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REVIEW

Intensity-modulated radiation therapy for nasopharyngeal carcinoma: a review

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Abstract
Introduction Advances in radiation therapy, such as intensity-modulated radiation therapy (IMRT), have allowed high-dose delivery to tumors while sparing normal tissues. However, IMRT requires careful delineation of target volumes to prevent marginal recurrences.
Results and discussion This review discusses the recent advances in the treatment of nasopharyngeal carcinoma with particular emphasis on IMRT. Multiple phase III trials that have relied on conventional radiotherapy have shown a survival benefit to concurrent chemoradiotherapy (CCRT) over radiotherapy (RT) alone. Two randomized trials using IMRT have demonstrated decreased xerostomia rates compared to conventional radiotherapy while still maintaining excellent local control rates, although follow-up was short. While modern locoregional results are excellent, 90 % or more, distant-metastasis-free rates are not as impressive, ranging from 66 to 93 % among studies.
Conclusion IMRT is an advanced technique, its excellent treatment outcomes have been reproduced in many single institution studies. Perhaps IMRT-delivered RT can replace the benefit provided by chemotherapy when added to conventional RT. Future studies should focus on reducing target volumes to minimize toxicity while dose-escalating for high-risk patients.

Keywords Intensity-modulated radiation therapy · Nasopharyngeal carcinoma · Radiotherapy

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Introduction

Nasopharyngeal carcinoma (NPC) can be difficult to treat because the nasopharynx is surrounded by many sensitive normal structures. Improved treatment has led to many patients living for decades after diagnosis and increased the importance of minimizing side effects. The development of new radiotherapy (RT) techniques has facilitated minimizing complications and late sequellae of treatment.

Intensity-modulated radiation therapy (IMRT) is a technique that allows the modification of each radiation beam, whether by shaping the field or changing the dose-intensity, and provides highly conformal dose delivery. This permits high-dose delivery to the tumor while simultaneously reducing dose to the normal tissues. It is commonly performed by using inverse planning which allows a computer to suggest a plan based on predetermined target dose parameters that the responsible physician finds clinically acceptable. The benefit of IMRT comes with a potential drawback in that as dose to the target volumes become more conformal, incorrect delineation of the target or normal structures can cause marginal or complete misses. Therefore, accurate delineation of target volumes and critical normal structures for IMRT is crucial. While clinical studies that demonstrate clinicians' abilities to do this reliably are just beginning to appear, dosimetric studies of IMRT for NPC have reported improved tumor coverage and normal tissue sparing [1–3].

Recent clinical studies, including two phase III trials, have demonstrated improved protection of salivary function using IMRT [4–6]. Subject to future studies, IMRT has become the gold standard means of delivering radiation therapy for NPC. This article therefore reviews recent advances in the treatment of NPC based on IMRT.

Intensity-modulated radiation therapy vs. older techniques

One of the biggest challenges of treating NPC using conventional techniques is to prescribe a tumoricidal dose to gross disease without causing clinically important toxicity in normal structures. Two-dimensional RT (2D-RT), typically with opposed lateral portals, did not permit equivalent sparing of normal structures without under-treating gross disease. Common toxicities with this technique, particularly with concurrent chemotherapy, included: xerostomia, occurring in over 90 % of patients and 70 % have reported moderate or severe symptoms [7, 8], mucositis, where significant mucositis have been reported from 33 to 64 % of patients [9–11], and dysphagia, where the most common dysfunction was pharyngeal retention ranging from 77 to 93.5 % [12–14]. Two-year locoregional recurrence rates ranged from 13 to 26.6 % and 5-year survival rates ranged from 43.5 to 70.6 % [15]. Three-dimensional conformal RT (3D-RT) was an improvement over 2D-RT, but still had difficulty covering the target when it was close to critical structures such as the brainstem. The benefit of IMRT over 2D-RT or 3D-RT is that it can improve coverage to disease while reducing dose to adjacent organs.

Dosimetric advantages of IMRT

Several institutions have shown an unquestionable dosimetric benefit of IMRT for NPC over conventional techniques [1, 3]. Hunt et al. showed that compared to 3D-RT, IMRT lowered doses to the spinal cord, mandible, and temporal lobes while increasing coverage to the retropharynx, skull base, and nodal regions [1]. Xia et al. compared IMRT, 3D-RT, and 2D-RT plans for locally advanced NPC [3]. They found that IMRT was able to achieve the same dose coverage to the target volume, while reducing dose to the parotid gland, optic chiasm, and brainstem.

An additional dosimetric advantage of IMRT is simultaneous delivery of different doses during every fraction of treatment. This can allow areas of subclinical disease to receive adequate lower doses compared to gross disease where doses can be substantially higher. This technique has been referred to in the literature by a variety of terms including simultaneous integrated boost, simultaneous modulated accelerated RT, or dose painting [16–18].

Clinical advantages of IMRT

Lee et al. reported one of the earliest clinical experiences of IMRT for NPC [19]. With a median follow-up of 31 months, the 4-year local progression-free rate was 97 % and the 4-year locoregional progression-free rate was 98 %. Furthermore, these excellent outcomes occurred despite the fact that the majority of these patients (70 %) had locally advanced disease. Subsequently, several institutions have reported their IMRT experience with similar outcomes. A prospective study from Hong Kong using IMRT alone for early-stage NPC reported a 3-year local control, distant metastases free, and overall survival rate of 100 % [20]. Kam et al. reported a 3-year local relapse-free survival rate of 92 % and 3-year nodal relapse-free survival rate of 98 % [21]. This study was similar to Lee et al. [19] in that the majority of patients (57 %) presented with locally advanced disease. Wolden et al. reported 3-year local control rates of 91 % and 3-year regional control rates of 93 %, of which 77 % of patients presented with stage III and IV disease [22]. Kwong et al. reported dose escalation results using IMRT for stage III and IV NPC [23]. The 2-year locoregional control rate was 95.7 %. Additional results of published IMRT series are summarized in Table 1.

Two phase III trials compared IMRT vs. conventional RT for early-stage NPC. Pow et al. [6] reported that IMRT was significantly better than conventional RT in regards to parotid sparing and improved quality of life. Kam et al. [4] showed that the incidence of observer-rated xerostomia was 39.4 % with IMRT compared to 82.1 % with conventional RT (p=0.01). Furthermore, patients who received IMRT had higher stimulated whole saliva flow rate and stimulated parotid flow rate. It is important to note that there was no statistical difference in patient-reported outcomes of xerostomia. Improvement in observer-rated xerostomia was not closely associated with patient-reported outcomes emphasizing the importance of monitoring both measured and patient-reported assessments. Similarly in Radiation Therapy Oncology Group (RTOG) 0225, which was a phase II study of IMRT with or without chemotherapy for NPC of all stages, the investigators were able to demonstrate the feasibility of delivering IMRT in a multi-institutional setting with reproducible excellent outcomes [5]. At 1 year from start of IMRT, only 13.5 % of patients had grade 2 xerostomia. For all patients, only two patients complained of grade 3 xerostomia and none had grade 4 xerostomia.

