gy	59.4	60–60.45	60	60
High-risk region, Gy/fraction	1.8	1.95–2.0	2	1.82
Low-risk region, Gy	50–54.12	54–55.8	50–54	54–60
Low-risk region, Gy/fraction	1.64–2.0	1.8	1.8–2.0	2
Margin around GTV, mm[a]	10	8–13	NA	13

Abbreviations: *RTOG* Radiation Therapy Oncology Group, *SKL* State Key Laboratory of Oncology in Southern China (Guangzhou), *PWH* Prince of Wales Hospital, Hong Kong, *GTV* gross tumor volume, *CTV* clinical target volume, *PTV* planning target volume

[a]Margin is for primary tumor (GTV70), which includes CTV expansion of GTV and PTV expansion

Table 8.3 Definitions of target volumes for gross disease

Target volumes	Definition and description
GTV_{70*} (The subscript 70 denotes the radiation dose delivered)	Primary: All gross diseases on physical examination and imaging (see above regarding the importance of MRI)
	Neck nodes: All nodes ≥1 cm or those with necrotic center
CTV_{70*}	GTV_{70} + ≥5 mm margin; around critical structures like the brainstem, 1 mm margin is acceptable
PTV_{70*}	CTV_{70} + 3–5 mm, depending on comfort level of daily patient positioning. Around critical structures like the brainstem, 1 mm margin is acceptable

Table 1.1 from: Lee NY, Le QT, O'Sullivan B, Lu JJ (2003) Chapter 1. Nasopharyngeal carcinoma. *Target Volume Delineation and Field Setup: A Practical Guide for Conformal and Intensity-Modulated Radiation Therapy*, with kind permission from Springer Science + Business Media
*PTV_{70} receives 2.12 Gy/fraction to 70 Gy over 33 fractions. For treatment of nodes that are small (i.e., ~1 cm), the lower dose of 63 Gy (PTV_{63}) can be considered at the discretion of the treating physician

Table 8.4 Definition of target volumes for high-risk subclinical region

Target volumes	Definition and description
$CTV_{59.4*}$	$CTV_{59.4}$ should encompass CTV_{70} with a 5-mm margin and regions at risk for microscopic disease which include
	Entire nasopharynx
	Anterior 1/2 or 2/3 of the clivus (entire clivus, if involved)
	Skull base (ensuring coverage of foramen ovale where V3 resides)
	Pterygoid fossa
	Parapharyngeal space
	Inferior sphenoid sinus (entire sphenoid sinus in T3-T4 disease)
	Posterior 1/3 of the nasal cavity/maxillary sinuses (ensuring coverage of pterygopalatine fossae where V2 resides)
	Inferior soft palate
	Retropharyngeal lymph nodes
	Retrostyloid space
	Bilateral nodal levels IB through V**
	Include cavernous sinus for advanced T3-T4 lesions
	Importance of reviewing bone window while contouring on CT scan to ensure coverage of skull base foramina
$PTV_{59.4*}$	$CTV_{59.4}$ + 3–5 mm, depending on the comfort of physician, but around critical structures like the brainstem, 1-mm margin is acceptable

Table 1.2 from: Lee NY, Le QT, O'Sullivan B, Lu JJ (2003) Chapter 1 Nasopharyngeal Carcinoma. *Target Volume Delineation and Field Setup: A Practical Guide for Conformal and Intensity-Modulated Radiation Therapy*. Reproduced with kind permission from Springer Science + Business Media
*High-risk subclinical dose ($PTV_{59.4}$): 1.8 Gy/fraction to 59.4 Gy, for lower-risk subclinical regions *excluding the nasopharynx/skull base regions where they are always considered high risk*, can consider 1.64 Gy/fraction to 54 Gy (PTV_{54}), i.e., N0 neck or low neck (levels IV and VB) at the discretion of the treating physician
Level IB can be omitted in node-negative disease.** At discretion of physician, level 1B may also be spared in low-risk node positive patients (e.g., isolated retropharyngeal nodes or isolated level IV nodes are considered low risk for level 1B involvement). At the same time, treatment of level 1B should be considered in node-negative patients with certain features (e.g., involvement of hard palate or nasal cavity)

