Clinical trials on Precision Radiotherapy in Head and Neck Carcinoma

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INTRODUCTION

- Radiotherapy is the main non-surgical treatment for squamous-cell carcinoma of the head and neck (HNSCC).

- High rates of local tumour control can be achieved :
- stage 1 and 2 == 5-year survival > 80% for
- stage 3 and 4 == 5-year survival 60–70%;

- However, long-term late sequelae of radiotherapy are highly prevalent and have severe adverse effects on quality of life (QoL).

- Radiation-induced xerostomia is the most commonly reported late side-effect of radiotherapy to the head and neck. Lack of saliva affects speech and swallowing and can accelerate dental caries.

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Acute effects

During treatment

Skin	**Erythema -desquamation**
Xerostomia	**Aqueous - Tenuous - Dry**
Mucositis	**erythema - mouth ulcers**
Dysphagia	**liquid diet - NGT & PEG**
Odynophagia	**pain requiring morphine**
Otitis	**Erythema – infection**
Taste	**altered sensation**
Fatigue	**minor to rehabilitating**

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Late effects

- Xerostomia
- Tissue fibrosis
- Osteoradionecrosis
- Telangiectasia
- Edema

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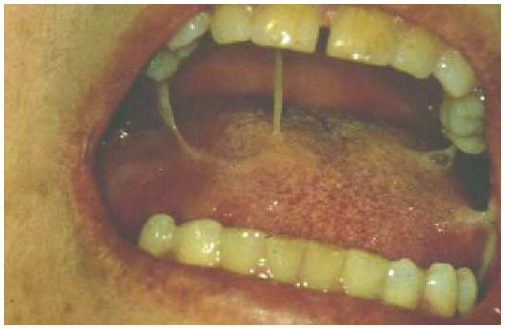
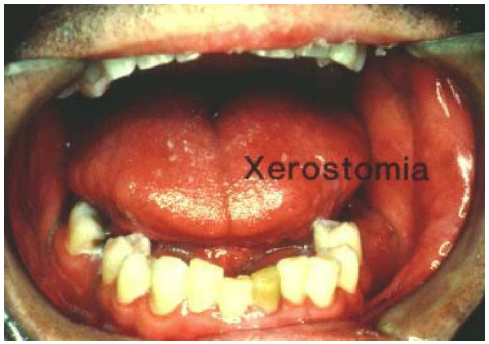
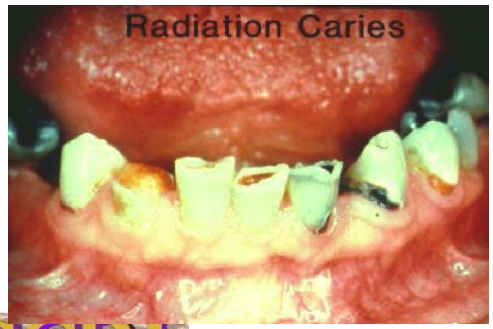


DRY MOUTH

Xerostomia can take form of thick saliva



Or total lack of salivation



Radiation Caries

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Paradigm Shift in Cancer Mx

Surgery	Chemotherapy	Radiotherapy
Radical	Nil	Wide Field
Conservative	H Dose	Involved F
NIL ?	Targeted	Conformal

ERA OF RADICAL TREATMENT GONE

Clinical Oncology 23 (2011) 613–624

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.elsevier.com/locate/clon

Original Article

The Impact of Clinical Factors on the Development of Late Radiation Toxicity: Results from the Medical Research Council RT01 Trial (ISRCTN47772397)

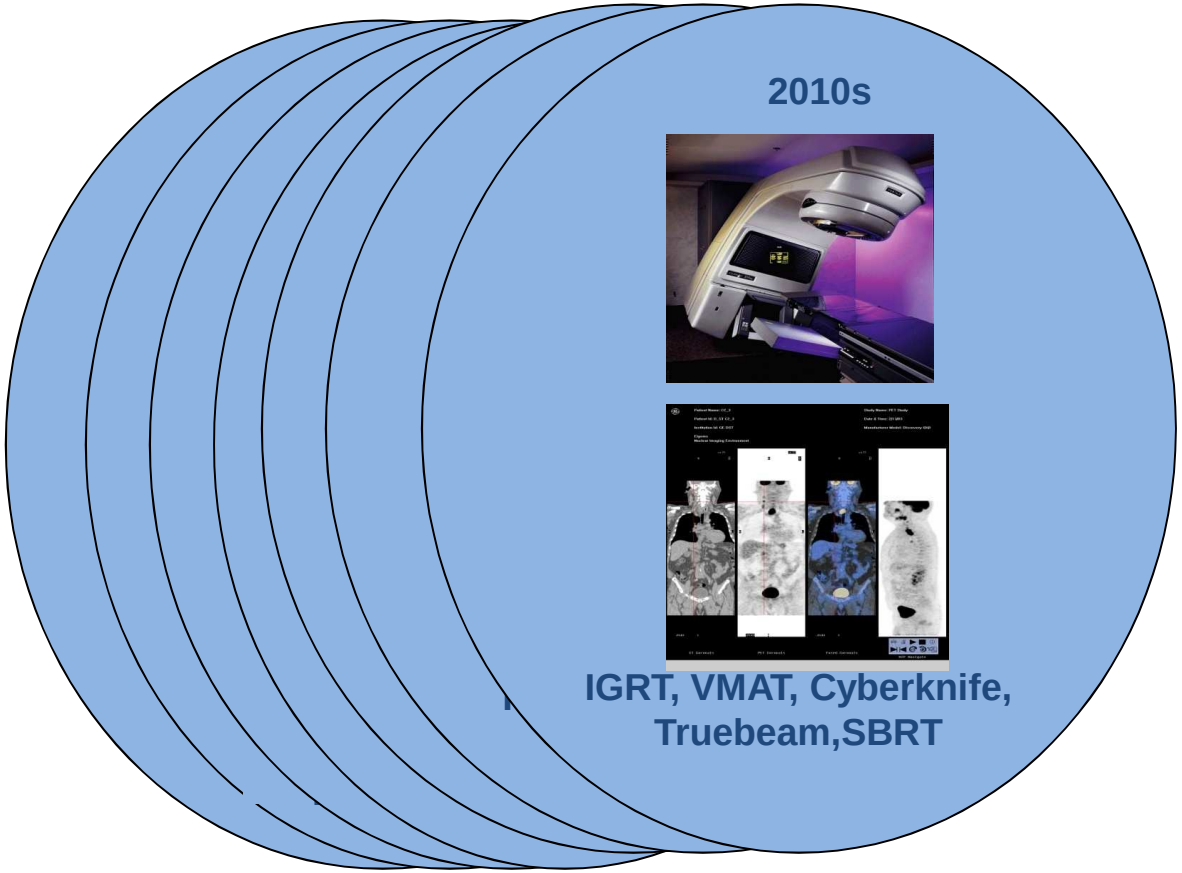
G.C. Barnett *†, G. De Meerleer ‡, S.L. Gulliford §, M.R. Sydes ||, R.M. Elliott ¶, D.P. Dearnaley **

- It is known that radiotherapy dosimetric factors, such as total dose, dose per fraction, volume irradiated, irradiation site and dose inhomogeneity, influence the development of late radiation toxicity

- Other factors, either environmental or genetic, may also predispose patients to the development of late toxicity. Examples of such factors include additional treatment (e.g. the use of systemic treatment or surgery) and patient characteristics (age,smoking history, body mass index, haemoglobin level & co-morbid conditions, such as DM, HT, vascular and connective tissue diseases)

The changing paradigm

Wide field radiation ***Conformal radiation***



Optimal Dose Delivery

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I M R T - Target volume

- IMRT requires a thorough understanding of target delineation in the complex H&N

- IMRT is a process
  - Planning
  - Information Transfer
  - Delivery
  - Verification

- IMRT allows you to customize your treatment delivery based on a specific planning objective

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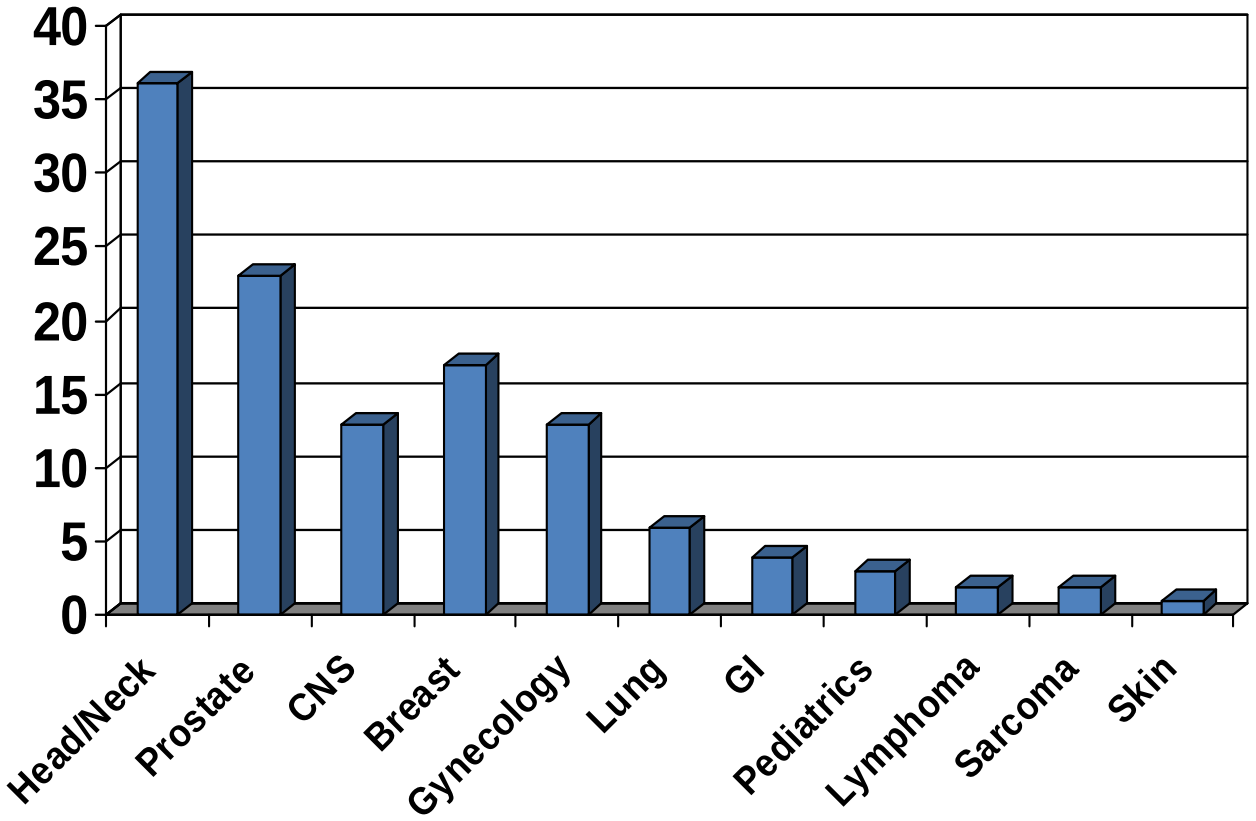
IMRT Clinical Studies



August 2002 Review of the Literature

Arno Mundt MD, University of Chicago

Rationale of IMRT in H & N Cancer

1. Anatomically complex H&N region
   - *an ideal option - IMRT.*
2. Lack of organ motion in the H&N region
   - *an ideal region for IMRT.*
3. Allows for dose escalation
   - *concomitant boost – ideal for H&N*

