CHAPTER 9

RADIOTHERAPY OF NPC: Current Strategies and Perspectives

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Abstract: Radiation therapy (RT) remains the mainstay of treatment for NPC patients without evidence of metastases. The goal of radiation therapy is to cure patients while preserving normal tissue function. Results from randomized clinical trials support the intensification of therapy with chemotherapy in combination with RT for locally advanced disease presentations. Parallel to the changing landscape of combined modality therapy in the management of NPC, there has been a rapidly changing landscape of technical RT planning, treatment delivery and treatment verification. Intensity-modulated radiation therapy (IMRT) in combination with image-guided radiation therapy (IGRT) strategies offer the potential for increasing accuracy of RT and limiting radiation dose to normal tissues, thereby, increasing the probability of cure and optimal quality of life. This chapter will review the principles of radiation planning as they apply to advanced radiation therapeutic strategies, the fundamentals of IMRT and IGRT and the emerging body of data demonstrating excellent results from IMRT. As well, the potential of IGRT in the management of NPC will be discussed. With the expectations of excellent loco-regional control, future efforts must be directed toward limiting RT-related toxicity. Despite excellent loco-regional control, some patients will still succumb to distant metastases. Evolving systemic strategies are being undertaken to reduce the probability of developing metastases. Combined modality therapy may cause more side effects. These efforts highlight the importance of reducing RT side effects. While RT can be used to re-treat patients with recurrent disease and palliate symptoms in incurable patients, this chapter will focus on the initial curative management of NPC.

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INTRODUCTION

Radiation therapy is the primary curative treatment modality for patient with NPC. For head and neck (H&N) radiation oncologists, RT planning for NPC is the most challenging H&N subsite due to the complexity of skull base anatomy and narrow safety margins due to near-by critical organs such as the cochlea, brainstem, brain, optic chiasm, spinal cord and mandible. However, a radiation oncologist can treat wider normal tissue margins than are accessible to the surgical oncologist as the near-by normal structure may tolerate radiation doses close to the prophylactic radiation dose required to sterilize microscopic disease. The nasopharynx is closely bounded by complex normal structures including the skull base superiorly, infratemporal fossa laterally and neurovascular bundle postero-laterally. Cancers of the nasopharynx have the propensity to invade these critical normal tissue regions which render the disease surgically unresectable. Even without invasion of these nearby structures, surgery is technically challenging and it is often not possible to obtain wide surgical normal tissue margins needed to ensure adequacy of resection and to minimize local (nasopharynx) recurrence. NPC surgery should only be undertaken in specialized centers of surgical expertise and excellence. Surgery dose have a role in the post-RT management of the neck. Patients should be considered for surgical salvage of regional (nodal) RT failure. The same surgical principles of salvage neck dissection for any H&N mucosal cancer can be applied to NPC. The incidence of isolated neck recurrences following RT is low in NPC. Hence, ≤5% of patients will be eligible for a neck dissection.[1-3] The local and regional control is excellent with single modality radiation therapy for early stage, nonbulky disease. Combined modality therapy with RT and chemotherapy for patients with locally advanced disease has been a major advancement in the management of NPC. The evolving role of chemotherapy and molecular targeted agents is discussed in Chapter 10 by Hui and Chan. Intensity-modulated radiation therapy (IMRT) is a form of 3-dimensional (3D) conformal radiation therapy. H&N RT targets are complex 3D volumes. The potential benefit of IMRT is the ability to plan and deliver highly conformal radiation that encompass H&N RT targets while limiting dose to nearby critical structures. Imaging a patient during a course of RT to ensure that the patient (and tumor) is in the same position as the RT plan is referred to as image guided-radiation therapy (IGRT). The ability to identify treatment set-up errors enables the implementation of corrective strategies for treatment set-up displacements or errors. IGRT offers the potential for increasing the accuracy of radiation treatments and potentially reducing late normal tissue injury by enabling the reduction of uncertainty planning margins (see PTV below) inherent in all RT plans. These uncertainty margins are in fact *normal tissue* margins. Large uncertainty margins may be a contributing factor to some radiation side effects. IGRT offers the potential to adapt to patient-specific changes during a course of therapy. The potential benefit is that treatment can be tailored to the individual instead of applying population-based treatment strategies.

Early clinical results with IMRT (with or without chemotherapy) have shown excellent loco-regional control. Unfortunately, approximately 20-30% of patients will still develop incurable metastases leading some people to view NPC as a systemic disease. RT is loco-regional treatment. If IMRT results consistently show excellent loco-regional control then future research efforts should be directed at limiting toxicity from RT which can be a significant cause of patient morbidity after several years and even decades of cure.

Tomotherapy[4] and Intensity Modulated Arc therapy (IMAT)[4,5] are forms of IMRT. There is limited clinical data in treating NPC with these two technologies. While there may be some practical differences between IMRT techniques related to technology-specific, planning software-specific and vendor-specific factors, this chapter will deal with the guiding principles of IMRT and a review of the clinical outcomes will be presented in context of other RT modalities. There are no clinical trials data to advocate for the use of any one specific IMRT technology.

PRINCIPLES OF RADIATION THERAPY PLANNING

The principles of radiation oncology planning have not changed with the implementation of advanced RT technologies. The radiation oncologist must apply the established oncologic and radiobiological principles in the conformal RT era. As newer technologies replace what is now state-of-the art RT, the fundamental principles will continue to apply. For example, the International Commission on Radiation Units and Measurements (ICRU) provides standards and guidelines for radiation target definition as well as planning and dose prescription. However, the principles of ICRU remain important in the conformal RT era and they are not specific to any technology.[6,7] These documents contain specific language that highlights this very important issue, "It must be stressed that the prescriptions of GTV(s) and CTV(s) are based on general oncologic principles and they are independent of any therapeutic approach…. Their definition must *precede* the selection of treatment modality and subsequent planning procedures."[6,7] CTV and GTV are defined below. It is relevant to review the principles of RT planning as they apply to NPC management. A new ICRU document (ICRU 83) specifically addresses IMRT but the RT target volume definitions have not changed.

Treatment Preparation and Planning

The preparation of a patient for RT requires a number of assessments and baseline investigations that are important to the long-term health of NPC patients. In addition to imaging staging tests, a thorough history and clinical examination is critical. A complete clinical assessment includes a direct flexible fiber-optic naso-laryngoscopic examination of the nasopharynx and complete evaluation of surrounding mucosal surfaces. A clinical assessment of the cranial nerves should be done in all patients. Clinical examination can provide invaluable information for tumor target localization during the planning process as disease can be directly visualized that may not be seen by modern imaging techniques. Patients should undergo pretherapy dental evaluation and counseling. Baseline audiometry and ocular evaluation is recommended.

