IMRT and IGRT in head and neck cancer: Have we delivered what we promised?

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Abstract

Intensity-modulated radiation therapy (IMRT) is a revolutionary new paradigm that aims at improving the therapeutic ratio by increasing the dose-gradient between target tissues and surrounding normal structures thereby offering probability of better loco-regional control with decreased risk of complications. IMRT is relatively intolerant to set-up uncertainties, warranting periodic image-guidance, making Image-Guided Radiation Therapy (IGRT) a natural corollary to IMRT. There are several challenges associated with the planning, delivery, and quality assurance of the IMRT and IGRT processes that must be addressed to realize the full potential of such exciting and promising technology. Given the complexities involved, it is quite intuitive to understand that IMRT and IGRT are resource-intensive, demanding increased labor, rigour, and expenses too. Other disadvantages associated with high-precision techniques include potentially increased risk of marginal failures, decreased dose homogeneity, and an increase in total body dose with increased risk of secondary carcinogenesis. The aim of this review is to define the role of IMRT and IGRT in contemporary head and neck oncologic practice through a critical appraisal of pertinent literature. Despite relatively short follow-up and limited clinical outcomes data, the weight of evidence suggests that loco-regional control is not inferior (either comparable or even better) and toxicity lesser with IMRT resulting in potentially improved quality-of-life, prompting the widespread adoption of such technology in community practice. Ongoing clinical trials in head and neck IMRT are currently addressing issues to optimize the IMRT process, adopting functional imaging for dose-painting, and incorporating adaptive re-planning strategies to further improve outcomes.

Keywords IMRT · IGRT · head-neck cancer · outcomes

Introduction

Radiation therapy has been an established and cost-effective treatment modality for the loco-regional control of a variety of cancers. It is estimated that 74% of patients with head neck cancers (HNC), need curative radiotherapy either as radical treatment or in the postopera-

tive adjuvant setting¹. Conventional radiotherapy for HNC (Fig. 1a), typically comprises of either a set of parallel opposed portals with or without matched low anterior neck field or a wedge pair portal based on two-dimensional fluoroscopic imaging designed to cover target volumes without major emphasis on shielding normal tissues resulting in considerable acute and late morbidity.^{2–4}

Fig. 1 Axial planning CT slice showing typical dose-wash of (a) conventional radiotherapy (2D-RT); (b) 3D-CRT; and (c) IMRT plan for head-neck cancer. Note the progressive high-dose conformation to the target volume and sparing of surrounding normal structures

Common acute toxicities of head-neck irradiation that are mostly self-limiting include mucositis, dysphagia, dysgeusia, and dermatitis that can lead to prolongation or discontinuation of treatment with potential adverse impact on outcomes.^{2,3} The most common and debilitating late toxicity is xerostomia - gross reduction in salivary output-leading to persistent dryness of mouth, oral discomfort, difficulty in speech and swallowing, impairment of taste, and deterioration of oro-dental hygiene.⁴ Some of the other late effects include subcutaneous fibrosis, hoarseness, and mucosal atrophy resulting in chronic dysphagia and increased risk of aspiration. Other potentially dangerous late complications such as radiation necrosis and myelopathy are rarely encountered in clinical practice. Over the years, major technological innovations have resulted in substantial improvements in planning, delivery and verification.⁵ The increasing use of computed tomography (CT) imaging for target volume delineation coupled with availability of computer-controlled treatment planning and delivery systems have progressively led to conformation of radiation dose to the target tissues (Fig. 1b) while sparing surrounding normal tissues, i.e. three-dimensional conformal radiotherapy (3D-CRT).

The advent of intensity-modulated radiation therapy (IMRT) in the last decade ushered in a new paradigm (Fig. 1c) that has completely revolutionized contemporary radiotherapy practice.⁶ The IMRT Collaborative Working Group⁷ of the National Cancer Institute defines IMRT as an advanced form of high-precision radiotherapy that uses non-uniform radiation beam intensities that have been determined using various computer-based optimization techniques to achieve the desired dose-distribution (Fig. 2). This definition (use of modulated beams with non-uniform intensities, delivering more than two intensity levels from a single beam direction and a single source position in space), excludes beams that use a transmission block with a single attenuation level, stan-

dard dynamic or static wedges, single-boost field inside the main field, as well as beams used in conformal arc delivery, GammaKnife and CyberKnife treatment. Determining the optimum beam fluence, such that the deliverable modulated fluence profiles result in a dose distribution that most closely match the desired one is an integral component of the IMRT planning and optimization process. IMRT is not only a technique for delivering optimized non-uniform beam intensities to a target volume, but it also provides a new approach to the entire treatment process.^{7–9} Clinical implementation of IMRT requires thorough knowledge of setup uncertainties, adequate selection of target volumes based on natural history of disease and patterns of spread, optimal delineation of target volumes and critical structures using multi-modality imaging, appropriate specification and dose prescription regarding dose volume constraints, and quality control of both the clinical and physical aspects of the whole procedure.^{7–9} High-precision techniques are relatively intolerant to set-up errors, mandating image-guidance for precise delivery. Image-guided radiation therapy (IGRT)^{10,11} thus represents a logical advancement in the field of high-precision radiotherapy and is a natural corollary to IMRT.

Cancers arising in the head and neck sites are in close proximity to several critical structures such as the spinal cord, brainstem, parotid glands, optic apparatus (eyes, optic nerves, chiasma), lacrimal glands, cochlea, and mandible. The promise of generating highly conformal and concave dose distributions around complex target volumes with steep dose-gradients makes IMRT ideally suited to HNC.^{6,12,13} The tolerance of surrounding organs at risk (OARs) is generally lesser than the prescription dose, which can be safely delivered with image-guided IMRT without compromising target volume coverage. The promise to reduce acute and late morbidity of treatment in conjunction with comparable or even better locoregional control and a potential positive impact on qua-

Fig. 2 Uniform intensity beam and resultant fluence-profile in 3D-CRT (left) as compared to modulated fluence from non-uniform intensity beams (right) typically used in IMRT

lity-of-life (QOL) and survival has prompted widespread adoption of IMRT and IGRT. This review aims to provide a brief overview of the current process of IMRT and IGRT followed by an attempt to define their role in contemporary head-neck oncologic practice through a critical appraisal of pertinent literature.

Planning in IMRT and IGRT context

Radiation therapy planning can be defined specifically though not only limited to the process of image-acquisition, volume delineation, dose-fractionation prescription, assigning of treatment fields and beam-modifiers, evaluation of dose distribution, and quality assurance before final approval for treatment delivery. The standard imaging technique used in radiotherapy planning is CT as it provides both anatomical detail for defining target volumes and the electron density data required for dose calculations. The terminology used in conformal planning has been laid down by the International Commission on radiation units and measurements (ICRU) Reports 50 and 62.^{14,15} Gross tumor volume (GTV) refers to the volume that includes gross tumor as defined by physical examination and imaging studies. Based on natural history of disease and patterns of spread, the GTV is expanded to create the clinical target volume (CTV) to

include areas at risk for harboring subclinical disease, which refers to microscopic deposits of tumor that are likely to be present but are not apparent on examination or imaging. Generally more than one CTV may be defined, based on the perceived risk of subclinical disease. The CTV is further expanded three-dimensionally to create the planning treatment volume (PTV) to account for daily set-up variability and/or organ motion that is expected during a course of fractionated radiotherapy.

Conformation of dose distribution to the target volumes with a high degree of precision and accuracy entails enormous complexity in both the planning as well as implementation process. IMRT can be considered as a 'chain of processes' (Fig. 3). At the heart of the process is the concept of 'inverse planning' in which the clinical objectives are specified mathematically and a computer optimization algorithm is used to automatically determine beam parameters (mainly beamlet weights) that will lead to the desired dose distribution.⁷ Optimization is an iterative process that balances the trade-off between target dose and coverage versus minimization of impact on normal tissues utilization a cost or objective function. The cost function is a mathematical description of criteria of treatment plan optimization (i.e. clinical objectives) and may be specified in terms of dose-limits, dose-volume limits, dose-response functions, or other formulations.⁷

Table 1. Disease-outcomes in large (≥ 100 patents) single-institution studies of IMRT in head neck cancers

Author (ref)	No. of pts (N)	Setting/points/dose	Median follow-up	Local/regional outcomes (yr)	Survival (yr)
Chao (17)	126	Radical/52 pts/ 68–72 Gy	#26 months	LRC: 79% & *84% (2-yr)	Not reported
		Post-op/74 pts/60–66 Gy		LRC: 90% & *93% (2-yr)	Not reported
Lee (18)	150	Radical/107 pts/70 Gy	25 months	LRC: 97% (2-yr) LRC: 95% (3-yr)	OS: 86% (2-yr) OS: 84% (3-yr)
		Post-op/43 pts/66 Gy	17 months	LRC: 83% (2-yr)	OS: 83% (2-yr)
Eisbruch (19)	133	Radical/60 pts/70 Gy	#32 months	LRC: 81% (3-yr)	DFS: #74% (3-yr)
		Post-op/73 pts/64 Gy		LRC: 84% (3-yr)	OS: #77% (3-yr)
Yao# (20)	150	Radical/99 pts/70–74 Gy	18 months	LC: 94% (2- & 3-yr)	DMFS: 87% (2-yr) & 81% (3-yr)
		Post-op/51 pts/60–64 Gy		LRC: 92% (2- & 3-yr)	OS: 85% (2-yr) & 82% (3-yr)
Studer (21)	115	Radical/80 pts/66–70 Gy	#18 months	LC: 81% (2-yr) RC: 86% (2-yr)	DMFS: 92% (2-yr) OS: 75% (2-yr)
		Post-op\$/35 pts/ 60–64 Gy		LC: 91% (2-yr) RC: 97% (2-yr)	DMFS: 88% (2-yr) OS: 79% (2-yr)
Schoenfeld (22)	100	All radical (> 85% treated with conc boost-72 Gy)	37 months	LC: 89% (3-yr) LRC: 87% (3-yr)	DFS: 78% (3-yr) OS: 71% (3-yr)

Pts = patients; yr = year; Post-op = post-operative; LC = local control; RC = regional control; LRC = locoregional control; DFS = disease-free survival; DMFS = distant-metastases free survival; OS = overall survival; conc = concomitant

*Refers to ultimate loco-regional control including surgical salvage

#Results pertain to entire study cohort including radical and post-operative IMRT

\$1 patient had received pre-operative radiotherapy

Fig. 3 Intensity-modulated radiation therapy (IMRT) process chain

Plan evaluation metrics must be clinically relevant and understandable, but, at the same time be able to differentiate between plans and thus provide assistance to the physician in decision-making.

