State of the art for radiotherapy of SCCHN
Head & neck cancer = 42,000 new cases/year in Europe

Cured

Less side effects
More organ & function preservation

Not cured

Local failure

More effective systemic treatment

Distant failure
Advances in radiotherapy for HNC

1) Lessons from randomized trials

2) IMRT : beyond parotid sparing ?

3) New approaches ?
Advances in radiotherapy for HNC

1) Lessons from randomized trials

2) IMRT: beyond parotid sparing?

3) New approaches?
Randomized trials
EBM level 1

Other randomized trials

GOITEC
Groupe d’Oncologie Radiothérapie Tête Et Cou
Radiotherapy oncology group for head & neck

MACH-NC
Meta-Analysis of Chemotherapy in Head & Neck Cancer
Lessons from randomized trials: 70 Gy / 7 weeks alone = Perhaps the worst we can do …!
Lessons from randomized trial … (II)

Altered Fractionation

Level of Evidence (EBM-1)

Use in routine practice

Chemo-RT

Cetuximab

IMRT

Induction

Chemo

Other EGFr targeting

Hypoxia targeting
Lessons from randomized trial … (II)

Level of Evidence (EBM-1)

Altered Fractionation

Hypoxia targeting

Other EGFr targeting

Use in routine practice

Chemo-RT

Cetuximab

IMRT

Induction Chemo
Concomitant chemo-RT

More efficient on tumor control / survival ...

But also more side effects ++ ... !

= is considered in Europe as a standard of care
Meta-Analysis of Chemotherapy in Head & Neck Cancer

Why CT-RT is a standard treatment?

- Local failure: RT + 5FU-platin (63.2%)
- Distant failure: RT + 5FU-platin (18.9%)
- RT (49.7%)

Pignon et al, Radiother Oncol 2009
Which type of concomitant CT-RT?

Which drugs?

Increasing / decreasing the dose intensity?
### Survival by type of concomitant CT

<table>
<thead>
<tr>
<th>Type of chemotherapy</th>
<th>No. Deaths / No. Entered</th>
<th>O-E Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
<th>p of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(a) Poly chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU and Platin</td>
<td>602 / 940</td>
<td>695 / 931</td>
<td>-92.2</td>
<td>317.6</td>
<td>0.75 [0.67;0.84]</td>
</tr>
<tr>
<td>5-FU or Platin</td>
<td>495 / 743</td>
<td>543 / 795</td>
<td>-45.8</td>
<td>250.0</td>
<td>0.83 [0.74;0.94]</td>
</tr>
<tr>
<td>Neither 5-FU nor Platin</td>
<td>62 / 115</td>
<td>85 / 129</td>
<td>-11.1</td>
<td>35.0</td>
<td>0.73 [0.52;1.01]</td>
</tr>
<tr>
<td>Subtotal (a)</td>
<td>1159 / 1798</td>
<td>1323 / 1855</td>
<td>-149.0</td>
<td>602.6</td>
<td>0.78 [0.72;0.85]</td>
</tr>
<tr>
<td><strong>(b) Mono chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono cisplatin</td>
<td>703 / 1151</td>
<td>739 / 1059</td>
<td>-102.6</td>
<td>341.8</td>
<td>0.74 [0.67;0.82]</td>
</tr>
<tr>
<td>Mono Other</td>
<td>1309 / 1875</td>
<td>1327 / 1877</td>
<td>-74.8</td>
<td>643.3</td>
<td>0.89 [0.82;0.96]</td>
</tr>
<tr>
<td>Subtotal (b)</td>
<td>2012 / 3026</td>
<td>2066 / 2936</td>
<td>-177.4</td>
<td>985.1</td>
<td>0.84 [0.78;0.89]</td>
</tr>
<tr>
<td><strong>Total (a … b)</strong></td>
<td>3171 / 4824</td>
<td>3389 / 4791</td>
<td>-326.4</td>
<td>1587.7</td>
<td>0.81 [0.78;0.86]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2_1 = 1.69$ p = 0.19
Which type of concomitant CT-RT?

