IMRT in Head and Neck Cancer: Beyond Parotid Sparing...

Prof. Jean Bourhis
Better and better target definition & delivery ...

- < 1950
- ≈ 1960
- ≈ 1990
- IMRT / stereo
- ≈ 2016
Head and neck cancer: radiation-induced side effects after CT-RT ...

- Significant impact on quality of life

- Xerostomia:
  - Most frequently Grade ≥ 2 were reported
  - Impact on quality of life increases with time

- Dysphagia:
  - Most frequently Grade ≥ 3 were reported
  - Major impact on quality of life
  - Impact more pronounced in first 12 months after completion of RT

- Trismus, Dental defect, Neck fibrosis ...
High dose (50-70 Gy)

Side Effects In HNC

Large volume (50 Gy in 800-1600 cc)
High dose: can we decrease the dose?

Side effects

Large volume
Small variations in dose → major impact

70 Gy + Cisplatin,

N= 840 patients randomized

Estimated percentage locoregional failure-free

0 1 2 3 4

Years following end of radiotherapy

Compliant plan by TMC

No adv impact

Adv impact

2P < 0.0001

＜ 10% PTV
Less than 66.5 Gy

＞ 10% of PTV
Less than 66.5 Gy

(Peters JCO 2010)
No compromise with the RT dose +++ (HPV ?)

but ... can we decrease safely
the _volume_ of RT ? to decrease side effects ?
GTV = 44 cc
High risk CTV
(+ 5 mm)

= 93 cc
PTV 50 Gy

= 879 cc
(95% isodose)
Tomotherapy)
PTV 50 Gy
3D RT
(95% isodose)

= 1489 cc
IMRT

1) Better normal tissue protection

2) Dose escalation to the tumor
   *Interesting if*:
   - Most relapses in the GTV
   - Dose effect relationship

3) Dose sculpting
Phase III study: 3D-CRT versus IMRT

- **3D-CRT**
  - 47 patients
  - 60-65 Gy in 30 fractions
  - $D_{\text{mean}}$ parotid glands:
    - Ipsilateral: 61.0 Gy
    - Contralateral: 61.0 Gy

- **IMRT**
  - 47 patients
  - 60-65 Gy in 30 fractions
  - $D_{\text{mean}}$ parotid glands:
    - Ipsilateral: 46.7 Gy
    - Contralateral: 25.4 Gy

Nutting et al, Lancet Oncol 2011
Gain with IMRT

Nutting et al, Lancet Oncol 2011
The PARSPORT trial
Dynamics of swallowing recovery after IMRT for locally advanced oropharyngeal SCC

Feng et al. JCO; 2010
Is parotid sparing compromising tumor control probability?
Does recurrence rate increase by using parotid-sparing IMRT in head and neck cancer?

No

Recurrences after conformal parotid-sparing radiotherapy for head and neck cancer

No.
Does recurrence rate increase by using parotid-sparing IMRT in head and neck cancer?

No

CLINICAL INVESTIGATION

MARGIN ON GROSS TUMOR VOLUME AND RISK OF LOCAL RECURRENT IN HEAD-AND-NECK CANCER

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Locoregional Failure Analysis in Head-and-Neck Cancer Patients Treated with IMRT

Gabriela Studer, Urs M. Luetolf, Christoph Glanzmann

Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer

Gordon O. Schoenfeld, M.D., Robert J. Amdur, M.D., Christopher G. Morris, M.S., Jonathan G. Li, Ph.D., Russell W. Hinerman, M.D., and William M. Mendenhall, M.D.

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Does recurrence rate increase by using parotid-sparing IMRT in head and neck cancer? *(more recent series)*

Clinical Investigation: Head and Neck Cancer

Patterns of Disease Recurrence Following Treatment of Oropharyngeal Cancer With Intensity Modulated Radiation Therapy

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INTENSITY-MODULATED RADIOTHERAPY IN THE TREATMENT OF OROPHARYNGEAL CANCER: CLINICAL OUTCOMES AND PATTERNS OF FAILURE

Megan E. Daly, M.D., Quynh-Thu Le, M.D., Peter G. Maxim, Ph.D., Billy W. Luo, Jr., M.D., Ph.D., Michael J. Kaplan, M.D., Nancy J. Fischbein, M.D., Harlan Pinto, M.D., and Daniel T. Chang, M.D.

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IMRT: beyond parotid sparing?
Uni or bilateral radiotherapy?