All patients should undergo a specialized planning computerized tomography (CT) scan with appropriate H&N immobilization usually consisting of a mask and head rest.[8] Magnetic resonance (MR) scan registration and fusion techniques facilitate gross disease delineation particularly when tumors are near or involve the skull base (Fig. 1A-C).[9] Positron Emission Tomography (18FDG-PET) can also provide important planning information (Fig. 1D).[10] Currently, imaging registration and fusion technologies used in the planning process are based on 'rigid' modeling which can not account for all patient deformation and rotation discrepancies between the primary

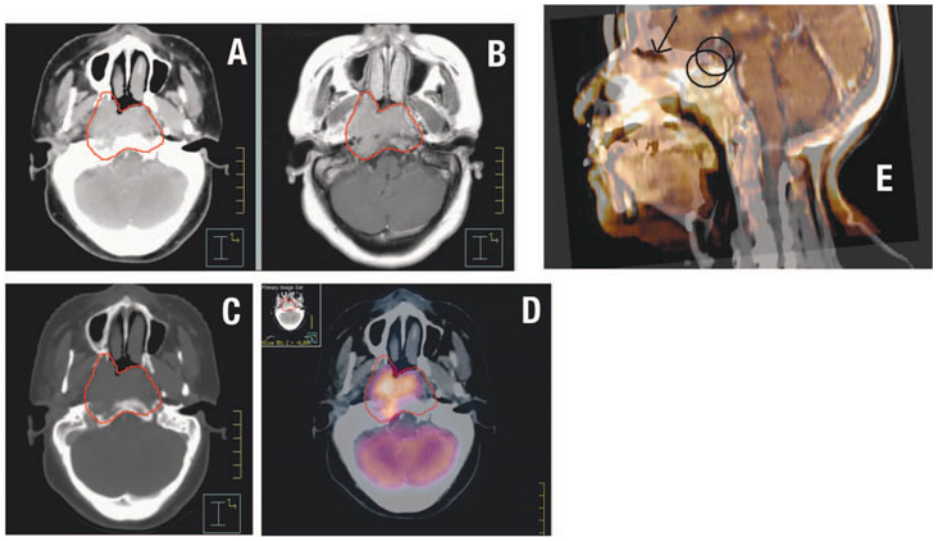

Figure 1. MR and PET Registration/Fusion with Planning CT scan. NPC is contoured. A) Planning CT scan; B) MR registered and fused to planning CT scan; C) Planning CT scan, 'bone' window setting; D) Planning CT scan registered and fused to PET scan; E) Registration/Fusion mismatch error intentionally created to demonstrate inaccuracy in overlay of optic chiasm (arrow points to displacement of chiasm within the circle regions).

planning scan and the secondary registration image modality e.g., MR scan. For a more detailed review of registration strategies, the reader is referred to references 11 and 12.[11,12] Care and caution must be taken when using secondary images to assist contouring of gross disease and critical normal organs. For example, any rotational mismatches between the fused planning CT and MR scans can adversely affect the accurate contouring of the optic chiasm as this anatomical region is very sensitive to these rotations (Fig. 1E).

Radiation Dose and Fractionation Schedule

A standard radiation total dose range for gross disease for mucosal H&N cancers is 66-70 Gy using a standard dose per fraction 1.8-2 Gy. This total and fractional radiation dose is relevant for NPC RT. Some centres routinely use an additional 'boost' to the nasopharynx. A radiation 'boost' is typically the final phase of radiation therapy used to only treat gross disease. A boost can be used after prophylactic RT has been delivered to regions at-risk for microscopic involvement or as a dose-escalation strategy. In Hong Kong, 'standard' dose-fractionation schedules for NPC were previously influenced by serious radiation therapy treatment unit shortages and large fractional doses, 3.8-4.2 Gy, were used until the early 1980s to minimize the total number of treatments.[13] In a NPC population-based model of 1008 early stage (Ho classification) patients treated between 1976-1985 with large fractional doses, Lee and colleagues examined possible radiobiological parameters predictive of local control and treatment toxicity. In this study, fraction size did not impact on local control.[14] She demonstrated an association

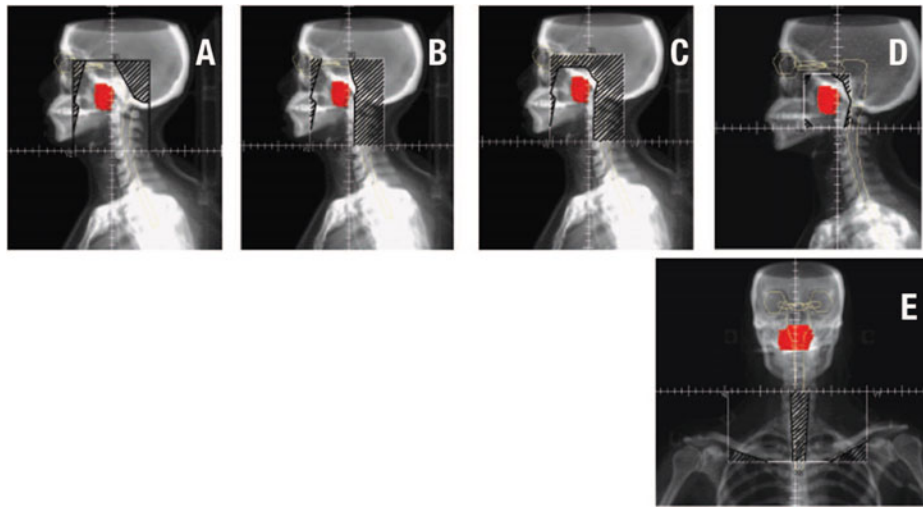

Figure 2. Example of Multi-phase 2DRT. NPC is shown. A) Phase 1 Lateral fields; B) Phase 2 Lateral fields with spinal cord shielding; C) Phase 3 Lateral fields with optic chiasm and optic nerve shielding; D) Nasopharynx boost lateral fields; E) Anterior low neck field with midline spinal cord and lung shields.

between larger fraction size, (3.5 Gy) and shorter (accelerated) overall treatment time with the development of symptomatic temporal lobe necrosis. This observation is consistent with the radiobiological principle that there may be increased late normal tissue damage when larger dose per fraction are delivered.[15,16]

The delivery of non-standard radiation dose per fraction or the use of non-standard RT schedules is termed altered fractionation. There is limited retrospective[17] and prospective[18] clinical data showing improved cancer control using altered fractionation and unacceptable normal tissue injury can result from the use of these regimens.[19] Therefore, altered fractionated schedules can not be recommended as standard of care for NPC patients.

Recently, technology driven factors have influenced dose-fractionation scheduling as well as radiobiological principles. 2-Dimensional RT (2DRT) requires multiple phases of treatment. Typically, an initial large radiation portal is used to encompass gross disease and routes of microscopic tumor spread. This initial phase can not be continued to a dose required to sterilize disease due to spinal cord dose constraints. A second phase is used to limit dose to the spinal cord. Following a so-called "microscopic" dose, subsequent phase(s) treat sites of gross disease only (Fig. 2). With IMRT, optimal dose conformation and tissue sparing may be better achieved with single phase therapy. Examples of this approach have been described as simultaneous integrated boost (SIB)[20] and simultaneous modulated accelerated radiation therapy (SMART) boost.[21] This strategy has also been commonly described as "dose painting". The key principle of these strategies is that the higher gross disease dose and lower microscopic dose must be delivered in one plan over the *same number of fractions*. This had lead to the emergence of non-standard fractional doses (<1.8 Gy or >2 Gy) (Fig. 3). Clinical trials are now investigating these dose-fractionation schedules.

