Current approaches in Radiotherapy Management of HNC

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26-27 November – NICE, FRANCE

www.excemed.org
Along with surgery, **radiotherapy** plays a key role in the management of **early** stage and locally **advanced** head and neck squamous-cell carcinomas (HNSCC)

- either **alone** or,
- more frequently **combined** with surgery and/or chemotherapy.
Staging
(CT head and neck, CT chest, ENT exam, +/- additional studies, e.g. PET)

Early-stage HNSCC
Stage I and Stage II

Careful evaluation of treatment goals and performance status
Organ preservation?
Performance status?
Patient's preferences?
Physician's preferences?

Locoregionally advanced HNSCC
Stage IVA/B and stage III, high-risk locations

Resectable?
No
Yes

Performance status?
Poor
Good

Careful evaluation of treatment goals
Organ preservation?
Performance status?
Patient's preferences?
Physician's preferences?

Radiation
(Single modality) level I evidence
Use in patients with poor performance status
Substantial functional impairment with surgery
Patient's/physician's preference

Surgery
(Single modality) level I evidence
Use in patients with adequate performance status
No significant functional impairment with surgery
Patient's/physician's preference

Chemoradiotherapy
- Radiation with concomitant cetuximab (level I evidence)
- Chemoradiotherapy at reduced intensity (expert opinion)
- Radiation single modality (expert opinion)
- Palliative measures (expert opinion)

If upstaging occurs or if high-risk features are present, adjuvant treatment is indicated

Chemoradiotherapy
- Locoregionally advanced disease (chemotherapy based; level I evidence)
- Radiation with concomitant cetuximab (level I evidence)
- For locoregionally advanced disease single modality radiation is not considered adequate (level I evidence)

Surgery
Level I evidence

Pathology review: high-risk features
Yes
No

Induction chemotherapy
- Expert opinion
- In high-risk situations, may help to reduce the risk of distal failure

Chemoradiotherapy
- Cisplatin—single agent 30% local failure rate (level I evidence)
- Combination chemo (cisplatin/ 5-FU, TFHX, etc.; level II evidence)

Radiation
(Single modality)
- Level II evidence
- Expert opinion (vs chemoradiation)
radiation therapy /surgery as a single modality are level I evidence
Organ preservation must be highly considered.
Head and Neck Cancer:
Multidisciplinary Management Guidelines
2015
Early stage cancer

- Early stage tumors (T1-2, N0, stade I and II) can be adequately treated with either surgery or radiotherapy (RT).

Treatment choice may be influenced by, tumor size, location, depth of invasion (tumor thickness), proximity to bone, growth patterns, degree of differentiation...

Surgery remains the mainstay of management for oral cavity tumours (Grade B)

Possibility of interstitial brachytherapy in (T1 and T2) cancers of the oral tongue and floor of mouth (remote from the mandible)
Advanced stage cancer

For advanced disease, \((T3, T4 N0 and T1-4 N+, Stage III and IV)\),

- **if resectable**: surgical resection, neck dissection, reconstruction and post-operative RT +/- chemotherapy (CT) (prognostic factors)

- **if not resectable**
  - Chemoradiotherapy (CRT) or (RT + Cetuximab)
  - Radical RT
Early stage cancer

- **T1-2, N0, stade I and II**: oropharyngeal carcinoma can be treated by either primary surgery or radiotherapy.

No high quality comparative studies

- **Brachytherapy** is possible for Tonsil, Soft Palate, Facial arch and base of tongue lesion

  ( < 5 cm )
• Superficial, exophytic,

• tonsillar region (which includes the fossa, anterior and posterior pillars), lateral pharyngeal wall

• Ulcerating, infiltrating,

• uvula, lingual junction area, furrow amygdalo-glosse, intermaxillary commissure, retromolar trigone
Advanced stage cancer

- (T3, T4 N0 and T1-4 N+, Stage III and IV):

Overall survival is improving in patients receiving radical surgery and adjuvant treatment

- Surgery followed by RT +/- CT (prognostic factors)
- CRT (platinum) Exclusive, after lymphadenectomy if necrotic node

However, functional results can be poor (speech and swallowing Function.....) Or the tumor/node is not resectable...