Since IMRT reduces toxicity compared to older techniques, it may increase patient compliance to chemoradiation. In RTOG 0225, 90 % of patients received the planned 70 Gy and 88 % with locally advanced disease received three cycles of concurrent cisplatin [5]. This compliance rate compared favorably to 63 % in the Intergroup 0099 trial, 52 % in the Hong Kong NPC-9901 trial, and 71 % in the

Table 1 Results from series treating NPC with IMRT with or without chemotherapy

Study	Year	Stage	No.	Median follow-up (months)	Time point (years)	Local control rate (%)	Regional control rate (%)	Distant met-free rate (%)	OS (%)
Lee et al. [19] (UCSF)	2002	All	67	31	4	97	98	66	88
Kwong et al. [20] (Hong Kong)	2004	T1 N0–1[a]	33	24	3	100	92	100	100
Kam [21] (Hong Kong)	2004	All	63	29	3	92	98	79	90
Wolden et al. [22] (MSKCC)	2006	All	74	35	3	91	93	78	83
Kwong et al. [23] (Hong Kong)	2006	III–IVB[a]	50	25	2	96	NA	94	92
RTOG 0225 [5]	2009	All	68	31	2	93	91	85	80
Tham et al. [32] (Singapore)	2009	All	195	37	3	90	NA	89	94
Lin et al. [29] (China)	2009	II–IV[a]	323	30	3	95	98	90	90
Wong et al. [33] (China)	2010	All	175	34	3	94	93	87	87
Lin et al. [28] (China)	2010	IIB–IVB[a]	370	31	3	95	97	86	89
Kam et al. [57] (Hong Kong)	2010	All	231	59	6	82	91	75	66
Ng et al. [30] (Hong Kong)	2011	All	193	30	2	95	96	90	92
Xiao et al. [34] (China)	2011	III–IVA[a]	81	54	5	95	NA	NA	75
Bakst et al [35] (MSKCC)	2011	II–IVB[a]	25	33	3	91	91	91	89
Xiayun et al. [37] (China)	2011	IIB–IVB[b]	54	30	3	95	98	86	88
Ma et al. [36] (Hong Kong)	2011	III–IVB[b]	30	32	2	93	93	93	90
RTOG 0615 [27]	2012	IIB–IVB[c]	42	30	2	NA	NA	91	91
Su et al. [31] (China)	2012	I–IIB[b]	198	51	5	97	98	98	NA

NPC nasopharyngeal carcinoma, *IMRT* intensity-modulated radiation therapy, OS overall survival, *UCSF* University of California at San Francisco, *MSKCC* Memorial Sloan-Kettering Cancer Center, *RTOG* Radiation Therapy Oncology Group, *NA* not available, *T* primary tumor stage

[a] AJCC Staging Manual 5th Edition [58]

[b] AJCC Staging Manual 6th Edition [59]

[c] AJCC Staging Manual 7th Edition [60]

Singapore randomized trial [24–26] all of which used non-IMRT techniques.

Treatment planning and target volumes

While IMRT is commonly used for many head and neck cancer sites, it is a tool that can be used at its full potential only if the technical aspects of treatment planning are well understood and the required methodology is disseminated throughout the Radiation Oncology community. This aspect of IMRT often receives the least attention in the literature, but may be the most important factor in achieving the results described above.

Based on a series of IMRT publications for NPC (Table 2), 13 studies have reported using treatment planning CT with 3 mm or less thickness [5, 20–23, 27–34], one study used 3 to 5 mm which may have been as a result of available technology at the time given that it was the first reported experience [19], while three studies did not report slice thickness [35–37]. Therefore, given the available data, we recommend using treatment planning CT with 3 mm or less thickness in areas that contain disease.

Fusion of MRI or PET scans with treatment planning CT images is highly encouraged to accurately delineate the target volumes. In the series listed on Table 2, all studies reported using MRI as part of pretreatment workup [5, 19–23, 27–37], among them, 13 studies either required or performed MRI on the vast majority of patients (95 % or more) [5, 19, 20, 23, 27–30, 32, 33, 35–37]. MRI has been demonstrated to be better at showing tumor extent than CT and should be part of pretreatment planning [38, 39]. In addition, PET was used in eight studies [19, 22, 27–29, 32, 34, 35], while the data was not available in nine studies [19–21, 23, 30, 31, 33, 36, 37]. Fused plans or co-registration was performed in ten studies [5, 21, 22, 27–30, 32, 33, 35].

The delineation of gross tumor volume (GTV) varies from institution to institution and we have summarized this in Table 2. In addition to the primary tumor, the GTV included nodes greater than 1 cm in diameter or nodes with necrotic center in four studies [5, 27, 33, 35]. In ten studies, the GTV also included involved lymph nodes without explicitly defining the criteria [19, 21, 22, 28–32, 34, 37]. Kwong et al. described the GTV as any macroscopic tumor and the whole nasopharynx, including bilateral Eustachian cushions and prevertebral muscles in one paper [20], while a subsequent paper described the GTV as the whole nasopharynx, tumor extending outside the nasopharynx, any skull

base erosion, and intracranial disease as well as enlarged neck nodes [23]. The criteria for defining involved lymph nodes remain controversial as many studies did not define this explicitly. However, in general, all lymph nodes that are PET positive or greater than 1 cm in short axis should receive definitive treatment.

The clinical target volume (CTV) varies even more than GTV from between institutions, due to different methods of contouring, including the margin around the GTV and the delineation of high-risk volumes. From the studies listed on Table 2, the CTV margin around the GTV was 1 cm in three studies [20, 21, 23], 0.5 cm or more in eight studies [5, 27–29, 31–34], and 0.2 cm or more in one study [30]. Two studies that did not include CTV described using a PTV with 1 cm margin beyond the GTV [22, 35]. Among those that described CTV margins, seven studies described shrinking the posterior margin if the CTV was close to critical structures like the brainstem [5, 21, 23, 27, 31, 33, 34]. Two studies reduced a 1-cm margin to 0.5 cm [21, 23], two studies reduced 0.5–1 cm margin to 0.2–0.5 cm [31, 34], and three studies reduced ≥0.5 cm margin to as small as 0.1 cm [5, 27, 33]. Based on these results, many studies used a 0.5-cm margin with an optional posterior margin reduction of 0.1–0.5 cm.

The delineation of CTV for high-risk regions varies greatly from institution to institution and we have summarized a list of studies that define target volumes in Table 3. In general, the clivus, skull base, inferior sphenoid sinus, cavernous sinus, pterygoid fossae, parapharyngeal space, posterior nasal cavity and maxillary sinus, retropharyngeal lymph nodes, and levels II through V are covered. For the clivus, eight studies covered the anterior third to half of the clivus if there was no involvement [20, 21, 27–30, 32, 37]. If there is any involvement, the clivus should be covered entirely. For the base of skull, six studies included the petrous tips and/or the foramen ovale [20, 21, 23, 27, 30, 32]. One study also included the foramen rotundum [27]; while two studies included the foramen spinosum [20, 23]. Coverage of the inferior orbital fissure was described in two studies [20, 23] and the anterior third to half of the arch of cervical vertebrae 1 (C1) was covered in four studies [20, 23, 28, 29]. Given the lack of data, it is unclear if the inferior orbital fissure or the anterior arch of C1 should be part of the CTV and this may be a potential area to spare. An example of delineation for GTV and CTV is shown in Fig. 1.

The greatest variability for cervical lymph node coverage is level I. In two studies, level Ia was covered electively if Ib nodes or the oral cavity was involved [21, 32]. Three studies covered level Ib routinely [5, 21, 33], three studies had the option to spare level Ib in N0 disease [27, 30, 32], and two studies did not cover level Ib [28, 29]. Based on the data, we do not recommend routinely covering level Ia. Additionally, level Ib is an area that may be potentially spared even with node positive disease. Two studies that did not cover level Ib reported 3-year locoregional control rates of 95–98 % despite having 80 % of patients with locally advanced disease [28, 29]. For retropharyngeal lymph nodes, the inferior border is at the hyoid bone in two studies [21, 40] and at the cranial edge of the second cervical vertebrae in two studies [28, 29]. It is important to note that in the consensus guideline by Gregoire et al. [41], the inferior border of the retropharyngeal node is defined as the cranial edge of the body of the hyoid bone.