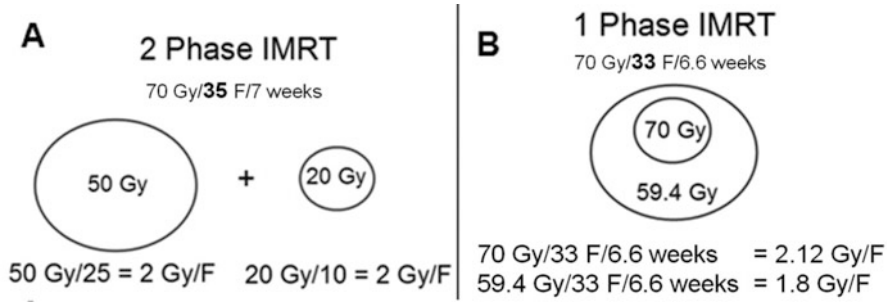

Figure 3. A comparison of two-phase IMRT dose-fractionation to an example of a one-phase IMRT dose-fractionation. A) 2-phase IMRT plan using 'standard' 2 Gy fractions (F) throughout treatment. B) 1-phase IMRT plan treated over 33 fractions. Prophylactic (microscopic) dose kept to 'standard' 1.8 Gy per fraction. Hence, gross disease is treated 2.12 Gy per fraction to desired total dose of 70 Gy.

Principles of ICRU 50/62

ICRU Report 50: Prescribing, Recording and Reporting Photon Beam Therapy was published in 1993. The supplement to ICRU 50, ICRU Report 62: Prescribing, Recording and Reporting Photon Beam Therapy was published in 1999. These documents provide important guidance to the definition of radiation therapy targets (GTV, CTV) and associated geometric expansions that account for uncertainties that may occur during a course of RT (PTV, PRV). Gross Tumor Volume (GTV) is defined as any gross tumor determined by clinical examination and imaging. Clinical Target Volume (CTV) is a normal tissue margin, encompassing GTV that accounts for subclinical spread of cancer. It is common that multiple CTV(s) are defined for volumes to be treated to separate gross disease or prophylactic doses of radiation i.e., CTVI, CTVII. These suffixes are not consistently applied in the current literature and suffixes indicating dose in Gray (Gy) are useful i.e., CTV70, CTV50. Planning Target Volume (PTV) is a volume that accounts for all geometric uncertainties that must be accounted for to ensure adequate CTV coverage with the prescription radiation dose. These uncertainties include internal motion (e.g., swallowing) and day to day treatment set-up errors (e.g., variations in H&N mask fitting). Thus, it is the PTV that is the planning target not the CTV. Similarly to PTV, a volume surrounding a clinically defined normal Organ-at-Risk (OR) is defined as Planning Organ-at-Risk Volume (PRV) accounting for geometric uncertainties around an OR (Fig. 4).[6,7]

In NPC RT planning, it is common for PTV margins to overlap with OR(s) and PRV(s) (Fig. 4). While compromises may need to be made in the planning process when PTV is near or overlaps critical structures such as the brainstem, it must be emphasized that the uncertainties inherent in PTV remain even in a clinically acceptable appearing RT plan. There are several strategies that can be used to define a clinically relevant PTV.[22] A commonly used population-based model, 'van Herk formulation', defines random and systematic error components of PTV. This 'margin recipe' can be used to derive a clinically relevant PTV from actual patient data. This is a population-based PTV model and it is not tailored to any one patient. Implicit in any clinical application of mathematical models is the needs to understand the basic assumptions. A major

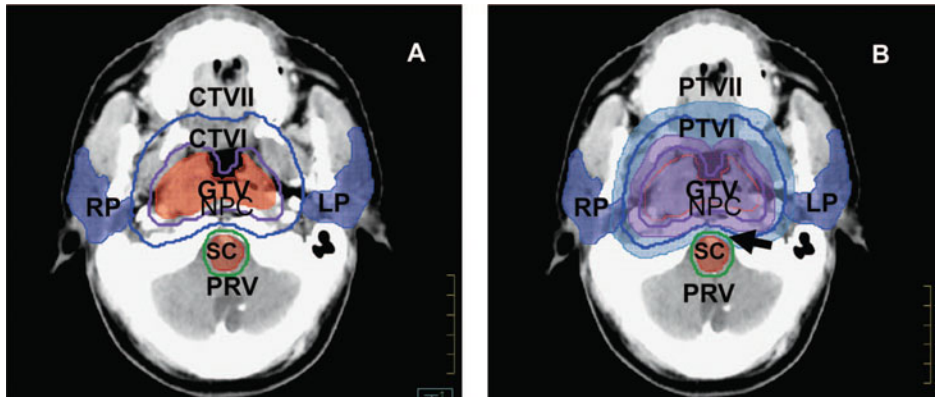

Figure 4. ICRU defined volumes. A) Primary tumor (GTV) encompassed by Clinical Target Volume to be treated to gross disease dose (CTVI) and microscopic dose (CTVII). Spinal cord (SC) is encompassed by Planning Organ at Risk Volume (PRV). Right (RP) and left (LP) parotid glands are shown as examples of Organs at Risk. B) CTVI and CTVII are expanded by 5 mm geometric margins to generate PTVI and PTVII. Note PTVII overlaps with spinal cord PRV.

assumption in the van Herk formulation is that all displacements and discrepancies of CTV during treatment are rigid displacements (superior-inferior, anterior-posterior, cranial-caudal). This model does not account for changes in patient shape (deformation) over a course of therapy.[23] It has been quantitatively shown that H&N patients are prone to deformation and rotational displacements during a course of RT.[24,25] PTV is a critical concept in RT planning and treatment delivery. Many RT centers do not have PTV margin data derived from their patient population. A 5 mm geometric PTV margin around is commonly used in practice in this setting and in some RT clinical trials.

Radiation Therapy Target Delineation

The increasing use of conformal radiation therapy techniques requires the radiation oncologist to delineate (contour, segment) many complex volumes including GTV and CTV. PTV is not a contoured volume but a geometric margin of uncertainty. The most critical information required for contouring is accurate clinical and radiologic staging. Other tumor factors such as histopathology subtype classification, does not impact the contouring process. Two challenges for the radiation oncologist include targeting of the neck and targeting of the primary.

There is limited data about the specific anatomic failure patterns after RT for NPC. Recurrences are commonly reported as local, regional and metastatic and this vernacular does not specify the anatomic regions bounding the primary site or neck in a way that is informative to the contouring process. As such, the radiation oncology discipline has adopted consensus guidelines for CTV delineation of the node-negative neck based on surgical pathologic data.[26] Guidelines for CTV contouring for node-positive disease have been proposed.[27] While practically useful, these guidelines may not reflect patterns of recurrence specific to NPC. One potential benefit of intensity-modulated radiation therapy (IMRT) is parotid sparing and avoidance of xerostomia (dry mouth).

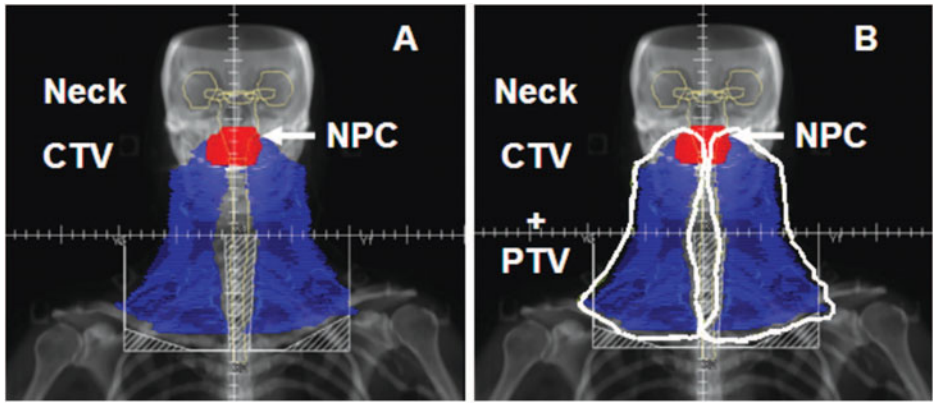

Figure 5. Conventional 2DRT fields compared to conformally delineated neck nodal targets. A) Typical lower neck anterior field does not encompass node-negative 'consensus' neck CTV (shown as shaded region). Primary tumor is shown (NPC). See reference 28 for node-negative CTV consensus. B) When a 5 mm PTV expansion is applied to CTV (PTV shown as white outline surrounding PTV), under-coverage of conformal target is more apparent.