A stringent quality assurance (QA) program is key to successful implementation of IMRT. The overall accu-

racy of IMRT depends upon mechanical isocentric accuracy of the delivery unit (gantry, collimator, couch), beam stability (at low monitor units and small field sizes), multi-leaf collimator (MLC) system (leaf-travel and position accuracy, reproducibility) and its characterization into the treatment planning system (MLC leaf-end and side leakage, tongue-and-groove effect, penumbra modeling). Well-defined guidelines for tolerance limits and action levels pertaining to various aspects of IMRT dosimetry including a credentialing mechanism has been proposed to ensure that what is planned is actually delivered.¹⁶

The implementation process of IMRT may be defined as an accurate registration of the patient geometry with the dose delivery geometry of the treatment unit using either two-dimensional or three-dimensional image-guidance. IGRT relies heavily on serially acquired image datasets^{12,13} using a variety of medical imaging platforms (e.g. stereoscopic X-ray guidance, CT-guidance, infra-red marker guidance) to account for changes in the position of the intended target before or during treatment delivery, that are then used to maximize targeting capabilities to deposit higher doses to target structures while minimizing

Table 2. Phase II studies of IMRT in nasopharynx, oropharynx, oral cavity, hypopharynx, and larynx

Author (ref)	No. of pts	Median dose	Median follow-up	Local/regional control (yr)	Survival (yr)	Acute toxicity	Late toxicity
Nasopharynx*							
Lee (23)	67	70–72 Gy	31 mths	LC: 97% (4-yr) RC: 98% (4-yr)	DMFS: 66% (4-yr) OS: 88% (4-yr)	≥ Gr3 mucosa – 24% ≥ Gr3 pharynx – 24%	Gr2 xerostomia-3% (2-yr) Gr4 hearing loss – 8%
Chong (24)	104	64–70 Gy	19 mths	LC: 98% (3-yr) RC: 99% (3-yr)	DMFS: 88% (3-yr) OS: 86% (3-yr)	Gr3 mucosa – 17% Gr3 skin – 2%	≥ Gr3 xerostomia-9% (1-yr)
Bucci# (25)	118	70 Gy	30 mths	LR: 96% (4-yr) RC: 98% (4-yr)	DMFS: 72% (4-yr) OS: 74% (4-yr)	No reported	Osteonecrosis < 1% Temporal lobe necrosis < 1%
Zhao (26)	122	68 Gy	20 mths	LRC: 93% (3-yr)	DMFS: 86% (3-yr) OS: 85% (3-yr)	Gr3 skin – 2% Gr3 mucosa – 15%	No reported
Kam (27)	63	66 Gy	29 mths	LC: 92% (3-yr) RC: 98% (3-yr)	DMFS: 79% (3-yr) OS: 90% (3-yr)	Gr3 mucosa – 41% Gr3 dysphagia – 5%	Gr2-3 xerostomia-23% (2-yr)
Kwong (28)	33	68–70 Gy	24 mths	LC: 100% (3-yr) RC: 93% (3-yr)	DMFS: 100% (3-yr) OS: 100% (3-yr)	Gr3 mucosa – 33% Gr3 skin – 26%	Gr3 xerostomia-40% (1-yr) 15% (2-yr)
Wolden (29)	74	70 Gy	35 mths	LC: 91% (3-yr) RC: 93% (3-yr)	DMFS: 78% (3-yr) PFS: 67% (3-yr) OS: 83% (3-yr)	Not reported	Gr3 hearing Loss – 15% Gr2 xerostomia – 32% (2-yr) Gr3 xerostomianone (2-yr)
Fang (30)	110	70.2 Gy	40 mths	LRC: 84% (3-yr)	DMFS: 83% (3-yr) OS: 85% (3-yr)	Worsening in all quality of life scores	Gradual recovery in quality of life scores over time
Oropharynx							
Chao (31)	74	66–70 Gy	33 mths	LRC: 87% (4-yr)	DMFS: 90% (4-yr) OS: 87% (4-yr)	Not reported	Gr2 xerostomia – 9 pts Gr3 trismus 1 pt
Lee (32)	41	70 Gy	31 mths	LC: 95% (3-yr) RC: 94% (3-yr)	DMFS: 86% (3-yr) OS: 91% (3-yr)	Not reported	PEG dependency – 4% (2-yr) Gr2 xerostomia – 12% (2-yr)
deArruda (33)	50	70 Gy	18 mths	LC: 98% (2-yr) RC: 88 (2-yr)	DMFS: 84% (2-yr) OS: 98% (2-yr)	Gr3 mucosa – 38%	Gr2 xerostomia-33%

(contd...)

Table 2. (contd...)

Author (ref)	No. of pts	Median dose	Median follow-up	Local/regional control (yr)	Survival (yr)	Acute toxicity	Late toxicity
Garden (34)	51	66–72 Gy	45 mths	LC: 96% (2-yr) LRC: 93% (2-yr)	DFS: 87% (2-yr) OS: 93% (2-yr)	PEG tubes-21 pts	Gr2 dysphagia – 3 pts Osteoradione necrosis – 1 pt
Huang (35)	71	70 Gy	33 mths	LC: 94% (3-yr) RC: 94% (3-yr)	OS: 83% (3-yr)	≥ Gr3 toxicity – 50%	Gr2 xerostomia-2 pts (2-yr) Osteoradione necrosis – 1 pt
Sanguineti (36)	50	66–78 Gy	33 mths	LC: 94% (3-yr) RC: 85% (3-yr)	Not reported	Not reported	Not reported
Daly (37)	107	66 Gy	29 mths	LRC: 92% (3-yr)	DMFS: 92% (3-yr) OS: 83% (3-yr)	Gr3 mucosa – 58% Gr3 skin – 5%	Any Gr3 toxicity – 6%
Oral cavity/hypopharynx/larynx							
Studer (38)	30	70 Gy	12 mths	LC: 43% (2-yr)	OS: 30% (2-yr)	PEG tubes-14 pts	No Gr3 xerostomia
	Rad 28 PO	60 Gy	19 mths	LC: 92% (2-yr)	OS: 83% (2-yr)		
Yao (39)	55	60–66 Gy	17 mths	LC: 85% (2-yr) LRC: 82% (2-yr)	DMFS: 89% (2-yr) OS: 68% (2-yr)	Not reported	Not reported
Studer (40)	29	60–71 Gy	16 mths	LC: 90% (2-yr)	DMFS: 93% (2-yr)	Not reported	Gr3 dysphagia – 1 pt Gr4 fibrosis – 2 pts
				RC: 93% (2-yr)	DFS: 90% (2-yr)		
Lee (41)	31	70 Gy	26 mths	LC: 86% (2-yr)	DMFS: 92% (2-yr)	Gr2 mucosa – 48%	Gr2 xerostomia (2-yr)
				RC: 94% (2-yr)	OS: 63% (2-yr)	Gr2 pharynx – 100%	Necrosis, fasciitis – 1 pt

Pts = patients; yr = year; mths = months; Gr = grade; LC = local control; RC = regional control; LRC = loco-regional control; DFS = disease-free survival; DMFS = distant-metastases free survival; OS = overall survival; Rad = radical; PO=post-operative; PEG = percutaneous endoscopic gastrostomy

*Several patients in many series of nasopharyngeal cancers received planned brachytherapy or radio-surgery boost

#Update of UCSF experience included the 67 patients initially reported by Lee et al

doses to collateral normal tissues to further enhance therapeutic ratio. IMRT and IGRT thus demand precision and accuracy that surpasses the requirements of conventional radiotherapy treatment planning and delivery techniques.^{7,9,12} It requires a coordinated team effort between the radiation oncologist, medical physicist, and radiation therapy technologist.

Current best evidence

There is no debate or controversy regarding the dosimetric superiority (Fig. 4) of IMRT in head-neck cancers

over two-dimensional conventional radiotherapy or even 3D-CRT. However, the key question whether that dosimetric advantage translates into a significant and meaningful clinical benefit remains unanswered.¹³ The correlation of dosimetric parameters with organ function and toxicity has generated robust and valuable dose-volume-toxicity relationship. These dose-volume constraints are now routinely applied as objectives in IMRT optimization to reduce OAR to acceptable levels.