The planning target volume (PTV) margin also varies similarly to CTV margin and is listed in Table 2. The PTV margin off of CTV was 0.5 cm or more in four studies [5, 27, 33, 37], 0.3 cm in five studies [21, 28–30, 32], and 0.2 cm in two studies [20, 23]. In the two studies with 0.2 cm margin, the CTV margin beyond GTV was 1 cm which is relatively large [20, 23]. There is no clear consensus on PTV margin but it is reasonable to use 0.3 to 0.5 cm based on the available data.

We list the studies that included organs at risk with dose constraints in Table 4. In general, the brainstem, spinal cord, eyes, optic nerves, chiasm, lens, temporal lobes, parotid glands, inner/middle ears, temporomandibular joints, mandible, oral cavity, and larynx are included. The dose constraints vary among institutions and there are few data that suggest one is superior to the others. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) provides recent data behind normal tissue complication probabilities [42].

For the brainstem, the maximum dose (dmax) was 56 Gy in four studies [20, 23, 33, 34], 54 Gy in five studies [5, 21, 27, 30, 36], and 50 Gy in one study [32]. In four studies, 1 % of the brainstem could not exceed 60 Gy [5, 27, 30, 33]. For the spinal cord, the dmax was 50 Gy in one study [23], 46 Gy in one study [20], and 45 Gy in seven studies [5, 27, 30, 32–34, 36]. In four studies, 1 % or 1 cc of the spinal cord could not exceed 50 Gy [5, 27, 30, 33]. For the eyes, the dmax was 58 Gy in two studies [20, 23] and 50 Gy in two studies [5, 30]. The mean dose (dmean) for the eyes was 50 Gy or less in two studies [20, 23] and 35 Gy or less in three studies [5, 30, 33]. The optic nerves and chiasm essentially have the same dose constraint. The dmax for the optic nerves and chiasm was 58 Gy in two studies [20, 23], 54 Gy in five studies [5, 21, 30, 33, 36], and 50 Gy in three studies [27, 32, 34]. The dmean was 50 Gy or less in two studies [20, 23] and two studies stated that 1 % of optic nerve and chiasm could not exceed 60 Gy [5, 30]. For the temporal lobes, the dmax was 67 Gy in one study [36], 65 Gy in one study [30], 60 Gy in four studies [5, 23, 33, 34], and 58 Gy in one study [20]. The dmean for the temporal lobes was 50 Gy or less in two studies [20, 23] and in three studies, 1 % of the temporal lobes could not exceed 65 Gy [27, 30, 33].

Table 2 Treatment planning techniques of series treating NPC with IMRT

Study	CT scan thickness and additional pretreatment imaging	Target volume delineation	RT prescription	Organs at risk contoured
Lee et al. [19] (UCSF)	3–5 mm MRI (100 %) PET = NA Fused plans done (NA)	GTV = primary tumor and positive neck nodes; CTV = GTV + margin, regional lymph nodes, entire nasopharynx, retropharyngeal lymph nodal regions, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus, and posterior third of the nasal cavity and maxillary sinuses; PTV = built-in system (based on Peacock or Corvus)	GTV=65–70 Gy at 2.12–2.25 Gy/fx CTV=60 Gy at 1.8 Gy/fx Clinically negative neck=50–60 Gy at 1.8–2 Gy/fx	Brainstem, spinal cord, optic nerves, chiasm, parotid glands, temporomandibular joints, middle and inner ears
Kwong et al. [20] (Hong Kong)	2.5 mm from pituitary fossa to angle of jaw; 5 mm elsewhere MRI (100 %) PET = NA	GTV = macroscopic tumor and whole nasopharynx including bilateral Eustachian cushions and prevertebral muscles and enlarged cervical lymph nodes; CTV = GTV + 1 cm, sphenoid sinus caudal to base of pituitary fossa, bilateral cavernous sinus, base of skull including medial one third of petrous temporal bones but excluding internal auditory canals and cochlea, inferior orbital fissures, foramen ovale, foramen spinosum, anterior one half of clivus, posterior one third of nasal cavity and antrum, medial pterygoid muscles and parapharyngeal space up to styloid process, anterior one half of the arch of C1 and prevertebral muscles inferior to C1, bilateral levels II, III, Va, and jugular lymphatics up to base of skull in poststyloid area; PTV = CTV + 2 mm margin as well as posterior parts of submandibular gland	GTV=68–70 Gy at 2–2.06 Gy/fx CTV = NA PTV=66–68 Gy at 1.9–2 Gy/fx	Lens, eyes, optic nerves, optic chiasm, pituitary, temporal lobes, brain, brainstem, inner ear, middle ear, external auditory meatus, temporomandibular joints, parotid glands, spinal cord
Kam [21] (Hong Kong)	2.5 mm spanning primary tumor, enlarged regional lymph nodes, optic pathway; 5 mm elsewhere. MRI (78 %) PET = NA Fused plans (78 %)	GTV = gross disease and enlarged lymph nodes + 2 mm margin; CTV = GTV + 1 cm margin (0.5 cm posterior), sphenoid sinus, cavernous sinus, petrous tips, foramen ovales, retropharyngeal nodes to bottom of hyoid bone, posterior third of nasal cavity and maxillary sinus, anterior half of clivus if intact or whole clivus if involved, whole parapharyngeal fat spaces, pterygoid fossae, regional lymphatics including levels Ib and V, level Ia included if submandibular or oral cavity involvement; PTV = CTV + 3 mm	GTV=66 Gy at 2 Gy/fx±8 Gy boost at 2 Gy/fx CTV = NA PTV=60 Gy at 1.82 Gy/fx Lower neck=54–60 Gy for N0 and 66 Gy for N+ at 2 Gy/fx	Brainstem, spinal cord, parotid glands, optic nerves, chiasm, lens, eyeballs, temporal lobes, temporomandibular joints, cochlea, vestibulocochlear nerves, external auditory canals, and oral mucosa
Wolden et al. [22] (MSKCC)	3 mm MRI (70 %) PET if clinically indicated (NA) Fused plans (77 %)	GTV = primary disease and involved lymph nodes; CTV = NA; PTVg = GTV + 1 cm margin (0.5 cm posterior); PTVm = PTVg, entire nasopharynx, bilateral retropharyngeal and cervical lymph nodes + 5 mm margin	Accelerated hyperfractionation using concomitant boost (n=59) Daily treatment (n=15)	Globes, optic nerves, optic chiasm, brainstem, spinal cord, cochlea, parotid glands, submandibular glands, oral cavity, and larynx

Table 2 (continued)