Steps of IMRT in H&N Ca …

Clinical Assessment…

- Pretreatment dental consultation
  - Extraction of bad teeth
  - Initiation of prophylactic fluoride therapy.
- Pretreatment ophthalmology and audiology consults
- Thyroid function tests baseline.
- Review of imaging studies and further workup

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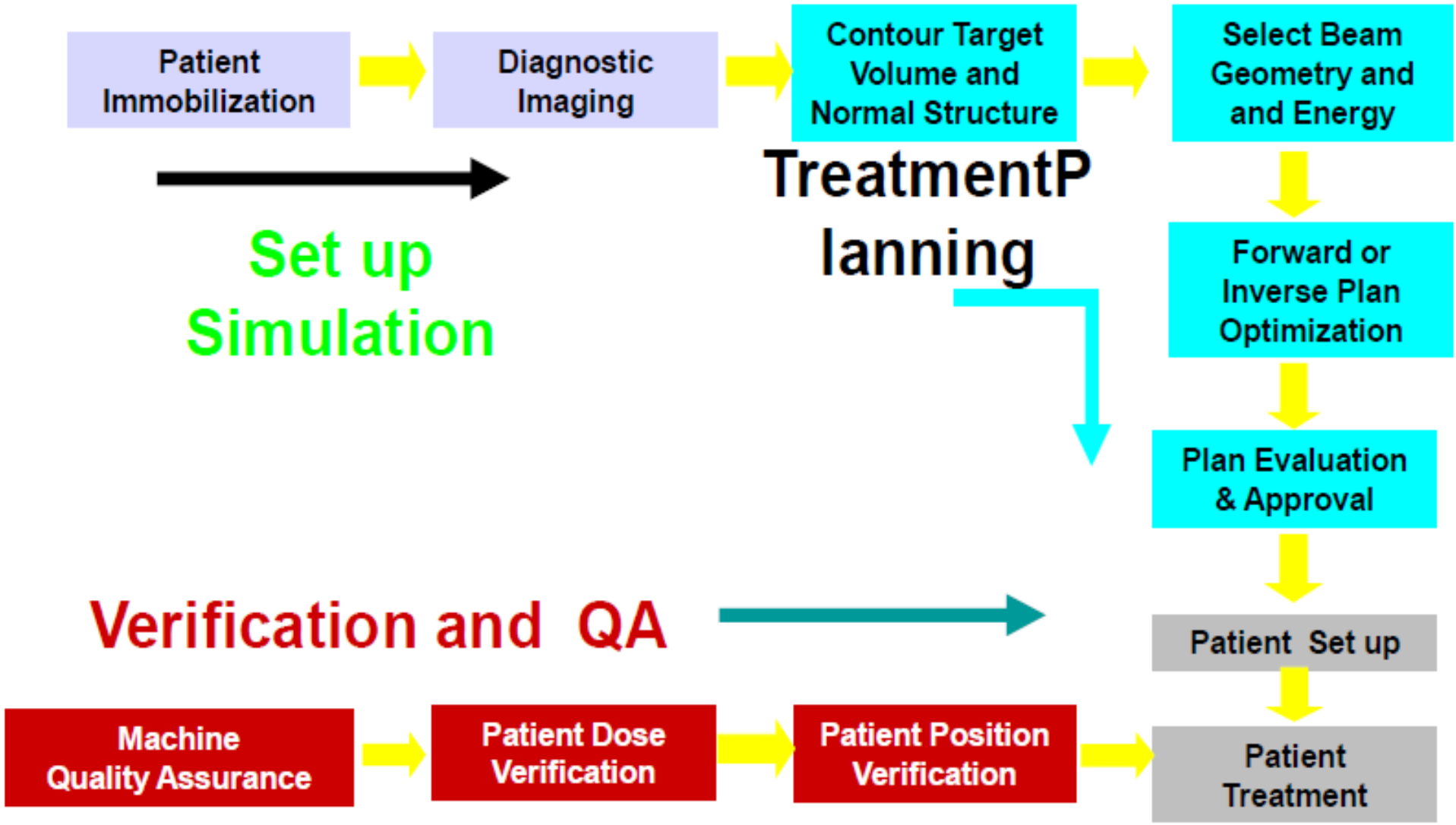
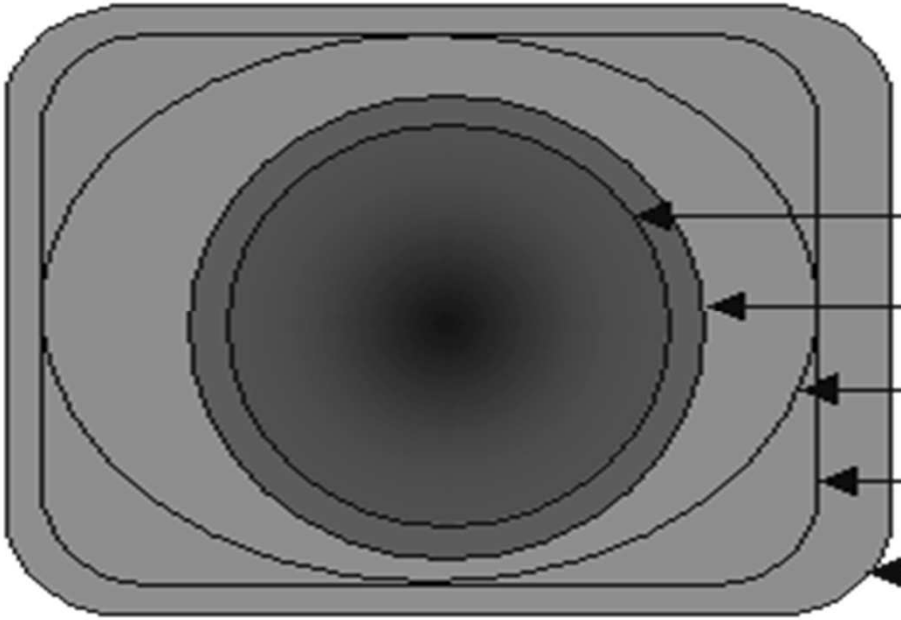
RADIOTHERAPY PROCESS



Target volume(s) should follow the recommendations of ICRU Reports 50 and 62.



GTV - Imaging and examination based
CTV - GTV + 7 mm margin
PTV - CTV + 5 mm margin

Gross Tumor Volume
Clinical Target Volume
Planning Target Volume
Treated Volume
Irradiated Volume

TABLE 1. Common Terminology Used in Radiation Therapy

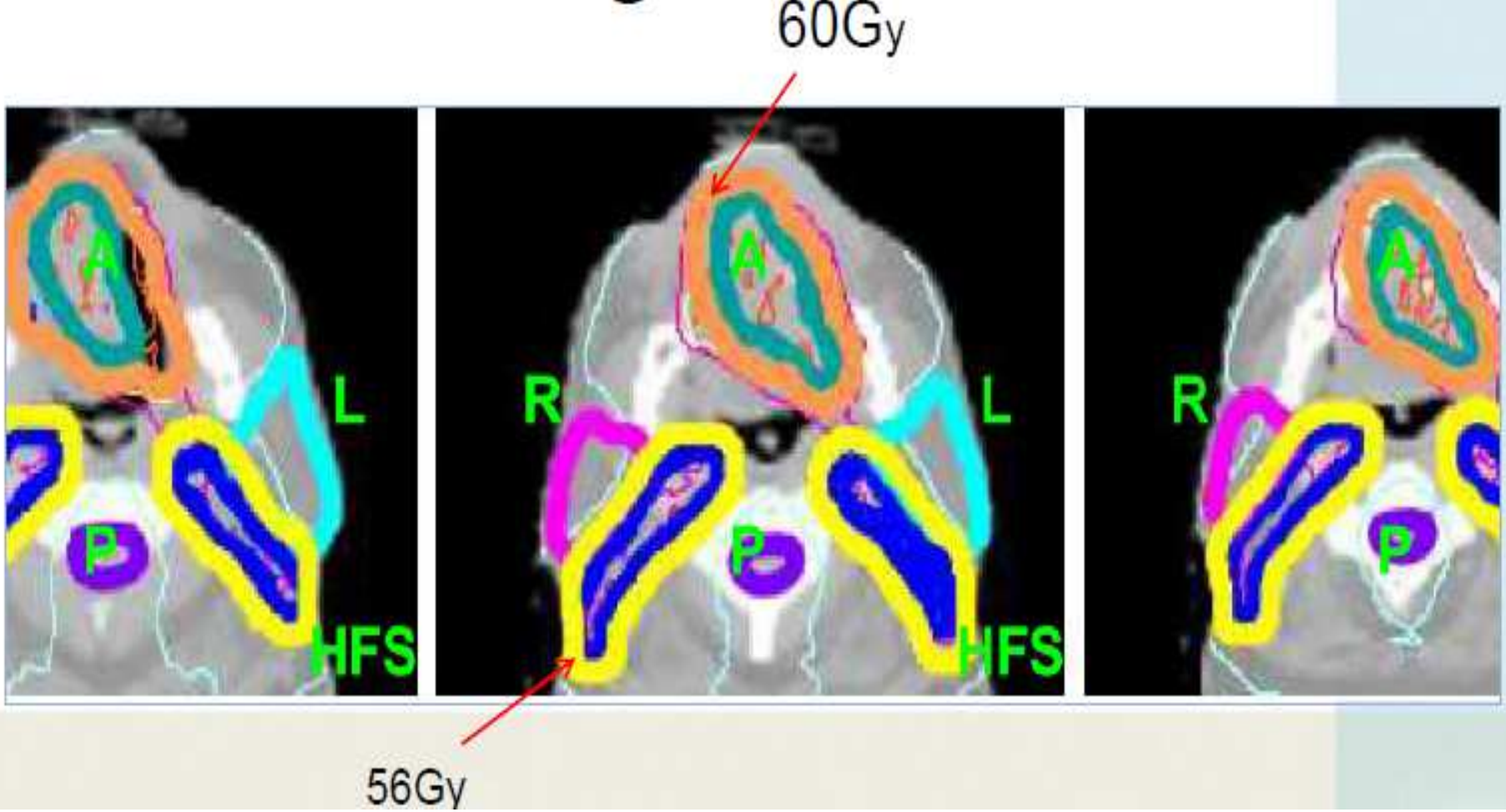
Term	Definition
Gross tumor volume (GTV)	Macroscopic tumor volume as detected by clinical examination and anatomic imaging (ultrasound, CT, MRI, PET)
Clinical target volume	GTV with margin added for subclinical microscopic spread
Planning target volume	Clinical target volume with margin added for organ motion and setup inaccuracy
Treatment volume	Tissue volume treated to substantial radiation dose (typically larger than planning target volume)
Metabolic tumor volume	Metabolically active tumor volume as detected by biologic imaging, for example, ^{18}F-FDG PET
Hypoxic tumor volume	Hypoxic tumor volume as detected by biologic imaging, that is, hypoxia or hypoxia-related PET tracers (^{18}F-FMISO, ^{18}F-fluoroazomycin arabinoside, ^{18}F-fluoroerythronitroimidazole), or blood oxygen level-dependent MRI

Prescription for Head Neck IMRT

- 95% prescription dose to cover 98% of high dose PTV
- Prescription dose to cover at least 91% of high dose PTV
- 95% dose to cover at least 95% of low risk PTV
- Avoid hotspots >107%
- Parotid
- PRV Spine
- Mandible

Treatment Planning in the IMRT Era

- "Dose Painting"



History

Eisbruch et al. (1998) reported on their use of IMRT in 15 patients with stage III/IV head and neck cancer requiring bilateral neck irradiation. The minimum primary planning target volume (PTV) dose in the IMRT plans was higher than that in the standard plans (95.2% and 91% of the prescribed dose, respectively); coverage of the ipsilateral jugular nodes was also improved, but coverage of the contralateral jugular or posterior neck nodes was similar to conventional treatment. With respect to the normal critical structures, both the magnitude of dose and the volume in the high-dose regions decreased with IMRT. The mean dose to all major salivary glands, particularly the contralateral parotid gland, was much lower. It was noted that despite the normal tissue sparing, the tumor target coverage was not compromised.

