# SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

## Initial Workup

- **History:**
  - Smoking
  - Viral infections
  - Exposure to radiotherapy
- **Pan-endoscopic evaluation under anesthesia (EUA):**
  - Inspection,
  - Palpation,
  - Direct and indirect endoscopy
- **Biopsy:**
  - Fine needle aspiration cytology (FNAC): core or excisional
- **Laboratory Investigations:**
  - CBC
  - Biochemistry.
- **Imaging:**
  - Chest x-ray.
  - CT primary and neck or MRI.
  - PET-CT for stage III or IV.

## Staging

Staging procedure according to AJCC 7$^{th}$ edition for different sites of head and neck H& N:

- Oral cavity
- Nasopharynx
- Oropharynx
- Hypopharynx
- Larynx
- Salivary gland
- Sinonasal tumor

Staging is actually the function of head and neck surgeons and radiation therapists as they will implement the initial treatment. The cases are referred to the medical oncology department for systemic therapy being advanced; metastatic; or recurrent.

## Pathology

- Squamous cell carcinoma (90%)
  - Well, moderately or poorly differentiated
  - Keratinized or non-keratinized.
- Verruocous carcinoma (< 5% indolent disease, rarely metastasize).
- Basaloid SCC or Spindle cell SCC.
- Sinonasal adenocarcinoma.
- Salivary gland tumor:
  - Mucoepidermoid carcinoma
  - Polymorphous low-grade adenocarcinoma
  - Adenoid cystic carcinoma

## Treatment

The multidisciplinary treatment approach should always be considered.

**Treatment of stage I and II head and neck cancer.**

### Single-modality therapy (Radiotherapy or Surgery)

Single-modality therapy using either radiation therapy or surgery had similar overall survival.

The choice is typically based upon:

Surgical accessibility of the tumor and

Functional outcomes and morbidity associated with each modality.

In general, surgery is used as the main modality of treatment in the oral cavity.

RT is more commonly used in other sites (Larynx, oropharynx, hypopharynx, and nasopharynx).

### Post-operative Radiotherapy

Indicated in:

Advanced T-stage (T3/T4).

Two or more positive lymph nodes (N2/N3).

Perineural or lymphovascular invasion.

### Post-operative Concurrent Chemo-radiotherapy

Indicated in:

Positive or close margins.

Extracapsular nodal extension.

**Treatment of locally advanced squamous cell carcinoma of the head and neck (Stage III, IVa or IVb, larynx, hypo and oropharynx and oral cavity).**

- Surgical treatment plus postoperative radiotherapy or chemo-radiotherapy.
- Organ preservation approaches for unresectable or potentially resectable patients want to preserve organ function.
- Definitive radiotherapy.
- Concurrent chemoradiotherapy
- Induction chemotherapy followed by radiotherapy
- Sequential treatment (induction chemotherapy followed by concurrent chemoradiotherapy)
- Adjuvant chemotherapy

**Correction of nutritional status and dental rehabilitation**

**1. Definitive Radiotherapy**

- Option for patients with:
  - Poor PS,
  - Multiple co-morbidities or
  - Elderly >70.
- A meta-analysis of chemotherapy in head and neck cancer (MACH-NC) found that older patients are less likely to benefit from the addition of chemotherapy to definitive locoregional treatment.

**2. Concurrent Chemoradiotherapy**

- Concurrent chemoradiotherapy is the standard approach in locally advanced disease.
- A meta-analysis of concurrent chemotherapy in head and neck cancer (MACH-NC) Concurrent chemotherapy was assessed in 50 trials that included 9605 patients.
- Mean follow-up was 5.6 years. Concurrent chemotherapy significantly decreased the risk of death compared with definitive local therapy alone (hazard ratio [HR] 0.81, 95% CI 0.78-0.86); this correlated with a 6.5% absolute decrease in mortality at five years (Pignon JP, et al).

**3. Induction Chemotherapy Followed by Radiotherapy Alone**

- There was no statistically significant effect on overall survival from induction chemotherapy compared with surgery and/or RT alone based on results of a meta-analysis of 31 trials with 5311 patients, (HR 0.96, 95% CI 0.90-1.02) (Blanchard P, et al).