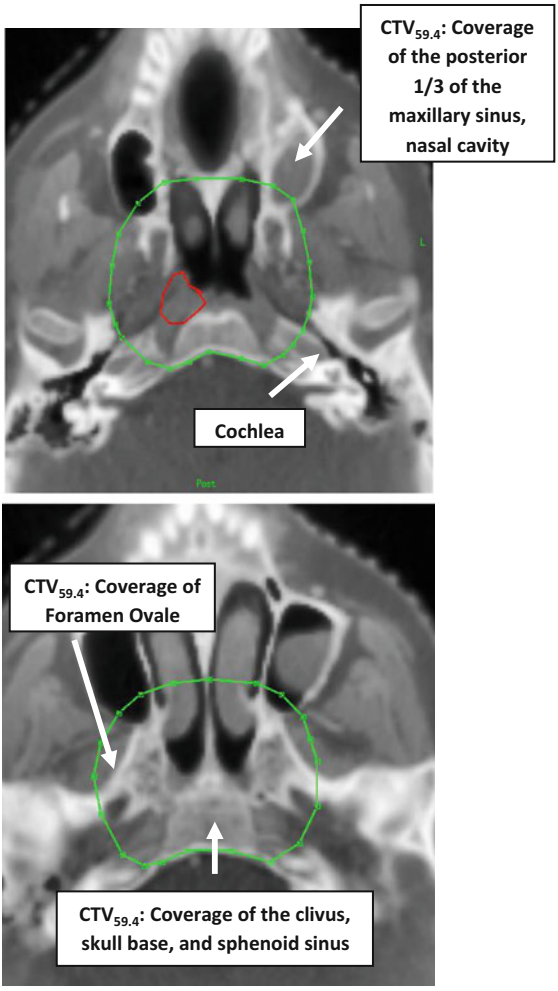

Fig. 8.2 Delineation of target volumes in a case of T1N1 nasopharyngeal carcinoma (NPC). GTV70 (inner contour, *red*) and CTV59.4 (*green*) contours in a patient with T1N1 NPC with coverage of the retropharyngeal and level II nodes (Figure 1.2 from: Lee NY, Le QT, O'Sullivan B, Lu JJ (2003) Chapter 1 Nasopharyngeal Carcinoma. *Target Volume Delineation and Field Setup: A Practical Guide for Conformal and Intensity-Modulated Radiation Therapy*, with kind permission from Springer Science + Business Media)

target volume [19]. Thus, attention must be paid to accurate target delineation to avoid marginal misses when using IMRT.

Reductions in high-risk subclinical volumes with IMRT have also been described. Lin et al. reported a prospective, single-institution study involving 323 patients with NPC; that study reduced the CTV suggested in the RTOG guidelines and resulted in excellent LCR outcomes [20]. One reduction involved the exclusion of upper deep jugular lymph nodes (level IIa above the C1 vertebrae) in the CTV. Treatment volume reductions may be important for reducing toxicity and even secondary primary tumors, the rate of which has been reported to be as high as 1 % among patients with NPC receiving definitive RT [21]. The next section reviews the guidelines used at the authors' institutions and some variations in those guidelines used at other institutions.

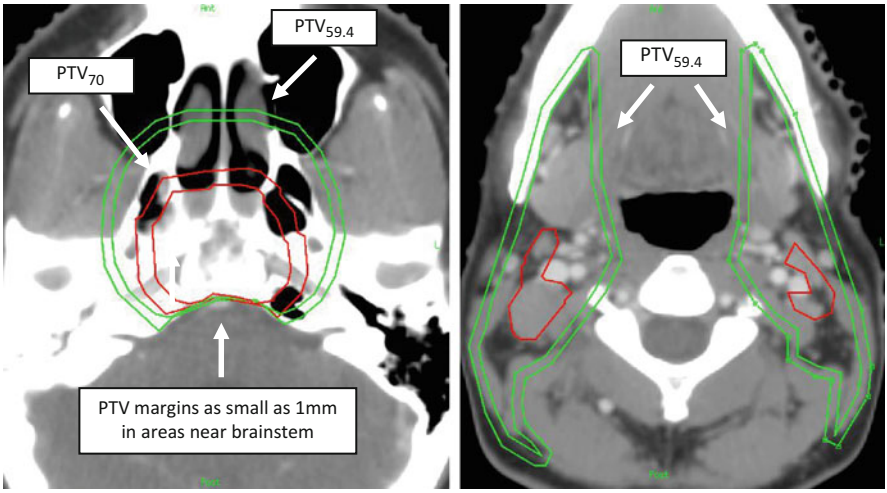

Fig. 8.3 Delineation of target volumes in a case of T3N2 nasopharyngeal carcinoma (NPC). PTV70 (*red*) and PTV59.4 (*green*) in a patient with T3N2 nasopharyngeal carcinoma (Figure 1.4 from: Lee NY, Le QT, O'Sullivan B, Lu JJ (2003) Chapter 1. Nasopharyngeal carcinoma. *Target Volume Delineation and Field Setup: A Practical Guide for Conformal and Intensity-Modulated Radiation Therapy*, with kind permission from Springer Science + Business Media)