Xerostomia is a very common consequence of prophylactic neck RT in patients treated with nonconformal techniques. Cannon et al reported parotid gland recurrences in NPC patients as a consequence of intentionally limiting dose to the parotid gland in an attempt to avoid xerostomia.[28] Thus in some patients, the parotid gland should be delineated as part of the nodal CTV. There is no established guideline for inclusion of the parotid in the neck nodal CTV and the challenge remains about when to include this region given the potential consequence of permanent xerostomia and increased risk of osteoradionecrosis of the mandible.

The use of the consensus guidelines for neck CTV delineation has resulted in a change in the neck CTV and PTV coverage compared to 2DRT (Fig. 5).[29] We reported less than 2% failure close to a midline spinal cord shield in the low neck that is typically used in 2DRT. [30] This spinal cord shield routinely shielded the medial PTV when applied to the consensus neck CTV. This issue highlights again the need for detailed anatomically-specific patterns of failure following conformal RT for NPC.

GTV delineation is a difficult clinical task and we have shown inter-observer variability among 6 experienced H&N radiation oncologists and 2 neuroradiologists when contouring GTV on contrast enhanced CT scan, noncontrast CT scan and PET-CT scans from patients with oropahrynx cancer.[31] Given that nasophraynx pimary site delineation is potentially a more complex task, it is possible that inter-observer variations in GTV and CTV delineation could be one determinant of loco-regional control and normal tissue toxicity.

Similar general principles are applied to CTV delineation across the world. It is generally accepted that CTV (to be treated to a prophylactic dose) must include gross disease and routes of subclinical spread with particular attention to the skull base and comprehensive neck nodal RT.[32-36] Seemingly subtle differences in CTV contouring may have significant normal tissue consequences. Table 1 lists the commonly accepted regions for CTV delineation as well as highlights some of the areas of uncertainty and possible normal tissue consequences of over-inclusion of normal tissues in the CTV.

Table 1. Clinical target volume in NPC

Clinical Target Volume (CTV)	Controversy/Uncertainty About Extent of Coverage	Potential Normal Tissue Consequence
Primary		
Nasopharynx		
Clivus	What extent of clivus should be included? Should 1/2-1/3 be included if clivus uninvolved and the entire clivus if involved or T3, T4?	brainstem
Skull base		
– *foramen lacerum*		
– *foramen ovale*		
– *foramen rotundum*		
– *petrous portion of temporal bone (including carotid canal)*	Should the carotid canals be excluded for T1, T2* or when primary involves contralateral nasopharynx?	brain, cochlea, middle ear
Sphenoid sinus	Should just the inferior sphenoid be included for T1, T2* disease or when uninvolved? Should the entire sphenoid if involved or T3,T4?	brain, optic chiasm
Cavernous sinus	Can the cavernous sinus be excluded for T1, T2*?	brain, brainstem, optic chiasm
Ethmoid sinus	Should the posterior 1/3 of bilateral ethmoid sinuses be included in all cases?	optic nerve, eye (retina), orbital muscles
Oropharynx (at least 1 cm uninvolved mucosal margin on primary disease)		
Nasal cavity (at least 1 cm uninvolved mucosal margin on primary disease)	Should the posterior 1/4-1/3 of bilateral nasal cavity be included for all cases?	nasal cavity mucosa, nasal hair follicles
Maxillary antrum	Should the posterior 1/4-1/3 of bilateral maxillary antrums be included for all cases?	muscles of mastication, nasal cavity mucosa, nasal hair follicles
Pterygoid fossae		
Parapharyngeal space		
Infratemporal fossa	What extent of infratemporal fossa coverage is required for early disease?	mandible, muscles of mastication
Lymph Node Region		
Retropharyngeal nodes	Should this nodal group be delineated inferiorly to the hyoid or caudal aspect of C2?	pharyngeal constrictor muscles
Level 2-5		
Level 1B	Can level 1B excluded in N0 cases or when level 2a is not involved?	mandible, submandibular gland, floor of mouth mucosa

*T2 category includes T2a, T2b

Radiation Therapy Quality

One of the criticisms of the landmark NPC Intergroup trial 0099 that demonstrated improved disease-free survival (DFS) and overall-survival (OS) in NPC pateints using concurrent and adjuvant cisplatin-based chemotherapy was the unexpectedly low 5-year DFS, 29% and OS, 37%, in the standard RT alone arm.[1,37] Several explanations have been suggested including the relatively high incidence of WHO Type 1 NPC (28%) in this North American study population. The 5-year DFS and OS of patients treated at the Princess Margaret Hospital (PMH) during a similar time period was 62% and 48% which was higher than the RT alone arm of Intergroup 0099 but lower than the combined chemotherapy and RT study arm. Single institutional experiences can not be directly compared to the results of a randomized trial. It is, however, noteworthy that the PMH results were in line with other major centers during this time period.[3] One potential confounding factor may have been that patients were treated with 2DRT without the routine use of a planning CT scan. However, no conclusions can be made about the quality of RT planning and delivery in the Intergroup 0099 trial as there was no centralized RT quality assurance review. The limitation of 2DRT planning without the use of a planning CT scan was demonstrated in patients treated at PMH during an overlapping era with Intergroup 0099.[8] There may be several medical advances over a period of years that could lead to improved patient loco-regional control, DFS and OS including advances in detection, diagnosis, staging, systemic therapy and advancements in RT planning/delivery. Several authors have reported improved RT loco-regional control outcomes when compared to prior institutional treatment time periods and RT technical advances may have played a role.[13,38,39] Excellent loco-regional control has been reported with early intensity-modulated radiation therapy (IMRT) experience as an example of advanced RT (Table 2). In a phase III trial of non-nasopharynx locally advanced H&N squamous cell carcinomas conducted by the Trans- Tasman Radiation Oncology Group (TROG) investigating standard concurrent chemoradiation with or without tirapazemine, all RT plans were subjected to expert peer review. Twenty-percent of patients were found to have major protocol deviations in the radiotherapy plan. These protocol deviations were, for the first time, associated with increased risk of death (HR = 1.56; $p \leq 0.0001$), any failure (HR = 1.65; $p < 0.0001$) and loco-regional failure (HR = 1.82; $p = 0.0002$).[40] Taken together, these data support that radiation quality is an important factor in determining outcome for NPC patients. Quality control is an important aspect of any RT department and quality assurance review should be a standard practice in all RT NPC trials.