Study	CT scan thickness and additional pretreatment imaging	Target volume delineation	RT prescription	Organs at risk contoured
Kwong et al. [23] (Hong Kong)	2.5 mm from 1 cm superior to tumor or pituitary fossa down to angle of jaw; 5 mm elsewhere. MRI (100 %)	GTV = whole nasopharynx, skull base erosion, intracranial disease	GTV=76 Gy at 2.17 Gy/fx	Eyeballs, optic nerves, optic chiasm, temporal lobes, brainstem, spinal cord, parotid glands, inner ears, middle ears, external ears, and temporomandibular joints
	PET = NA	GTVn = enlarged neck nodes	GTVn=72 Gy	
	Fused plans = NA	CTV = GTV + 1 cm margin (0.5 cm posterior if close to brainstem), sphenoid sinus, cavernous sinus, base of skull, petrous tip, inferior orbital fissures, foramen ovale, foramen spinosum, clivus, posterior third of nasal cavity and maxillary antrum, parapharyngeal spaces, prevertebral muscles, and anterior half of the arch of C1, poststyloid area cover regional lymphatic in neck including levels II, III, and Va	PTV=70 Gy at 2 Gy/fx	
		PTV = CTV + 2 mm margin	Lower neck=60 Gy for N0 and 66 Gy for N+ at 2 Gy/fx	
RTOG 0225 [5]	3 mm or less	GTV = gross disease, lymph node >1 cm or nodes with necrotic center	GTV, CTV_{70}, PTV_{70}=70 Gy at 2.12 Gy/fx	Brainstem, optic nerves, chiasm, spinal cord, mandible, temporomandibular joint, temporal lobes, parotid glands, tongue, inner/middle ears, eyes, lens, and glottic larynx
	MRI required (NA)	CTV_{70} = gross tumor volume ≥0.5 cm margin (as small as 0.1 cm margin if close to brainstem)	$CTV_{59.4}$, $PTV_{59.4}$=59.4 Gy at 1.8 Gy/fx	
	PET optional (NA)	$CTV_{59.4}$ = entire nasopharynx, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus, posterior third of nasal cavity and maxillary sinus, bilateral retropharyngeal lymph nodes, bilateral levels Ia, Ib, II, III, IV, and V	$CTV_{50.4}$=50.4 Gy at 1.8 Gy/fx	
	Fused plans optional (NA)	$CTV_{50.4}$ = low neck (if using anterior or anterior–posterior split beam technique)		
		PTV = CTV ≥0.5 cm margin		
Tham et al. [32] (Singapore)	3 mm in nasopharyngeal region; 5 mm elsewhere	GTV = gross disease and enlarged lymph nodes	PTV_70Gy=70 Gy at 2.12 Gy/fx	Brainstem, spinal cord, parotid glands, optic nerves, chiasm, lens, eyeballs, temporal lobes, temporomandibular joints, inner ear structures, auditory nerves, and oral mucosa
	MRI (95 %)	CTV_70Gy = GTV and entire nasopharynx	PTV_66Gy=66 Gy at 2 Gy/fx	
	PET/CT (18 %)	PTV_70Gy = CTV_70Gy + 0.3 cm margin	PTV_60Gy=60 Gy at 1.82 Gy/fx	
	Fused plans (95 %)	CTV_66Gy = GTV + 0.5 cm margin	Low neck (anterior split beam technique)=54–60 Gy at 2 Gy/fx	
		PTV_66Gy = CTV_66Gy + 0.3 cm margin		
		CTV_60Gy = sphenoid sinus, cavernous sinus, petrous tips, foramen ovale, retropharyngeal nodes to hyoid bone, posterior third of nasal		

Table 2 (continued)

Study	CT scan thickness and additional pretreatment imaging	Target volume delineation	RT prescription	Organs at risk contoured
		cavity and maxillary sinus, anterior half of clivus if intact or whole clivus if involved, parapharyngeal fat spaces, pterygoid fossae, bilateral levels II, III, IV, and V, level Ib covered if nodal disease on ipsilateral neck, level Ia covered if submandibular node or oral cavity involved by disease PTV_60Gy = CTV_60 Gy + 0.3 cm margin		
Lin et al. [29] (China)	3 mm	GTV-P = primary gross tumor volume	GTV-P, PTV of GTV-P=66–69.75 Gy at 2.2–2.25 Gy/fx	Brainstem, spinal cord, parotid glands, optic nerves, chiasm, lens, eyeballs, temporal lobes, temporomandibular joints, mandible, hypophysis
	MRI required after July 2005 (NA)	GTV-N = involved lymph nodes	GTV-N, PTV of GTV-N=66–66.65 Gy at 2.15–2.2 Gy/fx	
	PET if clinically indicated (NA)	CTV-1 = GTV + 0.5–1 cm margin, entire nasopharyngeal mucosa + 0.5 cm margin	PTV of CTV-1=60–60.45 Gy at 1.95–2 Gy/fx	
	Fused plans done (NA)	CTV-2 = nasopharyngeal cavity (posterior nasal cavity), maxillary sinus (0.5 cm anterior to posterior nasal aperture and maxillary mucosa), pterygopalatine fossa, posterior ethmoid sinus, parapharyngeal space, skull base, anterior third of clivus and cervical vertebra, inferior sphenoid sinus, cavernous sinus, retropharyngeal nodes from base of skull to second cervical vertebrae	PTV of CTV-2 and CTV-N=54–55.8 Gy at 1.8 Gy/fx	
		CTV-N = bilateral levels II, III, IV, and V, upper deep jugular nodes above C1 vertebrae included if clinically involved	Low neck (anterior split beam technique)=50.4 Gy at 1.8 Gy/fx	
		PTV = CTV + 0.3 cm margin		
Wong et al. [33] (China)	3 mm	GTV = gross disease and lymph nodes >1 cm or any node with necrotic center	PTV70=70 Gy at 2.12 Gy/fx (66 Gy at 2 Gy/fx if stage I)	Brainstem, spinal cord, optic nerves, optic chiasm, eyes, lens, temporal lobes, parotid glands, cochlea, and temporomandibular joints
	MRI required (NA)	CTV70 = GTV	PTV60=60 Gy at 1.82 Gy/fx	
	PET = NA	CTV60 = CTV70 + 0.5 cm margin (0.1 cm margin if close to brainstem), entire nasopharynx, retropharyngeal nodes, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus, posterior third of nasal cavity and maxillary sinus, bilateral upper deep jugular nodes, levels II, III, IV, V, and supraclavicular nodes	PTV54=54 Gy at 1.64 Gy/fx	
	Fused plans done (NA)	CTV54 = low-risk nodal regions		
		PTV = CTV + 0.5 cm margin (less if close to critical organ)		
Lin et al. [28] (China)	3 mm	GTV-P = primary gross tumor		

Table 2 (continued)