The contemporary practice of head neck IMRT has largely evolved from single-institution phase I–II prospective studies¹³ consistently demonstrating either comparable or even favorable outcomes in cancers arising

Fig. 4 Dose-wash in (a) upper axial, (b) lower axial, (c) coronal, and (d) sagittal plane of a simultaneous integrated boost (SIB)-IMRT plan delivering 70 Gy (violetpink) to gross disease (PTV70); 63 Gy (yellow) to high-risk elective volume (PTV63); and 54 Gy (green) to low-risk elective volume (PTV54) in 35 fractions. (e) Resultant dose-volume histogram showing exquisite sparing of the contra-lateral parotid gland

both from unspecified head-neck sites^{17–22} (Table 1) as well as specifically from nasopharynx,^{23–30} oropharynx,^{31–37} oral cavity,^{38,39} and pharynx/larynx^{40,41} (Table 2). The Kaplan–Meier estimates of loco-regional control at 2-to 4-years has varied from 80–100% across these studies (excepting for oral cavity) which is certainly not inferior (either comparable or even superior) to historical controls with similar stage disease treated with conventional techniques. Acute radiation toxicity (mucositis, dysphagia, xerostomia, and dermatitis) has generally been lesser with IMRT across most of the trials prompting better compliance to treatment. Most importantly, the incidence of moderate to severe late xerostomia ($\geq$ grade 2) as scored by the radiation therapy oncology group/European organization for research and treatment of cancer (RTOG/EORTC) morbidity criteria has been significantly lesser with the use of parotid sparing techniques, with gradual though partial recovery over time manifesting as subjective and objective improvement of late xerostomia-related symptoms resulting in preserved or improved health-related QOL. Due to relatively limited follow-up, the efficacy of IMRT for long-term outcomes is still not firmly established. The short-term survival estimates (distant-metastases free survival, disease-free survival, and overall survival) though have generally favored IMRT over conventional techniques.

The long-term local control and overall survival in sino-nasal cancers has traditionally been 50–60% and 40–

50% respectively using conventional techniques with unacceptably high rates of irreversible toxicity of the lacrimal gland and optic pathways. Recent reports^{42–49} delivering higher doses (60–70 Gy) with IMRT suggest potentially improved local control (60–85%) as well as overall survival (50–90%), at 2–4 years, albeit with shorter follow-up, with significantly reduced ocular toxicity (dry-eye syndrome and optic neuropathy) consistent with the dose-volume-toxicity profile of the lacrimal and optic apparatus (Table 3). Interesting applications of IMRT that currently evolving (Table 4) include curative intent re-irradiation in the setting of a delayed loco-regional recurrence or the emergence of a second new primary in a previously irradiated head-neck mucosal site;^{50–54} unknown primary with metastatic neck nodes requiring comprehensive mucosal and nodal irradiation^{55–57}; and thyroid cancers.^{58–60}

The favorable results from these prospective single-institution studies need to be interpreted with caution as they may be fraught with bias. Parallel developments in diagnosis and therapy resulting in stage migration due to improved diagnostic imaging e.g. 18-F-fluoro-deoxyglucose positron emission tomography (FDG-PET); increasing use of multi-modality imaging for better target delineation; improved planning and optimization algorithms; concurrent systemic therapy (chemotherapy and biological therapy); and more liberal use of better and aggressive supportive care (feeding tubes, narcotics, antibiotics,

Table 3. Summary outcomes in sino-nasal cancers treated with IMRT

Author (ref)	Patients	Median dose	Median follow-up	Local control	Overall survival	≥ Gr3 visual toxicity
Claus (42)	32	70 Gy	15 months	Not reported	80% (1-year)	None
Duthoy (43)	39	70 Gy	31 months	68% (4-year)	59% (4-year)	2 patients
Combs (44)	46	64 Gy	16 months	81% 2-year)	90% (3-year)	None
Chen [#] (45)	23	70 Gy	44 months	65% (5-year)	47% (5-year)	None
Daly (46)	36	70 Gy	39 months	58% (5-year)	45% (5-year)	None
Hoppe [#] (47)	30	60 Gy	23 months	Not reported	Not reported	None
Dirix (48)	25	60 Gy	27 months	81% (2-year)	88% (2-year)	None
Madani (49)	84	70 Gy	40 months	74.9% (3-year) 70.7% (5-year)	70.2% (3-year) 58.5% (5-year)	1 patient

[#]Both series also reported outcomes of conventional and three-dimensional conformal radiotherapy

growth factors) may have partially contributed to better outcomes in recent years as compared to historical controls.

To investigate whether the early success of IMRT in HNC reported by a few institutions could be reproduced in a multi-institutional setting, the RTOG embarked on two multicentre phase I/II trials. In the first study,⁶¹ 69 patients with early oropharyngeal cancer (T1-2, N0-1) requiring bilateral neck irradiation were accrued from 14 participating institutions on a prospective study of moderately accelerated, hypofractionated IMRT prescribing 66 Gy to primary tumor and involved nodes and 54–60 Gy to subclinical disease in 30 fractions over 6 weeks. At a median follow-up of 2.8 years for survivors, the 2-year estimated local/regional failure rate was 9%. Maximal late toxicities ≥ grade 2 were dermatitis (12%), mucositis (24%), salivary gland toxicity (67%), esophagitis (19%), and osteoradionecrosis (6%). Grade 2 or worse xerostomia was observed in 55% of patients at 6 months but reduced to 25% and 16% at 1-year and 2-years respectively. Preliminary data from the second study⁶² involving 68 patients with non-metastatic nasopharyngeal cancer treated with 70 Gy to gross disease and 59.4 Gy to elective volumes in 33 fractions with concurrent cisplatin for advanced-stage disease reported an estimated 2-year loco-regional progression free, distant metastasis-free, and overall survival of 89.3%, 84.7%, and 80.2% respectively. Acute grade 4 mucositis occurred in 4.4%, and the worst late grade 3 toxicities were esophagitis (4.7%), mucositis (3.1%), and xerostomia (3.1%). The rate of grade 2 xerostomia at 1-year was 13.5%, while no patient developed grade 4 late xerostomia.

The largest prospective single-arm study⁶³ in nasopharyngeal carcinoma included 323 patients treated on an institutional protocol of reduced volume IMRT to a dose of 66–69.75 Gy in 30–31 fractions and cisplatin-based concurrent chemotherapy for loco-regionally advanced disease. With a median follow-up of 30 months, the estimated 3-year local control, regional control, distant-

metastases free survival, disease-free survival, and overall survival was 95%, 98%, 90%, 85%, and 90% respectively. The commonly observed severe acute toxicities were grade 3 mucositis (27.5%), dermatitis (4.6%), and leucopenia (5.9%). The most commonly observed late toxicity was xerostomia. Over 94% of patients had grade 2 xerostomia at 3-months, which gradually improved over time, reducing to 63% at 1-year and to 8% at 2-years after radiotherapy.

In a non-randomized comparison,⁶⁴ 190 patients with non-metastatic nasopharyngeal cancer treated with IMRT were matched in a 1:1 ratio with 190 patients selected from a large institutional database of patients treated with conventional radiotherapy based on known prognostic factors (gender, age, T-stage, N-stage, chemotherapy, and hemoglobin). There were statistically significant differences in the loco-regional control (90.4% vs 78.3%, $P = 0.011$) and relapse-free survival (89.8% vs 80.7%, $P = 0.029$) favoring IMRT. However, the difference in 4-year progression-free survival; distant metastases-free survival; and overall survival, however, was no different between the two groups (79.4% vs 64.8%, $P = 0.251$; 88.6% vs 83.4%, $P = 0.857$; and 88.9% vs 75.8%, $P = 0.246$ respectively). The incidence of late xerostomia at 6-months, 1-, 2-, 3-, and 4-years was significantly lesser in the IMRT group, which also showed a quicker recovery over time than conventional radiotherapy.

Another large prospective non-randomized comparison of conventional radiotherapy (150 patients) with IMRT (91 patients) was recently reported by Vergeer and colleagues.⁶⁵ Patient-rated xerostomia, RTOG acute and late xerostomia, and QOL scores were measured at baseline (pre-radiotherapy) and at specified post-radiotherapy intervals. The use of IMRT resulted in a significant reduction of the mean parotid dose (27 vs 43 Gy; $P < 0.001$). At 6-months, 41% patients treated with IMRT reported moderate or severe xerostomia compared with 67% patients treated with 3D-CRT ($P < 0.001$). During treatment, significantly more patients in the 3D-CRT

Table 4. Evolving applications of IMRT in curative intent re-irradiation, CUP with metastatic neck nodes, and thyroid cancers

Author (ref)	No. of pts (N)	Median dose	Median FU	Local/regional control (yr)	Survival (yr)	Acute toxicity	Late toxicity
Curative intent re-irradiation							
Lu (50)	49	70 Gy	9 months	LC: 100% (1-yr)	Dist mets-3 pts	Gr3 mucosa-2 pts Gr3 skin-none	Not reported
Biagioli (51)	41	60 Gy	14 months	LRC: 38% (2-yr)	DFS-48.1% (2-yr) OS-48.7%(2-yr)	Gr3-4 toxicity-32%	Gr3-4 toxicity-6 pts
Lee (52)	105 74*	59.4 Gy	35 months	LRC: 42% (2-yr) 52% with IMRT	OS: 37% (2-yr) 57% with IMRT	Gr3-4 toxicity-23%	Gr3-4 toxicity-15%
Sulman (53)	74	60 Gy	25 months	LRC: 64% (2-yr)	OS-58% (2-yr)	Death-1 pt	Severe toxicity-20%
Duprez (54)	84	69 Gy	20 months	LRC: 40% (5-yr)	DFS: 15% (5-yr) OS: 20% (5-yr)	Gr3-4: 26 pts	Gr3-4: 11 pts 2 fatal hemorrhages
CUP with metastatic neck nodes							
Madani (55)	23	66 Gy	17 months	3 nodal failures	DMFS-76.3% (2-yr) OS-74.8% (2-yr)	Gr3 skin-7 pts Gr3 mucosa-11 pts	Gr3 xerostomia-2 pts Gr3 dysphagia-none
Klem (56)	21	66 Gy	24 months	LC: 90% (2-yr)	OS-85% (2-yr)	Gr3 skin-1 pt Gr3 mucosa-3 pts	Gr2 esophagus-3 pts Gr2 xerostomia-10 pts
Lu (57)	18	60–70 Gy	25 months	LC: 88.5% (2-yr)	DMFS-88.2% (2-yr) OS-74.2% (2-yr)	Worst acute toxicity was Gr3 mucositis	No significant late toxicity
Thyroid cancers							
Rosenbluth (58)	20	63 Gy	13 months	LC: 85% (2-yr)	DMFS: 46% (2-yr) OS: 60% (2-yr)	Gr3 mucosa-7 pts Gr3 skin-3 pts Gr3 pharynx-3 pts	Gr3-4 late toxicity-none
Urbano (59)	13	58.8 Gy	9 months	LC: 85% (crude)	OS: 69% (crude)	Gr3 skin-39% Gr3 mucosa-8% Gr3 pharynx-31%	Gr2 xerostomia-1 pt Hoarseness-3 pts
Schwartz (60)	131 57*	60 Gy	38 months	LRC:79% (4-yr) Same with IMRT	OS: 73% (4-yr) Same with IMRT	Not reported	≥ Gr4–12% overall 2% with IMRT

Pts = patients; FU = follow-up; yr = year; Gr = grade; Dist mets = distant metastases; LR = locoregional; LRC = loco-regional control; DMFS = distant-metastases free survival; OS = overall survival; CUP = carcinoma of unknown primary.