Radiation Therapy Treatment Strategies

2-Dimensional Radiation Therapy

The principles of 2DRT planning have been briefly discussed above. 2DRT planning is field-based with field placement usually using boney and sometimes soft-tissue surrogate for tumor unless a planning CT scan is used.[41] Retrospective series have shown excellent local and regional control with modern 2DRT with 5-year local control and regional control ranges 81-84% and 80-94%, respectively. In these series, 20-62% of the patients received chemotherapy.[2,42,43] To date, all RT trials evaluating the role of chemotherapy with RT have been done with 2DRT. Table 2 lists the results from randomized trials evaluating the role of concurrent chemotherapy with RT if local, regional or loco-regional control was reported.[1,37,44-46]

Table 2. Clinical results of 2DRT and IMRT in NPC

Institution	Year of Publication	Patient Number	Chemo-therapy	RT Technique	Total Dose	Reported Outcome Period	Local Control	Regional Control	Loco-regional Control	Metastases-Free Survival	Overall Survival	Ref.
Phase III concurrent chemoradiation trial												
Intergroup 0099#	1998, 2001	147	53%	2DRT	70 Gy Primary 66-70 Gy Nodes	3-year RT vs CRT	67% vs 92 %*	86% vs 91%*		65% vs 87%*	5-year 37% vs 67% (<0.001)	1,37
Taichung Veterans General Hospital	2003	284	50%	2DRT	70-74 Gy	5-year RT vs CRT	72.6% vs 89.3% (p = 0.0009)	92.% vs 96.8% (n.s.)		69.9% vs 78.7% (n.s.)	54.2 vs 72.3% (P = 0.0022)	45
Queen Mary Hospital#	2004	219	50% CRT 100% adjuvant chemo	2DRT +/– boost	66-68 Gy +/– boost	3-year RT vs CRT			72.4% vs 80% (n.s.)	30.6% vs 8.2% (p = 0.026)	76.8% v.s. 86.5% (p = 0.026)	46
Hong Kong Nasopharyngeal Cancer Group (NPC-9901)#	2006	348	49%	2DRT +/– boost	68 Gy +/– boost	3-year RT vs CRT	89.2% vs 95.3%*	92% vs 96.5%*	82% vs 92% (p = 0.005)	73% vs 76% (n.s.)	78% vs 78% (n.s.)	44
IMRT												
Non-randomized												
University of California-San Francisco	2004	118	90%	IMRT +/– brachytherapy boost	70 Gy +/– boost	4-year	96%	98%		72%	74%	33, 57, 58, 59
Queen Mary Hospital	2004	33 (early disease)		IMRT	68-70 Gy	3-year	100%	92.3%		100%	100%	34
Prince of Wales Hospital	2004	63	30%	IMRT+/– brachy-theapy boost	66 Gy +/– boost	3-year	92%	98%		79%	90%	60

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Table 2. Continued

Institution	Year of Publication	Patient Number	Chemo-therapy	RT Technique	Total Dose	Reported Outcome Period	Local Control	Regional Control	Loco-regional Control	Metastases-Free Survival	Overall Survival	Ref.
Non-randomized (continued)												
Queen Mary Hospital	2006	50 (locally advanced)	68%	IMRT	76 Gy	2-year			95.7%	94.2%	92.1%	21
Memorial Sloan-Kettering Cancer Center	2006	74	93%	IMRT	70 Gy Accelerated RT	3-year	91%	93%		78%	83%	61
Multi-center, China	2009	323	94%	IMRT	66-69.75 Gy	3-year	95%	98%		90%	90%	36
Phase II trial												
RTOG	2008	68	84%	IMRT	70 Gy	2-year (estimated)	92.3%	90.5%	90.5%	85.7%	79.1%	62
Phase III trial												
Queen Mary Hospital#	2008	82 (40 vs 42)		2DRT +/– boost vs IMRT	68 Gy +/– boost vs 70 Gy	4-year	71.7% vs 90.5% (p = 0.019)	100% vs 92.9 (n.s.)		90% vs 81.7% (n.s.)	91.7% vs 85% (n.s.)	63

#Study terminated early 2DRT—2-dimensional radiation therapy; IMRT—intensity-modulated radiation therapy; RT—radiation therapy alone arm; CRT—chemoradiation arm; *crude rate; n.s.—not significant.

Conformal Radiation Therapy

In distinction to 2DRT, a planning CT scan must be performed for *3-dimensional conformal radiation therapy* (3DCRT) planning. Planning is not field-based but 3D volume-based. RT planning decisions are made about radiation beam geometry, weighting and modifiers ('forward' planning). Simply put, radiation field parameters are still manipulated. However, the uniformity of a radiation beam intensity (fluence) across a beam from the treatment machine is not manipulated within the treatment unit head.

Intensity-modulated radiation therapy (IMRT) is similar to 3DCRT in that the planning and plan evaluation is volumetric. Target volumes and OR(s) doses are evaluated using dose-volume histograms. However, 'inverse' planning processes are applied in which dose-volume and dose priority objectives are stipulated at the beginning of the planning process and then computerized 'optimization' is done to meet the dose volume objectives.[47-49] It should be emphasized that the dose volume objectives should be based on clinical data where available for tumor control and normal tissue tolerances. Multi-leaf collimators within the treatment unit head modulate the intensity of the radiation beam within the treatment unit head and the fluence across a beam is non-uniform (Fig. 6). A detailed discussion about the technical aspect of IMRT is beyond the scope of this chapter and

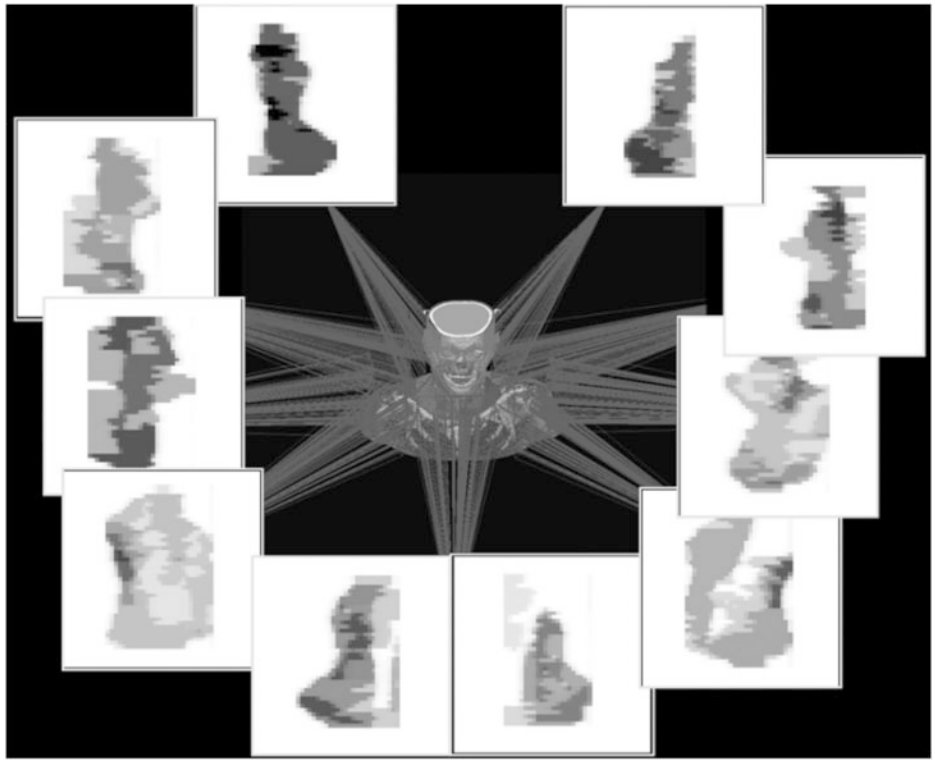

Figure 6. Nine field IMRT beam arrangement and fluence maps. Beam fluence (fluence map) is shown for each beam. The heterogeneity of each beam fluence map demonstrates the non-uniformity of beam intensity for IMRT-generated plans.