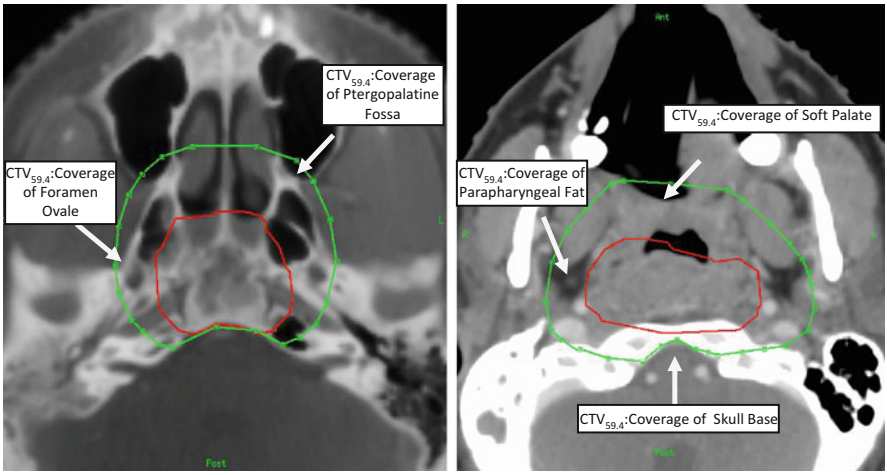

Fig. 8.4 Delineation of target volumes in a case of T3N2 nasopharyngeal carcinoma (NPC) with the use of different CT window settings. GTV70 (*green*) and CTV59.4 (*red*) in bone window (*left*) and soft tissue window (*right*) (Figure 1.5 from: Lee NY, Le QT, O'Sullivan B, Lu JJ (2003) Chapter 1. Nasopharyngeal carcinoma. *Target Volume Delineation and Field Setup: A Practical Guide for Conformal and Intensity-Modulated Radiation Therapy*, with kind permission from Springer Science + Business Media)

8.3.3.1 Gross Tumor Volume

Generally, the GTV is defined as the primary tumor and any involved lymph nodes. Involved lymph nodes are typically defined as any lymph node larger than 1 cm in diameter or those that show avidity on PET scanning.

Expansions around the GTV have included those for both a CTV and a PTV or a single, larger PTV expansion alone. The RTOG studies recommended the use of a CTV70, defined as a 0.5-cm margin with an optional posterior margin reduction of 0.1–0.5 cm (Table 8.3) as well as a PTV70 expansion of 0.5 cm. Variations on these expansions have included a larger CTV expansion of 1 cm [15, 22, 23] or the elimination of a CTV and the use of a larger PTV of 1 cm [12, 24]. The use of the latter method may avoid confusion with the CTVs described below for high-risk and low-risk subclinical regions.

8.3.3.2 High-Risk and Low-Risk Subclinical Regions

The CTV is generally defined as regions at high risk of harboring microscopic disease (Table 8.4). This volume can be treated to a lower dose of 59.4 Gy (CTV59.4), which includes all potential routes of spread for primary and nodal disease. Specifically, CTV59.4 typically covers the clivus, skull base, inferior sphenoid sinus, cavernous sinus, pterygoid fossae, parapharyngeal space, posterior nasal cavity and maxillary sinus, retropharyngeal lymph nodes, and neck levels II through V. The bilateral level IB can be spared in carefully selected patients without compromising LRC [20, 25]. Whether the inferior orbital fissure or the anterior arch of C1 can be spared remains unclear owing to a lack of data [16]. Variations also exist for the inferior border of the retropharyngeal lymph nodes. A consensus guideline published by Gregoire et al. defines the border as the cranial edge of the hyoid bone [26], but others have described it as the inferior border of the hyoid bone [22] and the cranial edge of the second cervical vertebrae [20, 25].

The low anterior neck can also be treated to a lower dose than the GTV because it is at low risk of harboring disease. This low-risk region can be treated separately with a dose of 50.4 Gy in 1.8 Gy per fraction using conventional anteroposterior (AP) or posteroanterior (PA) portals or with a dose of 54 Gy (CTV54) in 1.64 Gy per fraction in a single IMRT plan.

Finally, an additional CTV (CTV63) can be used at the discretion of the treating physician. A lower dose (63 Gy) can be used for a small-volume lymph node disease. Examples of the appropriate application of this intermediate dose would include the presence of small lymph nodes near the mandible or in the lower neck and close to the brachial plexus.

8.3.3.3 Planning Target Volume

The margin for the PTV also varies between institutions [16]. Most institutions have described the PTV as 0.2–0.5 cm beyond the CTV. The use of a PTV margin of 0.3–0.5 cm would be reasonable, as many published studies have shown an efficacy using these limits. Daily image guidance with kV imaging can facilitate margin reduction.