Study	CT scan thickness and additional pretreatment imaging	Target volume delineation	RT prescription	Organs at risk contoured
			GTV-P, PTV of GTV-P=66–69.75 Gy at 2.2–2.25 Gy/fx	Brainstem, spinal cord, parotid glands, optic nerves, chiasm, lens, eyeballs, temporal lobes, temporomandibular joints, mandible, and hypophysis
	MRI required after July 2005 (NA)	GTV-N = nodal gross tumor	GTV-N, PTV of GTV-N=66–66.65 Gy at 2.15–2.2 Gy/fx	
	PET if clinically indicated	CTV-1 = GTV + 0.5–1 cm margin, entire nasopharynx + 0.5 cm margin	PTV of CTV-1=60–60.45 Gy at 1.95–2 Gy/fx	
	Fused plans done (NA)	CTV-2 = nasopharyngeal cavity (posterior nasal cavity), maxillary sinus (0.5 cm anterior to posterior nasal aperture and maxillary mucosa), pterygopalatine fossa, posterior ethmoid sinus, parapharyngeal space, skull base, anterior third of clivus and cervical vertebra, inferior sphenoid sinus, cavernous sinus, retropharyngeal nodes from base of skull to second cervical vertebrae	PTV of CTV-2 and CTV-N=54–55.8 Gy at 1.8 Gy/fx	
		CTV-N = Bilateral levels II, III, IV, and V	Low neck (anterior split beam technique)=50.4 Gy at 1.8 Gy/fx	
		PTV = CTV + 0.3 cm margin		
Ng et al. [30] (Hong Kong)	3 mm MRI (100 %)	GTV_P = primary tumor GTV_N = involved lymph nodes	PTV1=70 Gy at 2–2.12 Gy/fx PTV2=59.4–61.25 Gy at 1.75–1.8 Gy/fx	Brainstem, spinal cord, optic chiasm, optic nerves, temporal lobes, pituitary, mandible, temporomandibular joints, lens, eyeballs, parotid glands, cochlea, tongue, and larynx
	PET = NA	CTV1 = GTV_P + 0.2–0.5 cm (smaller margin if close to critical structure), GTV_N + 0.5–1 cm margin, margin and whole nasopharynx	PTV3=52.5–59.4 at 1.75–1.8 Gy/fx	
	Fused plans (100 %)	CTV2 = CTV1, parapharyngeal spaces, posterior third of nasal cavity and maxillary sinus, pterygoid process, base of skull, lower half of sphenoid sinus, anterior half of clivus, petrous tips, bilateral retropharyngeal nodes, levels II, II, VA	Low neck (split beam technique)=50 Gy at 2 Gy/fx if N0 or 60–66 Gy at 2 Gy/fx if N+	
		CTV3 = Levels IV–VB		
		PTV = CTV + 0.3 cm margin		
Xiao et al. [34] (China)	3 mm	GTV = primary gross disease and positive lymph nodes	GTV (primary)=68 Gy at 2.27 Gy/fx	Brainstem, spinal cord, temporal lobes, lens, optic nerves, chiasm, parotid glands, temporomandibular joints, and mandible
	CT and MRI (37 %)	CTV1 = GTV + 0.5–1 cm margin (0.2–0.3 cm margin posteriorly) and whole nasopharynx	GTV (node)=60–66 Gy at 2–2.2 Gy/fx	
	CT, MRI and PET (54 %)	CTV2 = CTV1 + 0.5–1 cm margin (0.2–0.3 cm margin posteriorly), bilateral levels IIa, IIb, III, and Va (levels IV and Vb included if N+)	CTV1=60 Gy at 2 Gy/fx	
	Fused plans = NA	PTV margin = NA	CTV2=54 Gy at 1.8 Gy/fx	

Table 2 (continued)

Study	CT scan thickness and additional pretreatment imaging	Target volume delineation	RT prescription	Organs at risk contoured
Bakst et al [35] (MSKCC)	CT thickness = NA	GTVg = primary disease and nodes >1 cm or nodes with necrotic centers	PTVg=70.2 Gy at 2.34 Gy/fx	Globes, optic nerves, optic chiasm, brainstem, spinal cord, cochlea, parotid gland, submandibular glands, oral cavity, and larynx
	MRI required (NA)	PTVg = GTVg + 1 cm margin (0.5 cm posterior)	PTVm=54 Gy at 1.8 Gy/fx	
	PET (100 %)	PTVm = PTVg including potential routes of NPC spread, bilateral retropharyngeal and cervical lymph node regions + 0.5 cm margin		
	Fused plans (100 %)			
Xiayun et al. [37] (China)	CT thickness = NA	GTV = primary tumor and metastatic lymph nodes	PTVg=66–70.4 Gy at 2.2 Gy/fx	NA
	MRI required (NA)	CTV = whole nasopharyngeal cavity, anterior one-third of clivus (whole clivus covered if T3 or T4), pterygoid plates, parapharyngeal space, inferior sphenoid sinus, posterior one third nasal cavity and maxillary sinus, bilateral levels II, III and Va (levels IV and Vb if N+)	PTV60=60 Gy at 2 Gy/fx	
	PET = NA	PTVg = GTV + 0.5 cm margin	PTV54=54 Gy at 1.8 Gy/fx	
	Fused plans = NA	PTV60 = CTV + 0.5 cm margin		
		PTV54 = low-risk clinical target volume		
Ma et al. [36] (Hong Kong)	CT thickness = NA	PTV of primary tumor and involved lymph nodes	PTV primary and involved lymph node=66 Gy in 2 Gy/fx plus 8 Gy in 2 Gy/fx boost or 70 Gy at 2 Gy/fx	Brainstem, spinal cord, optic nerve, chiasm, lens, and temporal lobes
	MRI required (NA)	PTV of subclinical disease around tumor and upper/midneck	PTV subclinical disease and upper/midneck=60–62 Gy in 1.77–1.82 Gy/fx	
	PET = NA	PTV of lower neck	PTV of lower neck=54–56 Gy at 1.6–1.64 Gy/fx	
	Fused plans = NA			
RTOG 0615 [27]	3 mm or less	GTV = gross disease, lymph node >1 cm or nodes with necrotic center	GTV, CTV_{70}, PTV_{70}=70 Gy at 2.12 Gy/fx	Brainstem, optic nerves, chiasm, spinal cord, mandible, pituitary, temporomandibular joint, temporal lobes, parotid glands, oral cavity, inner/middle ears, eyes, lens, brachial plexus, esophagus (including postcricoid pharynx), and glottic larynx
	MRI required (NA)	CTV_{70} = gross tumor volume ≥0.5 cm margin (as small as 0.1 cm margin if close to brainstem)	$CTV_{59.4}$, $PTV_{59.4}$=59.4 Gy at 1.8 Gy/fx	
	PET optional (NA)	$CTV_{59.4}$ = entire nasopharynx, anterior 1/2 to 2/3 of clivus (entire clivus if involved), skull base (foramen ovale and rotundum bilaterally), pterygoid fossae, parapharyngeal space, inferior sphenoid sinus (entire sphenoid sinus in T3 or T4), posterior fourth or third of nasal cavity and maxillary sinus,	CTV_{54}, PTV_{54} (if one single IMRT plan)=54 Gy at 1.64 Gy/fx	

Table 2 (continued)

Study	CT scan thickness and additional pretreatment imaging	Target volume delineation	RT prescription	Organs at risk contoured
		bilateral retropharyngeal lymph nodes, bilateral upper deep jugular regions, levels IB (if N+), II, III, IV, and V. Cavernous sinus included if T3, T4, or bulky disease in roof of nasopharynx		
	Fused plans optional (NA)	CTV_{54}, CTV_{50} = low neck	CTV_{50} (if split-beam technique)=50 Gy at 2 Gy/fx	
		PTV = CTV ≥0.5 cm margin	Optional: CTV_{63}, PTV_{63} (small volume lymphd nodes)= 63 Gy at 1.91 Gy/fx	
Su et al. [31] (China)	3 mm	GTV = primary tumor (GTVnx) and involved lymph nodes	PTV of GTVnx=68 Gy 2.27 Gy/fx	Brainstem, spinal cord, temporal lobes, parotid glands, temporomandibular joint
	MRI (80 %)	CTV = GTVnx + 0.5–1 cm margin, entire nasopharynx mucosa + 0.5 cm margin	PTV of GTV (involved node)= 64–66 Gy at 2.13–2.2 Gy/fx	
	PET = NA	CTV2 = CTV + 0.5–1 cm margin (0.3–0.5 cm posterior if close to brainstem), retropharyngeal nodes, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus, posterior edge of nasal cavity and maxillary sinuses, and upper neck	PTV of CTV=60 Gy at 2 Gy/fx	
	Fused plans = NA	PTV margin = NA	PTV of CTV2=54 Gy at 1.8 Gy/fx	
			Low neck=50 Gy at 2 Gy/fx for N1 (no low neck if N0)	

NPC nasopharyngeal carcinoma, *IMRT* intensity-modulated radiation therapy, *CT* computed tomography, *RT* radiation therapy, *UCSF* University of California at San Francisco, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *NA* not available, *GTV* gross tumor volume, *CTV* clinical target volume, *PTV* planning target volume, *fx* fraction, *N* nodal stage, *C* cervical vertebrae, *MSKCC* Memorial Sloan-Kettering Cancer Center, *RTOG* Radiation Therapy Oncology Group, *T* primary tumor stage