**4. Sequential Treatment Approach**

- The role of induction chemotherapy prior to concurrent chemoradiotherapy remains controversial.
- The choice between either an ICT-based or a CRT-based organ-preserving protocol depends on various factors such as:
  - Anatomical subsite

- Foreseeable compliance/tolerance to treatment
- Performance status

- Patients with massive larynx cartilage invasion should be excluded from this approach.
- Concurrent chemoradiotherapy is preferable for:
  - Patients less likely to have distant metastases (N0 and N1 presentations)
  - Preservation of the larynx and sequential therapy
  - Selected patients with high risk of distant metastases (more extensive lymph node disease including bulky N2b, N2c, and N3).

**Supporting Evidence:**

| **TAX 324 trial** |
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| • TPF regimen (docetaxel, cisplatin and 5 fluorouracil) followed by concurrent carboplatin plus RT was superior to induction PF followed by the same chemoradiotherapy regimen. |
| **DeCIDE trial** |
| • 280 patients were randomly assigned to induction with two cycles of TPF followed by chemoradiotherapy or chemoradiotherapy alone.<br>• There was no statistically significant difference in OS, (HR, 0.91; 95% CI, 0.59-1.41).<br>• Differences in RFS and distant metastasis-free survival with induction chemoradiotherapy were not statistically significant (Cohen EEW, et al). |
| **PARADIGM trial** |
| • The study compared concurrent chemoradiotherapy vs sequential treatment.<br>• At a median follow-up of 49 months, there was no statistically significant difference in three-year overall survival, and no clear benefit in any subset (Haddad R, et al). |

## 5. Adjuvant chemotherapy

- In six trials with 2567 patients that assessed the impact of adjuvant chemotherapy, there was no improvement in overall survival compared with definitive local therapy alone (HR 1.06, 95% CI 0.95 – 1.16).

## 6. Surgery

- Patients with a poor response or residual disease after radical chemoradiotherapy detected clinically or radiologically would be offered surgical treatment.

## Chemotherapy Regimens

| Regimen | Drug | Dose | Duration/ cycle |
|---|---|---|---|
| **TPF** | Docetaxol | 75 mg/m$^2$ IV D1 | 21 day<br>GCSF support |
| | Cisplatin | 100 mg/m$^2$ IV D1 | |
| | 5FU | 1000 mg/m$^2$/day IV D1 – D4 | |
| **PF** | Cisplatin | 100 mg/m$^2$ IV day 1 | 21 day |
| | 5FU | 5-FU (1000 mg/m$^2$/ CI D1-D4 | |
| **Alternative to three weekly Cisplatinum** | | | |
| **Drug** | | **Dose** | **Duration/ cycle** |
| **Cisplatin** | | 40 mg/ m$^2$ | Weekly |
| **Carboplatin** | | AUC 1.5 or 2 | Weekly |

**Special Considerations:**

1. **TPF Regimen:**
   - When TPF regimen (docetaxel, cisplatin and 5 fluorouracil) was used in the induction treatment setting, it revealed a better local control and organ preservation, with a trend of OS improvement in many trials compared by to PF.

2. **Carboplatin vs. Cisplatin:**
   - Whether or not carboplatin is equally effective compared to cisplatin as a radiation sensitizer is not yet clear.
   - The combination of carboplatin plus 5-fluorouracil and or paclitaxel may also represent another alternative option when cisplatin is not feasible.

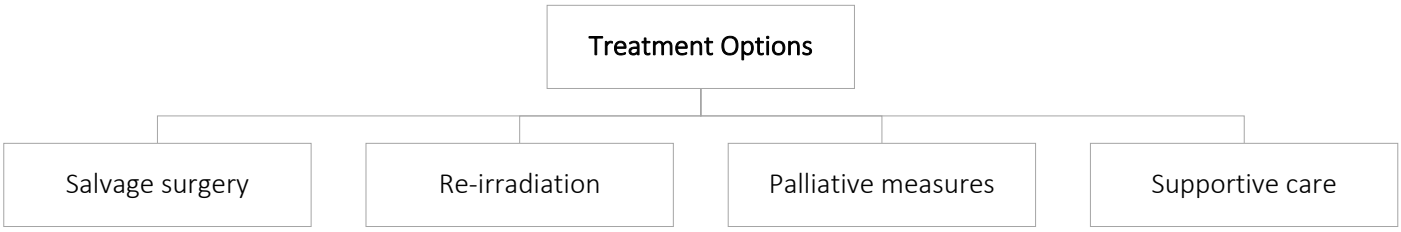
3. **Cetuximab:**
   - Cetuximab alone plus RT has yielded a higher response rate, longer DFS, and longer OS compared with radiotherapy alone. But this trial compared cetuximab plus RT with RT alone, which is no longer considered a standard.
   - The currently available data does NOT support the use of cetuximab with RT as an alternative to RT alone in elderly (≥65 years with KPS 60 to 80) and those with significant comorbidities.