Table 8.5 Normal tissue dose constraints

Critical structures	Constraints
Brainstem	Max <54 Gy or 1 % of PTV cannot exceed 60 Gy
Optic nerves	Max <54 Gy or 1 % of PTV cannot exceed 60 Gy
Optic chiasm	Max <54 Gy or 1 % of PTV cannot exceed 60 Gy
Spinal cord	Max <45 Gy or 1 cm^3 of the PTV cannot exceed 50 Gy
Mandible and TMJ	Max <70 Gy or 1 cm^3 of the PTV cannot exceed 75 Gy
Brachial plexus	Max <66 Gy
Temporal lobes	Max <60 Gy or 1 % of PTV cannot exceed 65 Gy
Other normal structures	Constraints
Oral cavity	Mean <40 Gy
Parotid gland	(a) Mean ≤26 Gy in one gland (b) Or at least 20 cm^3 of the combined volume of both parotid glands will receive <20 Gy (c) Or at least 50 % of one gland will receive <30 Gy
Cochlea	V55 <5 %
Eyes	Mean <35 Gy, Max <50 Gy
Lens	Max <25 Gy
Glottic larynx	Mean <45 Gy
Esophagus, postcricoid pharynx	Mean <45 Gy

8.3.4 Plan Assessment and Dose Constraints

For NPC, the organs at risk include the brainstem, spinal cord, optic nerves, chiasm, parotid glands, pituitary, temporomandibular (TM) joints, middle and inner ears, skin (in the region of the target volumes), oral cavity, mandible, eyes, lens, temporal lobe, brachial plexus, esophagus (including postcricoid pharynx), and glottic larynx (Table 8.5). In cases of advanced disease, we typically prioritize normal structure constraints, specifically the brainstem, spinal cord, and optic chiasm, over full coverage of the tumor. Ideally, at least 95 % of the PTV70 should receive 70 Gy. In addition, the minimum dose to 99 % of the CTV70 should be >65.1 Gy. The maximum dose received by 0.03 cm^3 of the PTV70 should be <80.5 Gy.

For the PTV59.4, 95 % of the volume should receive the prescription dose. The minimum dose to 99 % of the CTV59.4 should be >55.2 Gy. The maximum dose to 0.03 cm^3 of PTV59.4 should be 69.3 Gy.

8.4 Future Directions

Overall, LRC with IMRT is excellent, with rates generally exceeding 90 % in the current era when chemotherapy is included as part of the treatment. Future directions in therapy are now focusing on identifying patients with NPC who are more likely to experience local regional or, more commonly, distant failure after RT. These high-risk patients are likely to benefit from treatment intensification.

Monitoring levels of EBV DNA in plasma samples is one way to stratify patients in terms of risk, as this biomarker is showing great potential in the clinical setting. Many studies, including prospective and phase II studies, have established that pretreatment and posttreatment levels of EBV DNA are reliable indicators of tumor burden, predictors of recurrence and distant failure, and independent prognostic factors in EBV-related NPC [27–32]. Quantification of plasma EBV DNA has also been shown to be useful for monitoring patients with NPC and predicting the outcome of treatment [33]. A recent four-center study sought to harmonize EBV DNA assay methods, to bring us step closer to using EBV in biomarker-driven trials [34]. Indeed, we anticipate that an upcoming phase III study by the RTOG will incorporate plasma EBV DNA levels in treatment stratification.

Several imaging methods are also being used to identify patients with high-risk NPC that is more aggressive and more likely progress despite treatment. On the basis of evidence linking hypoxia with radioresistance [35], Chao et al. tested a PET-based technique to measure hypoxia with a Cu-ATSM [Cu(II)-diacetyl-bis(N(4)-methylthiosemicarbazone] tracer and considered the results promising [36]. Lee et al. also demonstrated the feasibility of using ^{18}F-labeled fluoromisonidazole (^{18}F-FMISO) PET/CT for guiding IMRT so as to allow the dose to radioresistant hypoxic regions to be escalated to 84 Gy (Fig. 8.5) [37]. Findings of

