Istituto del Radio "O. Alberti"
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More advanced treatments and new perspectives in the treatment of oropharyngeal carcinoma. Limited disease

IMRT to treat oropharyngeal carcinoma: limits and advantages

Dr. Sandro Tonoli

Introduction

- IMRT gives the possibility to obtain a better conformation of dose on complex volumes
- The clinical use of IMRT, but also 3D-CRT, requires a precise delineation of target volumes and organs at risk
- Any inaccuracy may impact on tumor control probability and normal tissue complication
- IMRT is not only a technical development but implies changes in the radiation oncologist mind

First of all… is IMRT safe?

- If we want to compare IMRT vs CRT we need information on
  - **Results in terms of LRC**
  - **Results in terms of QoL**
- Then we can analyze everything we like but it is secondary

Locoregional control of disease

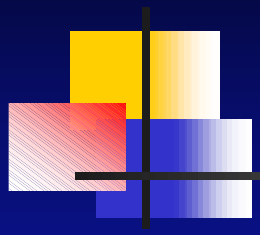
Is IMRT better than 3D-CRT in oropharyngeal cancer?

Comparison of clinical outcomes of IMRT for oropharyngeal carcinoma

Authors	stage	n. of pts	Median f.up (mo)	LC % 3 ys	RC % 3 ys	LRC 3ys %
Chao, Washington, 2004	III-IV	31	33	**	**	77#
Lee MDACC, 2006	III-IV	41	31	95	94	92
De Arruda MSKCC, 2006	III-IV	48	18	98*	88*	**
Garden, MDACC , 2007	I-III	51	45	96	**	94*
Sanguineti Texas, 2008	I-III	50	33	94	88	84
Huang UCSF, 2008	III-IV	71	33	94	94	90
Eisbruch Michigan		43	32	**	**	94

* 2 ys #4 ys

K. Huang and coll. S. Francisco - Cancer August 1, 2008, vol 113, n. 3



Results in terms of QoL

Health-related QoL outcomes following IMRT versus CRT for oropharyngeal SCC

- 26 patient treated using IMRT and 27 treated using CRT
- At 12 months after treatment the IMRT group had better HRQoL in all domains, including eating, speech, aesthetics and social disruption, compared with the CRT group

Table 4. Percentage of patients with high, medium, and low 12-month HNCI scores by type of radiation

HNCI domain/level of score	IMRT (n = 26)	CRT (n = 27)
Eating		
High	25.0	15.4
Intermediate	70.8	34.6
Low	4.2	50.0
Speech		
High	88.5	69.2
Intermediate	11.5	30.8
Low	—	—
Aesthetics		
High	92.3	80.8
Intermediate	7.7	7.7
Low	—	11.5
Social disruption		
High	84.6	69.2
Intermediate	15.4	30.8
Low	—	—

Abbreviations: HNCI = Head and Neck Cancer Inventory; IMRT = intensity-modulated radiation therapy; CRT = conventional radiation therapy.

Health-related QoL outcomes following IMRT versus CRT for oropharyngeal SCC

Mean eating scores

- At 3 month after RT, virtually the same for both groups
- Better improvement in the IMRT group at 1 year

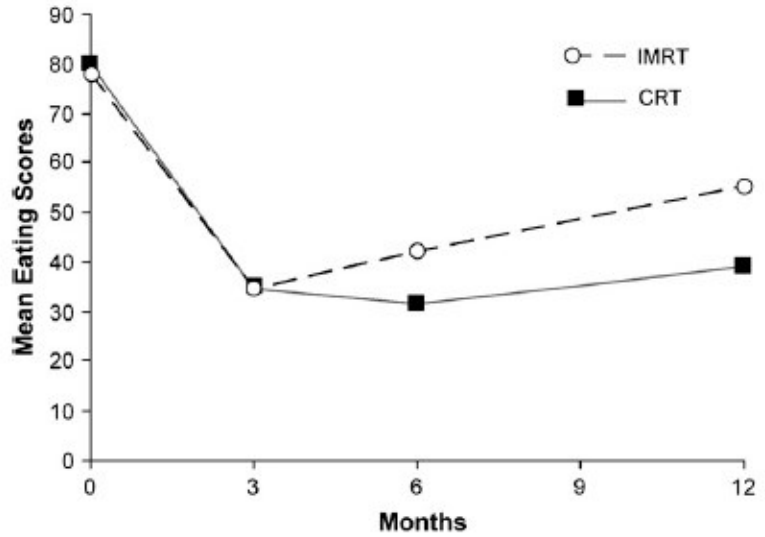


Fig. 1. Mean eating scores across the first year for patients treated using intensity-modulated radiotherapy (IMRT) compared with conventional radiation (CRT). The IMRT group included patients treated with IMRT after October 2002. Eating scores at 0 time point are pretreatment scores.