4. **Concurrent Cisplatin plus Cetuximab**
   - Concurrent treatment of cisplatin plus cetuximab does not appear to offer any advantages compared with concurrent cisplatin alone as reported in an early analysis of the randomized RTOG 0522 phase III trial.

## Treatment of Recurrent or Metastatic Disease

- Prognosis of patients with recurrent or metastatic disease usually poor.
- Treatment options depend on the stage of recurrence, metastatic site and previous line of treatment.

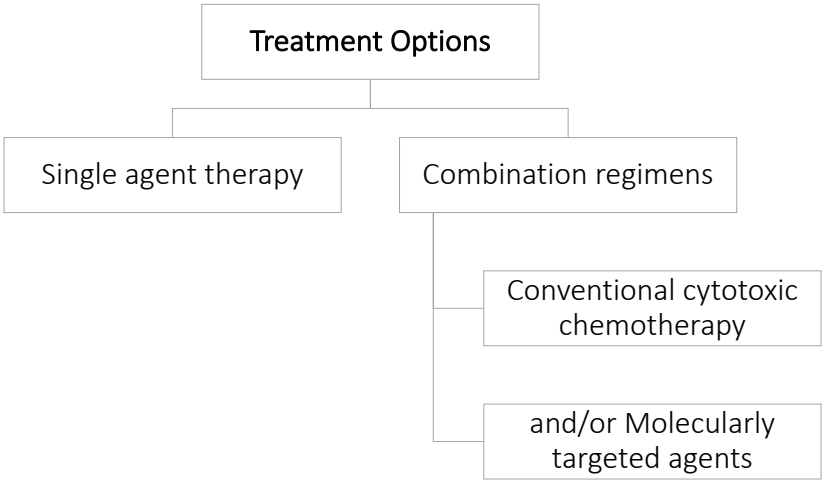
### Treatment of recurrent disease




**The following statements highlighting the basis of treating a recurrent disease:**

| **Salvage surgery** |
|---|
| Provides the best way for long term survival.<br>It depends on the site and volume of recurrent disease. |
| **Re-irradiation** |
| Re-irradiation is an alternative for patients who are not candidates for surgical salvage.<br>Patient selection depends on:<br>Site of recurrence, Tumor characteristic, surrounding, structure, previous dose given, duration between 1ry treatment and recurrence and the ability to tolerate toxicity. Re-irradiation post-operative in high-risk patients or as palliation. It can be given with or without chemotherapy. |
| **Systemic chemotherapy and best supportive care.** |

### Treatment of metastatic disease previously treated patients



| Favorable factors | Unfavorable factors |
|---|---|
| • Performance status (ECOG 0 or 1 versus 2).<br>• Poorly differentiated histology.<br>• Good response to chemotherapy | • Weight loss.<br>• Poor performance status.<br>• Prior radiation therapy.<br>• Active smoking.<br>• Significant comorbidity. |

## Treatment of metastatic disease previously untreated patients

Treatment option depends on performance status and comorbidities:

- Patients with a good PS and without serious comorbidities:
  - Platinum doublet-based chemotherapy regimens have a better response rate than single agents, without any survival benefit.
- Patients with a poor PS or significant comorbidities:
  - Offered single agent including non-platinum ones.