*These patients were treated with IMRT

group encountered worse acute xerostomia and mucositis. At 6-months, 32% patients treated with IMRT had ≥ grade 2 RTOG late xerostomia compared to 56% patients treated with 3D-CRT ($P = 0.002$).

There have been two randomized controlled trials (both in nasopharyngeal carcinoma) that have clearly demon-

strated the advantage of IMRT over conventional techniques. In the first such study,⁶⁶ 51 patients with stage II nasopharyngeal cancer (T2, N0/N1, M0) were randomly assigned to receive either conventional radiotherapy or IMRT with change in stimulated salivary flow rate as the primary outcome measure. Stimulated whole saliva flow

rate (SWSFR) and stimulated parotid flow rate (SPFR) were measured and EORTC QOL core questionnaire and head-neck module (QLQ-C30 and HN35) were completed preradiotherapy (baseline) and at 2, 6, and 12 months after radiotherapy. At 12 months postradiotherapy, 12 (50.0%) and 20 patients (83.3%) in the IMRT arm had recovered at least 25% of pre-radiotherapy SWSFR and SPFR respectively, compared with 1 (4.8%) and 2 patients (9.5%), respectively, in the conventional radiotherapy arm ($P < 0.05$). Global health scores showed continuous improvement in QOL after both treatments as compared to baseline ($P < 0.001$). However, at 12 months subscale scores for role-physical ($P = 0.011$), bodily pain ($P = 0.044$), and physical function ($P < 0.05$) were significantly better in the IMRT group. Importantly, there was substantial and consistent improvement in xerostomia-related symptoms over time in majority of patients in the IMRT arm in contrast to modest improvement in fewer patients in the conventional radiotherapy arm.

In the second study,⁶⁷ 60 patients with non-metastatic nasopharyngeal cancer (T1-2b, N0-1) were randomized to either two-dimensional conventional radiotherapy or IMRT with the incidence of observer-rated severe xerostomia at 1-year assessed by the RTOG/EORTC late radiation morbidity scoring system as the primary endpoint. Parallel assessment with patient-reported outcomes, SPFR, and SWSFR were also made at baseline (preradiotherapy), 6 weeks, 6 months and 1-year post-radiotherapy. Patients in the IMRT arm had significantly lesser grade 2 or worse xerostomia than those in the conventional radiotherapy arm both at 6-weeks (46.4% vs 85.7%; $P = 0.002$) and at 1-year (39.3% vs 82.1%; $P = 0.001$). The average fractional SPFR was significantly better with IMRT at 6-weeks (0.39 vs 0.09; $P < 0.0001$); 6-months (0.70 vs 0.04; $P < 0.0001$); and 1-year postradiotherapy (0.90 vs 0.05; $P < 0.0001$). On analyzing the trend of post-radiotherapy SPFR between 6 weeks and 1 year, significant improvement in fractional SPFR was observed for patients in the IMRT arm ($P < 0.05$, paired *t* test), but not in the conventional radiotherapy arm. The average fractional SWSFR was also significantly higher in the IMRT arm (0.41 vs 0.20; $P = 0.001$) at all time points.

In another phase III randomized controlled trial (PARSPORT),⁶⁸ recently presented and published in abstract form, 94 patients with pharyngeal tumors (80 oropharyngeal and 14 hypopharyngeal), stages T1-4, N0-3, M0, were randomized to either CT-planned conventional parallel opposed lateral fields (65 Gy/30 fractions/6 weeks) or parotid-sparing IMRT. The primary endpoint was incidence of $\geq$ grade 2 xerostomia at 1-year as assessed by the late-effects on normal tissues-subjective objective management analytic (LENTSOMA) scale. Secondary endpoints included acute toxicities and late RTOG radiation morbidity. With a median follow-up was

31.9 months, 1-year LENT-SOMA $\geq$ grade 2 xerostomia was observed in 74% patients in conventional radiotherapy arm as compared to 40% patients in the IMRT arm ($P = 0.005$). Corresponding values at 18 months were 71% and 29% respectively ($P = 0.004$). Acute radiotherapy related $\geq$ grade 2 fatigue was more prevalent in the IMRT group (76% vs 41% $P = 0.001$). The incidence, severity, and duration of acute mucositis and dermatitis were similar in the two arms. As expected, no significant differences were observed in loco-regional control and survival between the two arms.

A contemporary report⁶⁹ from a community-hospital setting in a developing country achieving outcomes similar to large academic institutions of the western world, is rather reassuring and ample testimony of the potential of applying such technology in routine clinical practice for larger benefit. Given these impressive results, IMRT has now been adopted as the standard approach in most co-operative group trials involving the head-neck. Two randomized controlled trials comparing 3D-CRT with IMRT in early to moderately advanced non-nasopharyngeal HNC with concurrent chemotherapy for bulky T2, T3, and/or N+ disease have recently been concluded at the authors institution, the data from which await publication (personal communication). Currently, there is a large ongoing multi-centre phase III trial (target accrual over 300 patients) wherein patients with locoregionally advanced cancers of the oral cavity, oropharynx or hypopharynx (stages III–IV) are being randomly assigned to an experimental two-phase IMRT (50 Gy/25 fractions to PTV1 followed by 25 Gy/10 fractions to PTV2) plus three-weekly concurrent cisplatin regimen against an active comparator comprising of conventional radiotherapy (50 Gy/25 fractions to PTV1 and 20 Gy/10 fractions to PTV2) plus similar chemotherapy (GORTEC 2004–01). The primary endpoint is loco-regional control at 2-years, while 2-year overall survival, late xerostomia, and QOL issues are secondary outcome measures.

Lessons from patterns of failure following IMRT

The therapeutic index of high-precision conformal radiotherapy is largely dependant on adequate selection and delineation of GTV, CTV, and OARs whose sparing can result in clinical benefit. Rapid advances in technology allow highly sophisticated treatment planning coupled to extremely accurate localization and precise radiation dose delivery. However, the technology for target volume delineation i.e. accurately defining what regions or tissues need to be targeted is still not very robust and continues to evolve. Consensus guidelines for target volume delineation in the neck both node negative⁷⁰ as well as node positive and post-operative setting⁷¹ have been

Fig. 5 (a) Axial planning CT of a patient with right sided oropharyngeal cancer treated with IMRT showing GTV (thin blue line), PTV (thick red line), and failure volume (Vf) at time of relapse (thick blue line). (b) Dose-volume histogram of PTV (dashed red line) and Vf (dashed blue line) showing an in-field failure in the high dose region (covered by >95% of the prescription dose)

adopted widely in routine clinical practice, but there continues to be widespread variation in the delineation of GTV at a given head and neck primary site even with multi-modality imaging.

The risk of retropharyngeal nodal failure in patients with locally advanced nonnasopharyngeal HNC is moderate, but exists even for the node-negative neck. This has prompted the inclusion of the entire retropharyngeal space bilaterally through the base of skull in the high-risk elective volume.¹⁹ However, it may be adequate to include the subdiaphragmatic space as the cranial-most target in the contra-lateral, clinically uninvolved neck. Another valid area of concern has been the incidence of marginal failure in the vicinity of the spared parotid gland.¹⁷ In recent times, this phenomenon of marginal peri-parotid failure has been increasingly recognized and reported.⁷² One of the early interim endpoints commonly employed in appraising the outcomes of high-precision techniques is the patterns of failure following treatment and their correlation with target volume coverage. It is indeed reassuring to note that the risk of marginal miss has not unduly increased after the introduction of conformal radiotherapy. In vast majority of single-institution series,^{17–22} the predominant pattern of failure following

IMRT for HNC has been ‘in-field’ (Fig. 5) within the GTV with marginal failure rate being around 10% (range 0–25%), that may serve as the basis of for designing further dose escalation studies.

What is the most optimal IMRT technique and fractionation for HNC?