(I)

Which drugs?

Decreasing the dose intensity of Chemo?
A randomized trial (USA, 1987) included in the MACH-NC database

Concomitant 20 mg / m2 / week: no benefit ...

OS; p=0.81

Cisplatin 20mg/m² qw + RT (n=149)
RT alone (n=159)
Gortec 99-02 trial, 2 versus 3 cycles

(257 patients who received at least 68 Gy)

PFS
HR = 1.44 (0.99-2.0)
p = 0.05

Survival
HR = 1.40 (0.96-2.0)
p = 0.07

Bourhis et al Lancet Oncol 2012
Gortec 99-02 trial, 2 versus 3 cycles

(patients who received at least 68 Gy)

Locoregional failures
HR = 1.52 (0.92-2.5)
p = 0.09

Distant metastases
HR = 1.82 (0.99-3.3)
p = 0.05

Bourhis et al Lancet Oncol 2012
Which type of concomitant CT-RT?

(I)

Which drugs?

*Increasing the dose intensity of RT?*
CT-RT:
No gain by increasing the dose intensity of RT

Patients at risk

<table>
<thead>
<tr>
<th>Years</th>
<th>No gain</th>
<th>Very accelerated RT alone</th>
<th>Accelerated RT + 2 cycles CT</th>
<th>Conventional RT + 3 cycles CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>278</td>
<td>279</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>174</td>
<td>161</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>127</td>
<td>118</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>103</td>
<td>93</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>75</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>48</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>
Which type of concomitant CT-RT?

(I)

Which drugs?

Decreasing the dose of RT?
Small variations in dose → major impact

70 Gy + Cisplatin,

N = 840 patients randomized

(Peters JCO 2010)
No compromise with the dose of RT

but … can we decrease safely the volume of RT to decrease side effects?
Evolution of SCCHN radiotherapy...

- 2-D: ≈ 1960
- 3-D: ≈ 1990
- IMRT / 4D: ≈ 2010

< 1950
GTV 70 Gy

= 44 cc
High risk 70 Gy
(+ 5 mm)

= 93 cc
Elective 50 Gy

= 879 cc
Tomotherapy)
50Gy
3D conformal RT
= 1489 cc
Gain with IMRT

Nutting et al, Lancet Oncol 2011
The PARSPORT trial
Advances in radiotherapy for HNC

1) Lessons from randomized trials

2) IMRT : beyond parotid sparing ?

3) New approaches ?
Beyond Parotid sparing: 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
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)*

Stem-cell sparing IMRT

N = 102 HNC patients randomized

Standard whole parotid sparing IMRT
Prevention of Dysphagia

RT Dose to the pharyngeal constrictor muscles (PCM) = variable 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
Swallowing sparing IMRT
Translation from DOSE reduction to RISK reduction

Van der Laan, et al. Radiother Oncol 2011
Carotid sparing IMRT: example in early glottic cancer

N = 23 patients treated at CHUV
Median Follow-up = 4 years,
Local control = 100%

<table>
<thead>
<tr>
<th>Bilateral carotid dose</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>V35 (ml)</td>
<td></td>
</tr>
<tr>
<td>Mean, SD</td>
<td>0.45, 0.37</td>
</tr>
<tr>
<td>Range</td>
<td>0.0-0.98</td>
</tr>
<tr>
<td>Median</td>
<td>0.16</td>
</tr>
</tbody>
</table>
Uni or bilateral radiotherapy?

- Well (very) lateralized tumors
- Minimal nodal involvement
- Other than base of tongue & soft palate tumors
The future: Adaptive RT with molecular imaging...
Advances in radiotherapy for HNC

1) Lessons from randomized trials

2) IMRT : beyond parotid sparing ?

3) New approaches ?
What else Can be Optimized?

De-escalation for HPV?

Molecular targeted agents

Induction CT?

Immunotherapy
De-escalation for HPV?