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History

Preliminary results of a retrospective study on the first 28 head and neck cancer patients treated with IMRT at Baylor College of Medicine was reported by Kuppersmith et al. (1999). The

The article highlighted the following clinical capabilities of IMRT: (1) decreased normal tissue doses during re-irradiation of previously treated patients; (2) cranial nerves could be traced to the base of skull while minimizing the dose to the parotid glands and other surrounding structures; varying doses could be administered to the primary site as opposed to the cranial nerves; (3) multiple targets could be treated simultaneously with an accelerated course and once-a-day fractionation while minimizing doses to adjacent normal structures. This technique was referred to as Simultaneous Modulated Accelerated Radiation Therapy (SMART).

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The SMART technique was used between January 1996 and December 1997 on 28 patients to treat various primary head and neck sites including oropharynx, nasopharynx, larynx, oral cavity, and sphenoid sinus (Butler et al. 1999).

Chao et al. (2000) implemented tomotherapy-based IMRT

Sultanem et al. (2000) reviewed the experience with IMRT in the treatment of nasopharyngeal carcinoma at the University of California, San Francisco. Thirty-five patients were treated: 4 (12%)

authors concluded that IMRT improved the target coverage, increased GTV dose, and improved sparing of the adjacent normal critical structures. Locoregional control for patients receiving concurrent chemotherapy was excellent.

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The advantage of IMRT is that, it spares the important vital structures such as salivary gland, mucosa of digestive tract, optic nerves, pharyngeal constrictors, brain stem and spinal cord. It also spares the oral and hypopharyngeal muscles which helps in normal deglutition and hence reduces radiation induced dysphagia. The ability of IMRT to spare cochlea reduces the incidence of radiation induced loss of hearing.[6] The highly conformal dose distributions attained by IMRT could improve tumor control rates in advanced cases, particularly those arising from the nasopharynx and sino-nasal regions because they facilitate the delivery of high doses to the tumor that is closely related to adjoining critical organs like the brainstem and optic nerves, without exceeding the normal tissue tolerance.[10]

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Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 4, pp. 981–991, 2006

0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2006.06.013

CLINICAL INVESTIGATION **Head and Neck**

XEROSTOMIA AND QUALITY OF LIFE AFTER INTENSITY-MODULATED RADIOTHERAPY VS. CONVENTIONAL RADIOTHERAPY FOR EARLY-STAGE NASOPHARYNGEAL CARCINOMA: INITIAL REPORT ON A RANDOMIZED CONTROLLED CLINICAL TRIAL

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Purpose: To compare directly the effect of intensity-modulated radiotherapy (IMRT) vs. conventional radiotherapy (CRT) on salivary flow and quality of life (QoL) in patients with early-stage nasopharyngeal carcinoma (NPC).

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The SF-36 comprises 35 statements divided into eight subscales: physical functioning, social functioning, role limitation-physical, role limitation-emotional, mental health, vitality, pain, and general health perception; one statement asks respondents to compare current health status with 1 year previously (26). For each subscale, raw data are transformed and summed on a 0–100 scale with a higher score indicating better health state. The SF-36 scale has been translated and validated for use in Hong Kong (27).

The EORTC QLQ-C30 (+3) questionnaire has 33 statements on QoL issues relevant to cancer patients (28–30). It comprises five multi-item functional scales: physical, role, emotional, cognitive, and social functioning; three symptom scales (fatigue, pain, nausea/vomiting); a global QoL scale; and six single items measuring additional symptoms/problems including dyspnea, sleep disturbances, and financial impact. All scales and single questions are scored on a categorical scale and numerically transformed to a score of 1–100.

The EORTC QLQ-H&N35 was designed for use in head-and-neck cancer patients (31). It comprises 35 questions assessing symptoms and side effects of treatment. There are seven multi-item scales assessing pain, swallowing, senses, speech, social eating, social contact, and sexuality, and 11 single items about teeth, mouth opening, dry mouth, sticky saliva, and coughing. The scales and single questions are scored on a categorical scale and numerically transformed to a score of 1–100. For EORTC core and H&N35 measures, a high score in functional scales and global QoL is indicative of high/healthy level of functioning, whereas for symptom scales/items, a high score indicates a high level of symptoms/problems. Translated versions of the EORTC core and H&N35 measures for use in Taiwan and Hong Kong were used (28).

Head and neck cancer related QOL questionnaire

Communication

- Talk to others
- Talk on phone
- Problems with clarity of voice
- Problems with volume of voice

Pain

- Shoulder or neck pain
- General physical problems
- Pain in mouth
- Frequency of use of pain medicines

Eating

- Problems chewing
- Dryness while eating
- Problems with taste
- Problems swallowing soft foods / solids
- Problems swallowing liquids
- Problems opening the mouth

Emotion

- Embarrassment about condition
- Concerns about appearance
- Emotional problems
- Financial worries
- Worry that condition will get worse
- Frustration about condition

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Methods and Materials: Fifty-one patients with T2, N0/N1, M0 NPC took part in a randomized controlled clinical study and received IMRT or CRT. Stimulated whole (SWS) and parotid (SPS) saliva flow were measured and Medical Outcomes Short Form 36 (SF-36), European Organization for Research and Treatment of Cancer (EORTC) core quetionnaire, and EORTC head-and-neck module (QLQ-H&N35) were completed at baseline and 2, 6, and 12 months after radiotherapy.

QoL was assessed with EORTC QLQC30, HN35, and the SF36 health survey and although QoL scores for some domains were better for IMRT patients, no improvements in patient-reported dry mouth symptoms on the HN35 questionnaire were noted.

Conclusions: IMRT was significantly better than CRT in terms of parotid sparing and improved QoL for early-stage disease. The findings support the case for assessment of health-related QoL in relation to head-and-neck cancer using a site-specific approach.

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(PARSPORT)

Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial

Christopher M Nutting, James P Morden, Kevin J Harrington, Teresa Guerrero Urbano, Shreerang A Bhide, Catharine Clark, Elizabeth A Miles, Aisha B Miah, Kate Newbold, MaryAnne Tanay, Fawzi Adab, Sarah J Jefferies, Christopher Scrase, Beng K Yap, Roger P A'Hern, Mark A Sydenham, Marie Emson, Emma Hall, on behalf of the PARSPORT trial management group*

Summary

Background Xerostomia is the most common late side-effect of radiotherapy to the head and neck. Compared with conventional radiotherapy, intensity-modulated radiotherapy (IMRT) can reduce irradiation of the parotid glands. We assessed the hypothesis that parotid-sparing IMRT reduces the incidence of severe xerostomia.

Lancet Oncol 2011; 12: 127–36
Published Online
January 13, 2011
DOI:10.1016/S1470-

PARSPORT

- Before the design of PARSPORT randomised trial, a few small single centre experiences had been published and a review of the published work on IMRT had been done. No randomised trials were identified.
- PARSPORT (CRUK/03/005) was approved by the national South-West Multicentre Research Ethics Committee (MREC 03/6/79) and the local ethics committees of all participating centres.
- PARSPORT trial was sponsored by the Royal Marsden NHS Foundation Trust and undertaken in accordance with the principles of Good Clinical Practice.

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PRIMARY END POINT :

Proportion of patients with XEROSTOMIA of Grade 2 or worse assessed by LENT SOMA Scale 1 year after RT.

SECONDARY END POINT:

i) Proportion of patients with any measurable Salivary flow after RT
ii) Acute and other late RT side effects.
iii) QUALITY OF LIFE – Included Xerostomia related (EORTC) & (Modified Xerostomia Questionnaire)
iv) PFS (RECIST)
v) OS

METHODS :

Multicentric Randomised phase 3 trial
UK based
Jan 2003 to Dec 2007

Inclusion criteria – Pharyngeal squamous cell carcinoma
(Oropharynx and Hypopharynx)
Any T , Any N, Non Metastatic
Both Primary and P/o
WHO PS- 0 or 1
No concomitant Chemotherapy
No Prophylactic Pilocarpine or Amifostine

Exclusion Criteria – Previous RT to Head & Neck
Previous Malignancy except non melanoma skin
cancer
Preexisting Salivary Gland disease
Tumour involving Parotid Gland

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PROCEDURE :

1) STAGING INVESTIGATIONS : Physical Examination
Biopsy
CT / MRI Neck
CXR
Blood Count / Biochemistry

2) CT Scan Based Radiation Planning :

a) 3D Conformal RT with Parallel opposed fields

b) Parotid Sparing IMRT

3) DOSES :

i) Primary Tumour & Involved Nodes – 65 Gy in 30 fractions

ii) Post op – 60 Gy in 30 fractions

iii) Post op gross residual – 65 Gy in 30 fractions

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Cont.

iv) <u>Elective Node</u> –

IMRT – 54 Gy in 25 fractions

Conventional – 50 Gy in 25 fractions

v) <u>Constraints</u> -

Spinal Cord - <50 Gy

Middle Ear & Inner Ear shielding

Parotid - <24 Gy to whole Contralateral Parotid (IMRT)

vi) <u>Acute Toxicity</u> –

Graded Weekly during RT upto 8 Weeks after treatment

NATIONAL CANCER INSTITUTE COMMON TOXICITY CRITERIA (VERSION 3)

vii) <u>Late Toxicities</u> –

At 3,6,12,18,24 months after RT

LENT SOMA & RTOG Scoring System

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Cont.

vii) Salivary Flow Measurements –

Before RT

4 weeks of RT

2 weeks after RT

3 , 6 , 12 , 18 , 24 months after RT

(Both Unstimulated and Sodium Citrate Stimulated Saliva from each

Parotid duct and floor of mouth were collected)

viii) Follow up –

Monthly in 1st year

2 monthly in 2nd year

3-6 monthly in 3rd year

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STATISTICAL ANALYSIS :

Assuming 1 year Xerostomia Rates of ~90% in conventional RT group, Sample Size of 84 patients is selected
To achieve
(30% Absolute difference between study groups).
(90% power, 5% two sided significance).

100 patients were to be enrolled to get 84 evaluable patients at end of 1 year.

Xerostomia rates were compared using chi square test.

Odds of grade 2 or worse Xerostomia at 12 & 24 months calculated with Logistic Regression model.