- CRT (platinum) or RT-Cetuximab (if CI Platinum)
  CT first if intensification needed
LARYNX / HYPOPHARYNX CANCER

T1-T2

• Glottic and supra-glottic :
  • **N0**: Unimodal treatment
    • Surgery: endoscopic or open partial surgery
    • Radiotherapy (IMRT* if Prophylactic treatment of the neck nodes)
    • no reported role for brachytherapy in the treatment of laryngeal or hypopharyngeal tumours.
  • **N+**: Multimodal treatment
    CRT or surgical procedures + post-operative RT +/- CT (prognostic factors)

• Subglottis :
  • organ preservation strategy reserving surgery for salvage
  • Total laryngectomy

• Hypopharynx:  RT +/- CT or partial surgery
LARYNX / HYPOPHARYNX CANCER

T3

- If resectable:
  
  organ preservation strategy (surgery for salvage)

- Evaluation: 2 - 4 weeks after the 3rd course of induction chemotherapy because of late replies (No place for the fourth cure)

- Preservation strategy is continued if good response
  
  RT for T3N0 responders, CRT for T3N+ responders

- If dissociated response: (not responder for Node’(s)), no surgery (on N) before Chemoradiotherapy

- If not: 3 options:
  
  - CRT (platinum),
  - Induction + CRT (bulky T + N)
  - RT + Cetuximab
• **Stage I (T1N0)** = exclusive Radiotherapy
  - (IMRT = Intensity Modulated RadioTherapy)

• **Stage II (T1 or T2 N0 N1 / N1)** = radiotherapy, + chemotherapy (platinum) if bulky disease or lymph node involvement

• **Stage III-IVB (any T3 or T4, any N2 or N3)** = CRT or CT first (platinum and taxanes) if bulky mass (T or N), or neurological symptoms, or near the chiasm...

• **Metastatic stage IV C** = CT (Cisplat-5FU) + taxanes?
Concomitant chemoradiotherapy CRT

- Radical setting:
  - \( \text{RT} = \text{Stage I} - \text{II} \)
  - \( \text{RT + CT (CRT)} = \text{Stage III- IV} \) « no resectables » with concordant PS

- Why RT-CT?
  - Historically, unresectable head and neck cancer treated with exclusive radiotherapy (RT) have a
    - 5-year survival rate less than 25 %.
  - De la Garza et al, in 1975 were the first in Mexico to use simultaneous with bleomycin and radiation.
    = significant initial benefit
  - Several phase III clinical trials have shown that CRT yields better results than RT alone: a significant 5-year local control and overall survival benefit.
• **level one evidence** of a significant **benefit** of the addition of chemotherapy in terms of **overall survival**.

• **absolute benefit** for chemotherapy of **4.5% at 5-years** HR=0.88 (p < 0.0001)

• The benefit is more pronounced for **concomitant chemotherapy**, with a hazard ratio of 0.81 (p < 0.0001) and a **5-year absolute benefit of 6.5%**.

• This survival benefit was mainly due to an improvement in the **locoregional control**, and only a marginal effect on distant metastases was observed.

• The **benefit** of concomitant chemotherapy **decreases with increasing age** of the patients (p = 0.003, test for trend).
Chemotherapy benefit was higher for concomitant administration.
Reduction of the risk of death is consistent in all tumour sites, and “young” patients.

Table 4: Risk reduction of death after concurrent chemotherapy and radiotherapy compared to no chemotherapy

<table>
<thead>
<tr>
<th>Subsite</th>
<th>Percentage reduction in risk of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>oropharynx</td>
<td>23%</td>
</tr>
<tr>
<td>larynx</td>
<td>22%</td>
</tr>
<tr>
<td>oral cavity</td>
<td>17%</td>
</tr>
<tr>
<td>hypopharynx</td>
<td>16%</td>
</tr>
</tbody>
</table>

Table 5: Risk reduction of death after concurrent chemotherapy by age

<table>
<thead>
<tr>
<th>Age</th>
<th>Percentage reduction in risk of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 or less</td>
<td>22-24%</td>
</tr>
<tr>
<td>60-70</td>
<td>12%</td>
</tr>
<tr>
<td>over 70</td>
<td>3%</td>
</tr>
</tbody>
</table>
the concomitant addition of chemotherapy to radiotherapy significantly improved overall survival ($p<0.0001$; absolute benefit at 5 years 6.3%).