## Chemotherapy Regimen

| Regimen | Drug | Dose | Duration |
|---|---|---|---|
| **PF** | Cisplatin | 100 mg/m$^2$ IV on day 1 | 21 day |
| | 5FU | 5-FU (1000 mg/m$^2$/CI) on D1 – D4 | |
| **PF + Cetuximab** | Cisplatin | 100 mg/m$^2$ IV on day 1 | 21 day |
| | 5FU | 5-FU (1000 mg/m$^2$/CI) on D1 – D4 | |
| | Cetuximab | 400 mg/m$^2$/ 1$^{st}$ dose, then weekly 250 mg/m$^2$ | |
| **Carboplatin/5FU ± Cetuximab** | Carboplatin | AUC 5 on D1 | 21 day |
| | 5FU | 5-FU (1000 mg/m$^2$/CI) on D1 – D4. | |
| | Cetuximab | 400 mg/m2/ 1st dose, then weekly 250 mg/m2 | |
| **Carboplatin/5FU/ leucovorin** | Carboplatin | AUC 1.5 | Weekly |
| | 5FU | 500 mg/m$^2$ | |
| | Leucovorin | 500 mg/m$^2$ | |
| **Taxane / Cisplatin or Carboplatin** | Paclitaxol or docetaxol | 75 – 100 mg/m$^2$ | 21 day |
| | Cisplatin OR | | |
| | Carboplatin | | |

**Special Considerations:**

- PF protocol is the first option with documented RR of 30%.
- Carboplatin is often considered to be less effective than cisplatin in head and neck cancer, in spite of the non-statistical significance in RR between both in many trials.
- Cetuximab plus cisplatin plus 5-fluorouracil increases overall survival compared with cisplatin plus 5-fluorouracil alone.
- Cetuximab could be continued as maintenance until disease progression or toxicity.
- When the quality of life is an issue weekly carboplatin, 5-fluorouracil, and leucovorin is the preferred choice.
- Single-agent regimen including; carboplatin, paclitaxel or cetuximab showed activity against these tumors and may be offered in this setting.

## Oligometastatic Site

- Patients with a limited number of distant metastases at presentation or relapse may benefit from aggressive treatment that includes eradication of all known sites of disease in whom disease in the primary site and regional lymph nodes has been completely controlled.
- In this setting, surgical metastasectomy can result in prolonged disease-free survival in a significant percentage of appropriately selected patients.
- Other approaches include stereotactic body radiation therapy.

## A disease that has progressed on or after platinum-containing

**Chemotherapy:**

- Factors in choosing a treatment regimen include:
  - Prior treatment history,
  - Patient performance status and comorbidities,
  - Expected toxicities.
- There is no evidence that second-line treatment prolongs survival.
- Single agents that can be offered include:
  - Methotrexate,
  - Cisplatin, Docetaxel,
  - Gemcitabine, and
  - Cetuximab.

## Tyrosine Kinase Inhibitor (TKI)

Afatinib; was approved in the 2nd line setting based on phase III LUX-Head and Neck RCT compared to methotrexate in patients with recurrent or metastatic H&N cancer.

Afatinib had greater PFS, relative to patients (2.6 months vs. 1.7 months; P =.03)

| Checkpoint inhibitors |
| --- |
| **Nivolumab; anti-PD-1 antibody (1a)**<br>It was approved based on CHECKMATE 141 phase III RCT including 361 patients with recurrent Head and Neck SCC whose disease had progressed within 6 months following platinum-based chemotherapy.<br>Nivolumab vs investigator choice (methotrexate, docetaxel, or cetuximab).<br>Significant OS benefit for nivolumab 7.5 months vs 5.1 (HR, 0.70; 97.73% CI, 0.51–0.96; P= .01). |
| **Pembrolizumab, anti-PD-1 antibody (2a)**<br>It was approved based on **KEYNOTE-012 and KEYNOTE-055.**<br>At 6 months, the overall survival rate was 59%, and the PFS was 23%, with an overall response rate of 18%. |

## Follow Up

**The patients will be followed up:**

- Every 3 months for the first 2 years,
- Every 4 – 6 months for years 3 to 5 then
- Annually.

**Follow up includes:**

- Clinical examination.
- Chest X-ray.
- Imaging study (CT scan or MRI of head and neck depending on the initial procedure).
- PET-CT scanning may be useful in the presence of doubtful findings.
- Treatment sequelae focusing on swallowing and respiratory dysfunctions.
- Evaluation of thyroid function (serum thyroid-stimulating hormone and sensitive TSH levels).
- Laboratory tests as clinically indicated.