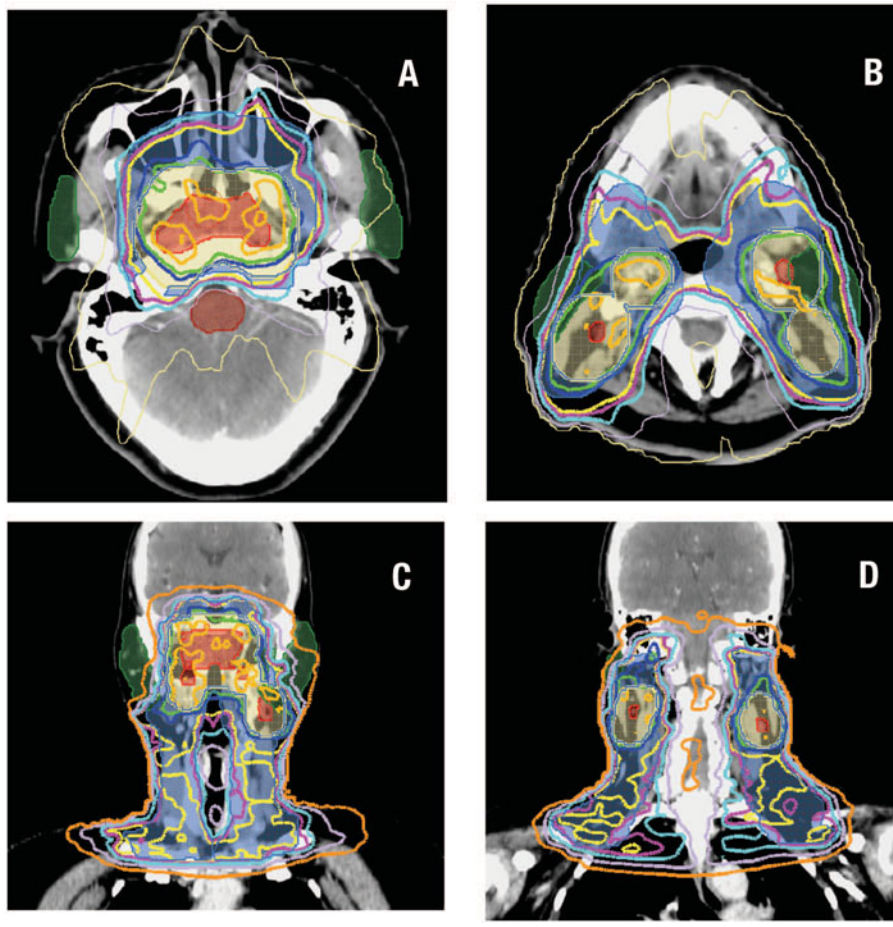

Figure 7. One-phase IMRT plan. Dose prescription are 70 Gy/35 fractions to gross disease PTV and 56 Gy/35 fractions to microscopic dose PTV. A) Axial dose distribution through primary; B) Axial dose distribution through upper neck; C,D) coronal dose distributions. Dose distributions demonstrate conformality of IMRT plans. Inner to outer shaded areas—GTV, PTV70 (to be treated to 70 Gy), PTV56 (to be treated to 56 Gy). Outer to inner lines—30Gy, 45 Gy, 53.2 Gy, 56 Gy, 58 Gy, 66.5 Gy, 70 Gy, 73.5 Gy isodose lines.

the reader is referred to reference 50.[50]A major success of conformal radiation therapies is the ability to create concave dose distributions (Fig. 7),[51] improve conformality of target coverage and create step dose gradients between target and normal tissue (Fig. 7). From the radiation oncology perspective, target delineation, uncertainty assessments, plan evaluation and treatment verification principles are the same for 3DCRT and IMRT.

There are no randomized studies comparing 3DCRT to IMRT. Several authors have shown that IMRT provides more conformal target coverage and normal tissue sparing[52-54] For early stage NPC, there may not be clinically apparent differences between IMRT and 3DCRT. In more advanced NPC, Hunt and colleagues from Memorial Sloan-Kettering Cancer Center (MSK) compared 2DRT, 3DCRT and IMRT planning for NPC. Twenty-three

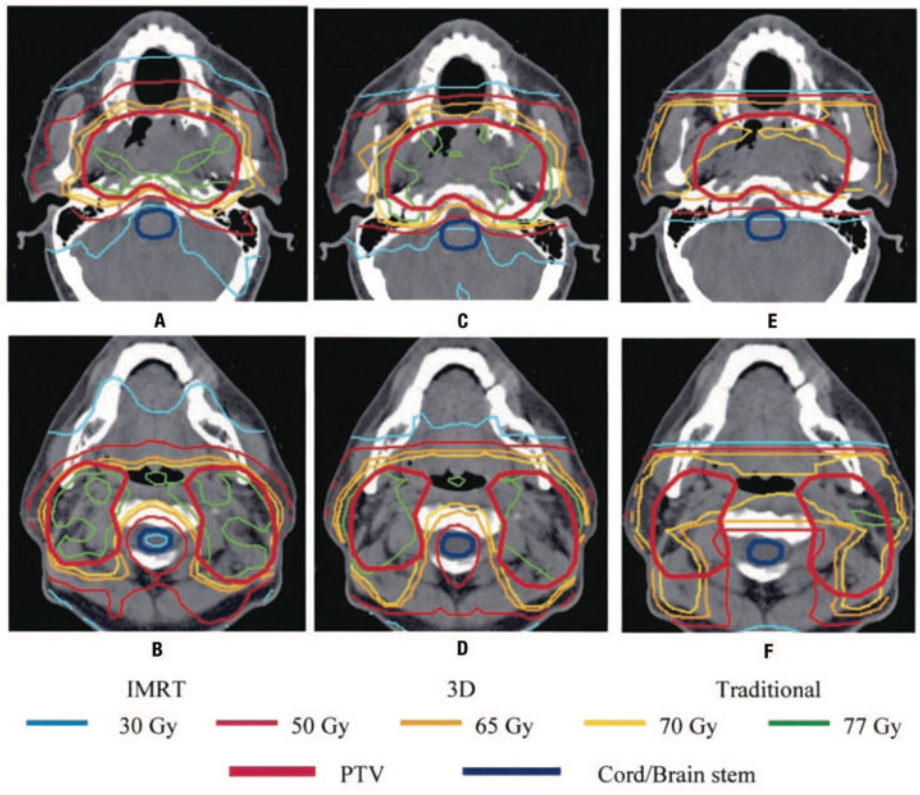

Figure 8. Axial dose distributions through nasopharynx and neck. IMRT (A,B) plan resulted in lower spinal cord maximum dose and better parapharyngeal, skull base, medial nodal coverage compared to 3DCRT (C,D) and 2DRT (E,F). Reprinted with permission from: Hunt MA, Zelefsky MJ, Wolden S, et al. Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer. International Journal of Radiation Oncology, Biology, Physics. 2001; 49(3):623-632. Copyright 2009 Elsevier.

patients were treated clinically with IMRT and a parallel planning study was performed for 2DRT and 3DCRT (Fig. 8). Hunt et al was able to achieve a lower spinal cord dose with IMRT compared to 3DCRT, 2DRT with maximum cord doses of 49 Gy, 44 Gy and 34.5 Gy, respectively. IMRT provided better target coverage in parapharyngeal region, skull base and medial nodal regions as well as lower dose to all normal tissues.[54] These authors and others have reported difficulty achieving parotid sparing dose-volume constraints. Unlike other H&N mucosal subsites, the retropharyngeal nodal region and level 2b must be prophylactically treated in all patients and the PTV volume surrounding this CTV will always overlap the parotid gland.[55,56] It is unlikely that a randomized trial comparing IMRT to 3DCRT will be possible as many centers will not have equal experience with both therapies.