consistent for all endpoints analysed (all $p<0.0001$):
- **PFS** = progression-free survival (HR 0.75, 95% CI 0.69–0.81),
- **LRC** = locoregional control (0.73, 0.64–0.83),
- **DC** = distant control (0.67, 0.59–0.75),
- and cancer mortality (0.76, 0.69–0.84).

but not adjuvant chemotherapy alone (0.87, 0.68–1.12) or induction chemotherapy alone (0.96, 0.80–1.16).

Further studies on the specific benefits of adjuvant chemotherapy after concomitant chemoradiotherapy are needed.
Overall, in Stade III-IV no resectables lesions, with concordant PS, the benefit of the addition of chemotherapy to locoregional treatment is consistent in all tumour locations of HNSCC, is predominant in the concomitant schedule and is lower in the oldest patients (over 70 y).
Adjuvant setting

Which **adverse risk features** will have impact on the need for postoperative adjuvant RT treatment?

1. **Related to the tumor**
   - tumor type (oral cancer ++)
   - size and grade (advanced = pT3 < pT4)
   - depth of invasion, bone invasion
   - perineural invasion
   - lymphovascular invasion
   - close or positive surgical margins (if reoperation not possible)

2. **Related to the nodes**
   - any positive lymph nodes, but especially **if more than one node is positive (N2b)**
   - positive nodes at level IV or V
   - Node > 3 cm (N2a) (3 cm = N1 can be discussed)
   - extracapsular lymph node spread (even when microscopic).

Locoregional control significantly decreases in the presence of **two or more indicators of poor prognosis**. To consider as they are associated with each other!!
Only formal criteria = extracapsular extension and/or positive surgical margins

The addition of concurrent chemotherapy (cisplatin) to postoperative radiotherapy improves LRC, DFS, and OS at 5 years (EORTC ;

Level  I evidence
Update at 10 years (RTOG study),

no statistically significant differences for any of the major endpoints of L-R control (the primary endpoint), DFS, or OS (secondary endpoints).

Significant improvements in L-R control and DFS from concurrent cisplatin persisted in the subgroup with R1 resection and/or N° RC + disease,

+ 2 or more lymph nodes
and/or microscopically involved resection margins
and/or extracapsular spread of disease,
How to improve the therapeutic ratio of RT

Most commonly, the therapeutic ratio is quantitatively defined as the ratio between tumour control probability and normal tissue complication probability

- Altered fractionated RT
- New radiation techniques

The objective of altered fractionated RT is to increase the dose intensity of RT by delivering a high total dose in an overall time as short as possible.

- Mainly, two types of altered fractionation regimens have been tested: accelerated and/or hyperfractionated RT.
Conventional:
- 70 Gy (daily 2 Gy/fraction = 35 fractions in 7 w (5 f/w

Accelereration:
- 70 Gy (daily 2 Gy/fraction = 35 fractions in 6 w (> 5 f/w
  - shortening the overall treatment time
  - reduce tumor cell repopulation between sessions to allow better local control probability.

Hyperfractionation:
- 81.6 Gy (daily 2 fractions of 1.2 Gy = 68 fr, in 7 w, 10 f/w
- “standard “ overall treatment time
- reduce late toxicity and allow to increase the total dose.
A meta-analysis MARCH Collaborative Group

- **15 randomised trials**: conventional and altered fractionation regimens: 6515 updated individual patient data

- **5 years LRC benefit = 6.4%** \((p < 0.0001)\)
  - which was particularly efficient in reducing primary tumor failures, whereas the effect on nodal disease was minimal

- **Absolute 5-year survival benefit = 3.4%** \((\text{Hazard Ratio (HR)}: 0.92; p=0.003)\)
  - Hyperfractionated (8% at 5 years)
  - significantly higher in younger patients (50 years or less) and there was no detectable benefit for patients over 70 years old.