What else Can we Optimize?

Molecular targeted agents

Induction CT?

Immunotherapy
ECOG 1308: HPV+ specific randomized trial

E1308 Induction followed by IMRT/Cetuximab

**ELIGIBILITY**
- Stage: III, IV A,B resectable
- Site: Oropharynx only
- HPV 16 ISH +ve or p16 IHC +
- N=83

**INDUCTION**
- (3 cycles)
  - Paclitaxel: 90mg/m2 qwk
  - Cisplatin: 75/m2 q21
  - Cetuximab: 250mg/m2 qwk

**RESPONSE**
- CR*
- IMRT 54Gy/27 fxs**
- Cetuximab 250mg/m2 qwk

*Complete response at primary site assessed by clinical and radiological exam.

**Patients with <CR at primary will receive 69.3Gy/33 Fxs with Cetuximab 250mg/m2 q wk**
RTOG 1016 - Cetuximab-RT vs. CT-RT if HPV(+) 

Eligibility 

- OPC 
- P16 (+) 
- Stage III / IV

Randomize to: 

1. RT 70 Gy/35f/6 wks + cisplatin x 2 
2. RT 70 Gy/35f/6 wks + cetuximab for 8 wks
De-escalation for HPV?

Molecular targeted agents

Induction CT?

Immunotherapy

What else Can be Optimized?
New insights for induction?

Phase III randomized study
TPF*† → cetuximab + RT vs carboplatin + 5-FU + RT

PFS (primary endpoint)

TPF*† → cetuximab + RT vs carboplatin + 5-FU + RT

www.clinicaltrials.gov/ct2/show/NCT01233843

2. Geoffrois L, et al. ASCO 2016 (Abstract No. 6000)
TPF related mortality in randomized trials

TPF related mortality (%)

0%

7%
TPF related mortality in randomized trials

TPF related Mortality (%)

Locally advanced N2-N3

Larynx preservation

Larynx preservation

Nasopharynx
TPF related mortality in randomized trials

TPF related mortality (%)

Locally advanced N2-N3
Locally advanced
Larynx preservation
Larynx preservation
Nasopharynx
Co-morbidies
What else Can we Optimize?

De-escalation for HPV?

Molecular targeted agents

Induction CT?

Immunotherapy
## Clinical trials of molecular targeted therapies in HNSCC

### EGFr targeting
- Gefitinib
- Cetuximab
- Others
  - Afatinib
  - Tirapazamine
  - Nimorazole
  - Celecoxib
  - COX2 inhib
  - Lapatanib
  - Gefitinib
  - Nimotuzumab

### V-EGF inhibitors
- Vandetanib
- Panitumumab
- Zalutumumab
- Afatinib
- Erolitinib
- Lapatanib
- Gefitinib
- Nimotuzumab

### mTOR inhibitor
- Rapamycin
- Everolimus
- Temsirolimus
- Temsirolimus

### PI3K inhibitor
- PX866
- BKM120
- Rigosertib
- BYL719

### Phase I-II
- Farnesyltransferase inhibitors
- PDK inhibitor
- AMPK activator
- MEK inhibitor
- Trametinib
- MET/VEGFR inhibitor
- FORETINIB
- E7050/Golvatinib
- MET inhibitor
- LY2801653

### Phase III
- Pazopanib
- Sorafenib
- Axitinib
- Sunitinib
- Bevacizumab
- ONYX-015 p53
- Advexin p53
- ONYX-015 p53
- AKT inhibitor
- Rapamycin
- Everolimus
- Temsirolimus
- Temsirolimus

### Others
- Nilotinib (c kit)
- Advexin p53
- ONYX-015 p53
- AKT inhibitor
- MK2206
- Rapamycin
- Everolimus
- Temsirolimus
- Temsirolimus
Clinical trials of molecular targeted therapies in HNSCC