Table 3 Clinical target volume delineation of series treating NPC with IMRT

	Clivus	Skull base	Sphenoid sinus	Cavernous sinus	Inferior orbital fissures	Pterygoid fossae	Parapharyngeal space	Cervical vertebrae (C) 1	Posterior nasal cavity and maxillary sinus	Retropharyngeal lymph nodes	Level I	Level II	Level III	Level IV	Level V
Lee et al. [19] (UCSF)	Y	Y	Y (inferior part)	NA	NA	Y	Y	NA	Y (posterior 1/3)	Y	NA	NA	NA	NA	NA
Kwong et al. [20] (Hong Kong)	Y (anterior 1/2)	Y (includes foramen ovale, foramen spinosum, and medial 1/3 petrous temporal bones)	Y	Y	Y	NA	Y (includes medial pterygoid muscles)	Y (anterior 1/2 of arch and prevertebral muscles)	Y (posterior 1/3)	Y	NA	Y	Y	NA	Y (Va only. Vb not mentioned)
Kam [21] (Hong Kong)	Y (anterior half if intact, whole if involved)	Y (petrous tips and foramen ovale)	Y	Y	NA	Y	Y	NA	Y (posterior 1/3)	Y (inferiorly to hyoid)	Y (Ib only. Includes Ia if Ib or oral cavity involved)	Y	Y	Y	Y
Kwong et al. [23] (Hong Kong)	Y	Y (includes petrous bone, foramen ovale, and foramen spinosum)	Y	Y	Y	NA	Y	Y (anterior 1/2 of arch and prevertebral muscles)	Y (posterior 1/3)	NA	NA	Y	Y	NA	Y (Va only. Vb not mentioned)
RTOG 0225 [5]	Y	Y	Y (inferior part)	NA	NA	Y	Y	NA	Y (posterior 1/3)	Y	Y (Ib only, Ia not mentioned)	Y	Y	Y	Y
Tham et al. [32] (Singapore)	Y (anterior half if intact, whole if involved)	Y (includes petrous tips and foramin ovale)	Y	Y	NA	Y	Y	NA	Y (posterior 1/3)	Y (inferiorly to hyoid)	Y (includes Ib if ipsilateral neck disease, Ia if Ib or oral cavity involved)	Y	Y	Y	Y
Lin et al. [29] (China)	Y (anterior 1/3)	Y	Y (inferior part and also include posterior ethmoid sinus, entire sphenoid sinus if involved)	Y	NA	Y	Y	Y (anterior 1/3)	Y (0.5 cm anterior to posterior nasal aperture and maxillary mucosa)	Y (inferiorly to cranial edge of C2)	N	Y (IIa included only if involved)	Y	Y	Y
Wong et al. [33] (China)	Y	Y	Y (inferior part)	NA	NA	Y	Y	NA	Y (posterior 1/3)	Y	Y (includes Ib, Ia not mentioned)	Y	Y	Y	Y
Lin et al. [28] (China)	Y (anterior 1/3)	Y	Y (inferior part and also include posterior ethmoid sinus, entire sphenoid sinus if involved)	Y	NA	Y	Y	Y (anterior 1/3)	Y (0.5 cm anterior to posterior nasal aperture and maxillary mucosa)	Y (inferiorly to cranial edge of C2)	N	Y	Y	Y	Y

Table 3 (continued)

	Clivus	Skull base	Sphenoid sinus	Cavernous sinus	Inferior orbital fissures	Pterygoid fossae	Parapharyngeal space	Cervical vertebrae (C) 1	Posterior nasal cavity and maxillary sinus	Retropharyngeal lymph nodes	Level I	Level II	Level III	Level IV	Level V
Ng et al. [30] (Hong Kong)	Y (anterior half)	Y (includes petrous tips)	Y (inferior half)	NA	NA	Y (pterygoid process)	Y	NA	Y (posterior 1/3)	Y	Y (Ib only, Ib may be spared in node negative disease)	Y	Y	Y	Y
Xiayun et al. [37] (China)	Y (anterior 1/3)	NA	Y (inferior part)	NA	NA	Y (pterygoid plates)	Y	NA	Y (posterior 1/3)	NA	NA	Y	Y	Y (if N1–N3)	Y (Va only. Vb if N1–N3)
RTOG 0615 [27]	Y (anterior half or 1/3 but entire clivus if involved	Y (includes foramen ovale and foramen rotundum)	Y (inferior part but entire sphenoid sinus if T3–T4)	Y	NA	Y	Y	NA	Y (posterior 1/4 to 1/3)	Y	Y (Ib only, Ib may be spared if node negative disease)	Y	Y	Y	Y
Su et al. [31] (China)	Y	Y	Y (inferior part)	NA	NA	Y	Y	NA	Y	Y	NA	Y	Y	Y (low neck excluded if node negative disease)	Y (low neck excluded if node negative disease)

NPC nasopharyngeal carcinoma, *IMRT* intensity-modulated radiation therapy, *C* cervical vertebrae, *UCSF* University of California at San Francisco, *Y* yes, *NA* not available, *RTOG* Radiation Therapy Oncology Group, *N* no

Fig. 1 Forty-four-year-old man with T4N1 NPC treated with definitive chemoradiation therapy. The PTV70 (*red*), PTV 59.4 (*blue*), and dose painting are shown above

There has been much interest in dose–function relationship of the parotid glands. Earlier studies showed that relative preservation of parotid function was achieved when the mean parotid dose was 26 Gy or less [43]. Another study observed a decreased incidence of xerostomia when the mean dose of at least one parotid gland was less than 25.8 Gy [44]. It should be noted that in both phase III studies by Kam et al. [4] and Pow et al. [44], the mean dose to the parotid glands were higher at 32.2 and 41 Gy, respectively, while still showing improved observer-rated salivary function. However, the patient-reported quality of life was not different in the study by Kam et al. [4]. This outcome may be due to the high mean parotid dose. In the recent PARSPORT study, a phase III trial comparing IMRT versus conventional RT for oropharynx and hypopharynx carcinoma, the authors demonstrated improved salivary function in