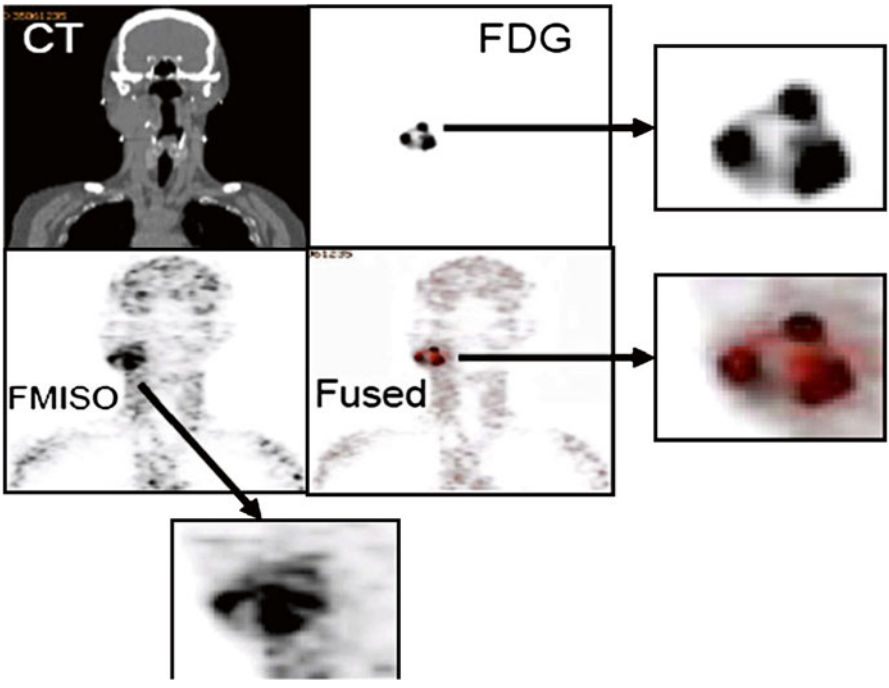

Fig. 8.5 Multimodality image acquisition, processing, and registration for ^{18}F-FMISO PET/CT-guided IMRT. Shown are computed tomography (CT) (*top left*), fluorodeoxyglucose (FDG) (*top right*), ^{18}F-fluoromisonidazole (^{18}F-FMISO) (*bottom left*), and fused FDG-^{18}F-FMISO (*bottom right*) images. Also shown are three enlarged areas from each scan type (From Lee et al. [37], with permission from Elsevier)

an ongoing trial, NCT00606294, are expected to show whether FMISO PET-guided visualization of hypoxia can be used to stratify patients in terms of risk.

Treatment intensification in the form of dose escalation is now an option with IMRT. Previous attempts at dose intensification with conventional RT were limited by toxicity [38, 39]. However, at least two dose-escalation studies have shown that IMRT can allow a safe dose escalation in NPC [22, 23]. In one of those studies, Kwong et al. used a prescribed dose of 76 Gy given in 35 fractions for T3-T4 NPC and found an excellent 2-year LCR rate of 96 % and acceptable toxicity [23]. In another such study, Kam et al. used a boost technique to provide a total dose of 74 Gy and also reported excellent LRC [22]. Although current dose levels have resulted in excellent LRC, dose escalation in selected patients with high-risk NPC may confer further benefits.

The use of adjuvant chemotherapy is another potential form of treatment intensification. Findings from the INT0099 trial indicated that the current standard of care should include adjuvant chemotherapy in addition to concurrent chemoradiation. However, results of a more recent phase III trial found no benefit from the use of adjuvant chemotherapy [40]; in that trial involving 508 patients, the 2-year failure-free survival rate was 86 % in the group with adjuvant chemotherapy and 84 % in the group without adjuvant chemotherapy ($P = 0.13$). Additional follow-up is needed, however, as the failure-free survival Kaplan-Meier curves may well separate over time. Moreover, that study was not designed to directly compare this therapy with that of INT0099. Nevertheless, patients with high-risk NPC may be more likely to benefit from adjuvant chemotherapy.

Interest has also been growing in the use of proton therapy in the form of intensity-modulated proton therapy (IMPT). IMPT plans have been shown to provide additional dosimetric advantage over IMRT by improving tumor coverage and reducing the mean dose to organs at risk (Fig. 8.6) [41]. We look forward to identifying potential benefit from protons in the clinical setting. Currently, an ongoing phase II trial at Massachusetts General Hospital is evaluating the potential for reduction in toxicity from the use of proton beam therapy (NCT00592501).

Adaptive RT is also being investigated for its potential to improve clinical outcomes. The rationale for this therapy is that significant anatomic changes during therapy, such as those resulting from loss of body weight or shrinkage in tumor volume (reportedly most severe after the first 2 weeks of treatment [42]), can lead to movement of the organs at risk into the planned radiation field. Conversely, marginal misses may occur if the tumor becomes displaced out of the treatment field, especially given the current efforts to reduce margins and treatment volumes to the greatest possible extent. The potential value of repeated treatment simulations is being considered and has shown some potential [42].

8.5 Conclusions

Clinical outcomes with IMRT have demonstrated clear dosimetric advantages, excellent LRC rates of more than 90 %, and lesser toxicity (specifically by improving salivary function) compared with conventional RT. The use of IMRT with

