Re-irradiation with curative intent for head and neck cancer ...

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Relatively high relapse rate?

Loco-regional

Distant

Risk of failure (%) vs Time from randomisation (years)

HR: 0.66

63.2%
50.2%
18.9%
16%

RT
RT + concomitant 5-FU / platin

Meta-Analysis of Chemotherapy in Head & Neck Cancer

Pignon JP et al 2009
Tumors that relapse may have a specific biological profile...

Resistance to cytotoxic agents etc...
Recurrence / second primary in previously irradiated area

**Treatment of choice =** salvage surgery

**Others :** Brachytherapy  
Re-irradiation  
Extreme 5FU-CDDP-Erbitux
Salvage surgery: not always successful ...

Ex: a series of 38 patients (over 25 years) with a local failure after RT for T1 glottic carcinoma (IGR)

Successful salvage
(= only 40%)

19 LT (50%)  8
9 LP        7
9 palliation -
1 n p       1
Large RT field for locally advanced cases

After RT-CT Salvage surgery may not be feasible

Fig. 4. Five-year rate of Grade 3–4 late toxicity of combined modality treatment (27 patients, RT+CT) vs. RT alone (17 patients, RT) assessed using three late toxicity scales simultaneously.

F Denis et al 2004
Locally advanced cases:

A series of 93 LR failure after CT-RT

(IGR, Temam et al)  

Only 38 could be operated (40%) with salvage procedure

Table 3. Indications for palliative treatment.

<table>
<thead>
<tr>
<th>Indications</th>
<th>No. of patients n = 55 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technically unresectable</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Low surgical curability</td>
<td>39 (71)</td>
</tr>
<tr>
<td>Poor health status</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>
2 predictors of outcome: initial stage and combined T + N relapse

P = 0.033, log rank test

Overall survival (mths)
Percent survival

Concurrent local and regional failure
Local or regional failure

P = 0.007, log rank test

Overall survival (mths)
Percent survival

Initial stage IV
Initial non-stage IV

P = 0.0005, log rank test for trend

Overall survival (mths)
Percent survival

Two predictors
One predictor
Zero predictor

P = 0.0007, log rank test
Table 2. Early and late post-operative complications

<table>
<thead>
<tr>
<th>Early complications &lt; 3 weeks</th>
<th>Surgery involving excisions of primary tumours (n=27)</th>
<th>Neck dissections exclusively (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with one or more complications</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Local infection/abscess</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Skin/soft tissue necrosis</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Fistula formation</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Partial/total flap necrosis</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Late complications &gt; 3 weeks</th>
<th>Surgery involving excisions of primary tumours (n=27)</th>
<th>Neck dissections exclusively (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with one or more complications</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Local infection/abscess</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Skin/soft tissue necrosis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Fistula formation</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pain/weakness of the shoulder</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* Vagus nerve injury
Full dose re-irradiation feasible in HNC?

- Feasible with increased, but acceptable toxicity
- **Limited volumes ++**, no re-irradiation of neurological structures
- **Curative potential** (13/169 pts > 5 years survivors, De Crevoisier series JCO 1998)
Feasibility of re-irradiation + 5FU / hydroxyurea

(E Vokes et al, 1988)
Feasibility of re-irradiation + concomitant chemotherapy (E Vokes et al, 1988)

RT-CT = 5FU 800 mg / m^2
hydroxyurea 1.5 g / j

5 x 2 Gy / week

6 cycles, overall time 11 weeks
Palliative

curative intent
Palliative treatments

Re-irradiation with curative intent
EXTREME (5FU, CDDP, Erbitux) : overall survival

HR (95% CI): 0.797 (0.644; 0.986)
Strat. log-rank test: 0.0362

Palliative re-irradiation?

Re-irradiation with curative intent
Previously Irradiated patients with recurrent HNC for palliation

Methotrexate 40 mg/m2 / week

Re-irradiation + CT
Phase III randomised trial

Randomized phase III trial (GORTEC 98-03) comparing re-irradiation plus chemotherapy versus methotrexate in patients with recurrent or a second primary head and neck squamous cell carcinoma, treated with a palliative intent

Radiother Oncol 2011

Table 4
Clinical response and patterns of failure.