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	Conventional radiotherapy (n=47)	IMRT (n=47)
Mean age at randomisation (years)	57·3 (10·2; 37·5–82·8)	59·5 (9·2; 44·1–77·1)
Number of women	12 (26%)	14 (30%)
WHO performance status		
0	42 (89%)	41 (87%)
1	5 (11%)	6 (13%)
Tumour site		
Oropharynx	40 (85%)	40 (85%)
Hypopharynx	7 (15%)	7 (15%)
Tumour stage		
T1	6 (13%)	6 (13%)
T2	27 (57%)	22 (47%)
T3	11 (23%)	16 (34%)
T4	3 (6%)	3 (6%)
Nodal stage		
N0	16 (34%)	23 (49%)
N1	9 (19%)	15 (32%)
N2a	7 (15%)	2 (4%)
N2b	10 (21%)	6 (13%)
N2c	1 (2%)	0
N2 (unknown)	1 (2%)	1 (2%)
N3	3 (6%)	0
AJCC* stage		
1 and 2	8 (17%)	15 (32%)
3 and 4	39 (83%)	32 (68%)
Neoadjuvant chemotherapy		
Yes	19 (40%)	20 (43%)
No	28 (60%)	27 (57%)
Type of radiotherapy		
Primary	32 (68%)	39 (83%)
Postoperative	15 (32%)	8 (17%)
Radiotherapy dose (Gy)		
Median dose to primary tumour and involved nodes	65·0 (65·0–65·0; 44)	65·0 (65·0–65·0; 47)
Median dose to elective nodes	50·0 (50·0–50·1; 43)	54·0 (54·0–54·1; 47)
Mean contralateral parotid dose†	61·0 (54·6–63·8; 43)	25·4 (23·2–28·0; 46)
Mean ipsilateral parotid dose†	61·0 (57·0–64·4; 43)	47·6 (39·9–54·5; 46)

Data are mean (SD; range); n (%); or median (IQR; n). IMRT=intensity-modulated radiotherapy. *American Joint Committee on Cancer—groupings based on TNM staging data collected. †Mann-Whitney test p<0·0001.

Table 1: Baseline characteristics and treatment details

RESULTS :

1) XEROSTOMIA :Grade 2 or worse

At 3 months: 62 patients

Conventional RT 33(87%) of 38 patients.

IMRT 29(76%) of 38 patients.

At 12 months: Total no. decreased

Conventional RT 25 (74%) of 34 patients.

IMRT 15 (38%) of 39 patients.

ORs 0.23, Absolute Reduction 35%

At 24 months: Conventional RT 20 (83%) of 24 patients.

IMRT 9(29%) of31 patients.

ORs 0.08, Absolute Reduction 54%

2) SIALOMETRY : Unstimulated Saliva Flow from Contralateral Parotid.

At 12 months: Conventional RT 0 (0%) of 25 patients.
IMRT 16 (47%) of 34 patients.

At 24 months : Conventional RT 0(0%) of 15 patients.
IMRT 7 (44%) of 16 patients.

Similar Results were obtained in Stimulated Saliva Flow Results.

	Conventional radiotherapy		IMRT	
	No measurable salivary flow* (n=25)	Measurable salivary flow (n=0)	No measurable salivary flow (n=18)	Measurable salivary flow (n=16)
Subjective xerostomia better than grade 2	6 (24%)	0	10 (56%)	12 (75%)
Subjective xerostomia grade 2 or worse	19 (76%)	0	8 (44%)	4 (25%)

Fisher's exact test for association (treatment groups combined) p=0·018. LENT SOMA=Late Effects of Normal Tissues Subjective-Objective Management Analytic. IMRT=intensity-modulated radiotherapy. *Measurable salivary flow was defined as any saliva collected from the Lashley cup apparatus.

Table 3: Concordance between unstimulated contralateral saliva flow and LENT SOMA subjective xerostomia at 12 months

Results Cont.

3) QUALITY OF LIFE : EORTC Global Health Status Score
(Higher Score better QOL)

At 12 months : Conventional RT 1.1
IMRT 3

At 24 months : Convetional RT 2.8
IMRT 8.3

HN 35 Subscale Scores for Dry mouth, senses, Sticky Saliva shows similar Results in favor of IMRT.

Results Cont.

4) <u>LOCOREGIONAL PFS</u> : PFS At 2 years

Conventional RT 80%
IMRT 75%

IMRT – 12 recurrances total
11 in high dose volume
01 in electively irradiated nodal region

Conventional RT – 07 recurrances total
05 in high dose volume
02 in both high dose & electively irradiated region

Results Cont.

4) <u>OVERALL SURVIVAL</u> :
(32 Deaths in Total) 02 years OS

Conventional RT : 76%
IMRT : 78%

DISCUSSION :

1) less Incidence of RT induced XEROSTOMIA in IMRT Arm.
2) Early Recovery of Saliva Flow in cases treated with IMRT.
3) Improved QOL in IMRT Arm.
4) Comparable PFS & OS in both Arms.
5) No significant effect of Neoadjuvant Chemotherapy on Incidence of Xerostomia.

Detailed Analysis of Dose Distribution to Salivary Glands including Parotid and its clinical correlation is Ongoing.

Initial Results suggest no correlation between salivary gland doses of RT and Xerostomia.

Impact of PARSPORT

- PARSPORT trial is the largest randomised trial of IMRT in head and neck cancer, and the only trial addressing squamous-cell carcinoma, the predominant form seen worldwide.

- The trial showed that IMRT reduces patient-reported xerostomia, allows recovery of salivary flow, and improves quality of life after treatment compared with conventional radiotherapy

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Merits and Demerits

A limitation of our trial was that it was not possible to mask the treatments from patients or clinicians because of differences in treatment delivery. However, results that

Our trial was too small to detect small differences in, or conclude non-inferiority of, locoregional PFS or overall survival. Although patients continue to be followed up for long-term survival, to show non-inferiority in overall survival to no more than 5% at 2 years (80% power, one-sided 5% significance) would need a randomised controlled trial of more than 900 patients. In this, and other, head and neck IMRT studies most tumour recurrences happen within the high-dose volume. Recurrences have not been noted in the spared parotid tissue in patients treated with IMRT or surgery,[21,38] suggesting that a large study to show non-inferiority in this tumour type is probably both impractical and inappropriate. Our trial has shown a clinically and statistically significant reduction in xerostomia, improved salivary flow, and improved QoL, and thus strongly supports a role for IMRT in HNSCC.

Int. J. Radiation Oncology Biol. Phys., Vol. 5

0360-3016/03/$–see front matter

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doi:10.1016/S0360-3016(03)00361-4

CLINICAL INVESTIGATION **Head and Neck**

QUALITY OF LIFE AFTER PAROTID-SPARING IMRT FOR HEAD-AND-NECK CANCER: A PROSPECTIVE LONGITUDINAL STUDY

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Purpose: Parotid-sparing intensity-modulated radiotherapy (IMRT) for head-and-neck cancer reduces xerostomia compared with standard RT. To assess potential improvements in broader aspects of quality of life (QOL), we initiated a study of patient-reported QOL and its predictors after IMRT.

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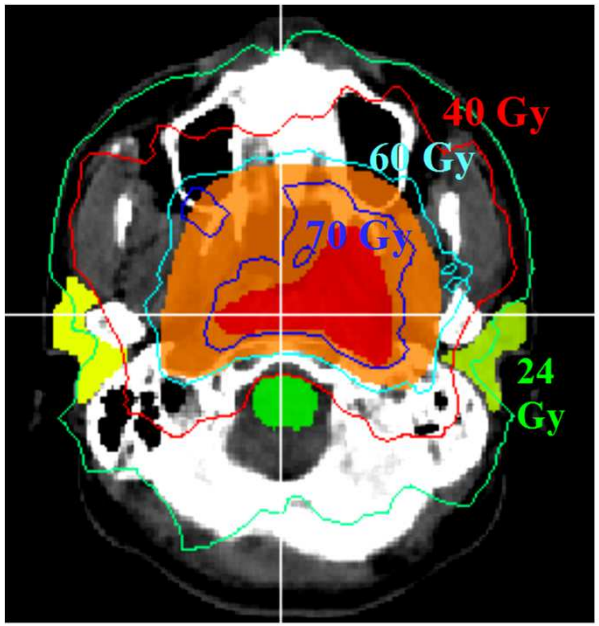
IMRT for NPC

RTOG Protocol H-0225 (Lee & Garden)

Stage: I-IVb

Histology:

WHO I-III



R E G I S T E R

IMRT:

2.12 Gy/F/d X 33 F to ≥ 95% of GTV

1.8 Gy/F/d X 33 F to ≥ 95% of CTV

Chemotherapy (≥T2b or N+)

Concurrent: Cisplatin x 3

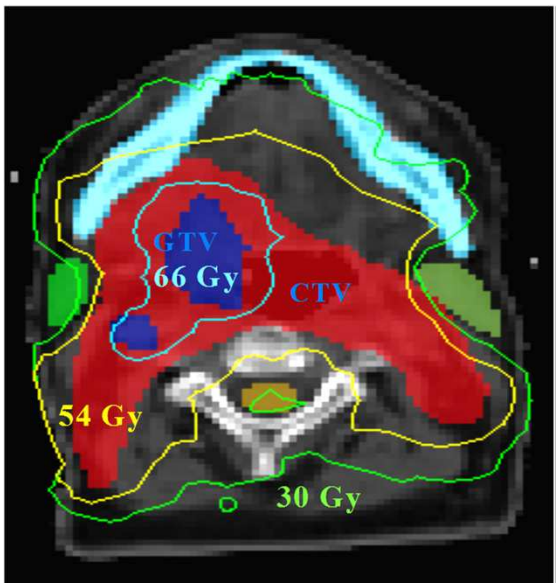
Adjuvant: Cisplatin + 5-FU

IMRT for Oropharyngeal SCC

RTOG Protocol H-0022 (Eisbruch & Chao)

Stage: T1-2 N-1

Site:
Tonsil, BOT, Soft Palate



R E G I S T E R

Gross disease PTV:

66 Gy/30 FX

Subclinical disease PTV:

54-60 Gy/30 FX

Boost of 4-6 Gy/2-3 FX to the tumor PTV allowed

IMRT for Oropharynx Cancer

- 2000-June 2003: 133 patients
- Age: 30-75 (53) years; 85% male
- Site: tonsil-52%; tongue base-40%
- T1-2(x): 114; T3-4: 19
- Chemotherapy: 28 (T3-4 or N2-3)
- 3-Y local control: 95%
- 3-Y overall survival: 93%

Garden et al., 2005

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Table 1. Locoregional Control After IMRT for Head and Neck Cancer

Study	No. of Patients	Primary Site	RT		Follow-Up (months)		Control		
			Definitive	Postoperative	Median	Range	Local (%)	Regional (%)	Interval (years)
Chao et al[19]	126	Various	52	74	26	12-55		85	2
Lee et al[5]	67	NPX	67	0	31	7-72		98	4
Chao et al[20]	74	OPX	31	43	33	9-60		87	4
Eisbruch et al*[21]	133	Various, non-NPX	60	73	32	6-107		82	3
Kam et al[33]	63	NPX	63	0	29	8-45	92	98	3
Kwong et al[34]	33	NPX	33	0	29	11-42	100	92	3

Abbreviations: IMRT, intensity-modulated radiotherapy; RT, radiotherapy; NPX, nasopharynx; OPX, oropharynx.

*Patients treated from 1994 to 2002; three-dimensional conformal radiotherapy was used before 1996, and IMRT thereafter.