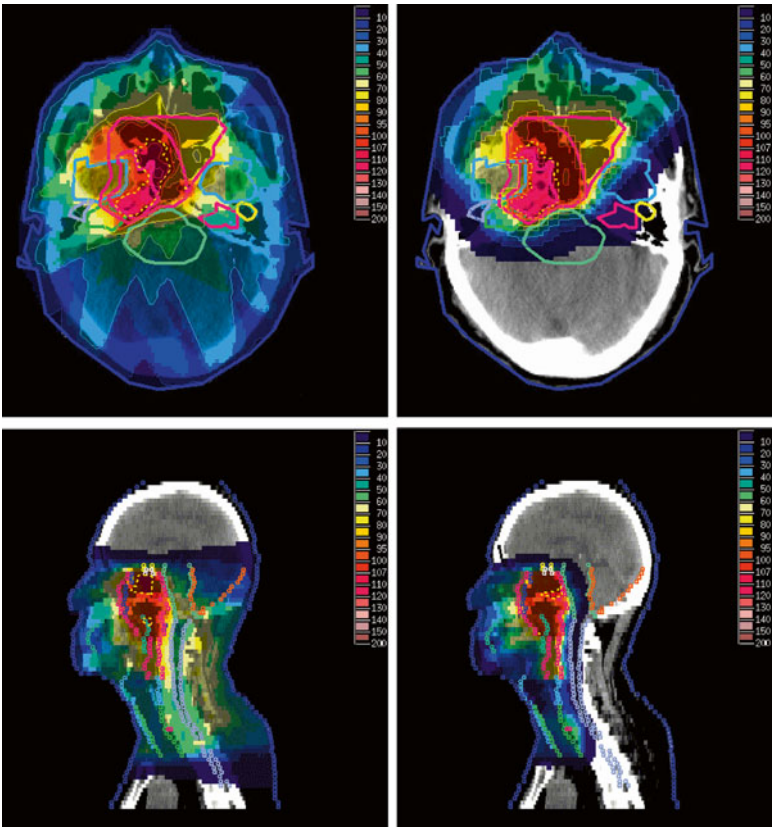

Fig. 8.6 Dosimetric comparison of treatment plans for intensity-modulated radiation therapy (IMRT) vs. intensity-modulated proton therapy (IMPT). Dose distributions are shown for IMRT plans (*left*) and IMPT plans (*right*) for a patient with T4N1N0 nasopharyngeal carcinoma. *Dotted lines* denote 95 % of the prescribed dose to the gross tumor volume. Figure 2 from Taheri-Kadkhoda et al. [41] (License accessible at: http://creativecommons.org/licenses/by/2.0/legalcode)

specific target volume guidelines has been replicated successfully in a multi-institutional setting in the United States.

Further improvements in toxicity after IMRT will rely on either further reductions in margins within treatment volumes or the use of adaptive RT. Proton therapy also shows promise in terms of further sparing critical structures. Regarding approaches to improve disease control, dose escalation with IMRT is now feasible and could be considered for cases of particularly aggressive NPC. The use of imaging parameters and biomarkers, such as EBV DNA levels, also shows promise for risk stratification and consequent treatment intensification for high-risk NPC.

References

1. Yu MC (1990) Diet and nasopharyngeal carcinoma. FEMS Microbiol Immunol 2(4):235–242
2. Thompson LD (2007) Update on nasopharyngeal carcinoma. Head Neck Pathol 1(1):81–86
3. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, Forastiere AA, Adams G, Sakr WA, Schuller DE, Ensley JF (1998) Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 16(4):1310–1317
4. Hunt MA, Zelefsky MJ, Wolden S, Chui CS, LoSasso T, Rosenzweig K, Chong L, Spirou SV, Fromme L, Lumley M, Amols HA, Ling CC, Leibel SA (2001) Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer. Int J Radiat Oncol Biol Phys 49(3):623–632
5. Xia P, Fu KK, Wong GW, Akazawa C, Verhey LJ (2000) Comparison of treatment plans involving intensity-modulated radiotherapy for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 48(2):329–337
6. Chambers MS, Garden AS, Kies MS, Martin JW (2004) Radiation-induced xerostomia in patients with head and neck cancer: pathogenesis, impact on quality of life, and management. Head Neck 26(9):796–807
7. Eisbruch A, Ship JA, Dawson LA, Kim HM, Bradford CR, Terrell JE, Chepeha DB, Teknos TN, Hogikyan ND, Anzai Y, Marsh LH, Ten Haken RK, Wolf GT (2003) Salivary gland sparing and improved target irradiation by conformal and intensity modulated irradiation of head and neck cancer. World J Surg 27(7):832–837
8. Blanco AI, Chao KS, El Naqa I, Franklin GE, Zakarian K, Vicic M, Deasy JO (2005) Dose-volume modeling of salivary function in patients with head-and-neck cancer receiving radiotherapy. Int J Radiat Oncol Biol Phys 62(4):1055–1069. doi:10.1016/j.ijrobp.2004.12.076
9. Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH, Leung WK (2006) Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 66(4):981–991
10. Kam MK, Leung SF, Zee B, Chau RM, Suen JJ, Mo F, Lai M, Ho R, Cheung KY, Yu BK, Chiu SK, Choi PH, Teo PM, Kwan WH, Chan AT (2007) Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 25(31):4873–4879
11. Lee N, Harris J, Garden AS, Straube W, Glisson B, Xia P, Bosch W, Morrison WH, Quivey J, Thorstad W, Jones C, Ang KK (2009) Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. J Clin Oncol 27(22):3684–3690
12. Lee AW, Lau WH, Tung SY, Chua DT, Chappell R, Xu L, Siu L, Sze WM, Leung TW, Sham JS, Ngan RK, Law SC, Yau TK, Au JS, O'Sullivan B, Pang ES, O SK, Au GK, Lau JT, Hong Kong Nasopharyngeal Cancer Study Group (2005) Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol 23(28):6966–6975
13. Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, Chua ET, Yang E, Lee KM, Fong KW, Tan HS, Lee KS, Loong S, Sethi V, Chua EJ, Machin D (2005) Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol 23(27):6730–6738
14. Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, Akazawa P, Weinberg V, Fu KK (2002) Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys 53(1):12–22
15. Kwong DL, Pow EH, Sham JS, McMillan AS, Leung LH, Leung WK, Chua DT, Cheng AC, Wu PM, Au GK (2004) Intensity-modulated radiotherapy for early-stage nasopharyngeal