In a seminal series of reports, University of California-San Francisco (UCSF) investigators reported their IMRT single institution experience.[32,57-59] In their last report, 118 patients with Stage I-IV NPC (AJCC 1997) were included. The total IMRT dose was

70 Gy/33 fractions but 22% of patients received a brachythrapy boost. Ninety percent of patients received chemotherapy. The median follow-up was 2.5 years. The estimated 4-year local and regional control was 96% and 98%, respectively. Unfortunately, 28% of patients developed metastases and the OS was 74%. Skull base necrosis and temporal lobe necrosis was observed.[57] In an earlier report 5/67 patients experienced Grade 5 hearing loss but 29/67 presented with T3/4 disease and comprehensive skull base radiotherapy was likely required.[59] Lin et al reported similar excellent loco-regional control is a recent large series of 323 patients.[36] Table 2 lists recent reported series demonstrating excellent loco-regional control with IMRT.[32-34,36,57-61]

The Radiation Therapy Oncology Group (RTOG) conducted a Phase II study to evaluate the generalizability of the UCSF results. A preliminary report of RTOG 0522 showed an estimated 2-year local and regional control for 68 patients accrued to this trial was 92.3% and 90.5%, respectively with a median follow-up of 2 years. Distant metastases-free survival was 85.7%.[62] It should be noted that all participating centers had to obtain centralized IMRT quality assurance accreditation before being allowed to accrue patients to this study. A small randomized phase III from Queen Mary Hospital comparing IMRT to 2DRT in early stage NPC was terminated early because of marked differences in local control favoring IMRT. Eighty-two patients were enrolled in this trial before trial closure. The 4-year local control was 90.5% vs 71% ($p = 0.019$) for IMRT and 2DRT, respectively after a median follow-up of 4 years (Table 2).[63]

The excellent loco-regional control with IMRT even in advanced stage disease to date is extremely promising and the emerging data demonstrates reproducibility of results in major centers with experience with NPC. These data support the routine use of IMRT to treat NPC patients even in the absence of a large randomized trial.

IMAGE-GUIDED RADIATION THERAPY (IGRT)

Image-guided radiation therapy (IGRT) refers to patient imaging acquired during a course of radiation therapy to verify the patient position during the treatment. Historically, all radiation treatments have incorporated some form of image guidance. The most rudimentary IGRT is the well established practice of acquiring 2D 'beam's eye' views of radiation treatment fields. The imaging format is usually a mega-voltage (MV) image acquired just prior to treatment or during treatment. These images may be in hardcopy or electronic portal imaging (EPIDs) formats. Typically, the radiation oncologist will review the image after the patient has been treated and continue therapy with or without a set-up error or 'displacement' correction. This strategy is referred to as 'off-line'. 'On-line' strategies require a verification image assessment at the treatment unit where set-up correction can be performed prior to therapy. More advanced strategies employ frequent verifications throughout a course of treatment and daily IGRT has been implemented by some centers.

The major advances in IGRT have been the development of technologies that enable acquisition of full 3D verification images 'in the treatment room'. A detailed review of 'in room' IGRT technologies is beyond the scope of this text and readers are refereed to reference 24. 'In room' technologies all employ either MV or kilo-voltage (kV) CT imaging. More recently, 'in the treatment unit' technologies have been developed. kV cone-beam CT scan (CBCT) imaging is an example of this technology in which a CBCT unit is incorporated into the treatment unit.[64-66] Using CBCT, volumetric or

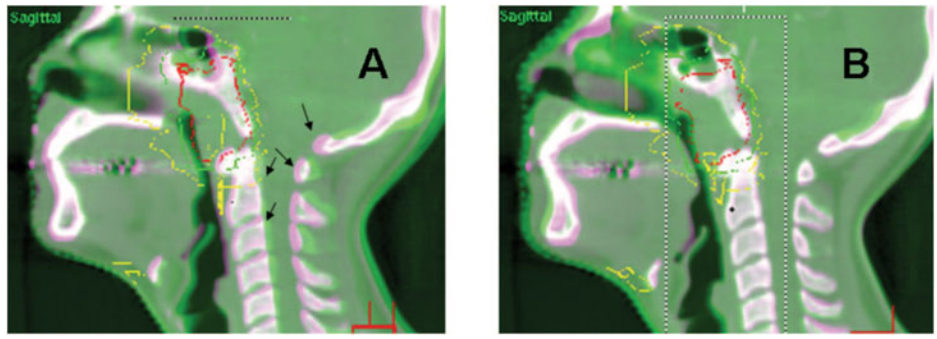

Figure 9. Three-dimensional (3D) image-guided radiation therapy (IGRT). A) Overlay of planning CT scan (reference scan) and 3D image acquired using a cone-beam CT scan (IGRT scan) at the treatment unit. Only a representative sagittal plane is shown. Double image (highlighted by arrows) is seen between the reference scan and the IGRT scan due to set-up errors (displacements) that were detected prior to treatment. It is important to note that axial and coronal planes are also captured of a 3D image and displacement corrections are made in 3D. B) Double image is not apparent as the displacements were corrected for prior to treatment by applying treatment couch shifts to offset displacements. Note that the rectangle defines a region of interest (ROI) for image-guided analyses of displacements and corrections.

3D image datasets can be acquired during a course of RT. Image matching protocols can be developed to match internal surrogates of the target volume such as bone (bone-matching). Tumor-matching or normal-tissue matching i.e., soft tissue matching can also be performed. Patient volumetric data is usually acquired in a region of interest (ROI). For NPC patients, the skull base should be included in the ROI (Fig. 9). Skull base bone matching is a good surrogate for nasopharynx tumors which do not move day to day relative to bone. The clivus is a useful surrogate for the brainstem.

Concern has been raised about the additional patient radiation dose from the acquisition of IGRT images and the potential for second cancers.[67,68] For CBCT, this dose depends on many factors specific to the image matching technology and imaging acquisition parameters. Phantoms studies performed at PMH recorded single scan doses in the rage of 1.6-2.3 cGy for institutional scan protocols.[69] Others have reported higher doses.[67,68] Additional radiation dose can be partially accounted for by including the total imaging dose in the dose calculations if there is a clinical concern about the additional dose.