- **no benefit** was seen for distant metastasis.
The update identified a total of 40 trials, representing 12,003 patients:

CRT ≥ Hyperfractionated Schedule
(indirect comparison meta-analysis)

Overview
Systematic Review and Meta-analysis of Conventionally Fractionated Concurrent Chemoradiotherapy versus Altered Fractionation Radiotherapy Alone in the Definitive Management of Locoregionally Advanced Head and Neck Squamous Cell Carcinoma

T. Gupta †, S. Kannan ‡, S. Ghosh-Laskar ‡, J.P. Agarwal ‡

Overall survival

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>AFRT Events</th>
<th>CCRT Events</th>
<th>Total O-E</th>
<th>Variance</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORO 93.01</td>
<td>38</td>
<td>52</td>
<td>13.75</td>
<td>21.9549</td>
<td>14.1%</td>
<td>0.57 [0.37, 0.87]</td>
<td>0.57 [0.37, 0.87]</td>
</tr>
<tr>
<td>GORTEC 99.02</td>
<td>279</td>
<td>184</td>
<td>21.2422</td>
<td>100.8073</td>
<td>64.8%</td>
<td>0.81 [0.67, 0.98]</td>
<td>0.81 [0.67, 0.98]</td>
</tr>
<tr>
<td>TMH</td>
<td>65</td>
<td>38</td>
<td>-7.07824</td>
<td>16.44954</td>
<td>10.6%</td>
<td>0.65 [0.40, 1.05]</td>
<td>0.65 [0.40, 1.05]</td>
</tr>
<tr>
<td>CMU</td>
<td>48</td>
<td>14</td>
<td>-4.955</td>
<td>63.911</td>
<td>4.1%</td>
<td>0.46 [0.21, 1.00]</td>
<td>0.46 [0.21, 1.00]</td>
</tr>
<tr>
<td>POMER</td>
<td>104</td>
<td>35</td>
<td>-3.12332</td>
<td>9.9244</td>
<td>6.4%</td>
<td>0.73 [0.39, 1.38]</td>
<td>0.73 [0.39, 1.38]</td>
</tr>
</tbody>
</table>

Total (95% CI) 557 560 100.0% 0.73 [0.62, 0.86]

Favours [CCRT] Favours [AFRT]

No form of acceleration can potentially compensate fully for the lack of concurrent chemotherapy.
Altered Fractionation

- Where radiotherapy is the primary treatment modality, hyperfractionated schedules can be considered as an alternative approach for patients with head and neck cancer (except T1-3 glottic or supraglottic) unable to receive or decline concurrent chemotherapy or other systemic therapies.
Recurrence in head and neck cancer:
- 20% to 30% of high-risk postoperative patients
- 30% of patients treated with definitive chemoradiotherapy.

Bernier J, N Engl J Med 2004;350:
Brockstein B, Ann Oncol 2004

In addition, patients with HNC are at risk for second primary malignancies, at a rate of up to 3% per year in the head and neck region.

- **Surgical salvage = preferred treatment approach** (only 25% of the patients)
- Radiotherapy +/- chemotherapy
- Chemotherapy
- Best Palliative Care
If significant risk of further local recurrence:
Reirradiation with chemotherapy (Vokes Protocole):

<table>
<thead>
<tr>
<th>RT</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 w</td>
<td>3 w</td>
</tr>
</tbody>
</table>

50 up to 60 Gy
hydroxyurea and 5-fluorouracil

Phase III multicenter trial (GORTEC-GETTEC 99-01) = Vokes vs Observation

L-R control (reduced by a factor of 2) and DFS (the primary endpoint) were improved in patients receiving postoperative reirradiation and chemotherapy (HR of 1.68), although there was no apparent difference in OS compared with those observed after surgery

level 1 evidence ++

Janot F; J Clin Oncol 2008
Vokes EE; Ann Oncol 1996
IORT = Intra Operative RadioTherapy

- If surgery is considered for recurrent cancer, the use of intraoperative RT should be a consideration, in addition to postoperative irradiation.