carcinoma: a prospective study on disease control and preservation of salivary function. Cancer 101(7):1584–1593
16. Wang TC, Riaz N, Cheng S, Lu J, Lee N (2012) Intensity-modulated radiation therapy for nasopharyngeal carcinoma: a review. J Radiat Oncol 1(2):129–146
17. Lonneux M, Hamoir M, Reychler H, Maingon P, Duvillard C, Calais G, Bridji B, Digue L, Toubeau M, Gregoire V (2010) Positron emission tomography with [18F]fluorodeoxyglucose improves staging and patient management in patients with head and neck squamous cell carcinoma: a multicenter prospective study. J Clin Oncol 28(7):1190–1195
18. Abdel Khalek Abdel Razek A, King A (2012) MRI and CT of nasopharyngeal carcinoma. AJR Am J Roentgenol 198(1):11–18
19. Lee NY, Zhang Q, Pfister DG, Kim J, Garden AS, Mechalakos J, Hu K, Le QT, Colevas AD, Glisson BS, Chan AT, Ang KK (2012) Addition of bevacizumab to standard chemoradiation for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial. Lancet Oncol 13(2):172–180
20. Lin S, Pan J, Han L, Zhang X, Liao X, Lu JJ (2009) Nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy: report on the 3-year outcome of a prospective series. Int J Radiat Oncol Biol Phys 75(4):1071–1078
21. Kong L, Lu JJ, Hu C, Guo X, Wu Y, Zhang Y (2006) The risk of second primary tumors in patients with nasopharyngeal carcinoma after definitive radiotherapy. Cancer 107(6):1287–1293
22. Kam MK, Teo PM, Chau RM, Cheung KY, Choi PH, Kwan WH, Leung SF, Zee B, Chan AT (2004) Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: the Hong Kong experience. Int J Radiat Oncol Biol Phys 60(5):1440–1450
23. Kwong DL, Sham JS, Leung LH, Cheng AC, Ng WM, Kwong PW, Lui WM, Yau CC, Wu PM, Wei W, Au G (2006) Preliminary results of radiation dose escalation for locally advanced nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 64(2):374–381
24. Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ (2006) Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. Int J Radiat Oncol Biol Phys 64(1):57–62
25. Lin S, Lu JJ, Han L, Chen Q, Pan J (2010) Sequential chemotherapy and intensity-modulated radiation therapy in the management of locoregionally advanced nasopharyngeal carcinoma: experience of 370 consecutive cases. BMC Cancer 10:39
26. Gregoire V, Levendag P, Ang KK, Bernier J, Braaksma M, Budach V, Chao C, Coche E, Cooper JS, Cosnard G, Eisbruch A, El-Sayed S, Emami B, Grau C, Hamoir M, Lee N, Maingon P, Muller K, Reychler H (2003) CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines. Radiother Oncol 69(3):227–236
27. Twu CW, Wang WY, Liang WM, Jan JS, Jiang RS, Chao J, Jin YT, Lin JC (2007) Comparison of the prognostic impact of serum anti-EBV antibody and plasma EBV DNA assays in nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 67(1):130–137
28. Leung SF, Chan AT, Zee B, Ma B, Chan LY, Johnson PJ, Lo YM (2003) Pretherapy quantitative measurement of circulating Epstein-Barr virus DNA is predictive of posttherapy distant failure in patients with early-stage nasopharyngeal carcinoma of undifferentiated type. Cancer 98(2):288–291
29. Leung SF, Zee B, Ma BB, Hui EP, Mo F, Lai M, Chan KC, Chan LY, Kwan WH, Lo YM, Chan AT (2006) Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. J Clin Oncol 24(34):5414–5418
30. Wang WY, Twu CW, Lin WY, Jiang RS, Liang KL, Chen KW, Wu CT, Shih YT, Lin JC (2011) Plasma Epstein-Barr virus DNA screening followed by (1)(8)F-fluoro-2-deoxy-D-glucose positron emission tomography in detecting posttreatment failures of nasopharyngeal carcinoma. Cancer 117(19):4452–4459