JCO, 2006

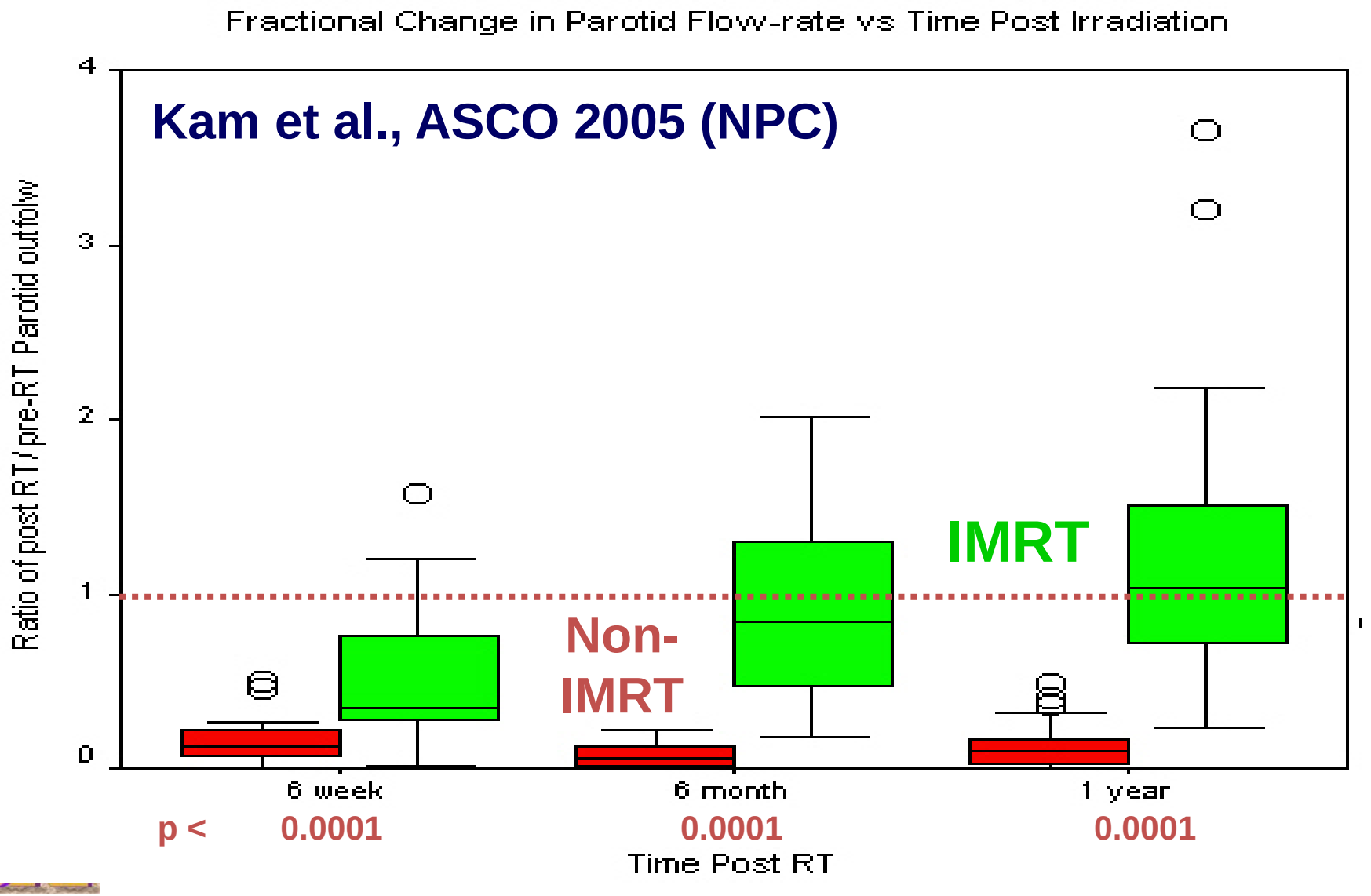
Cont..

- **IMRT for HNC, ASTRO 2003**
  Nancy Lee, MSKCC N.Y.
- **Approx. 150 papers reported on outcome of HNC treated with IMRT**
- **End points of these trials were local control and xerostomia.**
- **Mean parotid dose < 26 Gy has resulted in objective & subjective salivary function preservation and improved QOL**
- **IMRT resulted in 82% improvement in xerostomia as compared to 40% with 3 DCRT.**

- **Local control**

		IMRT(%)	3DCRT(%)
T1, T2		92 – 100	64 – 95
T3, T4		92 – 94	44 – 68
T1, T2	NPC	92	70 – 90
T3, T4	NPC	87 – 94	30 - 70
	Ophx.		

Recovery of Saliva Flow (A vs C)



Ontario

Cancer Care Ontario

Action Cancer Ontario

Evidence-Based Series 21-3-3-EDUCATION AND INFORMATION 2013

The Role of IMRT in Head & Neck Cancer

B. O'Sullivan, R.B. Rumble, P. Warde,
and members of the IMRT Indications Expert Panel

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RECOMMENDATIONS

If the reduction of xerostomia and improved quality of life are the main outcomes of interest, then IMRT is the recommended treatment for all nasopharyngeal, oropharyngeal, hypopharyngeal, laryngeal, oral cavity, and unknown primary cancers where lymph node regions requiring inclusion in the treatment volume would result in irreparable damage to salivary function if 2D EBRT or 3D EBRT were used due to their inability to maintain salivary doses within their tolerance limits (<26 Gy mean dose). The data provided are applicable to locally advanced disease but are equally applicable to early-stage disease and rare sites (e.g. salivary gland tumours) requiring RT that would otherwise damage these normal structures. In addition, these principles hold for skin malignancy where advantages in sparing normal tissue while achieving target coverage are also relevant.

KEY EVIDENCE

Kam MKM, Leung SF, Zee B, Chau RMC, Suen JJS, 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(31):4873-9.

Kwong D, McMillan A, Pow E, Sham J. A randomized trial comparing intensity modulated radiotherapy versus 2-dimensional radiotherapy for Stage II nasopharyngeal carcinoma. Proc Annu Meet Am Soc Radiat Oncol. 2008;72(1):1.

Nutting C, A'Hern R, Rogers MS, Sydenham MA, Adab F, Harrington K, et al. First results of a phase III multicenter randomized controlled trial of intensity modulated (IMRT) versus conventional radiotherapy (RT) in head and neck cancer (PARSPORT: ISRCTN48243537; CRUK/03/005). J Clin Oncol. 2009;27(18 Suppl):6006.

Lee N, Harris J, Garden AS, Straube W, Glisson B, Xia P, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. J Clin Oncol. 2009;27(22):3684-90.

Eisbruch A, Harris J, Garden AS, Chao CK, Straube W, Harari PM, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys. 2010;76(5):1333-8.

RECOMMENDATIONS

If blindness is to be minimized or avoided, IMRT is indicated in the definitive or adjuvant RT setting for nasal and paranasal sinus cancers or other sites where the disease is juxtaposed to the optic apparatus. The latter would include diseases such as skin malignancy and sarcomas, in addition to epithelial cancers, since ocular toxicity is often a major barrier to safe treatment planning for lesions in these locations.

KEY EVIDENCE

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(1):141-7.

Madani I, Bonte K, Vakaet L, Boterberg T, De Neve W, Madani I, et al. Intensity-modulated radiotherapy for sinonasal tumors: Ghent University Hospital update. Int J Radiat Oncol Biol Phys. 2009;73(2):424-32.

Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-based Medicine: How to practice and teach EBM. 2nd ed. Edinburgh, London: Churchill Livingstone; 2000.

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RECOMMENDATIONS

If osteoradionecrosis is to be minimized or avoided, IMRT is indicated in the definitive or adjuvant RT of tumours in the oral cavity, oropharynx, paranasal sinuses, and nasopharynx where significant doses of RT are required and would be applied to the mandible if 2D EBRT or 3D EBRT were used.

KEY EVIDENCE

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(1):141-7.

Ben-David MA, Diamante M, Radawski JD, Vineberg KA, Stroup C, Murdoch-Kinch CA, et al. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. Int J Radiat Oncol Biol Phys. 2007;68(2):396-402.

Studer G, Studer S, Zwahlen R, Huguenin P, Gratz K, Lutolf U, et al. Osteoradionecrosis of the mandible: minimized risk profile following intensity-modulated radiation therapy (IMRT). Strahlenther Onkol. 2006;182(5):283-8.

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RECOMMENDATIONS

If treatment-related outcomes (local control, overall survival) are the main outcomes of interest, there are no randomized data to support or refute a recommendation of IMRT over 2D EBRT or 3D EBRT in any head and neck site. However, NPC should ordinarily be treated with IMRT based on treatment-related outcomes as should nasal and paranasal sinus cancer.

KEY EVIDENCE

Kam MKM, Leung SF, Zee B, Chau RMC, Suen JJS, 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(31):4873-9.

Kwong D, McMillan A, Pow E, Sham J. A randomized trial comparing intensity modulated radiotherapy versus 2-dimensional radiotherapy for Stage II nasopharyngeal carcinoma. Proc Annu Meet Am Soc Radiat Oncol. 2008;72(1):1.

Lee N, Harris J, Garden AS, Straube W, Glisson B, Xia P, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. J Clin Oncol. 2009;27(22):3684-90.

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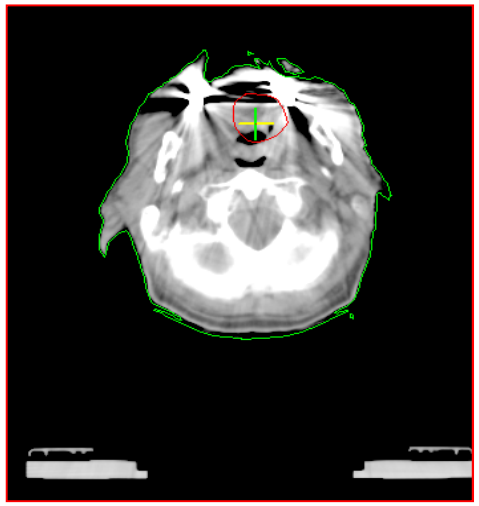
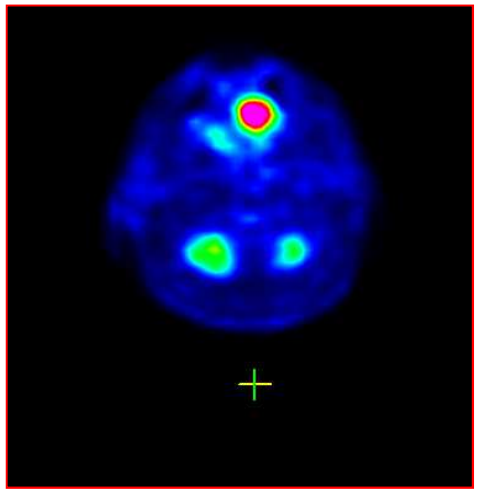
PET Scores over others!



CT, MRI

Anatomical imaging



PET is functional imaging

Active viable tumor

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Indian Journal of CANCER

SYMPOSIUM

Year : 2010 | Volume : 47 | Issue : 2 | Page : 126--133

PET/CT-guided radiation therapy planning: From present to the future

T Gupta[1], **S Beriwal**[2],

[1] Department of Radiation Oncology, Advanced Centre for Treatment Research and Education in Cancer (ACTREC), Tata Memorial Centre, Navi Mumbai, India

[2] Department of Radiation Oncology, University of Pittsburg Cancer Institute, Pittsburg, PA, USA

Innovations in Radiotherapy Planning of Head and Neck Cancers: Role of PET

Esther G.C. Troost[1], Dominic A.X. Schinagl[1], Johan Bussink[1], Otto C. Boerman[2], Albert J. van der Kogel[1], Wim J.G. Oyen[2], and Johannes H.A.M. Kaanders[1]

[1]Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; and [2]Department of Nuclear Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

CONCLUSION

^{18}F-FDG PET is the gold standard for noninvasive functional imaging in oncology. In head and neck tumors, ^{18}F-FDG PET is not recommended for detection of the primary tumor, and its value for metastatic lymph nodes is still a matter of debate. With regard to staging of the primary tumor, ^{18}F-FDG PET may influence the treatment decision if distant metastases or second primary tumors are detected.