Table 4 Organs at risk dose constraints of series treating NPC with IMRT

	Brainstem	Spinal cord	Eyes	Optic nerves	Optic chiasm	Lens	Temporal lobes	Parotid glands
Kwong et al. [20] (Hong Kong)	Dmax=56 Gy; Dmean= 50 Gy; <5 % volume overdose	Dmax=46 Gy; Dmean= 40 Gy; <5 % volume overdose	Dmax=58 Gy; Dmean= 50 Gy; <5 % volume overdose	Dmax=58 Gy; Dmean= 50 Gy; <5 % volume overdose	Dmax=58 Gy; Dmean= 50 Gy; <5 % volume overdose	NA	Dmax=58 Gy; Dmean= 50 Gy; <5 % volume overdose	Dmax=66 Gy; Dmean= 20 Gy; <50 % volume overdose
Kam [21] (Hong Kong)	Dmax=54 Gy	Dmax=45 Gy	NA	Dmax=54 Gy	Dmax=54 Gy	Dmax=6 Gy	Dmax=67 Gy	NA
Kwong et al. [23] (Hong Kong)	Dmax=56 Gy; Dmean= 50 Gy; <5 % volume overdose; <0.01 cc more than 58 Gy	Dmax=50 Gy; Dmean= 45 Gy; <5 % volume overdose; <0.01 cc more than 48 Gy	Dmax=58 Gy; Dmean= 50 Gy; <5 % volume overdose; may relax dose constraint on ipsilateral side	Dmax=58 Gy; Dmean= 50 Gy; <5 % volume overdose; may relax dose constraint on ipsilateral side	Dmax=58 Gy; Dmean= 50 Gy; <5 % volume overdose	NA	Dmax=60 Gy; Dmean= 50 Gy; <5 % volume overdose	NA
RTOG 0225 [5]	Dmax=54 Gy; 1 % PTV cannot exceed 60 Gy	Dmax=45 Gy or 1 cc of PTV cannot exceed 50 Gy	Dmean <35 Gy	Dmax=54 Gy; 1 % PTV cannot exceed 60 Gy	Dmax=54 Gy; 1 % PTV cannot exceed 60 Gy	ALAP	Dmax=60 Gy; 1 % PTV cannot exceed 65 Gy	Dmean ≤26 Gy (at least 1 gland); at least 20 cc of combined volume of both parotid glands receive <20 Gy; at least 50 % of one gland receive <30 Gy
Tham et al. [32] (Singapore)	Dmax=50 Gy	Dmax=45 Gy	NA	Dmax=50 Gy	Dmax=50 Gy	Dmax=10 Gy	NA	D_{50} <30 Gy
Wong et al. [33] (China)	Followed RTOG 0225 [5]							
Ng et al. [30] (Hong Kong)	Dmax=54 Gy; 1 % volume <60 Gy	Dmax=45 Gy; 1 cc <50 Gy	Dmax=50 Gy; Dmean <35 Gy	Dmax=54 Gy; 1 % volume <60 Gy	Dmax=54 Gy; 1 % volume <60 Gy	Dmax=6 Gy; 1 % volume <10 Gy	Dmax=65 Gy; 1 % volume <65 Gy	Dmean=26 Gy; 50 % volume <30 Gy (at least 1 gland)
Xiao et al. [34] (China)	Dmax=56 Gy	Dmax=45 Gy	NA	Dmax=50 Gy	Dmax=50 Gy	Dmax=5 Gy	Dmax=60 Gy	Dmax=40 Gy
Ma et al. [36] (Hong Kong)	Followed Kam et al. [21]							
RTOG 0615 [27]	Dmax=54 Gy; 1 % PRV cannot exceed 60 Gy	Dmax=45 Gy; 1 % PRV cannot exceed 50 Gy	Dmax=50 Gy	Dmax=50 Gy; PRV Dmax=54 Gy	Dmax=50 Gy; PRV Dmax=54 Gy	Dmax=25 Gy	NA	Dmean ≤26 Gy (at least 1 gland); at least 20 cc of combined volume of both parotid glands receive <20 Gy; at least 50 % of one gland receive <30 Gy

	Pituitary gland	Inner ears/cochlea	Middle ears	External auditory meatus	Temporomandibular joints	Mandible	Oral cavity/tongue	Glottic larynx	Oral mucosa
Kwong et al. [20] (Hong Kong)	Dmax=45 Gy; Dmean= 25 Gy; <5 % volume overdose	Dmax=58 Gy; Dmean= 50 Gy; <5 % volume overdose	Dmax=58 Gy; Dmean= 50 Gy; <5 % volume overdose	Dmax=58 Gy; Dmean= 50 Gy; <5 % volume overdose	Dmax=58 Gy; Dmean=50 Gy; <5 % volume overdose	NA	NA	NA	NA
Kam [21] (Hong Kong)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kwong et al. [23] (Hong Kong)	NA	NA	NA	NA	NA	NA	NA	NA	NA
RTOG 0225 [5]	NA	Dmean <50 Gy	Dmean <50 Gy	NA	Dmax=70 Gy; 1 cc of PTV cannot exceed 75 Gy	Dmax=70 Gy; 1 cc of PTV cannot exceed 75 Gy	Dmax=55 Gy; 1 % PTV cannot exceed 65 Gy	Dmean <45 Gy	NA
	NA	NA	NA	NA	NA	NA	NA	Dmax=38 Gy	Dmax=40 Gy

Table 4 (continued)

	Pituitary gland	Inner ears/cochlea	Middle ears	External auditory meatus	Temporomandibular joints	Mandible	Oral cavity/tongue	Glottic larynx	Oral mucosa
Tham et al. [32] (Singapore)									
Wong et al. [33] (China)	Followed RTOG 0225 [5]								
Ng et al. [30] (Hong Kong)	Dmax=60 Gy; 1 % volume <65 Gy	Dmean <50 Gy	NA	NA	1 % volume<70 Gy; 1 % volume <75 Gy	1 % volume< 70 Gy; 1 % volume <75 Gy	1 % volume<70 Gy; Dmean <55 Gy	Dmean<30 Gy; Dmean <45 Gy	NA
Xiao et al. [34] (China)	NA	NA	NA	NA	Dmax=50 Gy	Dmax=50 Gy	NA	NA	NA
Ma et al. [36] (Hong Kong)	Followed Kam et al. [21]								
RTOG 0615 [27]	NA	No more than 5 % received 55 Gy or more	NA	NA	Dmax=70 Gy; 1 cc cannot exceed 75 Gy	Dmax=70 Gy; 1 cc cannot exceed 75 Gy	Dmean <40 Gy	Dmean <45 Gy	NA

NPC nasopharyngeal carcinoma, *IMRT* intensity-modulated radiation therapy, *Dmax* maximum dose, *Dmean* mean dose, *NA* not available, *RTOG* Radiation Therapy Oncology Group, *PTV* planning target volume, *ALAP* as low as possible, D_{50} dose to 50 % of organ, *PRV* planning organ at risk volumes

observer and patient-reported outcomes [45] Despite treating different sites, it is still interesting to find that while the mean ipsilateral parotid dose was 47.6 Gy, the mean contralateral parotid dose was 25.4 Gy which may have attributed to the improved patient-reported quality of life.

Early-stage nasopharyngeal carcinoma

For stage I NPC, the standard treatment is RT alone. The location of the nasopharynx near critical structures makes surgical approaches limited. Historical long-term survival for early-stage NPC patients who received conventional RT alone ranged from 60–80 % [46, 47]. A larger, modern study from Hong Kong reported 5-year local control and overall survival as high as 91 and 90 %, respectively, for early-stage NPC using predominantly conventional RT [48]. It is possible that the results were improved due to greater number of available linear accelerators and higher number of pretreatment MRIs. Because long-term xerostomia is a well-known problem after head and neck RT, investigators have looked into parotid-sparing techniques with IMRT. In 2004, Kwong et al. not only reported excellent results for early-stage NPC with IMRT but also showed progressive recovery of salivary function [20]. At 1 year after IMRT, 60 and 47 % of patients recovered at least 25 % of their baseline stimulated parotid salivary (SPS) flow and stimulated whole salivary (SWS) flow, respectively. By 2 years, SPS and SWS flow improved to 86 and 71 %, respectively.

In the previously mentioned phase III studies of early-stage NPC treated with IMRT, Kam et al. [4] and Pow et al. [6] were able to show no difference in local control while improving xerostomia. In addition, in RTOG 0225 [5], with a median follow-up of 2.6 years, no early-stage patients who were treated with IMRT alone developed locoregional failure. Thus, it seems fair to conclude that IMRT controls over 90 % of stage I NPC and simultaneously protects the parotids to the degree that restoration of function can be expected in 50 % of patients after 1 year.