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>R-RT (23) n (%)</th>
<th>Ch-T (20) n (%)</th>
<th>Total (43) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>4 (17%)</td>
<td>2 (10%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>2 (9%)</td>
<td>2 (10%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (13%)</td>
<td>4 (20%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Progression</td>
<td>14 (61%)</td>
<td>14 (70%)</td>
<td>28 (65%)</td>
</tr>
<tr>
<td>Overall response (CR + PR)</td>
<td>6 (26%)</td>
<td>2 (10%)</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>Loco-regional recurrence</td>
<td>14 (61%)</td>
<td>11 (55%)</td>
<td>25 (58%)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>5 (22%)</td>
<td>5 (25%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>Second cancer</td>
<td>2 (9%)</td>
<td>5 (25%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>
Palliative scenario:
methotrexate versus reirradiation + chemotherapy

Overall Survival

logrank: chi2 at 1 ddl = 0.184, p = 0.6684

R-RT ChT

At risk

30 7 2 1
27 6 2 1 1
Palliative re-irradiation

Re-irradiation with curative intent

Definitive RT-CT

Post-operative RT-CT
Palliative re-irradiation

Re-irradiation with curative intent

Definitive RT-CT

Post-operative RT-CT
Re-irradiation + concomitant chemo: experience at IGR

(De Crevoisier et al JCO 1998 N= 106 head and neck cancer patients)

• Previously irradiated area (mean cumulat. dose 115 Gy) Inoperable

• Feasibility and relatively good immediate tolerance

• Survival 24 % at 2 years
  14 % at 5 years (with CR)
Re-irradiation + concomitant chemo: experience at IGR

(De Crevoisier et al JCO 1998 N= 106 head and neck cancer patients)

• Main prognostic factor: size of the field (2D) (reflecting the tumor volume)

• Late effects:

  37% G 2-3 neck fibrosis,
  4% ostéoradionécrosis,
  17% mucosal necrosis
  23% severe trismus (< 5 mm).
105 patients with recurrent HNC (1996-2005)

Median cumulative dose 121 Gy

75% with concomitant chemo

Acute Grade 3–4 toxicities 23%

Severe Grade 3–4 late complications 12 patients

18 patients long term survivors with no evidence of disease
Palliative re-irradiation

Re-irradiation with curative intent

Definitive RT-CT

Post-operative RT-CT
Re-irradiation after salvage surgery in HNC?

- **Limited data** (few Phase II series)

- **Few large series**: ex, 25 patients (De Crevoisier, Cancer 2001)

- **Feasible, perhaps increased toxicity compared to Re-RT alone**?

  Ex. Bone necrosis, 16% versus 4%

  (De Crevoisier 1998 & 2001)
Reirradiation for Head-and-Neck Cancer: Delicate Balance Between Effectiveness and Toxicity
F Hoebers, et al 2011

• 58 patients re-RT with curative intent.

  Definitive Re-RT 53%,
  Salvage surgery + Re-RT 47%.

• Median cumulative dose 119 Gy

• Serious late toxicity ≥ Grade 3: 20 of 47 evaluable patients (43%).

• Approximately 1 in 3 patients survived re-RT without recurrence and severe complications.
Post-operative re-irradiation + chemo: how useful?
(JCO, Janot et al 2008)

Salvage surgery

- 60 Gy + chemo
- Wait and see = reference arm
Post-operative re-irradiation + chemo
: a randomized trial (JCO, Janot et al 2008)

- HNSCC: recurrence or second primary

- Previous RT >= 45 Gy

- Salvage surgery with macroscopically complete resection
  *(debulking not allowed)*

- **Limited** target volume ++
  - Tumor bed & zone at risk,
  - Spinal cord exclusion
  - No prophylaxia / nodes
  - Within 6 weeks after surgery
Acute toxicity $\geq$ grade 3 in the RT-CX arm

*(JCO, Janot et al 2008)*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosa</td>
<td>17</td>
</tr>
<tr>
<td>Skin</td>
<td>7</td>
</tr>
<tr>
<td>Pharynx</td>
<td>7</td>
</tr>
<tr>
<td>Larynx</td>
<td>6</td>
</tr>
<tr>
<td>General condition</td>
<td>4</td>
</tr>
<tr>
<td>Hand foot syndrom</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
</tbody>
</table>
Treatment potentially related deaths in the RT-CX arm

(JCO, Janot et al 2008)

- **3 from acute toxicity** (< 6 months): 2 fatal infections and one hemorrhage

- **2 from late toxicity**: one extensive mucosal necrosis (13 months) + one laryngeal oedema (16 months)
Late toxicity (Gr 3-4) at 2 years from randomization

*(JCO, Janot et al 2008)*

<table>
<thead>
<tr>
<th></th>
<th>RT-CT n=18 (3 missing)</th>
<th>« Wait and see » n=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sub-cutaneous</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Larynx</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Number of pts</td>
<td><strong>7 (39%)</strong></td>
<td><strong>2 (10.5%)</strong></td>
</tr>
</tbody>
</table>
Loco-regional control (time from randomization)

(JCO, Janot et al 2008)