Technique

With the increasing prevalence of IMRT in the clinic, radiation oncologists are now confronted with the choice of the optimal IMRT technique and fractionation for different disease sites and stages in the head and neck. One issue is whether patients with complex anatomy should undergo an extended whole-field technique, in which the entire target volume from the head till lower neck is included in a single IMRT plan, or a splitfield IMRT technique, in which the target volumes superior to the vocal cords are treated with an IMRT plan matched to a conventional low anterior neck field. Although published guidelines regarding choosing the most optimal technique are lacking, most patients are treated on physician and/or institutional preference for a particular technique. In gen-

eral, cancers involving the nasopharynx and oropharynx are best treated with the split-field IMRT technique to minimize the dose to the glottic larynx. The extended whole-field IMRT technique should be preferred whenever glottic larynx is either part of the target volume (as in cancers arising from the larynx, hypopharynx, and unknown head-and-neck primary) or gross disease extends inferiorly and close to the glottic larynx⁷³

Delivery

Head-neck IMRT is commonly delivered using MLCs either in the dynamic mode (DMLC) or segmental mode (SMLC) on a conventional linear accelerator. The advantage of DMLC is the ability to deliver the desired intensity profile with a high degree of fidelity. The SMLC method resembles treatment with multiple static fields that can be more easily verified. However, the use of SMLC requires that the desired profile be approximated by discrete intensity levels, which may lead to degradation in the delivered dose distribution. Both delivery modes produce comparable results dosimetrically⁷⁴ in terms of PTV coverage, OAR sparing, conformality, and homogeneity; but have important differences in terms of delivery times (15–20% longer with SMLC) and monitor units (15–20% higher with DMLC) which can impact upon the choice.⁷⁵

More recently, newer and improved modes of IMRT planning and delivery have been developed. Helical TomoTherapy (TomoTherapy Inc, Madison, WI)⁷⁶ has emerged as a promising and novel platform wherein a 6 MV linear accelerator mounted on a ring-gantry continuously rotates around the patient to deliver radiation in a helical mode, collimated and modulated by binary MLCs, as the patient translates through the ring. Volumetric modulated arc therapy (VMAT) using intensity-modulated arcs has also emerged in parallel. Two such systems are currently commercially available – RapidArc (Varian Medical Systems, USA)⁷⁷ and VMAT ERGO++ (Elekta, Sweden).⁷⁸ To achieve the desired level of modulation, the instantaneous dose-rate, MLC leaf-position, and gantry rotational speeds are continuously varied by the optimizer. VMAT ERGO++ uses a novel aperturebased algorithm during a single gantry arc of up to 360 degrees. Both these forms of volumetric modulated rotational systems aim to maintain or improve target volume coverage, reduce OAR doses, and reduce beam-on time per fraction to increase patient throughput as compared to conventional IMRT.

Fractionation

Another issue in head-neck IMRT pertains to the most optimal fractionation scheme to be employed. Given the multitude of target volumes with variable risk of harboring subclinical disease and resultant clonogen density

mandating differential dosing to elective volumes, HNC lends itself intuitively to the simultaneous integrated boost (SIB) paradigm (Fig. 4). A single-phase IMRT plan using the SIB paradigm obviates the need for sequential planning and summation for plan evaluation. However, some centres do employ a two-phase IMRT plan to further reduce the dose to parotid glands and preserve salivary function. In an international survey,⁷⁹ 12 different types of IMRT dosefractionation schedules for head-neck cancers were reported. Conventional fractionation (70–72 Gy at daily 2 Gy/fraction) was used in only 3 centres, while 11 centres used altered fractionation regimens. Reported schedules included accelerated fractionation (6 fractions/week), modestly accelerated hypofractionation (≤ 2.2 Gy/fraction), dose-escalated hypofractionation (≥ 2.3 Gy/fraction), hyperfractionation, continuous acceleration, and concomitant boost schedule. The reasons for dose fractionation variability include desire for dose escalation, differences in irradiated volume, number of target volumes, concurrent systemic treatment, overall treatment time, resource-constraints, variable margins, late tissue toxicity, and use of separate low anterior neck fields. Such variability in IMRT fractionation renders any meaningful comparison of treatment results difficult and mandates standardization to ensure uniformity both across and within institutions.

Role of hadron therapy and radio-surgery

Particle-beam therapy

Protons deposit most of their energy in the ‘Bragg’ peak, the depth of which is dependent on the energy of the proton beam that can be controlled very precisely. Since protons have no exit dose, normal tissues beyond the target receive very minimal radiation, making them an attractive option for skull-base tumors. The intensity of the proton radiation can also be modulated using the pencil-beam scanning technique to achieve intensity-modulated proton therapy. The best results for protons in HNC have been in advanced sino-nasal malignancies. In a series of 102 patients⁸⁰ treated to a median dose of 71.6 Gy with protons, the 5-year local control was 86% (median follow-up-6.6 years), with very low rates of ocular toxicity. The largest study⁸¹ of fast-neutrons in salivary gland cancers reported a 6-loco-regional control and cause-specific survival of 59% and 67% respectively, with a 10% incidence of grade 3–4 late toxicity at a median follow-up of 36 months establishing the efficacy of such therapy.

Radio-surgery

Single fraction radio-surgery has been used in nasopharyngeal cancers generally as a boost following com-

pletion of fractionated external beam radiotherapy with good efficacy, but moderate toxicity. In addition, it continues to be used occasionally in arterio-venous malformations, paragangliomas, and melanomas arising in the head-neck. With wider availability of radio-surgery systems, there has been recent renewed interest in using either single-fraction short-course hypo-fractionated stereotactic body radiotherapy (SBRT) for head-neck cancers. In a recent report,⁸² 55 lesions arising in the head-neck in 44 patients as primary, recurrent, or metastatic cancers were treated using single-dose (13–18 Gy) or hypo-fractionated SBRT (36–48 Gy in 5–8 fractions). Tumor control at 1-year was 83.3% and 60.6% in the primary and recurrent groups respectively, with only grade 1–2 acute mucosal toxicity. In another larger study,⁸³ 85 patients with recurrent previously irradiated squamous cell carcinoma of the head and neck were treated with hypofractionated SBRT to a median dose of 35 Gy (range: 15–44 Gy). There was no re-irradiation related grade 4–5 toxicity. The 1-year and 2-year local control and overall survival was 51.2% and 30.7%, and 48.5% and 16.1%, respectively. In another study,⁸⁴ 36 patients (44 sites) were treated using CyberKnife robotic radio-surgery system (Accuray, Sunnyvale, CA) as re-irradiation for locally recurrent HNC to doses of 18–40 Gy (median-30 Gy) in 3 to 5 fractions to the 65%–85% iso-dose line for 3–5 consecutive days. Acute grade 3 toxicity was noted in 13 patients, while 3 patients developed severe late complications (bone and soft-tissue necrosis). The 1-year and 2-year overall survival was 52% and 31% respectively.

Image-guidance in HNC

Set-up errors, though undesirable, are an inherent part of the radiation therapy process. It is widely accepted that there are two types of set-up errors, systematic and random errors. Systematic component of the displacement pertains to an error during the planning (preparation) process (such as laser misalignment) that is propagated and present during the entire course of treatment while random errors are errors of execution that represent day-to-day variation in the set-up of the patient. The conventional method of verifying patient positioning has been through a set of periodically acquired two-dimensional portal images (either through films or electronic portal images). However, they suffer from poor image quality and can visualize only bony anatomy rendering detection of soft-tissue changes difficult. The highly conformal dose distributions produced by IMRT are less tolerant to set-up uncertainties.^{7–9} The routine availability of on-line electronic portal imaging devices (EPID) on the current generation of linear accelerators has led to an improved understanding of treatment uncertainties and the need to reduce them. In conventional head neck radiotherapy

using EPID verification, systematic and random errors have varied from 1–3 mm, necessitating a 4–5.5 mm CTV to PTV margin applying published margin generating recipes.⁸⁵ The development and commercial availability of advanced on-line imaging technologies for volumetric verification has provided further impetus for testing IGRT in the clinic. An ideal IGRT system should be equipped with the ability to efficiently acquire and compare three-dimensional volumetric data of soft tissues including tumors and a process to apply a clinically meaningful intervention to account for treatment uncertainty and set-up errors. An exhaustive discussion on currently available IGRT systems is beyond the scope of this article and the reader is referred to an excellent contemporary review.¹⁰ Helical TomoTherapy, an integrated platform for planning, verification, and delivery of IMRT uses the 6 MV (degraded to 3.5 MV for imaging) treatment beam for daily imaging prior to delivery (Fig. 6). The MVCT image is automatically co-registered with the planning CT to detect translational and rotational errors that can be corrected by applying the couch shifts automatically. Cone-beam CT (CBCT) is a novel form of volumetric in room imaging that can minimize patient positioning inaccuracies. Images taken from a CBCT just prior to treatment can be overlaid on the original planning CT to detect positioning errors with millimeter accuracy (Fig. 7). It is reassuring to note that residual set-up uncertainty with volumetric imaging (CBCT or MVCT) have generally been very low for head-neck sites.^{86,87} A valid concern with daily CBCT as well as MVCT verification has been a modest increase (0.3–0.5 Gy) in dose over the entire duration of treatment.

Resource implications of introducing IMRT/IGRT in the clinic

While concerns have been raised regarding the resource-intensive nature of IMRT and IGRT, only a few actual studies have addressed this issue by measuring the additional time and human resource burden imposed by their introduction in clinical practice. One of the first such study⁸⁸, prospectively collected data on the planning, quality assurance, and treatment times on an initial group of HNC patients treated with IMRT. A comparative group of patients with advanced HNC undergoing 2- or 3-phase conventional radiotherapy planning, requiring matched photon and electron fields, was also timed. Although, overall 22 head-neck IMRT planning time (including contouring, planning and QA) was significantly longer (median 14.8 vs 10.4 h; $P < 0.001$) for IMRT, the median treatment delivery time per fraction was comparable (median 11.2 vs 12 min) to a conventional 2- or 3-phase HNC treatment encompassing volumes similar to IMRT. An overall reduction in

Fig. 6 Co-registration of planning kVCT (grayscale) with daily acquired MVCT images (light-blue) prior to delivery. Set-up errors in lateral, longitudinal, vertical directions (translational displacements) and rotational axis (roll) can be corrected by applying the shifts automatically

radiographer man hours per patient of 4.8 h was recorded whereas physics time was increased by 4.9 h per patient. In the most comprehensive assessment of time-manpower resource burden in HNC (related to immobilization, image-acquisition, contouring, planning, QA, verification, and delivery), Murthy et al.⁸⁹ demonstrated significantly longer overall person-hours for IMRT compared to 3D-CRT (48.5 vs 37.3 person-hours; $P < 0.001$), with most of this difference being due to increased daily delivery time per fraction for IMRT (median 0.9 vs 0.6 person-hours; $P < 0.001$) and additional patient-specific QA (done only in IMRT group). With an aim to measure the mean duration of treatment per fraction⁹⁰ associated with image-guided IMRT and impact of learning curve if any, time measurements were performed on Helical TomoTherapy

on a group of 72 patients initially and 27 patients later after 1 year (one-third were HNC patients). The average treatment time on TomoTherapy after clinical implementation was 25 min which was no different after 1 year negating any impact of a learning curve.