Intermediate-stage nasopharyngeal carcinoma

For patients with stage II disease, there currently is too little data to be sure if RT alone is sufficient. A recent phase III study from China randomized 230 NPC patients with T1-2N1M0 or T2N0M0 disease with parapharyngeal space involvement to 2D-RT versus concurrent chemoradiotherapy (CCRT) [9]. Chemotherapy consisted of weekly cisplatin. With a median follow-up of 5 years, the study showed improvement in overall survival (95 vs 86 %), progression-free survival (88 vs 78 %), and distant-metastasis-free

survival (95 vs 84 %) of CCRT compared to 2D-RT while there was no significant difference in locoregional control (93 vs 91 %). However, it is important to be aware that in this trial all patients were treated using 2D-RT. Patients also did not have chest CT screening as part of their pretreatment evaluation, thus some pre-existing distant metastases may have been missed. Additionally, 31 patients (13 %) upon restaging to the 2010 AJCC staging system were reclassified as stage III.

While this study showed that CCRT is recommended for stage II disease treated with 2D-RT, it is important to consider whether chemotherapy is simply compensating for 2D-RT since none of these patients were treated with IMRT. It is possible that IMRT may provide better locoregional control and therefore reduce or eliminate the benefit of chemotherapy. Perhaps a phase III trial using IMRT with or without concurrent chemotherapy for stage II NPC would be helpful in answering the question.

Locally advanced nasopharyngeal carcinoma

Intergroup 0099 was the first phase III study to establish CCRT as the standard of care for locally advanced NPC [24]. However, this study was questioned due to its poor results in the RT-only arm and its higher incidence of non-endemic histology. Subsequently, nine additional phase III randomized trials investigating RT versus CCRT with or without adjuvant chemotherapy have been published (Table 5) [9, 26, 49–55]. Of the ten trials, seven have shown an overall survival benefit with CCRT [9, 24, 26, 49, 50, 54, 55]. A meta-analysis of eight randomized trials demonstrated that chemotherapy provided an absolute overall survival advantage of 6 % at 5 years and that the benefit was greatest with concomitant chemotherapy while induction and adjuvant chemotherapy were inconclusive [56]. These studies have confirmed the benefit of CCRT as the treatment of choice for locally advanced NPC.

Table 5 Phase III trials comparing 2D-RT alone versus CCRT, with or without adjuvant chemotherapy

Study	Year	Stage	Median follow-up (months)	Time point (yr)	Arms	No.	LRC (%)	DFS (%)	Distant-metastasis-free survival (%)	OS (%)
INT 0099 [24]	1998	III–IV[a]	60	5	RT	69	NA	29	NA	37
					CCRT + AC	78		58		67
Chan et al. [49, 61]	2002	Ho's N2/N3 or node ≥4 cm	66	5	RT	176	NA	52	NA	59
					CCRT	174		60		70
Lin et al. [54]	2003	III–IV[a]	65	5	RT	143	NA	53	70	54
					CCRT	141		72	79	72
Kwong et al. [51]	2004	Ho's T3 or N2/3 or node ≥4 cm	37	3	RT	109	72	58	71	77
					CCRT	110	80	69	85	87
Wee et al. [26]	2005	III–IV[b]	38	2	RT	110	NA	57	70	78
					CCRT + AC	111		75	87	85
Lee et al. [25, 53]	2005	Any T, N2–3[b]	71	5	RT	176	78	53	68	64
					CCRT + AC	172	88	62	74	68
Zhang et al. [43]	2005	III–IV[b]	24	2	RT	56	NA	83	80	77
					CCRT	59		96	92	100
Lee et al. [52]	2006	T3–4, N0–1[b]	35	3	RT	49	85	68	81	83
					CCRT + AC	47	81	73	89	87
					AF	48	78	63	77	73
					CCAF + AC	50	94	88	97	88
Chen et al. [50]	2008	III–IV[b]	29	2	RT	158	92	73	79	80
					CCRT + AC	158	98	85	87	90
Chen et al. [9]	2011	II–III[c]	230	5	RT	114	91	78	84	86
					CCRT	116	93	88	95	95

2D-RT two-dimensional radiotherapy, *CCRT* concurrent chemoradiation therapy, *yrs* years, *LRC* locoregional control, *DFS* disease-free survival, *OS* overall survival, *INT* intergroup, *RT* radiotherapy, *AC* adjuvant chemotherapy, *NA* not available, *N* regional lymph node stage, *T* primary tumor stage, *AF* accelerated fractionation, *CCAF* concurrent chemotherapy with accelerated fraction, *M* distant metastasis stage

[a] AJCC Staging Manual 4th Edition

[b] AJCC Staging Manual 5th Edition [58]

[c] AJCC Staging Manual 7th Edition [60]

It is important to note that none of the randomized trials comparing CCRT to RT utilized IMRT (Table 5). Yet, when comparing outcomes of multiple retrospective and prospective studies assessing IMRT, it appears that IMRT is equivalent or better than conventional RT. How much improvement can be attributed to IMRT and/or to the 3D imaging required for IMRT? Perhaps we are better treating tumors near vertebral bodies or critical structures that can only be adequately encompassed by IMRT, or perhaps CT- and MRI-based imaging has improved target volume delineation. It is possible that chemotherapy compensates for suboptimal RT techniques, and maybe concurrent chemotherapy with IMRT is enough to treat locally advanced NPC without adjuvant chemotherapy.

While IMRT achieves excellent locoregional control, chemotherapy is still needed to manage undetected micrometastasis. The previously mentioned early IMRT experiences from Lee et al. and Wolden et al. showed moderate distant-metastasis-free rates of 66 and 78 %, respectively, despite good locoregional control [19, 22]. Given that the predominant failure of locally advanced NPC with CCRT is distant metastasis, newer systemic strategies are being studied with the use of IMRT. Two recent phase II trials looked at the addition of targeted agents to CCRT using IMRT. In the first study, Ma et al. [36] used cetuximab with CCRT and found a 2-year distant-failure-free rate of 93 %. RTOG 0615, which was a phase II trial looking at the addition of bevacizumab to standard chemoradiation for locally advanced NPC, showed a promising 2-year distant-metastasis-free rate of 91 % [27]. While the delivery of concurrent cisplatin was different, the outcome of distant control appears to be improved compared with the historical rates of 70–80 %.

Potential future studies

As mentioned previously, the different margin sizes from various studies beg the question: what is the optimal margin size? With excellent locoregional control rates from IMRT (Table 1), perhaps our current CTV and PTV margins are too large. In the era of modern imaging and finer resolution, maybe we can reduce the margins and thereby decrease toxicity without compromising outcomes. Furthermore, it is possible that we are unnecessarily treating certain structures that do not improve outcome. One potential area is the sparing of the submandibular glands. Is it safe to spare the submandibular glands even in node positive patients? If so, perhaps we can further preserve salivary function in NPC patients.

Additionally, perhaps we should consider dose-escalating or boosting tumors that are likely to recur locoregionally despite IMRT. Patients with larger primary tumors would be the ideal cohort. With IMRT, it is now possible to further dose-escalate safely.

Conclusions

In conclusion, IMRT has allowed improved dose delivery to NPC tumors while reducing dose to normal tissues. Many dosimetric and clinical studies of IMRT have shown better treatment plans and clinical outcomes than older techniques. While IMRT is now regularly used for NPC, understanding the technical aspects of treatment planning is needed to maximize the true benefit of this technology.

The treatment for stage I NPC is RT alone while stage II and locally advanced NPC is CCRT. Perhaps IMRT can replace the benefit provided by chemotherapy when added either adjuvantly or concurrently to conventional RT. Future studies should focus on sparing and reducing target volumes in the face of excellent locoregional outcomes while dose-escalating for tumors likely to recur.

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