Loco-regional control

Chemo-reirradiation
No treatment

logrank: p < 0.0001

No. of patients at risk

0% 20% 40% 60% 80% 100%
0 1 2 3 4 5 Years

- 65 35 18 9 6 3
- 65 19 7 7 5 2
### First carcinological event (time from randomization)

*(JCO, Janot et al 2008)*

<table>
<thead>
<tr>
<th></th>
<th>RT-CT</th>
<th>Wait/see</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 65</td>
<td></td>
<td>N= 65</td>
</tr>
<tr>
<td>Local relapse</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Nodal relapse</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Metastases</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Snd primary</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>
Progression free survival (main end point, time from randomization)

(JCO, Janot et al 2008)

Chemo-reirradiation
No treatment

logrank : p = 0.008
Overall survival (time from randomization)

(JCO, Janot et al 2008)

No. At risk

<table>
<thead>
<tr>
<th>Years</th>
<th>Chemo-reirradiation</th>
<th>No treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

logrank : p = 0.495
What are the recommendations for Re-irradiation ...?

• Which dose?

• Concomitant TTT?

• Cumulative total dose to the organs in series:
  (spinal cord, brainstem, optic nerve ...)

• Which volume?
What are the recommendations for Re-irradiation ...?

• Which dose?

• Concomitant TTT?

• Cumulative total dose to the organs in series:
  (spinal cord, brainstem, optic nerve ...)

• Which volume?
Location of recurrences after Re-RT

F Hoebers, et al 2011

- 82% (18 cases) high-dose area (≥60 Gy)
- 4% intermediate-dose area (46–59 Gy)
- 0% elective area (46 Gy)
- 14% outside the RT field.
Location of recurrences after Re-RT

F Hoebers, et al 2011

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- 14% outside the RT field.
What are the recommendations for Re-irradiation ...?

• Which dose?

• **Concomitant TTT**?

• Cumulative total dose to the organs in series:
  (spinal cord, brainstem, optic nerve ...)

• Which volume?
Re-RT alone or Re-RT + drug?

- **Historically**: Vokes RT-CT regimen

- **More toxicity with chemo?** +20% if concomitant chemo in *F Hoebers series, 2011*

- **Ongoing Gortec regimen**
  - **RT bifractionated**, 1.2 Gy twice daily, up to 66 Gy
  - **Cetuximab** weekly (250 mg/m2)
  - **Overall time**: 5.5 weeks

- **Other**: 6 x 6 Gy + Cetuximab, GTV < 3 cm (*Lartigau*)
What are the recommendations for Re-irradiation ...?

• Which dose?

• Concomitant TTT?

• Cumulative total dose to the organs in series: (spinal cord, brainstem, optic nerve ...) : no re-irradiation

• Which volume?
What are the recommendations for Re-irradiation ...?

• Which dose?

• Concomitant TTT?

• Cumulative total dose to the organs in series: (spinal cord, brainstem, optic nerve ...)

• Which volume?
No dose

93 cc

GTV

44 cc
SALVAGE RE-IRRADIATION FOR RECURRENT HEAD AND NECK CANCER

Nancy Lee, M.D.,* Kelvin Chan, B.A.,* Justin E. Bekelman, M.D.,* Joanne Chung, B.A.,*
James Mechalakos, Ph.D.,† Ashwatha Narayana, M.D.,* Suzanne Wolden, M.D.,*  
Ennapadam S. Venkatraman, Ph.D.,§ David Pfister, M.D.,§ Dennis Kraus, M.D.,§  
Jatin Shah, M.D.,§ and Michael J. Zelefsky, M.D.*

Departments of *Radiation Oncology, †Medical Physics, and ‡Biostatistics, and Divisions of §Head and Neck Oncology, Department of Medicine, and §Head and Neck Surgery, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY
What volume / dose should we recommend for re-irradiation?

**The secret** .... GTV + small margin = < 50 cc to < 100 cc  No prophylaxia +++

**IMRT / stereo are mandatory** *(decreases by a factor 2 the volume compared to 3D conformal RT)*

**Doses** adapted to the volume ...

Not < 60 Gy equivalent, as high as possible if small volumes (imaging).

80-90% of the relapses after Re-irradiation are within the GTV ...

University of Michigan 96% recurrences were within the GTV; No RT to areas of potential subclinical disease was given…
Re-irradiation : conclusions

- **Resectable** : Salvage surgery treatment of choice, Re-RT, volume and indication discussed case by case with the surgeon

- **Unresectable** *(relatively common situation)*
  - Difficult to manage : delicate balance efficacy / toxicity...
  - Full dose re-irradiation with IMRT +/- concomitant chemo = the only potential curative alternative to palliative chemo
  - Feasibility of this approach ++, but is associated with a curative potential and limited side effects only in a low proportion of patients.