Marucci L
Head Neck. 2008 Jun
## Table 2 IMRT Reirradiation Studies for Recurrent Second Primaries in the Head and Neck

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>RT Regimen (Chemotherapy)</th>
<th>Median OS (Median Follow-Up in Months)</th>
<th>1-Year Survival (%)</th>
<th>Toxicity, % (Number of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulman et al(^{13})</td>
<td>78</td>
<td>Median RT dose 60 Gy (49% CT)</td>
<td>28 (NR)</td>
<td>75</td>
<td>grade 3-5 died</td>
</tr>
<tr>
<td>Lee et al(^{14})</td>
<td>105 (74 IMRT)</td>
<td>Median RT dose 59.4 Gy (74% CT)</td>
<td>25 (35)</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Popovtzer(^{15})</td>
<td>66</td>
<td>Median RT dose 64 Gy (71% CT)</td>
<td>(42)</td>
<td>40% 2-year OS</td>
<td>Late grade 3: 11 (4); 2 deaths</td>
</tr>
<tr>
<td>Zwicker et al(^{16})</td>
<td>38</td>
<td>Median RT dose 49 Gy (50% concurrent CT)</td>
<td>17 (NR)</td>
<td>63</td>
<td>Acute: 6 (2) grade 4</td>
</tr>
<tr>
<td>Sher et al(^{17})</td>
<td>35</td>
<td>Median RT dose 60 Gy</td>
<td>23 (28)</td>
<td>59</td>
<td>Late: 21 (8) grade 0-3, deaths: 0</td>
</tr>
<tr>
<td>Goldstein et al(^{18})</td>
<td>41</td>
<td>Median RT dose 61.1 Gy (curative) 54.5 Gy (palliative)</td>
<td>10.2 (NR)</td>
<td>39</td>
<td>Acute + late, grade 3 or 4: 68 (28) Deaths: 0</td>
</tr>
<tr>
<td>Chen et al(^{19})</td>
<td>21</td>
<td>Median RT dose 66 Gy</td>
<td>NR (20)</td>
<td>65</td>
<td>Cumulative toxicity: NR Deaths: 0</td>
</tr>
</tbody>
</table>
Stereotaxy / Cyberknife + Cetuximab

major clinical advantage in keeping the **overall treatment time short** in a population with a poor clinical prognosis

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**Small volume**

\[\text{size max} = 6 \text{ cm in one diameter}\]

- 36 Gy in six fractions of 6 Gy, over 11 or 12 days
- Concomitant cetuximab beginning with a test dose of 400 mg/m2 the week before SBRT.
- During the two weeks of SBRT and for the following 2 weeks, the patients received a weekly cetuximab dose of 250 mg/m2 in the form of 4 injections

- median follow up of 11.4 months.
- According to RECIST criteria evaluable in 49/60 patients, complete response was observed in 24 patients (49.0%), partial response in 10 (20.4%), stable disease in 11 (22.5%) and progressive disease in 4 patients (8.2%).
- The one-year OS rate was 47.5% (95% CI: 30.8–62.4).
Radiotherapy +/- Chemotherapy?

Not one study has ever shown a conclusive benefit to re-irradiation with concurrent chemotherapy compared with re-irradiation without chemotherapy.

Concurrent chemotherapy should be considered in highly functioning patients with bulky tumors or who develop recurrence shortly after their initial RT.

With IMRT (higher doses), no need to combine with chemotherapy? no split course, non altered fractionated treatment...
1. In patients with early cancer,
   Surgery remains the mainstay of management, if adequate performans status and no significant functional impairment, but Superficial, exophytic lesion (and tonsil area, pharyngeal wall) are rather treated by radiotherapy

2. In operable patients with locally advanced carcinoma,
   -- Adjuvant radiotherapy should be discussed in the presence of high risk factors, the addition of chemotherapy will be indicated in extracapsular extension and/or positive surgical margins = Only formal criteria

3. If NOT operable but medically fit for chemotherapy, (especially those aged 70 or under),
   Concurrent chemoradiotherapy should be considered rather than radiotherapy alone if:
   organ preservation is being pursued
   the primary tumour is unresectable.
4. Altered fractionated / hyperfractionated schedules ++++
increased total dose can be considered as an alternative approach for patients with head and neck cancer (except T1-3 glottic or supraglottic) unfit for concurrent chemotherapy or other systemic therapies.

5. Reirradiation:

- With IRMT, in selected case, possibility to deliver a continuous treatment with no gap (and no chemotherapy)

- Futur : Role of stereotaxy ...protontherapy
Thanks you !!!