Approved
- Gefitinib
- Cetuximab

V-EGF inhibitors
- Vandetanib
- Afatinib
- Lapatanib
- Nimotuzumab

EGFr targeting

Others
- Zalutumumab
- Panitumumab
- Erolitinib
- Afatinib
- Lapatanib
- Gefitinib
- Nimotuzumab

mTOR inhibitor
- Axitinib
- Sorafenib

PI3K inhibitor
- Pazopanib
- Sunitinib
- Bevacizumab

AKT inhibitor
- Erolitinib
- Zalutumumab

MEK inhibitor
- Panitumumab
- Afatinib
- Lapatanib

AMPK activator
- Nimotuzumab

PDK inhibitor
- Erolitinib
- Zalutumumab

Nilotinib (c-kit)

MET inhibitor
- Erolitinib
- Zalutumumab

Other targets
- KK inhibitor
- PDK inhibitor
Randomized Phase III trials testing EGFr targeting in HNSCC: cetuximab is the exception (and ---does not work with CT-RT RTOG 05-22…)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of action</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>EGFR TKI</td>
<td>negative</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR TKI</td>
<td>negative</td>
</tr>
<tr>
<td>Afatinib</td>
<td>EGFR/HER2 TKI</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR Chimeric MAb</td>
<td>positive</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>EGFR Humanized MAb</td>
<td>negative</td>
</tr>
<tr>
<td>Zalutumumab</td>
<td>EGFR MAb</td>
<td>negative</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>EGFR/HER2 TKI</td>
<td>negative</td>
</tr>
</tbody>
</table>

The only EGFr targeting agent working (ADCC ?)…
Adaptive RT

RT-CT

Altered fractionation

CT-RT ...

Cetuximab + RT

+ 13%

+ 10%
Adding cetuximab to CT-RT?
RTOG H05-22: Phase III (940 pts)

Stage III-IV

The addition of cetuximab to RT-cisplatin:

- No benefit in PFS / OS.
- More mucositis and skin reactions...
Adding chemotherapy to cetuximab-RT ? GORTEC 2007-01

= Treatment intensification with a cetuximab backbone.

Endpoints:
- Primary endpoint: PFS
- Secondary endpoint: Cumulative incidence of loco-regional progression

Erbitux 400mg/m² then 250mg/m² weekly; carboplatin 70mg/m²/d; 5-FU 600mg/m²/d

1. www.clinicaltrials.gov/ct2/show/NCT00609284;

* Off-label regimen for Erbitux
GORTEC 2007-01

**Progression-free survival**

- **Primary endpoint met (PFS)**

- **PFS at 3 years (95% CI):**
  - CT-Erbitux-RT**: 52.3% (45–59)
  - Erbitux-RT: 40.5% (34–48)

- **HR** 0.73 (0.57–0.94)
- 2-sided log-rank p=0.015

- **No. at risk:**
  - CT-cetux-RT**: 14 11 3 5 2
  - Cetux-RT: 4 4 5 0 3 9 20 12 97 6 4 1

- **Median follow-up of 4.4 years (CT-cetux-RT), 4.6 years (cetux-RT)**

*HR adjusted for N (0 vs 1–2), T (0–2 vs 3–4) and center in Cox model

**Off-label regimen for Erbitux**

Bournis J, et al. ASCO 2016 (Abstract No. 6003)
Optimisation of RT-CT

New molecular targeted agents

New induction CT

Combination with Immunotherapy
Activated T cell
Inhibitors of PD-1 and PD-L1 prevent the tumour cell from binding to PD-1, enabling the T cell to remain active.

“PD-1 inhibitors = the highest response rate of any single-agent immunotherapy,”
State of the art for radiotherapy of SCCHN

- **RT-CT**:  
  - RT-CT = a Standard of care  
  - Importance of RT / CT dose and of RT-QA & IMRT  
  - No need to increase the dose-intensity of RT  
  - Beyond parotid sparing ?

- **New approaches** …
  
  - Induction CT ?
  - HPV / de-escalation ?
  - New combinatory approaches with immunotherapy