Future perspectives

Molecular-imaging guided IMRT

Although CT-based IMRT planning can still be considered the gold-standard, use of multi-modality imaging and fusion, particularly with FDG-PET/CT is coming into vogue. One distinct advantage of PET/CT in head-neck IMRT planning is the potential for improved tumor

delineation, reduced intra-observer and inter-observer variability leading to standardization of treatment volumes across individuals and institutions.⁹¹ Integrated PET/CT systems produce anatomic and metabolic images with the patient in the same position and during a single procedure, greatly simplifying image registration. Studies that have examined the role of FDG–PET/CT in the context of IMRT planning have concluded that there are substantial quantitative and qualitative differences between PET-derived and CT-derived tumor volumes in a significant proportion of patients.⁹¹ Recent reports of improved outcomes with PET/CT-guided IMRT^{92,93} in HNC, though encouraging, would need to be confirmed in a larger patient population before widespread adoption in clinical practice. With a better understanding of the molecular biology of cancer, there has been an increasing demand to develop novel PET tracers to image various aspects of cell biology. Novel non-FDG tracers⁹¹ include markers of hypoxia (18F-fluoromisonidazole, 64Cu-ATSM, 18F-fluoroazomycin-arabinofuranoside, and 18FEF5); tumor proliferation (18F-fluorothymidine); and amino acid metabolism (11C-methionine, 11C-tyrosine, and 18F-fluoroethyltyrosine). Integration of such contemporary molecular biology tools including functional

imaging with radiation therapy planning could provide a closer view of the biologic pathways involved in tumor initiation, progression, and radiation response that could be used for differential dosing. Theragnostic imaging⁹⁴ to individualize radiation dose prescription and delivery in four-dimensions including time has tremendous potential to emerge as the next paradigm in radiation oncology.

Adaptive radiation therapy

The current standard of radiation therapy planning involves obtaining a set of images prior to initiation of treatment. A plan is then generated on that dataset and delivered over a course of the next 6–7 weeks, with a possibility of significant changes in the patient's anatomy based on shrinkage of the primary tumor or involved lymph nodes and loss of overall body weight.⁹⁵ Application of the original plan to the now altered anatomy can significantly alter dose-distribution and dose-volume statistics to target volumes as well as OARs.⁹⁶ Adaptive radiotherapy allows for adaptation of the treatment plan in response to the changes that occur, to maximally spare normal tissues while maintaining complete coverage of the target volume. Medial translation of the parotid glands from tumor regression and patient weight loss tend to bring the parotids into higher dose regions thereby increasing mean parotid dose.^{97–99} Though the resultant increase in mean parotid dose may seem small and insignificant, parotid being a radiosensitive gland,¹⁰⁰ even small changes in dose can have a large impact (decrease of salivary function at a rate of 5% per 1 Gy increase in mean parotid dose). The anticipated benefits of adaptive radiotherapy are highly intuitive and desirable, but there are significant barriers and challenges to its widespread adoption.¹¹ First, it is unclear when and how often adaptive re-planning should be done. Attempts are underway to identify the optimal re-planning schedule, which must take into account the technical difficulties and the time required to create a new plan. Secondly, new technologies such as deformable image registration and robust auto-segmentation in conjunction with higher computational power will be necessary to facilitate easy re-planning. Finally, the additional resource-burden imposed by such adaptive strategies with modest clinical benefits would need appropriate justification for policy-makers and administrators.

Conclusion

IMRT has emerged as a revolutionary high-precision radiotherapy paradigm that increases the dose-gradient between target tissues and surrounding normal structures with tremendous potential to improve outcomes. Since, such techniques are relatively intolerant to set-up errors;

Fig. 7 (a) Automatic co-registration of planning CT with kV Cone-Beam CT on the treatment console showing a marginal set-up error (note the fine blurring in the fused area). (b) Same patient after applying online correction showing excellent soft-tissue and bony anatomy match

they should be complimented with IGRT, i.e. periodic volumetric image-guidance. Several challenges associated with the planning, delivery, and quality assurance of the IMRT and IGRT processes must be addressed to realize the full potential of such exciting and promising technology. Although, there is lack of adequately powered randomized controlled trials, the weight of evidence from large phase II prospective trials firmly supports the use of IMRT in conjunction with IGRT for a wide variety of cancers arising in the head-neck region. Despite relatively modest follow-up and limited clinical outcomes data, it is well appreciated that toxicity (both acute and late) is lesser with IMRT, while loco-regional control is either comparable or even better than conventional radiother-

apy, thereby resulting in potentially improved quality-of-life, prompting the widespread adoption of such technology in clinical practice. The resource-intensive nature of IMRT and IGRT demands increased labor, rigour, expenses, and mandates good coordination amongst the radiotherapy team. Recent advances in molecular imaging provide unique opportunities to unravel and understand biological pathways involved in initiation and progression of cancers. Data from recently concluded and ongoing trials in head-neck IMRT/IGRT addressing various issues pertaining to optimization of processes, theragnostic imaging, and adaptive re-planning, should be able to provide deeper insights to help improve outcomes in head-neck cancers.

References

1. Delany G, Jacob S, Barton M. Estimation of an optimal external beam radiotherapy utilization rate for head and neck carcinoma. *Cancer*. 2005;103:2216–2227.
2. Trotti A. Toxicities in head and neck cancers: a review of trends and issues. *Int J Radiat Oncol Biol Phys*. 2000;47:1–12.
3. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: A systemic literature review. *Radiother Oncol*. 2003;66:253–262.
4. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol*. 2008;26:3770–3776.
5. Bernier J, Hall AJ, Giaccia A. Radiation oncology: a century of achievements. *Nat Rev Cancer*. 2004;4:737–747.
6. Gregoire V, De Neve W, Eisbruch A, Lee N, Van den Weyngaert D, Van Gestel D. Intensity-modulated radiation therapy for head and neck carcinoma. *Oncologist*. 2007;12:555–564.
7. Intensity Modulated Radiation Therapy Collaborative Working Group. Intensity-modulated radiotherapy: Current status and issues of interest. *Int J Radiat Oncol Biol Phys*. 2001;51:880–914.
8. Ezzell GA, Galvin JM, Low D, Palta JR, Rosen I, Sharpe MB, et al. Guidance document on delivery, treatment planning, and implementation of IMRT: Report of the IMRT subcommittee of the AAPM Radiation Therapy committee. *Med Phys*. 2003;30:2089–2115.
9. Hartford AC, Palisca MG, Eichler TJ, Beyer DC, Devineni VR, Ibbot GS, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for Intensity-Modulated Radiation Therapy (IMRT). *Int J Radiat Oncol Biol Phys*. 2009;73:9–14.
10. Jaffray D, Kupelian P, Djemil T, Macklis RM. Review of image-guided radiation therapy. *Expert Rev Anticancer Ther*. 2007;7:89–103.
11. Nath SK, Simpson DR, Rose BS, Sandhu AP. Recent advances in image-guided radiotherapy for head and neck carcinoma. *J Oncol*. 2009;2009:752135.
12. Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. *J Clin Oncol*. 2006;24:2618–2623.
13. Veldeman L, Madani I, Hulstaert F, De Meerleer G, Mareel M, De Neve W. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. *Lancet Oncol*. 2008;9:367–375.
14. International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy. Bethesda, MD: ICRU;1993.
15. International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy (supplement to ICRU Report 50). Bethesda, MD: ICRU;1999.
16. Palta JR, Liu C, Li JG. Quality assurance of intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2008;71 (suppl): S108–S112.
17. Chao KS, Ozygit G, Tran B, Chengiz M, Dempsey JF, Low DA. Patterns of failure in patients receiving definitive and postoperative IMRT for head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2003;55:312–321.
18. Lee N, Xia P, Fischbein NJ, Akazawa P, Akazawa C, Quivey JM. Intensity-modulated radiation therapy for head-and-neck cancer: the UCSF experience focusing on target volume delineation. *Int J Radiat Oncol Biol Phys*. 2003;57:49–60.
19. Eisbruch A, Marsh LH, Dawson LA, Bradford CR, Teknos TN, Chepeha DB, et al. Recurrences near base of skull after IMRT for