IMRT reduce radiation-induced morbidity and improves health-related QoL: results of a non randomided prospective study using a standardized follow-up program

- From 2000, prespective assesment of acute and late morbidity (RTOG and HRQoL)
- 2000-2004: 3DCRT (150 pts)
- 2004-> IMRT (91 pts)
- Significant reduction of the mean dose of the parotid gland (27 vs 43 Gy) with IMRT
- At 6 month
  - xerostomia (G2 or higher) lower after IMRT vs 3D- CRT
  - Positive effect on several general and H&N specific HRQoL dimensions

MARIJE R. VERGEER, IJROBP, Vol. 74, N. 1, 1–8, 2009, Amsterdam

IMRT reduce radiation-induced morbidity and improves health-related QoL: results of a non randomided prospective study using a standardized follow-up program

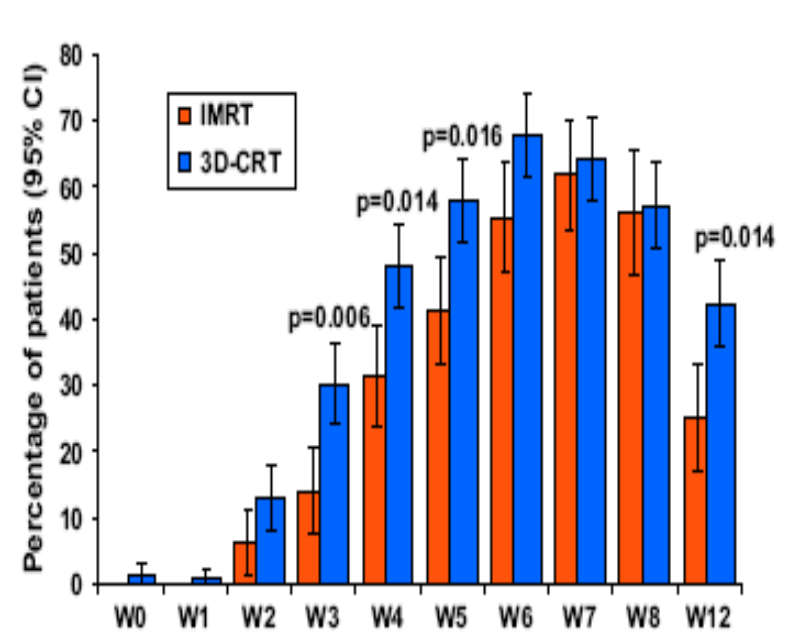
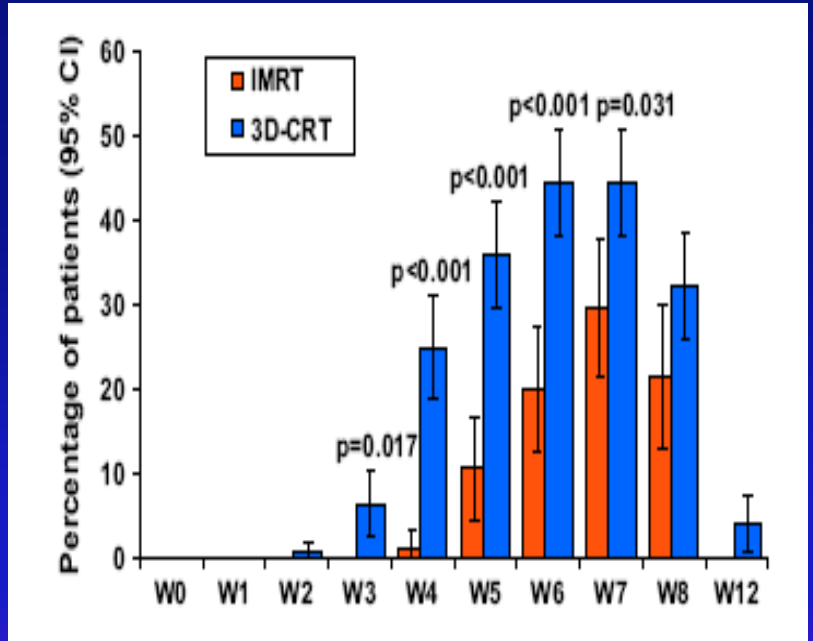


Fig. 2. Acute xerostomia Grade 2 according to Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring System.



Note:The prevalence of grade 3 or higher mucositis was significantly lower among IMRT-treated patients. This is most likely due to the SIB-technique used with a lower dose per fraction and a longer overall treatment time of radiation for the elective part of the target volume.