For radiotherapy planning in head and neck cancer, ^{18}F-FDG PET can provide important information complementary to CT. On the basis of PET information, the volume irradiated to high dose-levels may be reduced, thus facilitating the sparing of normal structures and the escalation of

Impact of PET-CT in H & N Cancer

Author	Patients	Change of GTV using PET	Increase in GTV	Decrease in GTV	Remarks
Rahn, 1998	22(prim)	41%	41%	0%	No image fusion
	12(recur)	58%	58%	0%	
Nishioka, 2002	21	71%	0%	71%	PET/CT/MRI fusion
Ciernik, 2003	12	50%	17%	33%	Integrated PET-CT
Daisne, 2004	29	93%	18%	75%	CT-PET image fusion
Paulino, 2005	40	100%	-	-	PET/CT/MRI and surgical specimen image fusion

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PET/CT in radiotherapy planning for head and neck cancer

Katie Newbold* and Ceri Powell

The Royal Marsden National Health Service Trust, London, UK

Edited by:
Ilja F. Ciernik, Städtisches Klinikum Dessau, Germany

Reviewed by:
Jesper Thygesen, Aarhus University Hospital, Denmark
Chaitanya Divgi, Columbia University, USA

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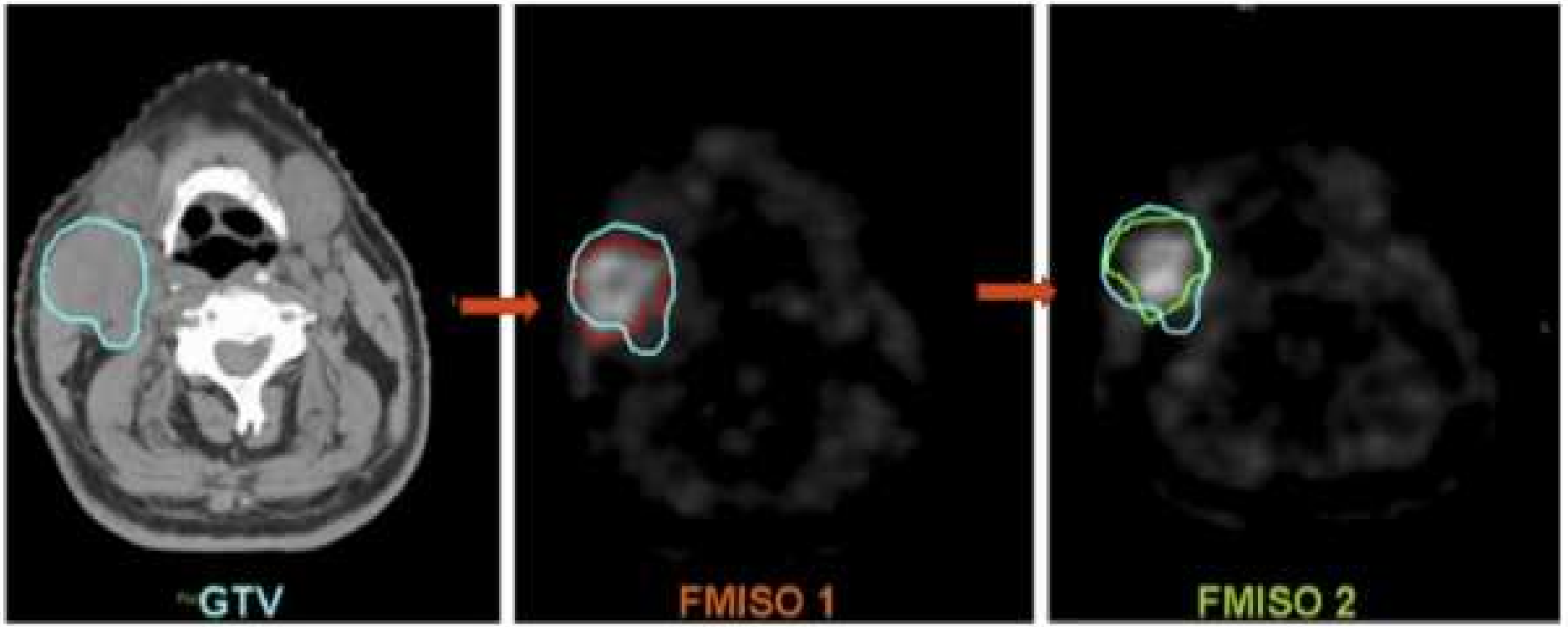
Katie Newbold, Thyroid Unit, The Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, UK.
e-mail: katienewbold@me.com

The use of PET/CT as an adjunct in radiotherapy planning is an attractive option in head and neck cancer (HNC) for several reasons. First, with potentially better identification of the disease extent, i.e., staging, the risk of geographical miss of radiation delivery to the gross tumor volume is reduced. Second, in characterizing the biological behavior of the disease for example, areas of hypoxia, rich or poor vascularity, or high cell proliferation, PET/CT can identify biological target volumes either for escalation of radiation dose or to predict the requirement for the addition of a radiosensitizer or alternative treatment strategies. ^{18}F-FDG is the most common tracer used in oncology studies, but many other tracers have been investigated with several entering clinical practice, although these remain predominantly in the research domain in HNC.

Keywords: head and neck cancer, PET-CT, biological target volume, radiotherapy, biomarkers

Work under progress

- **Hypoxia targeting**
- **Dose escalation**



Change in hypoxic area (and therefore boost target volume) 3 days apart in 4/7 patients

IGRT

- Image Guided Radiation Therapy

- WHY ??
  - Set up error
  - Intra & Inter fraction organ movement
  - Daily verification
  - Accurate Treatment Delivery

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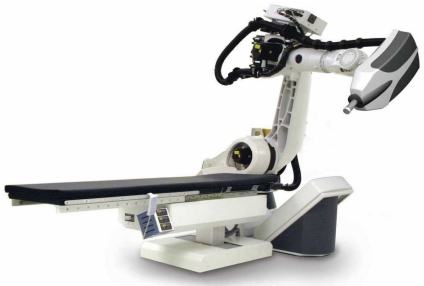
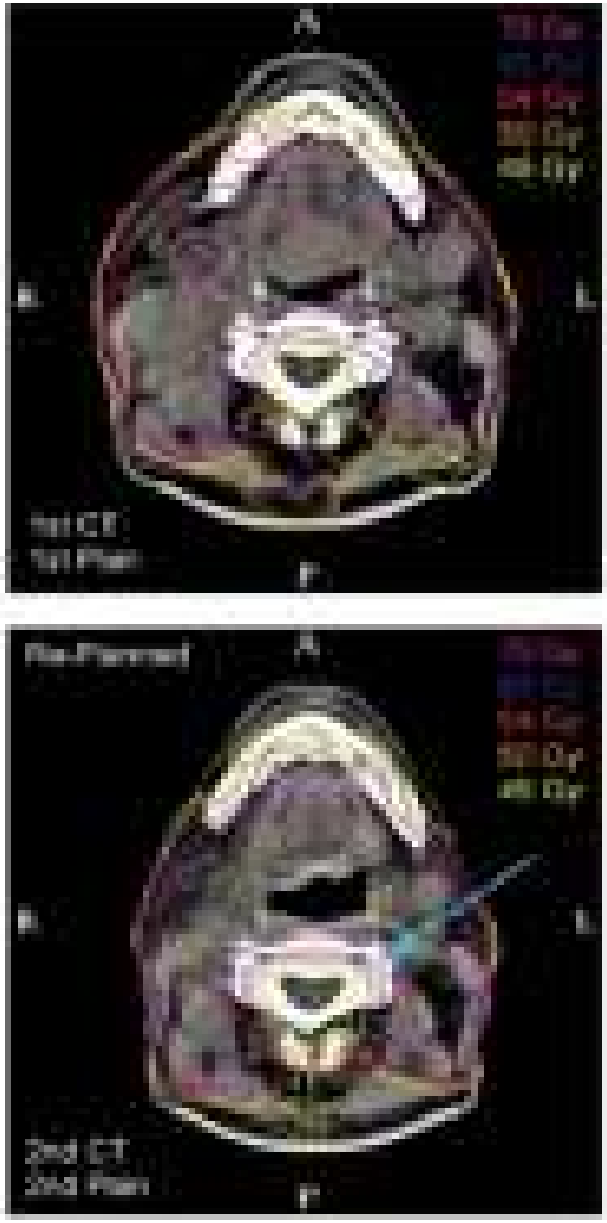
Types of IGRT

- Portal Imaging
- EPID – Electronic Portal Imaging Device
- USG guided RT
- In room CT
- KV Cone beam CT
- MRI guided RT
- Tomotherapy



Adaptive Radiotherapy



Adaptive Radiotherapy (ART)

ART is the process of altering the treatment plan in response to changes observed during radiation treatment. Deformation of targets, normal structures as well as patient anatomy may happen during a 6-7 week course of radiotherapy. For example large exophytic tumours of HPV origin and nasopharyngeal tumours often experience significant tumour regression during the course of treatment. It may be possible to replan and adjust for interval regression of the exophytic component of the disease to limit the occurrence of oral mucositis. These situations are currently being investigated by several groups to alleviate the problems of target deformation during a treatment course. Besides physical deformation in targets there could also be a biological variation with redistribution of tumour cells through the phases of cell cycle and reoxygenation of previously hypoxic cells, converting radio resistant cells to radio sensitive in some cases and vice versa. Disadvantage being changes in the patients anatomy from weight loss and tissue oedema may also occur during treatment. Soft tissue resolution is quite limited compared to bony anatomy.[10]

Adaptive Planning

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 5, pp. 1360–1368, 2010

0360-3016/10/$–see front matter

doi:10.1016/j.ijrobp.2009.04.005

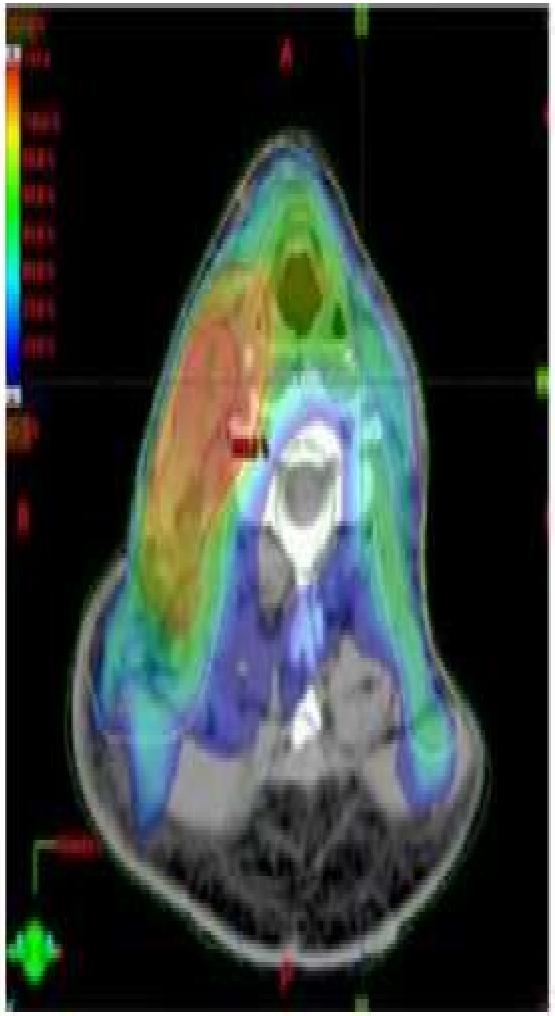
CLINICAL INVESTIGATION **Head and Neck**