- head and neck cancer: implications for target delineation in high neck and for parotid sparing. *Int J Radiat Oncol Biol Phys.* 2004;59:28–42.
20. Yao M, Dornfeld KJ, Buatti JM, Skwarchuk M, Tan H, Nguyen T, et al. Intensity-modulated radiation treatment for head-and-neck squamous cell carcinoma-the University of Iowa experience. *Int J Radiat Oncol Biol Phys.* 2005;63:410–421.
 21. Studer G, Huguenin PU, Davis JB, Kunz G, Lutolf UM, Glanzmann C. IMRT using simultaneous integrated boost (SIB) in head and neck cancer patients. *Radiat Oncol.* 2006;1:7.
 22. Schoenfeld GO, Amdur RJ, Morris CG, Li JG, Hinerman RW, Mendenhall WM. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2008;71:377–385.
 23. Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: An update of the UCSF experience. *Int J Radiat Oncol Biol Phys.* 2002;53:12–22.
 24. Chong Z. Improved local control with intensity-modulated radiation therapy in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2004;60 (suppl): S317
 25. Bucci M, Xia P, Lee N, Fishbein N, Kramer A, Weinberg V, et al. Intensity-modulated radiation therapy for carcinoma of the nasopharynx: An update of the UCSF experience. *Int J Radiat Oncol Biol Phys.* 2004; 60 (suppl):S317–S318.
 26. Zhao C, Lu L, Han F, Huang S, Lin C, Deng T, et al. Preliminary results of Intensity modulated radiotherapy alone for 122 patients with untreated nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2005;63 (suppl):S382.
 27. Kam MK, Teo PM, Chau RM, Cheung KY, Choi PH, Kwan WH, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: The Hong Kong experience. *Int J Radiat Oncol Biol Phys.* 2004;60:1440–1450.
 28. Kwong DL, Pow EH, Sham JS, McMillan AS, Leung LHT, Leung WK, et al. Intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: A prospective study on disease control and preservation of salivary function. *Cancer* 2004;101:1584–1593.
 29. Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: Update of the Memorial Sloan-Kettering experience. *Int J Radiat Oncol Biol Phys.* 2006;64:57–62.
 30. Fang FM, Chien CY, Tsai WL, Chen HC, Hsu HC, Lui CC, et al. Quality of life and survival outcome for patients with nasopharyngeal carcinoma receiving three-dimensional conformal radiotherapy vs intensity-modulated radiotherapy – a longitudinal study. *Int J Radiat Oncol Biol Phys.* 2008; 72:356–364.
 31. Chao KS, Ozyigit G, Blanco AI, Thorstad WL, Deasy JO, Haughey BH, et al. Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. *Int J Radiat Oncol Biol Phys.* 2004;59:43–50.
 32. Lee NY, de Arruda FF, Puri DR, Wolden SL, Narayana A, Mechalakos J, et al. A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;66:966–974.
 33. de Arruda FF, Puri DR, Zhung J, Narayana A, Wolden S, Hunt M, et al. Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: The Memorial Sloan-Kettering Cancer Center experience. *Int J Radiat Oncol Biol Phys.* 2006;64:363–373.
 34. Garden AS, Morrison WH, Wong PF, Tung SS, Rosenthal DI, Dong L, et al. Disease-control rates following intensity-modulated radiation therapy for small primary oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2007;67:438–444.
 35. Huang K, Xia P, Chuang C, Weinberg V, Glastonbury CM, Eisele DW, et al. Intensity-modulated chemo-radiation for treatment of stage III–IV oropharyngeal carcinoma. *Cancer.* 2008;113:497–507.
 36. Sanguineti G, Brandon Gunn G, Endres EJ, Chaljub G, Cheruvu P, Parker B. Patterns of loco-regional failure after exclusive IMRT for oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2008; 72:737–746.
 37. Daly ME, Le QT, Maxim PG, Loo BW, Kaplan MJ, Fischbein NJ, et al. Intensity-modulated Radiotherapy in the Treatment of Oropharyngeal Cancer: Clinical Outcomes and Patterns of Failure. *Int J Radiat Oncol Biol Phys.* 2009 (in press).
 38. Studer G, Zwahlen RA, Graetz KW, Davis BJ, Glanzmann C. IMRT in oral cavity cancer. *Radiat Oncol.* 2007;2:16.
 39. Yao M, Chang K, Funk GF, Lu H, Tan H, Wacha J, et al. The failure patterns of oral cavity squamous cell carcinoma after intensity-modulated radiotherapy – the University of Iowa experience. *Int J Radiat Oncol Biol Phys.* 2007;67:1332–1341.
 40. Studer G, Lutolf UM, Davis JB, and Glanzmann C. IMRT in hypopharyngeal tumors. *Strahlenther Onkol.* 2006;182:331–335.
 41. Lee NY, O'Meara W, Chan K, Della-Bianca C, Mechalakos JG, Zhung J, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for loco-regionally advanced laryngeal and hypopharyngeal cancers. *Int J Radiat Oncol Biol Phys.* 2007;69:459–468.
 42. Claus F, Boterberg T, Ost P, De Neve W. Short term toxicity profile for 32 sino-nasal tumors patients treated with IMRT: Can we avoid dry eye syndrome? *Radiation Oncol.* 2002;64: 205–208.
 43. Duthoy W, Boterberg T, Claus F, Ost P, Vakaet L, Bral S, et al. Post-operative intensity-modulated radiotherapy in sino-nasal carcinoma: Clinical results in 39 patients. *Cancer* 2005;104:71–82.
 44. Combs SE, Konkel S, Schulz-Ertner D, Munter MW, Debus J, Huber PE, et al. Intensity-modulated radiotherapy (IMRT) in patients with carcinomas of the paranasal sinuses: Clinical benefit for complex shaped target volumes. *Radiat Oncol.* 2006;1:23.

45. Chen AM, Daly ME, Bucci MK, Xia P, Akazawa C, Quivey JM, et al. Carcinomas of the paranasal sinuses and nasal cavity treated with radiotherapy at a single institution over five decades: Are we making improvement? *Int J Radiat Oncol Biol Phys.* 2007;69:141–147.
46. Daly ME, Chen AM, Bucci MK, El-Sayed I, Xia P, Laplan MJ, et al. Intensity-modulated radiation therapy for malignancies of the nasal cavity and paranasal sinuses. *Int J Radiat Oncol Biol Phys.* 2007;67:151–157.
47. Hoppe BS, Stegman LD, Zelefsky MJ, Rosenzweig KE, Wolden SL, Patel SG, et al. Treatment of nasal cavity and paranasal sinus cancer with modern radiotherapy techniques in the postoperative setting—The MSKCC experience. *Int J Radiat Oncol Biol Phys.* 2007;67:691–702.
48. Dirix P, Nuyts S, Vanstraelen B, Nulens A, Hermans R, Jorissen M, et al. Postoperative intensity-modulated radiotherapy for malignancies of the nasal cavity and paranasal sinuses. *Radiother Oncol.* 2007;69:1042–1050.
49. Madani I, Bonte K, Vakaet L, Boterberg T, De Neve W. Intensity-modulated radiotherapy for sinonasal tumors: Ghent University Hospital update. *Int J Radiat Oncol Biol Phys.* 2009;73:424–432.
50. Lu TX, Mai WY, Teh BS, Zhao C, Han F, Huang Y, et al. Initial experience using intensity-modulated radiotherapy for recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2004;58:682–687.
51. Biagioli M, Harvey M, Roman E, Racz LE, Wolfson AH, Mutyala S, et al. Intensity-modulated radiotherapy with concurrent chemotherapy for previously irradiated, recurrent head and neck cancers. *Int J Radiat Oncol Biol Phys.* 2007;69:1067–1073.
52. Lee N, Chan K, Bekelman JE, Zhung J, Mechalakos J, Narayana A, et al. Salvage re-irradiation for recurrent head and neck cancers. *Int J Radiat Oncol Biol Phys.* 2007;68:731–740.
53. Sulman EP, Schwartz DL, Le TT, Ang KK, Morrison WH, Rosenthal DI, et al. IMRT re-irradiation for head and neck cancers: disease control and morbidity outcomes. *Int J Radiat Oncol Biol Phys.* 2009;73:399–409.
54. Duprez F, Madani I, Bonte K, Boterberg T, Vakaet L, Derie C, et al. Intensity-modulated radiotherapy for recurrent and second primary head and neck cancer in previously irradiated territory. *Radiother Oncol.* 2009;93:563–569.
55. Madani I, Vakaet L, Bonte K, Boterberg T, De Neve W. Intensity-modulated radiotherapy for cervical lymph node metastasis from unknown primary cancer. *Int J Radiat Oncol Biol Phys.* 2008;71:1158–1166.
56. Klem ML, Mechalakos JG, Wolden SL, Zelefsky MJ, Singh B, Kraus D, et al. Intensity-modulated radiotherapy for head neck cancer of unknown primary: toxicity and preliminary efficacy. *Int J Radiat Oncol Biol Phys.* 2008;70:1100–1107.
57. Lu H, Yao M, Tan H. Unknown primary head and neck cancer treated with intensity-modulated radiotherapy: to what extent the volume should be irradiated. *Oral Oncol.* 2009;45:474–479.
58. Rosenbluth BD, Serrano V, Happersett L, Shaha AR, Tuttle MR, Narayana A, et al. Intensity-modulated radiotherapy for the treatment of non-anaplastic thyroid cancer. *Int J Radiat Oncol Biol Phys.* 2005;63:1419–1426.
59. Urbano TG, Clark CH, Hansen VN, Adams EJ, Miles EA, Nair HM, et al. Intensity modulated radiotherapy (IMRT) in locally advanced thyroid cancer: acute toxicity results of a Phase I study. *Radiother Oncol.* 2007;85:58–63.
60. Schwartz DL, Lobo MJ, Ang KK, Morrison WH, Rosenthal DI, Ahamad A, et al. Postoperative external beam radiotherapy for differentiated thyroid cancer: Outcome and morbidity with conformal therapy. *Int J Radiat Oncol Biol.* 2009;74:1083–1091.
61. Eisbruch A, Harris J, Garden AS, Chao CKS, Straube W, Harari PM, et al. Multiinstitutional trial of accelerated hypofractionated intensity modulated radiation therapy for early oropharyngeal cancer (RTOG-00-22). *Int J Radiat Oncol Biol Phys.* 2009 (in press).
62. Lee N, Harris J, Garden AS, Straube W, Glissin B, Xia P, et al. Intensity-modulated radiotherapy with or without chemotherapy for nasopharyngeal carcinoma: Radiation Therapy Oncology Group phase II trial 0225. *J Clin Oncol.* 2009;27:3684–3690.
63. Lin S, Pan J, Han L, Zhang X, Liao X, and Lu JJ. Nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy: report on the 3-year outcome of a prospective series. *Int J Radiat Oncol Biol Phys.* 2009;75:1071–1078.
64. Zhang Y, Lin ZA, Pan JJ, Zheng Z, Yang L, Lin SJ, et al. Concurrent control study of different radiotherapy for primary nasopharyngeal carcinoma intensity modulated radiotherapy versus conventional radiotherapy. *Chin J Cancer* 2009;28:1143–1148.
65. Vergeer MR, Doornaert PA H, Rietveld DHF, Leemans CR, Slotman BJ, Langendijk JA. Intensity-modulated radiotherapy reduces radiation induced morbidity and improves health related quality of life: results of a non-randomized prospective study using standardized follow-up program. *Int J Radiat Oncol Biol Phys.* 2009;74:1–8.
66. Pow EHN, Kwong DLW, Macmillan AS, Wong MCM, Sham JST, Leung LHT, et al. Xerostomia and quality of life after intensity modulated radiotherapy vs conventional radiotherapy for early-stage nasopharyngeal carcinoma. Initial report on a randomized controlled trial. *Int J Radiat Oncol Biol Phys.* 2006;66:981–991.
67. Kam MKM, Leung SF, Zee B, Chau RMC, Suen JSJ, Mo F, et al. Prospective randomized study of intensity modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. *J Clin Oncol* 2007;25:4873–4879.
68. Nutting C, A'Hern R, Rogers MS, Sydenham MA, Adab F, Harrington K, et al. First results of a phase III multicentre randomized controlled trial of intensity modulated