MARIJE R. VERGEER, IJROBP, Vol. 74, N. 1, 1–8, 2009, Amsterdam

Intensity-modulated chemoradiation for treatment of stage III and IV Oropharyngeal carcinoma

- 71 patients, 2000-2004
  - GTV 70 Gy in 2.12 Gy/fr
  - CTV high-risk 59.4 Gy in 1.8 Gy/fr
  - CTV low-risk 54 in 1.64 Gy/fr
- 3-ys LC, LRC, OS were 94%, 90% and 83%
- Late xerostomia:
  - grade 0 in 16 patients
  - Grade 1 in 31 patients
  - Grade 2 in 24 patients

K. Huang and coll. S. Francisco – Cancer August 1, 2008, vol 113, n. 3

So, IMRT seems better than 3DCRT….

Should everyone use IMRT to treat these tumors?

Some Notes…

- Selection bias in IMRT series
- When IMRT is compared to 3DCRT from the same era, there is no difference in outcome (Hodge et al IJROBP 69, 2007)
- Better outcome due to a change in the disease (HPV related cases?)

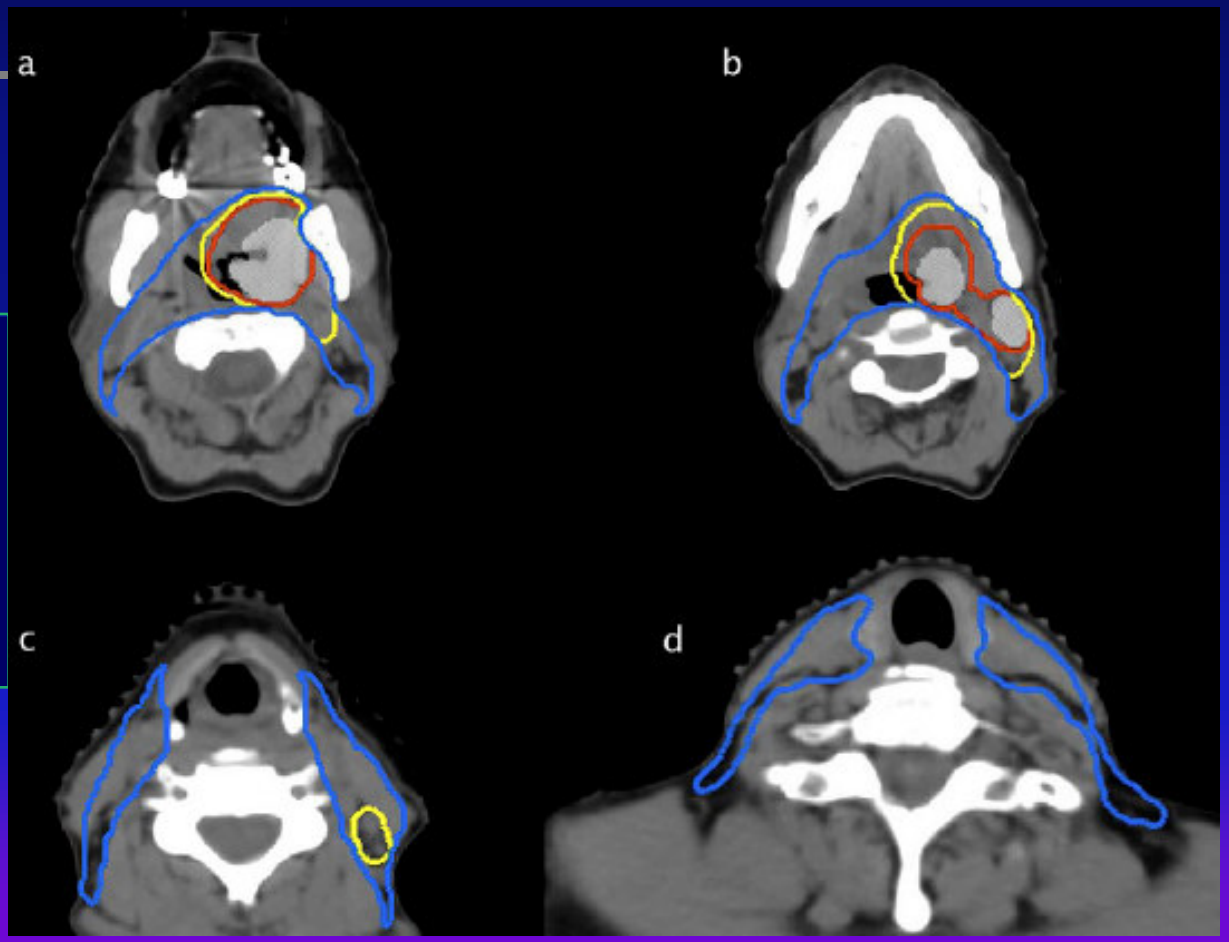
Patterns of locoregional failure after exclusive IMRT for oropharyngeal carcinoma