One potential benefit of IGRT is to ensure that the radiation treatment doses are reflective of the actual treatment plan delivered each day. These daily set-up variations can result in delivered radiation doses that do not accurately reproduce the original plan resulting in potential underdosing of the tumor.[70] Moreover, the delivered dose to normal structures can be unexpectedly high. Han et al reported increased parotid gland and spinal cord dose if daily IGRT was not used for conformal tomotherapy.[71] Similar results were reported by others.[72] As discussed previously, PTV uncertainties are made up of systematic and random errors. Off-line correction strategies decrease systematic errors only. Whereas, on-line corrective strategies will reduce both systematic and random errors.[73] The potential benefit of daily online corrective strategies is that PTV margins can be reduced if both systematic and random error components are reduced. PTV margins are normal tissue margins. By reducing PTV margins, normal tissue toxicity could potentially be reduced.[74]

ADAPTIVE RADIATION THERAPY

The changing view of a course of RT has evolved from being regarded as a static process to one that is dynamic (Fig. 10). Quantitative data is emerging confirming what was known to the experienced H&N oncologist, that anatomical changes during a course of radiation therapy are complex.[24,25,75] Current clinically implemented IGRT corrective strategies address rigid patient displacements well and some minor rotations can be adjusted. However, patient deformational changes are not accounted for. PTV margin recipes are derived from population data and may not be ideal for individual patients. Adaptive radiation therapy refers to adapting to individual patient changes during a course of RT. Adaptive radiation therapy was first described for non-H&N cancers but is now being investigated in H&N cancer and NPC patients.[76] Rapidly advancing technologies will enable complex replanning during treatment without delaying treatment or causing undue resource burden. These technologies include the evaluation of deformable registration technologies so that deformational changes can see and adjusted for.[77-80] Investigators

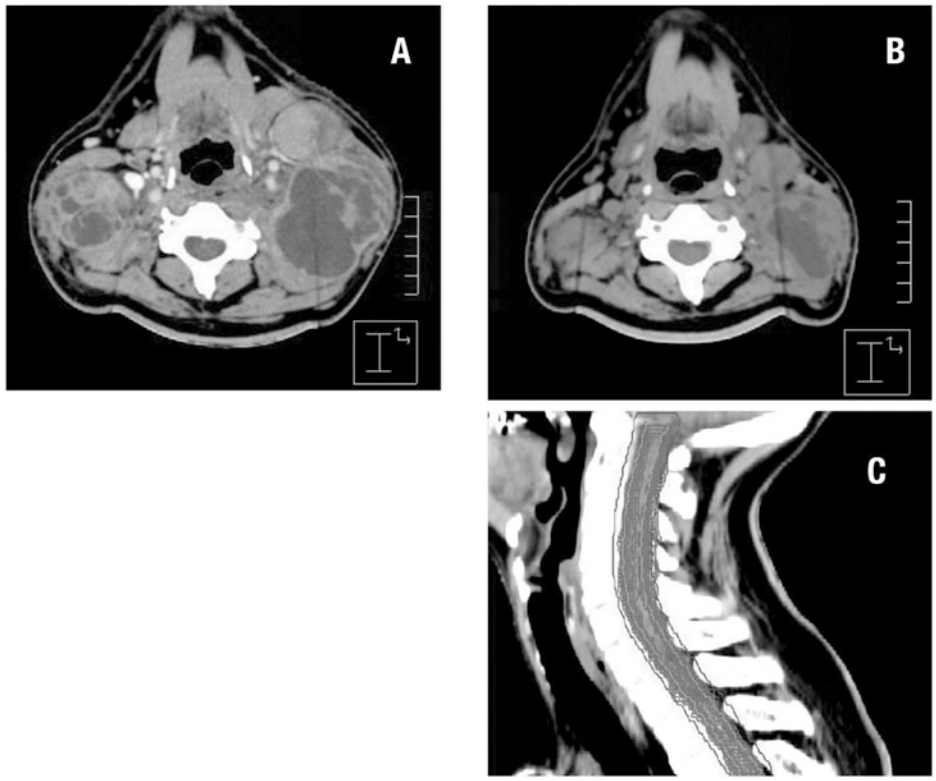

Figure 10. Examples of tumor and normal tissue changes during a course of radiation therapy illustrating that a course of radiation therapy is a dynamic process. A) Bulky bilateral neck lymphadenopathy (arrows). B) Lymph nodes have markedly shrunken by week 3 of a 7 week treatment necessitating replanning of IMRT. C) Shaded region is comprised of 35 spinal cord contours acquired from daily cone-beam CT scans over a 7 week course of IMRT. Spinal cord PRV is shown as outline. Note that shaded area is outside of PRV posteriorly demonstrating day to day spinal cord position variability.

are exploring the use of CBCT as the replanning CT scan so that additional planning CT scans do not have to be acquired.[81] In the future, radiation medicine practioners will be able to respond to treatment changes quickly. As novel molecular diagnostic and therapeutics emerge, the triggers for replanning radiation therapy may be changes in tumor microenvironment such as oxygenation.

Whether IGRT and adaptive radiation therapy will result in better outcomes is unknown. In view of the reported long-term toxicities from RT (see below), relatively small dosimetric changes may have clinical implications for normal tissues doses on the steep part of the dose response curve.

Another divergent approach to treatment changes is 'robust IMRT' modeling. Instead of replanning RT to adapt to changes, IMRT planning is modeled to account for changes such as breathing in thorax irradiation.[82] Currently, robust IMRT planning is a novel research concept.

LONG-TERM TREATMENT TOXICITY

RT for NPC can lead to serious long-term sequalae. Serious long-term toxicities have been for 2DRT and include Sensorineural hearing loss,[83-86] temporal lobe and brain necrosis,[87,88] osteoradionecrosis,[89] cranial nerve palsies,[90] optic neuropathy,[91] endocrine dysfunction,[92] carotid artery stenosis,[93] second cancers.[94] The baseline incidences of these unfortunate morbidities are unclear as some of the data comes from high dose per fraction RT or dose escalation experiences. Whether CT-based 2DRT planning, 3DCRT and IMRT can decrease the incidence of these late side effects will take years to establish. The potential to limit dose to parotid glands and decrease the probability of xerostomia is well documented.[95-101] Pow et al reported preliminary results of a small randomized clinical trial comparing IMRT and 2DRT. Better quality of life (QoL) and improved measured salivary flow at 12 months was observed in the IMRT group.[102] In a recent publication by Eisbruch et al,[103] there were no osteoradionecrosis complications in 176 patients treated with IMRT between 1996-2005 and followed for a minimum of 6 months. The tolerance limits for some organs are being better defined. In 26 patients, Eisbruch et al reported that the lowest dose delivered to the pharyngeal constrictor muscles to cause dysphagia and aspiration was 50 Gy.[104] However, some authors have reported concerns about IMRT toxicities. Rosenthal et al reported acute symptoms of headache, nausea and vomiting, scalp alopeca and oral cavity mucositis with IMRT related to the lower doses to the brainstem (>36 Gy), occipital scalp (>30 Gy) and anterior mandible (>34 Gy). Longer term concerns have been raised regarding of carotid artery complications related to higher carotid artery dose than with non IMRT techniques. The risk of second cancers has also been raised.[105-107]

CONCLUSION

To date, RT and systemic treatment strategies have been to intensify therapies. Strictly speaking, IMRT and 3DCRT can be considered *intensified* therapies as mean target doses tend to higher than with 2DRT. With improvements in target coverage, tumor margins receive higher doses than with 2DRT. Loco-regional control rates of greater than >90% have been reported by several institutions but a significant proportion of patients

will still develop metastatic disease. Patients who have undergone RT for NPC are at long-term risk of RT injury. Is it appropriate to ask, should future therapies be directed toward *de-intensification* of loco-regional therapies with *intensification* of systemic therapies? The loco-regional control of Human Papilloma virus-associated oropaharynx squamous cell carcinoma is also excellent with radiation therapy.[108] Interestingly, efforts are underway to develop clinical trials to investigate de-intensification treatment strategies in this group of patients. There are significant differences between these two patient populations including the lack of salvage surgical options for patients with locally recurrent NPC. While de-intensification is provocative, the potential consequences may be devastating if loco-regional failures increase. Dose *de-intensification* strategies should only be explored in clinical trials setting. IMRT results still need longer term confirmation. Current research strategies should include efforts to reduce radiation dose to normal tissues through improvements in conformal RT and implementation of IGRT.

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