31. Tang LQ, Chen QY, Fan W, Liu H, Zhang L, Guo L, Luo DH, Huang PY, Zhang X, Lin XP, Mo YX, Liu LZ, Mo HY, Li J, Zou RH, Cao Y, Xiang YQ, Qiu F, Sun R, Chen MY, Hua YJ, Lv X, Wang L, Zhao C, Guo X, Cao KJ, Qian CN, Zeng MS, Mai HQ (2013) Prospective study of tailoring whole-body dual-modality [18F]fluorodeoxyglucose positron emission tomography/computed tomography with plasma Epstein-Barr virus DNA for detecting distant metastasis in endemic nasopharyngeal carcinoma at initial staging. J Clin Oncol 31(23):2861–2869
32. Wang WY, Twu CW, Chen HH, Jiang RS, Wu CT, Liang KL, Shih YT, Chen CC, Lin PJ, Liu YC, Lin JC (2013) Long-term survival analysis of nasopharyngeal carcinoma by plasma Epstein-Barr virus DNA levels. Cancer 119(5):963–970
33. Lin JC, Wang WY, Chen KY, Wei YH, Liang WM, Jan JS, Jiang RS (2004) Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. N Engl J Med 350(24):2461–2470
34. Le QT, Zhang Q, Cao H, Cheng AJ, Pinsky BA, Hong RL, Chang JT, Wang CW, Tsao KC, Lo YD, Lee N, Ang KK, Chan AT, Chan KC (2013) An international collaboration to harmonize the quantitative plasma Epstein-Barr virus DNA assay for future biomarker-guided trials in nasopharyngeal carcinoma. Clin Cancer Res 19(8):2208–2215
35. Brizel DM, Sibley GS, Prosnitz LR, Scher RL, Dewhirst MW (1997) Tumor hypoxia adversely affects the prognosis of carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 38(2):285–289
36. Chao KS, Bosch WR, Mutic S, Lewis JS, Dehdashti F, Mintun MA, Dempsey JF, Perez CA, Purdy JA, Welch MJ (2001) A novel approach to overcome hypoxic tumor resistance: Cu-ATSM-guided intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 49(4):1171–1182
37. Lee NY, Mechalakos JG, Nehmeh S, Lin Z, Squire OD, Cai S, Chan K, Zanzonico PB, Greco C, Ling CC, Humm JL, Schoder H (2008) Fluorine-18-labeled fluoromisonidazole positron emission and computed tomography-guided intensity-modulated radiotherapy for head and neck cancer: a feasibility study. Int J Radiat Oncol Biol Phys 70(1):2–13
38. Wolden SL, Zelefsky MJ, Hunt MA, Rosenzweig KE, Chong LM, Kraus DH, Pfister DG, Leibel SA (2001) Failure of a 3D conformal boost to improve radiotherapy for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 49(5):1229–1234
39. Jen YM, Lin YS, Su WF, Hsu WL, Hwang JM, Chao HL, Liu DW, Chen CM, Lin HY, Wu CJ, Chang LP, Shueng PW (2002) Dose escalation using twice-daily radiotherapy for nasopharyngeal carcinoma: does heavier dosing result in a happier ending? Int J Radiat Oncol Biol Phys 54(1):14–22
40. Chen L, Hu CS, Chen XZ, Hu GQ, Cheng ZB, Sun Y, Li WX, Chen YY, Xie FY, Liang SB, Chen Y, Xu TT, Li B, Long GX, Wang SY, Zheng BM, Guo Y, Sun Y, Mao YP, Tang LL, Chen YM, Liu MZ, Ma J (2012) Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. Lancet Oncol 13(2):163–171
41. Taheri-Kadkhoda Z, Bjork-Eriksson T, Nill S, Wilkens JJ, Oelfke U, Johansson KA, Huber PE, Munter MW (2008) Intensity-modulated radiotherapy of nasopharyngeal carcinoma: a comparative treatment planning study of photons and protons. Radiat Oncol 3:4
42. Bhide SA, Davies M, Burke K, McNair HA, Hansen V, Barbachano Y, El-Hariry IA, Newbold K, Harrington KJ, Nutting CM (2010) Weekly volume and dosimetric changes during chemoradiotherapy with intensity-modulated radiation therapy for head and neck cancer: a prospective observational study. Int J Radiat Oncol Biol Phys 76(5):1360–1368
43. Su SF, Han F, Zhao C, Chen CY, Xiao WW, Li JX, Lu TX (2012) Long-term outcomes of early-stage nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy alone. Int J Radiat Oncol Biol Phys 82(1):327–333