- 2002-2006: 50 patient eligible
  - Definitive IMRT without chemo
  - No pretreatment radical surgery
  - Minimal follow up
- Median follow up: 32.6 months
  - 3 local and 6 regional failure

G. Sanguineti e coll. – Galveston, Texas
IJROBP vol 72, 2, 737-746, 2008

Patterns of locoregional failure after exclusive IMRT for oropharyngeal carcinoma

- GTV: Colorwash gray
- CTV3: blu line
- CTV2: yellow line
- CTV1: red line



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Patterns of locoregional failure after exclusive IMRT for oropharyngeal carcinoma

- 9 failures /50 patients
  - 4 in the neck treated electively to the lowest dose level
  - Retrospective identification of initial positive lymph nodes that might have justified the subsequent failure
  - 5 failures in proximity of the high-dose volume
  - Most failures around the high-dose region were "true failures" with no apparent technical causes

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IMRT for oropharyngeal carcinoma: impact of tumor volume

- 1997-2001
- 31/74 patients treated with definitive IMRT
- LRC 77% (4 years from diagnosis)
- multivariate analysis: GTV and nGTV independent factors determining LRC and DFS
- GTV: the only indipendent factor with an impact on DMFS

Impact of the type of imaging modality on target volumes delineation and dose distribution in pharyngo-laryngeal SC carcinoma: comparison between pre- and per-treatment studies

- 18 patient (oropharynx, larynx/hypopharynx)
- CT, MRI and FDG-PET pretreatment and during treatment (46 Gy)
- Coregistration: manual delineation of GTVs on CT and MRI, automatic on FDG-PET

Geets X. Et coll. – Rad Onc 78 (2006) 291-297

Impact of the type of imaging modality on target volumes delineation and dose distribution in pharyngo-laryngeal SC carcinoma: comparison between pre- and per-treatment studies

- Results:
- GTVs based on FDG-PET
  - are smaller (vs CT or MRI)
  - impact on the delineation of CTV and PTV
- FDG-PET based CRT results in smaller irradiated volumes with significant dose sparing to the parotid glands

Geets X. Et coll. – Rad Onc 78 (2006) 291-297

Impact of the type of imaging modality on target volumes delineation and dose distribution in pharyngo-laryngeal SC carcinoma: comparison between pre- and per-treatment studies

- Results:
  - tumor volume re-assessment during treatment with CT-scan or MRI is feasible and results in smaller TVs compared to the pre-treatment CT
  - The use of per-treatment images with CT- scan or MRI impacts on dose distribution with increase normal tissue sparing

Impact of the type of imaging modality on target volumes delineation and dose distribution in pharyngo-laryngeal SC carcinoma: comparison between pre- and per-treatment studies

- Warning!
  - Integration of FDG-PET: proper methodology to avoid introduction of inaccuracies
  - To which extend one could safely reduce the TVs during radiotherapy?
  - All the delineated volumes were ultimately registered on the pre-treatment planning CT, but **during RT anatomy changes** (deformation of external neck contour, tumor shrinkage with shift of the normal structures, parotid shrinkage)

FDG-PET/CT guided intensity modulated head and neck radiotherapy: a pilot investigation

- 63 consecutive patients with H&N tumors (75% oropharynx)
- GTV-CT: designed on CT readings of the study's radiology consultants
- GTV-PET: created according to FDG-PET/CT fusion imaging, consisted of all areas of increase FDG uptake
- No prophylactic treatment of all FCG-PET/CT negative nodal levels
- Single high dose CTV (GTV + 1-2 cm)