- Well (very) lateralized tumors
- Minimal nodal involvement
- Other than base of tongue & soft palate tumors
Carotid sparing IMRT: example in early glottic cancer

N = 23 patients treated at CHUV
Median Follow-up = 4 years,
Local control = 100%
van Luijk et al 2012:

- **Parotid stem cells**: necessary for the maintenance of organ function

- Reductions of RT dose to some parts of the gland allow the **parotid to regenerate**

- Stem cells located in the **central part of the major ducts** of the parotid

- **Proton RT to this central part of the gland** resulted in a significant reduction in saliva production in rats
Parotid stem cells sparing

- Region of major salivary ducts most radiosensitive part
- Stem cells located along salivary ducts (*mouse, rat, humans*)

C-kit positive cells
The cranio-ventral region contains the major ducts

Most predictive of saliva dysfunction at 1 year (van Luyck, N = 36 patients)
Stem-cell sparing IMRT
Planning comparison study

Based on planning comparison: expected reduction severe xerostomia (<25% salivary at baseline): 50% ▶ <20%
Ongoing randomized trial *(Groningen, Netherlands)*

N = 102 HNC patients randomized

Stem-cell sparing IMRT

Standard whole parotid sparing IMRT
Swallowing sparing IMRT

Pharyngeal constrictor muscles = variables for tube feeding dependence

DOSE VOLUME PARAMETERS

OTHER FACTORS

• Sex
• Age
• Tumour-stage
• Nodal-stage
• RT technique
• Chemotherapy
• Fractionation
• Site
• Baseline dysphagia
• Weight loss

Christianen, et al. Radiother Oncol 2012
Grade ≥ 2 dysphagia at 6 months

Superior PCM

Supraglottic area

Christianen, et al. Radiother Oncol 2012
Swallowing sparing IMRT
From DOSE reduction to RISK reduction …

Van der Laan, et al. Radiother Oncol 2011
Planning comparison
Standard IMRT versus swallowing sparing IMRT (SW-IMRT)

- **Standard IMRT:**
  - Dose reduction parotid glands
  - No dose constraints for superior PCM and supraglottis
  - $D_{\text{mean}}$ superior PCM = 64 Gy
  - $D_{\text{mean}}$ supraglottis = 60 Gy

- **Swallowing sparing IMRT:**
  - Dose reduction parotid glands
  - Dose reduction superior PCM and supraglottis
  - $D_{\text{mean}}$ superior PCM = 54 Gy
  - $D_{\text{mean}}$ supraglottis = 30 Gy
The future: Adaptive RT with molecular imaging ...?
Adaptive Radiotherapy

Dose sculpting based on functional imaging

Ex: Ga68-RGD imaging angiogenesis ... (CHUV)
Proton better than IMRT?
Head and neck: need for spot scanning (PSI)

Courtesy PSI
Protons (IMPT) vs. IMRT

Cozzi et al, Zeit Med Phys 2004
Avoiding IMRT ?...
EORTC-GORTEC-SAKK Intergroup
“Best-of”: TOS versus IMRT in early stage OPC

Assess eligibility:
Stage I/II
OPC $T_{1,2}N_0M_0$

Stratification for:
HPV-status, T, sub-site, institution, baseline-MDADI

Baseline function/QoL-status/MRI or CT-neck c contrast, CT-chest, pan-endoscopy, adequate trans-oral access

CT or MRI after 8-10 weeks:
CR – observation
PR – endoscopy, biopsy, salvage
NR – endoscopy, biopsy, salvage

1. Dysphagia related QoL (MDADI)
2. QoL/function
3. OS, DSS, PFS
4. LC, LRC
At 3, 6, 9 months, 1 year and 2 years

Risk-stratified
RT 60Gy for PI/LVI/CM or CRT 66Gy for pN1 with ECS and R1

Basic science package

Trans-oral surgery + uni-or bilateral selective neck dissection

IMRT+SIB 66-70Gy definitive dose, 54.25Gy prophylactic dose
Up-coming ASCO
2007-01 & 02 GORTEC randomized trials

- **≤ N2a**
  - RT
  - RT + Erbitux
  - RT + Carbo-5FU + erbitux
  - 406 pts included

- **>= N2b**
  - RT
  - RT + platin-5FU x 3
  - TPF x 3
  - Erbitux + RT
  - 370 pts included
GORTEC 2015-03 / Debio

Randomized phase II in locally advanced HNSCC (stage III / IV, HPV- if oropharynx)

- CDDP-RT + Placebo
- CDDP-RT + Debio 11-43
Phase II: primary end point LRC at 15 months (60% in the Bonner study) to 80%. 57 patients / arm (114 patients)
Since November 2012: Labeled by INCA (French National Cancer Institute) as a cooperative intergroups GORTEC-GETTEC-GERCOR