- (IMRT) versus conventional radiotherapy (RT) in head and neck cancer (PARSPORT: ISRCTN 48243537; CRUK/03/005). *J Clin Oncol* 2009;27:s18(suppl; abstr LBA6006).
69. Nangia S, Chufal KS, Tyagi A, Bhatnagar A, Mishra M, Ghosh D. Selective nodal irradiation for head and neck cancer using intensity-modulated radiotherapy: application of RTOG consensus guideline in routine clinical practice. *Int J Radiat Oncol Biol Phys*. 2010; 76:146–153.
 70. Grégoire V, Levendag P, Ang KK, Bernier J, Braaksma M, Budach V, et al. CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines. *Radiother Oncol*. 2003;69:227–236.
 71. Gregoire V, Eisbruch A, Hamoir M, Levandag P. Proposal for the delineation of the nodal CTV in the node-positive and post-operative neck. *Radiother Oncol*. 2006;79: 15–20.
 72. Cannon DM, Lee NY. Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head neck cancer. *Int J Radiat Oncol Biol Phys*. 2008;70:660–665.
 73. Lee N, Mechalakos J, Puri DR, Hunt M. Choosing an intensity-modulated radiation therapy technique in the treatment of head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2007;68:1299–1309.
 74. Longobardi B, De ME, Fiorino C, Dellocia I, Broggi S, Cattaneo GM, Calandrino R. Comparing 3D-CRT and inversely optimized IMRT planning for head and neck cancer: equivalence between step-and-shoot and sliding window technique. *Radiother Oncol*. 2005;77:148–56.
 75. Chui CS, Chan MF, Yorke E, Spirou S, Ling CC. Delivery of intensity-modulated radiation therapy with a conventional multi-leaf-collimator: comparison of dynamic and segmental methods. *Med Phys*. 2001;28:2441–2449.
 76. Chen AM, Jennelle RL, Sreeraman R, Yang CC, Liu T, Vijayakumar S, et al. Initial clinical experience with helical tomotherapy for head and neck cancer. *Head Neck* 2009;31:1571–1578.
 77. Vanetti E, Clivo A, Nicolini G, Fogliata A, Ghosh-Laskar S, Agarwal JP, et al. Volumetric modulated arc radiotherapy for carcinomas of the oro-pharynx, hypopharynx and larynx: A treatment planning comparison with fixed-field IMRT. *Radiother Oncol*. 2009;92:111–117.
 78. Bedford JL. Treatment planning for volumetric modulated arc therapy. *Med Phys*. 2009;36:5128–5138.
 79. Ho KF, Fowler JF, Sykes AJ, Yap BK, Lee LW, Slevin NJ. IMRT dose fractionation for head neck cancer: variation in current approaches will make standardization difficult. *Acta Oncol*. 2009;48:431–439.
 80. Chan AW and Liebsch NJ. Proton radiation therapy for head and neck cancer. *J Surg Oncol*. 2008;97:697–700.
 81. Douglas JG, Koh WJ, Austin-Seymour M, Laramore GE. Treatment of salivary gland neoplasms with fast neutron radiotherapy. *Arch Otolaryngol Head Neck Surg*. 2003;129:944–948.
 82. Siddiqui F, Patel M, Khan M, McLean S, Dragovic J, Jin JY, et al. Stereotactic body radiation therapy for primary, recurrent, and metastatic tumors in the head and neck region. *Int J Radiat Oncol Biol Phys*. 2009;74:1047–1053.
 83. Rwigyema JC, Heron DE, Ferris RL, Gibson M, Quinn A, Yang Y, et al. Fractionated stereotactic body radiation therapy in the treatment of previously-irradiated recurrent head and neck carcinoma: Updated report of the university of Pittsburgh experience. *Am J Clin Oncol*. 2009 (in press).
 84. Roh KW, Jang JS, Kim MS, Sun DI, Kim BS, Jung SL, et al. Fractionated stereotactic radiotherapy as re-irradiation for locally recurrent head and neck cancers. *Int J Radiat Oncol Biol Phys*. 2009; 74:1348–1355.
 85. Gupta T, Chopra S, Kadam A, Agarwal JP, Devi PR, Ghosh-Laskar S, et al. Assessment of three-dimensional set-up errors in conventional head and neck radiotherapy using electronic portal imaging device. *Radiat Oncol*. 2007;2:44.
 86. Zeidan OA, Langen KM, Meeks SL, Manon RR, Wagner TH, Willoughby TR, et al. Evaluation of image-guided protocols in treatment of head and neck cancers. *Int J Radiat Oncol Biol Phys*. 2007; 67:670–677.
 87. Schubert LK, Tome WA, Meheta MP, Soisson ET, Mackie TR, Ritter MA, et al. A comprehensive assessment by tumor site of patient set-up using daily MVCT imaging from more than 3,800 helical tomotherapy treatments. *Int J Radiat Oncol Biol Phys*. 2009;73:1260–1269.
 88. Miles EA, Clark CH, Urbano MT, Bidmead EA, Dearnaley DP, Harrington KJ, et al. The impact of introducing intensity-modulated radiotherapy into routine clinical practice. *Radiother Oncol* 2005;77:241–246.
 89. Murthy V, Gupta T, Kadam A, Ghosh-Laskar S, Budrukkar A, Phurailatpam R, et al. Time trial: A prospective comparative study of the time-resource burden for three-dimensional conformal radiotherapy and intensity-modulated radiotherapy in head and neck cancers. *J Can Res Ther*. 2009;5:107–112.
 90. Bijdekerke P, Verellen D, Tournel K, Vinh-Hung V, Somers F, Bieseman P, et al. Tomotherapy: implications on daily workload and scheduling patients. *Radiother Oncol*. 2008;86:224–230.
 91. Ford EC, Herman J, Yorke E, Wahl RL. 18F-FDG PET/CT for image-guided and intensity-modulated radiotherapy. *J Nucl Med*. 2009;50: 1655–1665.
 92. Rothschild S, Studer G, Seifert B, Huguenin P, Glanzmann C, Davis JB, et al. PET/CT staging followed by Intensity-Modulated Radiation Therapy (IMRT) improves treatment outcome of locally advanced pharyngeal carcinoma: a matched-pair comparison. *Radiat Oncol*. 2007;2:22.
 93. Vernon MR, Maheshwari M, Schultz CJ, Michel Michelle A, Wong SJ, Campbell BH, et al. Clinical outcomes of patients receiving integrated PET/CT-guided radiotherapy for head and neck

- carcinoma. *Int J Radiat Oncol Biol Phys.* 2008;70:768–684.
94. Bentzen SM. Dose painting and theragnostic imaging: biologically targeted dose distributions in external beam radiation oncology. *Cancer Treat Res.* 2008;139:41–62.
95. Barker JL, Garden AS, Ang KK, O'Daniel JC, Wang H, Court LE, et al. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/Linear accelerator system. *Int J Radiat Oncol Biol Phys.* 2004;59: 960–970.
96. Hansen EK, Bucci MK, Quivey JM, Weinberg V, Xia P. Repeat CT imaging and re-planning during the course of IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2006;64:355–362.
97. Kuo YC, Wu TH, Chung TS, Huang KW, Chao KS, Su WC, et al. Effect of regression of enlarged neck lymph nodes on radiation doses received by parotid glands during intensity-modulated radiotherapy for head-and-neck cancer. *Am J Clin Oncol.* 2006;29:600–605.
98. O'Daniel JC, Garden AS, Schwartz DL, Wang H, Ang KK, Ahamad A, et al. Parotid gland dose in intensity-modulated radiotherapy for head and neck cancer: is what you plan what you get? *Int J Radiat Oncol Biol Phys.* 2007;69:1290–1296.
99. Lee C, Langen KM, Lu W, Haimerl J, Schnarr E, Ruchala KJ, et al. Assessment of parotid gland dose changes during head and neck cancer radiotherapy using daily megavoltage computed tomography and deformable image registration. *Int J Radiat Oncol Biol Phys.* 2008;71: 1563–1571.
100. Blanco AI, Chao KS, EI Naqa I, Franklin GE, Zakarian K, Vicic M, et al. Dose-volume modeling of salivary function in patients with head-and-neck cancer receiving radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005;62:1055–1069.