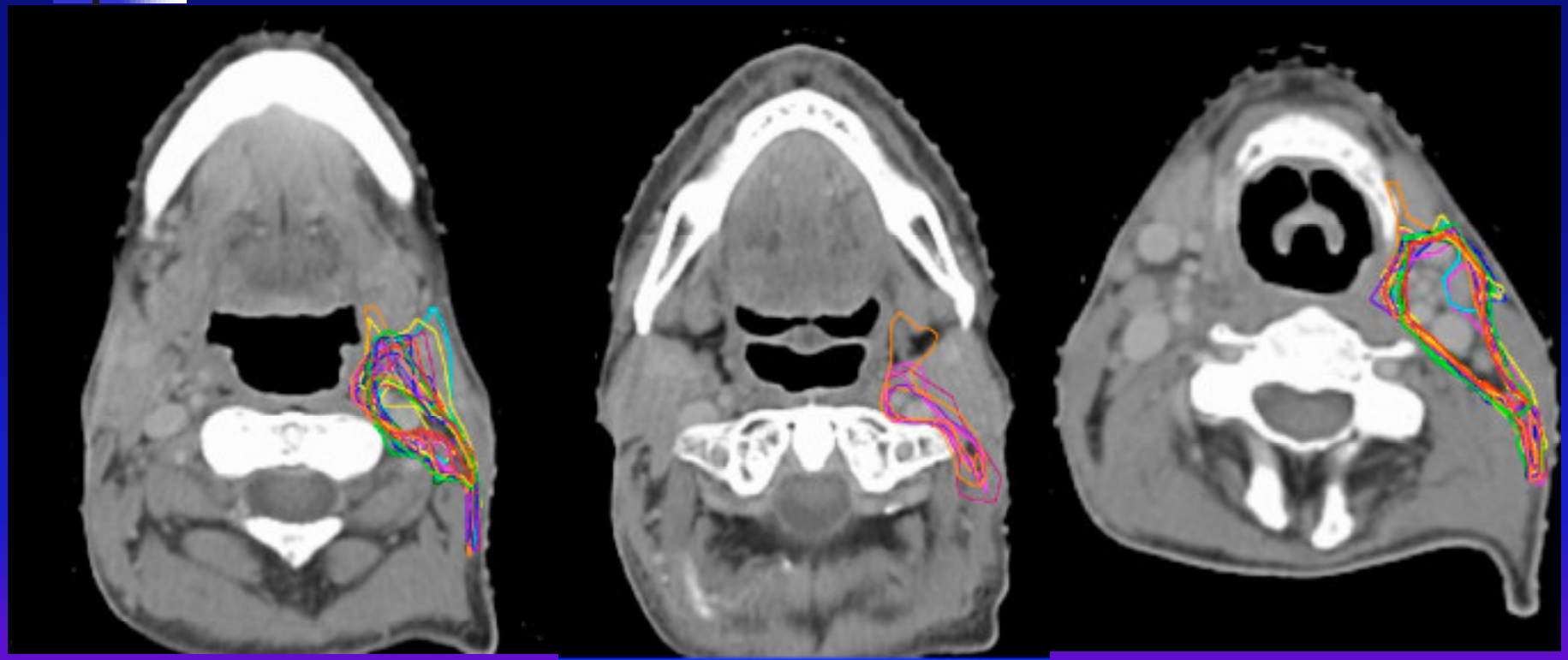
FDG-PET/CT guided intensity modulated head and neck radiotherapy: a pilot investigation

- 26 neck side underwent dissection (14 unilateral, 6 bilateral)
- FDG-PET/CT localized 26 of 27 pathologically involved nodal levels (96% sensitivity) and provided 98.5% (68 of 69) specificity.
- Negative and positive predictive values for nodal level staging were 98.5% e 96%
- The planning did not suffer a geographic nodal miss in this series when correlated with pathology results

FDG-PET/CT guided intensity modulated head and neck radiotherapy: a pilot investigation

- Multimodality imaging can facilitate individualized H&N IMRT treatment that intensifies treatment of disease, while protecting normal tissue
- The authors do no recommend routine clinical use of FDG-PET/C- directed IMRT planning until the accuracy of this imaging strategy is fully verified

Anyway differences between observers will always exist!



Importance of patient examination to clinical quality assurance in H&N radiation oncology

- 134 consecutive patient
- Peer review (H&N examination and imaging review to confirm target localization) led to changes in the treatment plans for 66% of patients
- Most of these changes were minor but
- 11% of the changes were major and could have potentially affected the therapeutic outcome or normal tissue toxicity

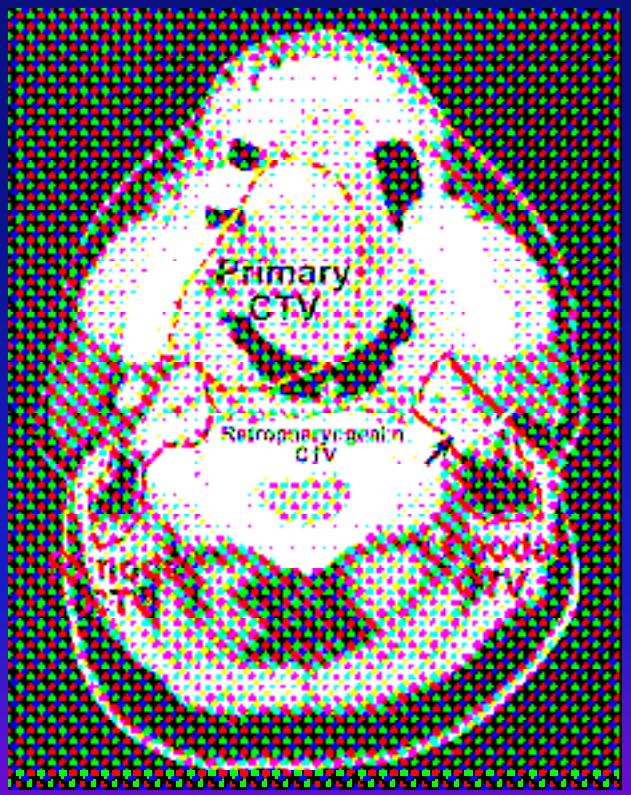
Rosenthal DI et al – Head Neck 2006; 28: 967-973

How to spare parotid irradiation?