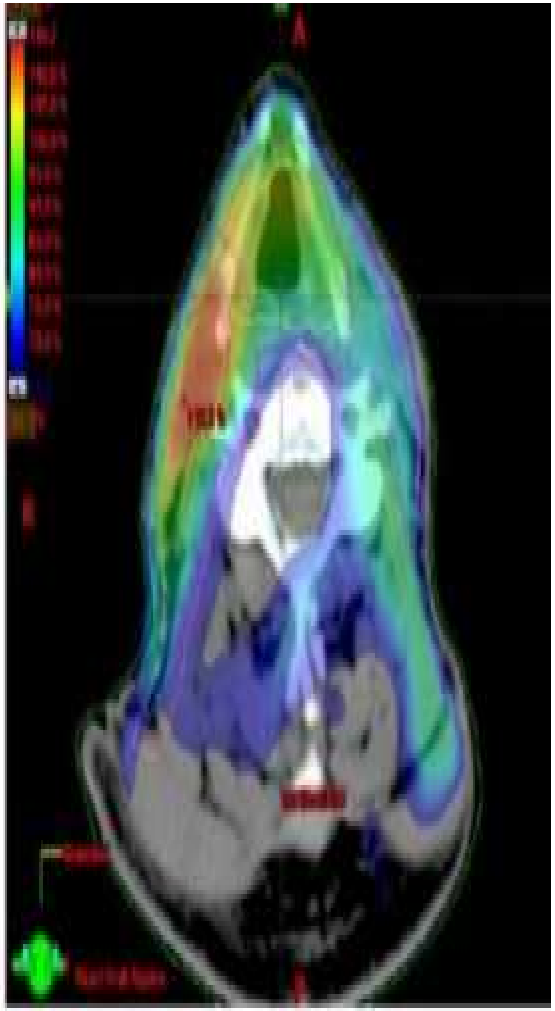
WEEKLY VOLUME AND DOSIMETRIC CHANGES DURING CHEMORADIOTHERAPY WITH INTENSITY-MODULATED RADIATION THERAPY FOR HEAD AND NECK CANCER: A PROSPECTIVE OBSERVATIONAL STUDY

SHREERANG A. BHIDE, F.R.C.R.,*† MARK DAVIES, B.SC.,‡ KEVIN BURKE, M.SC.,‡ HELEN A. MCNAIR, M.SC.,‡ VIBEKE HANSEN, PH.D.,† Y. BARBACHANO, M.SC.,§ I. A. EL-HARIRY, PH.D.,† KATE NEWBOLD, F.R.C.R.,‡ KEVIN J. HARRINGTON, F.R.C.R.,*† AND CHRISTOPHER M. NUTTING, F.R.C.R.†

*Institute of Cancer Research, 237 Fulham Road, London SW6 6JB, United Kingdom; †Head and Neck Unit, Royal Marsden NHS Foundation Trust Hospital, London SW3 6JJ, United Kingdom; ‡Department of Radiation Oncology, Royal Marsden NHS Foundation Trust Hospital, London and Sutton, United Kingdom; and §Department of Statistics, Royal Marsden NHS Foundation Trust Hospital, London and Sutton, United Kingdom

- Before and After – Adaptive Planning





- Greatest reduction in CTV 1, 3.2 % between week 0 & 2 (significant)
- Statistically significant reduction in volume of CTV 2 , 10.5% and 5 5 between wk 0 & 2 and 2 &4 respectively
- Parotid shrinks 14 % and 16% , wk 0&2, wk 2& 4 respectively
- Significant reduction in minimum dose to CTV and increase in mean dose to parotid

SBRT in Head and Neck Cancer

- Stereotactic approach – used since decades, well established track records in cranial lesions
- Stereotactic approach – initially started with cranium but now moved out of cranium
- Delivers biologically similar dose as conventional
- Fewer fractions, increased dose per fraction
- Dedicated or adapted linear accelerators
- Allows optimizations of conformality and tumor coverage with sparing of normal tissues

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SBRT in H&N Cancer

- Indications
- Target Definition
- Fractionation
- Constraints
- Efficacy
- Toxicity profile
- QOL

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SBRT in head and neck cancer

- Salvage option for unresectable recurrent, previously irradiated head and neck cancer
- Palliative radiotherapy metastasis to head and neck region from primary GI/Breast Cancer
- Definitive treatment of 2nd primary – unresectable & heavily irradiated earlier

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Looking into the history of SBRT

- First report on use of this technique – Kondziolka and Lunsford in 1991
- SBRT has been use for boost in Ca Nasopharynx
- Series of publications from Standford University – stereotactic boost as 7-15 Gy in one fraction 2-6 weeks after conventional 66 Gy
- Results 2 year local control 100%

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Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 5, pp. 1493–1500, 2009

0360-3016/09/$–see front matter

ELSEVIER

Heron et al. IJROBP 2009

CLINICAL INVESTIGATION **Head and Neck**

STEREOTACTIC BODY RADIOTHERAPY FOR RECURRENT SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK: RESULTS OF A PHASE I DOSE-ESCALATION TRIAL

Table 2. Patient enrollment and prior radiotherapy dose by dose tier

Dose tier	Subjects (*n*)	Prior RT dose (mean Gy/no. of fx)	Prior spinal cord dose (mean Gy)	Dose/fx (Gy)	No. of fx	Total dose (Gy)	Mean volume of GTV receiving PD (%)
1	3	69.2/36	45.5	5	5	25	98.4
2	3	69.6/35	45.2	6.4	5	32	96.7
3	3	66/30	40.7	7.2	5	36	95
4	6	68.5/36	44.6	8.0	5	40	92
5	10	66.8/35	45.1	8.8	5	44	94

Abbreviations: RT = radiotherapy; fx = fraction; GTV = gross tumor volume; PD = prescription dose.

Early Experience

- All patients were treated to the 80% isodose line, which was intended to cover >90% of the target volume

- Critical structure constraints were as follows:

✓ Spinal Cord maximum dose: <8 Gy
✓ Larynx: < 20 Gy
✓ Mandible: < 20 Gy
✓ Parotid: variable
✓ Brainstem: <8 Gy
✓ Oral Cavity: variable

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Table 3. Patient responses by dose tier

Response	Dose (Gy)					Total
	25	32	36	40	44	
Complete response	1	0	1*	0	0	2
Partial response	1*	0	1*	1	2	5
Stable disease	0	3	0	3	6	12
Progressive disease	0	0	0	2	2	4
Not evaluable	1	0	1	0	0	2

* Responses not confirmed.

In the present study,

Short term SBRT was feasible and safe.

The overall response rate in this group of heavily pre-treated patients was 28% (CR + PR)

No Grade 3 or 4 toxicities were noted among our patients.

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Heron et al. IJROBP 2009

Contouring and Margins

Radiotherapy and Oncology 106 (2013) 90–95

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Radiotherapy and Oncology

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Head and neck cancer

Target delineation in stereotactic body radiation therapy for recurrent head and neck cancer: A retrospective analysis of the impact of margins and automated PET-CT segmentation

Kyle Wang [a], Dwight E. Heron [a,b,*], David A. Clump [a], John C. Flickinger [a,c], Gregory J. Kubicek [a], Jean-Claude M. Rwigema [a], Robert L. Ferris [a,b], James P. Ohr [d], Annette E. Quinn [a], Cihat Ozhasoglu [a], Barton F. Branstetter [b,e]

Assessment of the impact of retrospectively adding margins/automated PET volumes to the gross tumor volume (GTV) in patients with post-SBRT recurrences.

- However, there is no standard regarding the use of such margins for hypofractionated techniques such as SBRT for rSCCHN

- Furthermore, the addition of margins has differed greatly between institutions studying this technique: Roh – 2-3mm , Siddiqui – ‘‘slight’’ margin , Unger – 2-10mm , Cengiz – none.

At our institution, SBRT for rSCCHN was first investigated in 2003 using doses of 12–36 Gy and fraction sizes from 3 to 6 Gy. We have typically contoured and treated the GTV with no margin

(GTV = CTV = PTV)

Dose and efficacy

ORIGINAL ARTICLE

Safety and efficacy of hypofractionated stereotactic body reirradiation in head and neck cancer: Long-term follow-up of a large series

Marie-Adele S. Kress, MD,[1]* Neilayan Sen, BA,[1] Keith R. Unger, MD,[1] Christopher E. Lominska, MD,[2] John F. Deeken, MD,[1] Bruce J. Davidson, MD,[1] Kenneth A. Newkirk, MD,[1] Jimmy Hwang, MD,[1] K. William Harter, MD[1]

[1]Departments of Radiation Oncology, Medical Oncology, and Head and Neck Surgery, Lombardi Comprehensive Cancer Center, Georgetown University Hospital, Washington, DC, [2]Department of Radiation Oncology, The University of Kansas Hospital, Kansas City, Kansas.

Accepted 10 May 2014
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.23763

fractionation scheme was 30 Gy in 5 fractions. The maximum doses to the spinal cord, brainstem, and optic nerve from SBRT alone were recorded when the target volume was in close proximity and were 21 Gy, 37 Gy, and 34 Gy, respectively.

Table 3 SBRT reirradiation for head and neck cancer

Clinical trial	*Voynov et al. 2006*	*Heron et al. 2009*	*Unger et al. 2010*	*Roh et al. 2009*	*Ozyigit et al. 2009*	*Vargo et al. 2012*
n	22	25	65	36	24	34
Initial therapy dose	median BED_{10} 97.8 Gy (70.1 – 190.3 Gy)	median, 64.7 Gy	median 67 Gy (32–120 Gy)	median, 70.2 Gy (39.6 – 134.4 Gy)	median, 70 Gy (48–70 Gy)	median 61.2 Gy (42–157 Gy).
Interval	n/s	13 months (range, 5–94 months)	26 months (range, 2–318 months)	24 months (range, 3.1–252.6)	38 months (range, 10–242 months)	53 months (range, 1–302 months)
Re-irradiation dose	5 (1 – 8) x 5 Gy (3 – 16 Gy)	5 x 5 Gy 5 x 6.4 Gy 5 x 7.2 Gy 5 x 8.0 Gy 5 x 8.8 Gy	5 (2–5) x 6 Gy (4–12Gy) median 30 Gy (21–35 Gy)	3 x 10/13 Gy 5 x 5/8 Gy	5 x 6 Gy	median dose of 40 Gy in 5 fractions (interquartile range, 30–44 Gy)
Target size (median)	TV 19.1 cm^3 (range, 2.5 – 140.3 cm^3)	TV 44.8 mm^3 (range, 4.2–216.6 mm^3)	Target volume 75 cm^3 (range, 7–276 cm^3)	GTV 22.6 cm^3 (range, 0.2 to 114.9 cm^3)	TV 63.4 cm^3 (range 26.3–170.4 cm^3)	TV 19,6ml (range, 4.5 – 103.9 ml)
Median follow-up time	19 months (range 11–40 months)	n/s	16 months	17.3 months	24 months	10 months (range, 0–55 months)
Local control	26% @ 2 years	n/s	30% @ 2 years *	61% @ 1 year 52.2% @ 2 years	82% @ 2 years	77% @ 6 months 59% @ 1 year
Overall survival	22% @ 2 years	median 6 months (95% CI 5–8 months)	12 months 41% @ 2 years *	52.1% @ 1 year 30.9% @ 2 years	cancer specific survival 64% @ 2 years	76% @ 6 months 59% @ 1 year
Toxicity	1/22 grade 2, 1/22 grade 3 mucositis No grade 4/5 toxicitiy	3/25 grade 1 1/25 grade 2 No grade 3–5 toxicities	19/65 acute grade 1–3 toxicities 6/65 late grade 4 toxicities: arterial bleeding, soft tissue necrosis, fistula formation 1 treatment related death	13/36 grade 3 acute toxicities 3/36 late toxicity: 1 bone necrosis, 2 soft tissue necrosis	5/24 severe late side effects (grade ≥ 3)	Acute/late grade 3 toxicity was 15/6%, with no grade 4–5 toxicity