- 1° step: in limited disease (T1-2 N0-2b) is it necessary to treat contralateral node levels?
- Obviously it depends on the subsite (tonsil ? base of tongue), the presence of omolateral nodes and the volume of T
- If yes, which ones and how?

Recurrences near base of skull after IMRT for H&N cancer: implication for target delineation in high neck and for parotid gland sparing

- 133 patients, [80 with oropharyngeal cancer (43 exclusive RT, 37 postoperative RT)]
- No contralateral clinical nodes but high risk
- The subdigastric node was defined as the superior-most target in the upper neck (Level II) in the clinically non-involved side of the neck, contralateral to the main bulk of the primary tumor



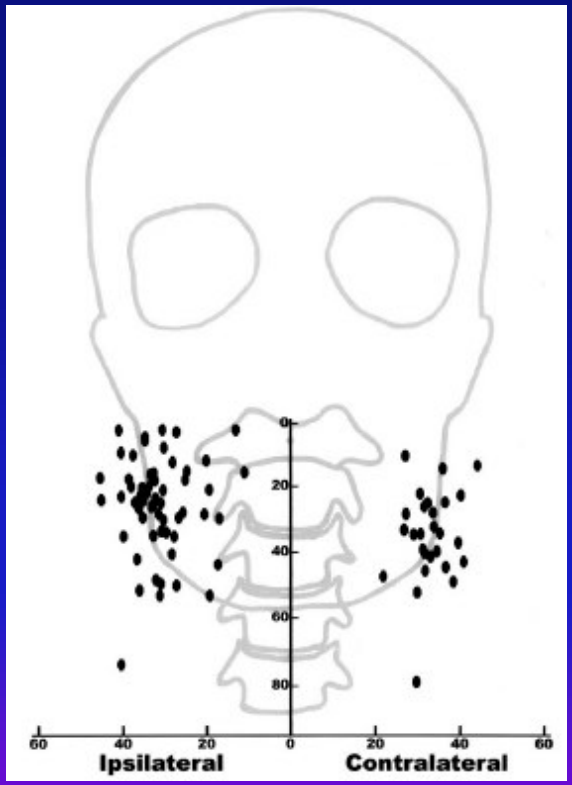
Recurrences near base of skull after IMRT for H&N cancer: implication for target delineation in high neck and for parotid gland sparing

- 21/133 (15%) LR recurrences
- 17 in field, 4 marginal
- No recurrences contralateral cranial to the subdigastric nodes
- Three (marginal) retropharyngeal node recurrences therefore target area extended to the level of C1 retropharyngeal
- 82% of cases contralateral dose to the parotid below 26 Gy

Location of cervical lymph node metastases in oropharyngeal and hypopharyngeal carcinoma: implication for cranial border of elective nodal target volumes

- 40 oropharyngeal tumors
- No retropharyngeal metastatic lymph nodes were found

- *"Contralateral metastatic lymph nodes are more caudally located than are ipsilateral metastatic lymph nodes.*



Most cranial metastatic lymph nodes

Pètra M. Prins-Braam et coll Utrecht, The Netherlands – IJROBP, vol. 58, 1 132-138, 2004

Location of cervical lymph node metastases in oropharyngeal and hypopharyngeal carcinoma: implication for cranial border of elective nodal target volumes

- *In elective irradiation, lowering the cranial border of the contralateral nodal target volume with 20 mm below the base of skull should be considered"*
- Influence of lowering the cranial border of the Level II radiation field on the probability of radiation induced xerostomia: 30% of reduction in the complication rate lowering the cranial border from C1 to C2 using IMRT
- *Lowering the border at the ipsilateral site is not advised*

Pètra M. Prins-Braam et coll Utrecht, The Netherlands – IJROBP, vol. 58, 1 132-138, 2004

Dose-effect relationship for the submandibular salivary glands and implication for their sparing by IMRT

- Several studies showed significant correlation between patient-reported xerostomia scores and salivary output, whereas other did not
- Sparing of the salivary glands alone is not sufficient to prevent symptoms of dry mouth
- Importance of the submandibular glands in secreting saliva in non stimulated state
- Lack of mucin in the parotid saliva

C.A. Murdoch-Kinch et al. IJROBP, 72, 2,373-382,2008

Dose-effect relationship for the submandibular salivary glands and implication for their sparing by IMRT

- 148 H&N patients
- Selective salivary flow rate measurement from Wharton's duct
- Correlation with dose to SMGs

Results

- SMG salivary flow rates depended on mean dose with recovery over time up to a threshold of 39 Gy.
- Substantial SMG dose reduction to below this threshold and without target underdosing is feasible in some patients, at the expense of modestly higher doses to some other organs.