Radiotherapy and Oncology 104 (2012) 91–95

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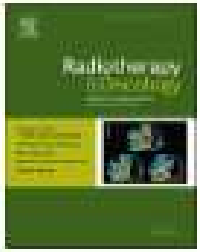

QoL in head and neck cancer

Prospective evaluation of patient-reported quality-of-life outcomes following SBRT ± cetuximab for locally-recurrent, previously-irradiated head and neck cancer

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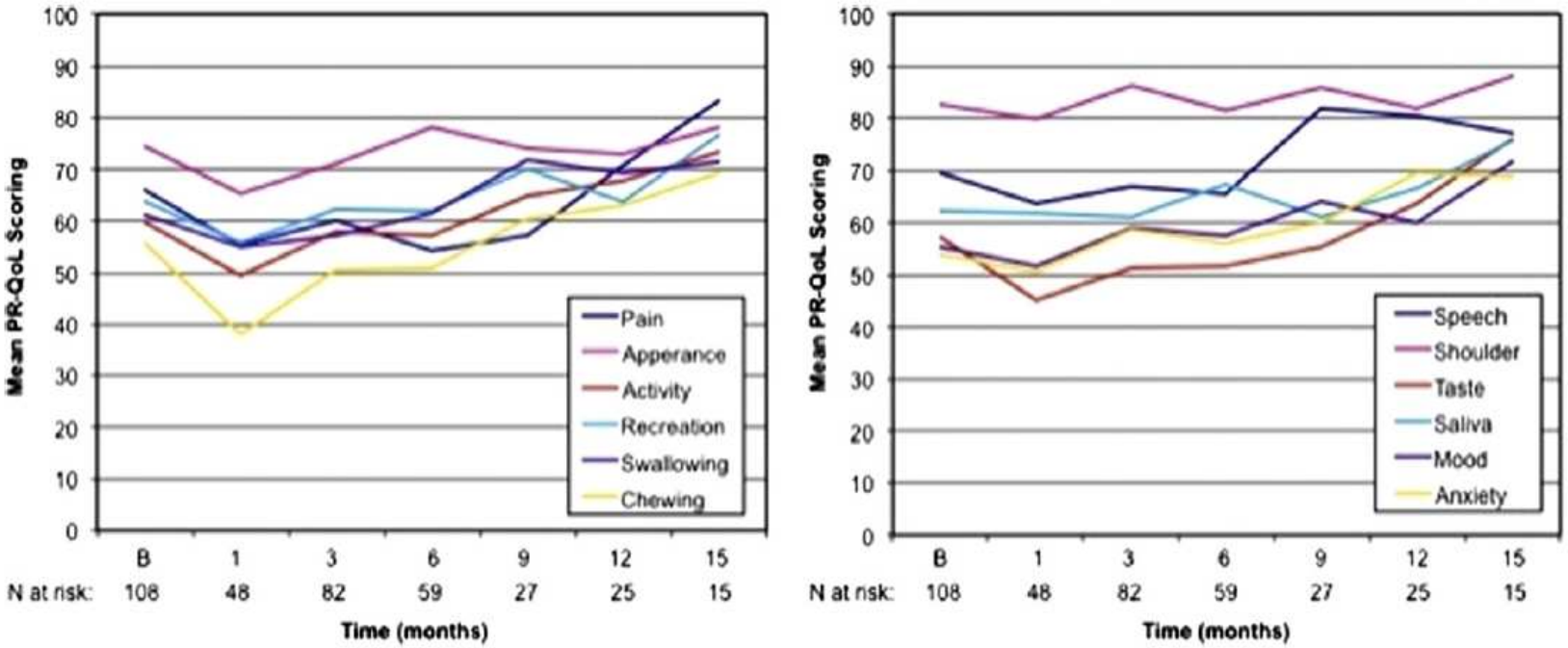

Fig. 2. Mean PR-QoL values for head and neck specific domains over time from baseline to 15-months. PR-QoL, patient-reported quality-of-life; B, baseline.

PR-QoL scores across domains as a function of time for select domains showing statistically significant increases from baseline to 15-months.

	Swallowing	Speech	Saliva	Activity	Recreation
Baseline (n = 108)	61.4 ± 33.6	69.6 ± 30.6	57.9 ± 28.7	57.4 ± 23.8	63.7 ± 28.1
1-Month (n = 48)	54.9 ± 32.8	63.7 ± 30.8	61.9 ± 35.1	49.5 ± 25.7	55.9 ± 26.7
3-Months (n = 82)	57.2 ± 34.0	67.2 ± 31.5	61.3 ± 32.0	57.9 ± 24.8	62.3 ± 25.7
6-Months (n = 59)	61.5 ± 32.7	65.5 ± 28.8	67.3 ± 30.6	57.3 ± 31.0	62.0 ± 28.2
9-Months (n = 27)	71.9 ± 27.8	82.1 ± 19.5	61.1 ± 29.1	64.8 ± 27.1	70.2 ± 25.5
12-Months (n = 25)	69.5 ± 36.7	80.4 ± 24.5	66.7 ± 28.5	68.0 ± 29.3	64.0 ± 32.3
15-Months (n = 15)	71.6 ± 25.6	77.1 ± 28.4	75.7 ± 19.7	73.3 ± 20.0	76.7 ± 22.1
Wilcoxon signed-rank baseline to 15-months	p = 0.025	p = 0.017	p = 0.041	p = 0.032	p = 0.039

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Baseline characteristics for patients completing evaluable UW-QoL-R questionnaires.

Baseline characteristics	All patients (n = 108)
Concurrent cetuximab	
SBRT + cetuximab	51 (47%)
SBRT alone	57 (53%)
Age (years), median (range)	66 (32–90)
Gender	
Male	74 (69%)
Female	34 (31%)
Primary site	
Larynx	19 (18%)
Nasopharynx	6 (6%)
Oropharynx	21 (19%)
Oral cavity	26 (24%)
Salivary glands/para-nasal sinuses	26 (24%)
Other	10 (9%)
Tumor volume (cm^3), median (range)	30.0 (2.5–165.6)
Prior RT dose (Gy), median (range)	68.4 (25–170.6)
Months from prior RT, median (range)	23 (2.2–1221)
Prior surgery	74 (69%)
Prior chemotherapy	67 (62%)

QOL was preserved - SBRT re-irradiation, as evidenced by progressive improvements in PR-QOL noted throughout the duration of clinical follow-up across all domains in a validated PRQOL assessment tool independent of age, use of cetuximab, tumor volume, and interval since prior irradiation.

GCRI

Experience in metastatic head and neck

- Siddiqui et al -15 patients who had primary cancers in lung, breast and brain and renal cell carcinoma and gastric adenocarcinoma

- Response Rate (CR + PR) 87%

- Good symptomatic relief

GCRI

Experience of SBRT in primary treatment

- Experience in primary treatment is limited
- Need to treat the primary and the involved nodes to high dose and need to cover elective nodal areas
- However in unusual and special circumstances SBRT can be employed
- Two series 10 and 13 patients –
- CR – 82% and 84% respectively
- PR – 69 % and 62 % respectively

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frontiers in ONCOLOGY

CLINICAL CASE STUDY
published: 28 October 2014
doi: 10.3389/fonc.2014.00238

Stereotactic body radiotherapy as primary therapy for head and neck cancer in the elderly or patients with poor performance

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Conclusion: Head and neck squamous cell carcinoma presents a unique challenge in the elderly, where medical comorbidities make it difficult to tolerate conventional radiation, often given with a systemic sensitizer. For these individuals, providing a shortened course using SBRT may offer an effective alternative.

GCRI

- Feasibility study using SBRT to deliver 8.5 Gy * 5 fractions to T1a vocal cord at Erasmus Medical Center, Netherlands

SBRT is also being explored as a treatment option for the management of squamous cell carcinoma of the vocal cord. Levendag *et al*. recently described a novel 4D conformal technique for treating a single vocal cord with SBRT.[52] Using this technique, it was feasible to irradiate one vocal cord within 1-2 mm accuracy, thus sparing the contra lateral vocal cord and contralateral normal tissues. They propose this technique may be a competitive alternative to laser surgery for early glottic cancer by preserving vocal cord function. A feasibility study using SBRT to deliver 8.5 Gy x 5 fractions to T1a vocal cord lesions is currently underway at the Erasmus Medical Center, Rotterdam, Netherlands. There has been other promising single institution experience using SBRT as part of primary treatment in head and neck cancer.[53 54]

SIDE EFFECTS

Esophageal stenosis (Biaglioli 2007)	Bleeding (Biaglioli 2007, Duprez 2007)
Osteonecrosis of the mandible or, for nasopharynx patients, of the first cervical vertebrae or bone of the skull base (Claus 2001, Platteaux 2010, Janssen 2010, Kasperts 2005, Law 2002, Mendenhall 2008, Strojan 2014) 10%	Neurologic damage like deafness, temporal lobe necrosis, optic or base of skull nerves damages. (Claus 2001, RTOG 9610 Spencer 2008, Platteaux 2010, Mendenhall 2008 Mendenhallo 2008)
Prolonged enteral nutrition (Claus 2001, Platteaux 2010, Spencer 2008)	Soft tissues fibrosis, trismus, palatal fibrosis. (Dawson2001, De Crevoisier 200,Kasperts 2006, Chua 2006, Mendenhall 2008)
Mucosae and/or soft tissues necrosis and fistulae. (De Crevoisier 2001, Janssen 2010)	Dry eye syndrome and ocular dysfunction (keratitis, corneal ulceration) (Duprez 2009)
Pain (Spencer 2008)	Larynx damage (Spencer 2008)
Severe epistaxis (Chua 1999)	Radiation-induced sarcoma (Mendenhall 2008)
Hypopituitarism (Mendenhall 2008)	Xerostomia (Mendenhall 2008)
Vascular stenosis and trombo-embolic events (Wong 2006)	Carotid blowout syndrom 2.6% (Strojan 2014)

Carotid artery blowout syndrome (CBS)

- Carotid artery blowout syndrome (CBS) is a serious and often fatal complication in reirradiation

- Published data reveal that CBS rates can be high in reirradiation with SBRT, especially in patients with tumors wrapping the carotid artery, nearby skin involvement, or necrosis at time of recurrence

GCRI

Dose Constraints

- No exact dose constraint established for Carotid artery

- To delineate the carotid artery and define it as an organ at risk to prevent hot spots of >100 Gy (EQD 2) on significant carotid sheath volumes . Similarly, in the Turkish study, all the patients who developed CBOS had received a maximal carotid artery dose of >34 Gy.

GCRI

Take home message….

- IMRT is the treatment of choice in Head and Neck Carcinoma
- IGRT and Adaptive Radiotherapy
- SBRT in head and neck cancer - selective cases
- Smaller PTV margins, Sharper dose fall-off can allow for geographic misses if target localization and immobilization are not accurate
- More complex, more beams/arc increase the overall treatment time - decrease dose rate! – newer gadgets

Biology is the King

Imaging is Queen

Technique is merely Manservant