C.A. Murdoch-Kinch et al. IJROBP, 72, 2,373-382,2008

Radiotherapy for Head and Neck cancer: is the "next level" down?

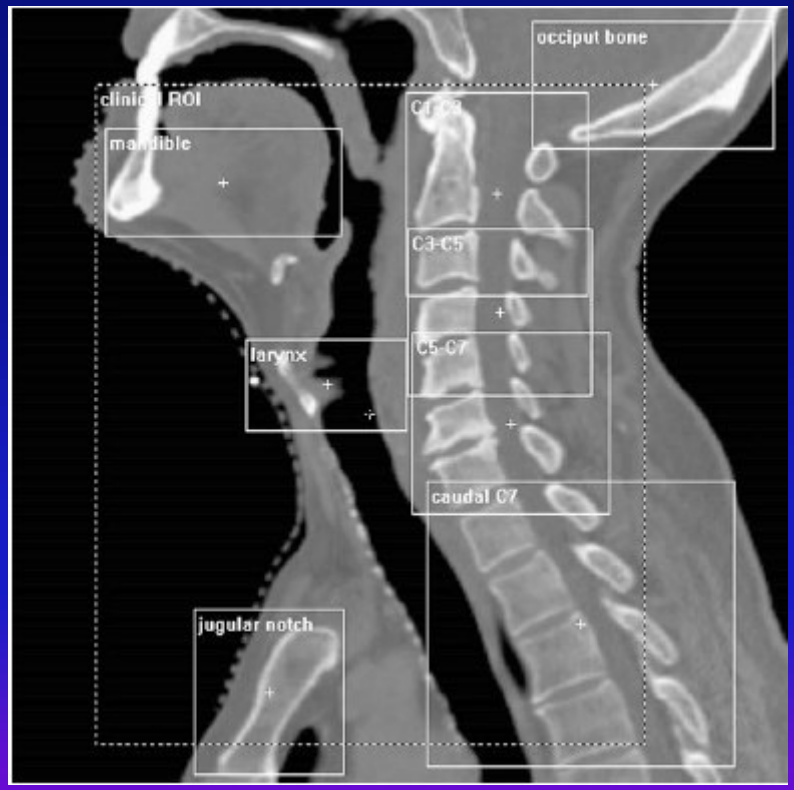
- Cannon and Lee reported three node positive patients with head-and-neck carcinomas (nasopharynx, 2 patients; tonsil, 1 patient) treated with definitive IMRT and concomitant chemotherapy .
- All had positive Level 2 nodes and received bilateral parotid sparing IMRT to reduce the risk of late xerostomia.
- Two patients developed a recurrence in the periparotid nodes, and 1 patient developed a recurrence in a parotid tail node that likely spread out of the node to the skin adjacent to the parotid tail.

Radiotherapy for Head and Neck cancer: is the "next level" down?

- "in our experience, we are usually unable to meaningfully spare the parotid (mean dose = 26 GY) if clinically positive Level 2 nodes are present in the side of the neck…"
- H&N cancer is relatively uncommon
- Treatment techniques are more demanding than dose used of many more common malignancies
- There is no standard method of defining the CTV
- The majority of practices (= 95%) do not track and report their outcomes

Setup uncertainties of anatomical sub-regions in H&N cancer patient after offline CBCT Guidance

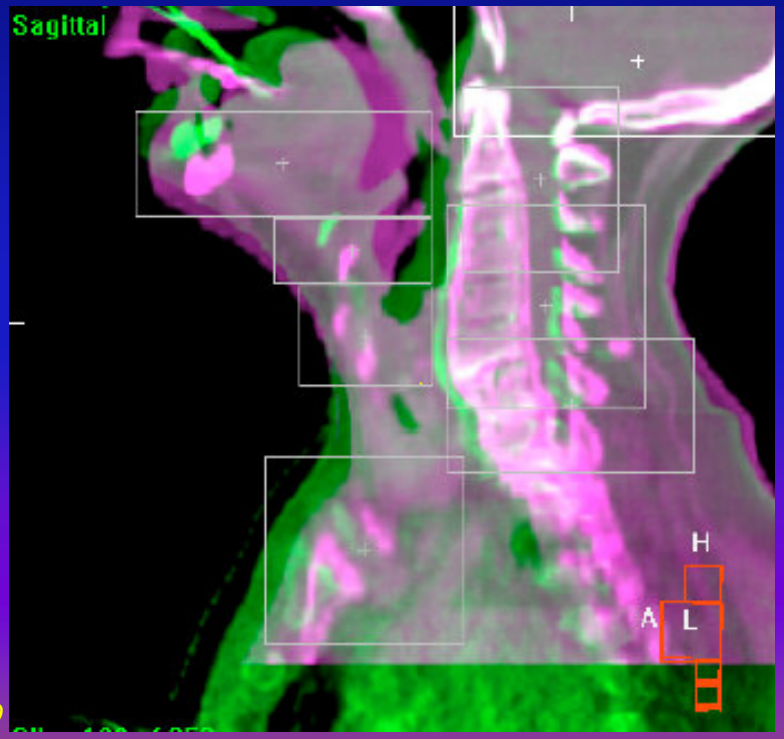
- For routine offline patient setup verification,
- CBCT scans before treatment
- delivery at regular intervals during the full course of treatment.
- 312 scans, on average 8.2 scans per patient.

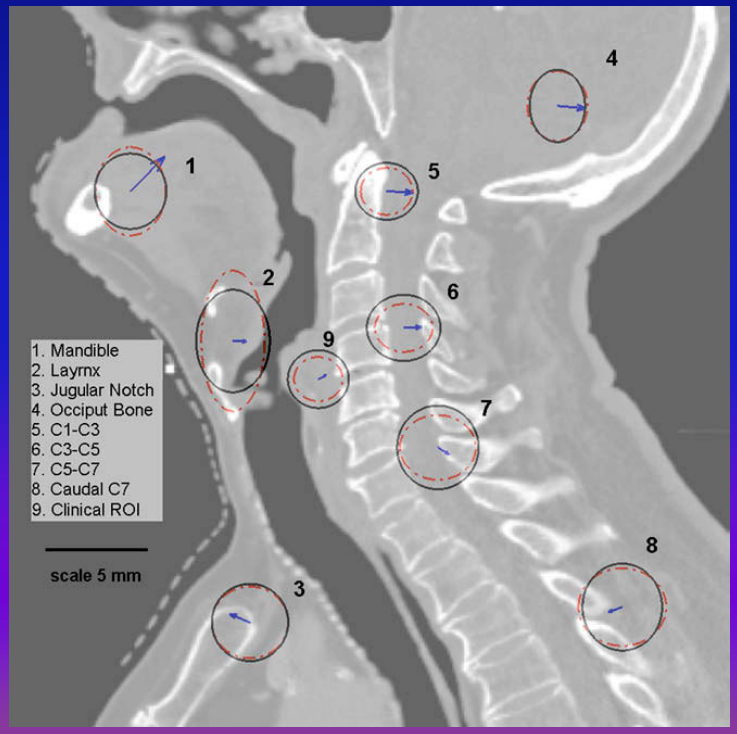


S. Van Kranen et alt, Amsterdam, JIROBP 73, 5, 1566-2573,2009

Setup uncertainties of anatomical sub-regions in H&N cancer patient after offline CBCT Guidance

- The neck shows flexibility despite immobilization
- If all movement are referred to C1-C3, the residual set up error increased with distance





Setup uncertainties of anatomical sub-regions in H&N cancer patient after offline CBCT Guidance

- Low incidence of time trends,
- Local setup errors with H&N cancer patients predominantly occur randomly and cannot generally be attributed to progressive change

- Isotropic margin of 5 mm:
  - Adequate for global patient set up uncertainty
  - Sufficient for the ROI containing C1-C3 o C3-C5
  - Insufficient considering deformations

S. Van Kranen et alt, Amsterdam, JIROBP 73, 5, 1566-2573,2009

Limitations of IMRT

- Certain dose distributions not physically achievable
- Objectives are sometimes difficult to define
- Uncertainties
  - Imaging devices: real extension of the disease
  - Definition of CTV
  - Positioning, distortions, intra and inter-fraction motion
- Inadequacies of planning, QA and delivery tools

IMRT pros and con

- More conformality
- Possibility to spare better the OARs
- Probably better TCP

- Commissioning
- Time consuming
  - Delineation of VOIs and OARs
  - Time for treatment delivery
- Hot and cold spots

Machines do not treat cancer!

- You need:
  - good radiologists
  - good radiation oncologists
  - good physicists
  - good radiation therapists

- Thank you for your attention