Indian clinical practice consensus guidelines for the management of very advanced disease of squamous cell carcinoma of head and neck

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In patients with very advanced (unresectable/inoperable/recurrent or metastatic) disease, a multidisciplinary approach must be considered when evaluating recurrent or distant metastasized disease to decide next course of treatment (surgery or re-irradiation, with or without chemotherapy). For patients with newly diagnosed but unresectable disease, the treatment goal is the cure. While for the recurrent disease group, the goal is either cure (if surgery or radiation remains feasible) or palliation (if the patient has received previous radiotherapy [RT] and the disease is unresectable). For patients with metastatic disease, the goal is palliation or prolongation of life.

Newly diagnosed (MO) T4b, N0–3/Unresectable nodal disease/Unfit for surgery

Chemotherapy and radiotherapy (CT/RT)

For patients who are unsuitable for surgery or with unresectable disease due to anatomical difficulty, chemoradiotherapy (CTRT) (evidence level [EL] 2; Grade C)11 or RT with cetuximab should be considered than RT alone. High-dose cisplatin with RT is effective.

CT regimens for cisplatin suitable patients include (a) three-weekly cisplatin 100 mg, (b) nimotuzumab + weekly 30 or 40 mg/m² cisplatin, (c) weekly cisplatin 30 or 40 mg/m², (d) cisplatin + paclitaxel, or (e) cisplatin + infusional 5-fluorouracil (FU). However, CT regimens for cisplatin unsuitable patients include (a) weekly cetuximab, (b) weekly nimotuzumab, (c) carboplatin + infusional 5-FU, (d) 5-FU + hydroxyurea, or (e) carboplatin + paclitaxel.

For high-risk patients, typically 70 Gy (2.0 Gy/fraction) and for low-to-intermediate risk patients, 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction) of radiation are recommended.
**Induction CT**

Induction CT followed by RT is also one option.\(^{[2,3]}\)

Cisplatin-based induction CT regimens are as follows:

- Docetaxel 75 mg/m\(^2\) on day 1 + cisplatin 75 mg/m\(^2\) on day 1 + 5-FU 750 mg/m\(^2\)/day for 5 days every 3 weeks for three cycles
- Paclitaxel 175 mg/m\(^2\) on day 1 + cisplatin 100 mg/m\(^2\) on day 2 + 5-FU 500–750 mg/m\(^2\)/day from day 2 to day 6 every 3 weeks for three cycles
- Cisplatin 100 mg/m\(^2\) on day 1 + 5-FU 1000 mg/m\(^2\)/day for 4 days every 3 weeks for three cycles.

**Definitive RT**

High-risk patients should be treated with conventional fractionation (0–72 Gy [2.0 Gy/fraction] daily Monday–Friday in 7–7.5 weeks) or concomitant boost accelerated RT (72 Gy/6 weeks [1.8 Gy/fraction], large field; 1.5 Gy boost as second daily fraction during last 12 treatment days) or 66–70 Gy (2.0 Gy/fraction; 6 fractions/week accelerated).

If partial response: definitive RT/concurrent CTRT. Low-to-intermediate risk patients should be given 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction) of radiation doses.

**Palliative RT**

- 50 Gy in 20 fractions or 37.5 Gy in 15 fractions (if well tolerated, consider adding 5 additional fractions to 50 Gy) or
- 30 Gy in 10 fractions or 30 Gy in 5 fractions: Give 2 fractions/week with ≥3 days between the two treatments or 44.4 Gy in 12 fractions, in three cycles (for each cycle, give 2 fractions 6 hours apart, for 2 days in a row, and treatments must exclude spinal cord after second cycle).

**Systemic therapy**

Single-agent systemic therapy including cisplatin/carboplatin/paclitaxel/docetaxel/5-FU/methotrexate/cetuximab/gemcitabine/capecitabine combination CT may be considered. Immunotherapy alone or in combination with CT has improved survival and need to be considered. Metronomic CT has also shown to improve progression-free survival and quality of life and also is a valuable option.

**Metastatic (M1) disease at initial presentation**

Locoregional treatment prior to beginning systemic therapy may be considered. Single agents and combination systemic therapy regimens are both used.

Combination systemic therapy includes:

- Cisplatin or carboplatin/5-FU/cetuximab\(^{[4]}\) (EL 1; Grade A)
- Pembrolizumab monotherapy or pembrolizumab for patients with a programmed death-ligand 1 (PD-L1) tumor proportion score (percentage of tumor cells with membranous PD-L1 staining) ≥50%. Pembrolizumab is recommended as a single agent in patients with a combined positive score (CPS) ≥20, and in combination with or without platinum plus FU in patients with CPS ≥1 and <20 (EL 1; Grade A)\(^{[5,6]}\)
- Nivolumab is recommended as single agent if disease has progressed during or within 6 months of platinum-based therapy (EL 1; Grade A)\(^{[7]}\)
- Cisplatin/5-FU
- Cisplatin or carboplatin/docetaxel or paclitaxel
- Cisplatin or carboplatin/docetaxel/cetuximab
- Cisplatin or carboplatin/paclitaxel/cetuximab.

Single-agent systemic therapy with cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, cetuximab, gemcitabine, or capecitabine can be considered.

**Recurrent or persistent disease**

In patients with recurrent or metastatic disease, palliative treatment should be considered. Symptomatic relief, particularly, pain and the management of nutrition, is important in the overall management. Using chemotherapeutic agents (like cisplatin plus 5-FU, carboplatin plus paclitaxel, or carboplatin plus docetaxel) is recommended. Addition of cetuximab can improve overall survival.\(^{[4,8]}\)

Patients who progress following initial treatment with systemic platinum-based CT (with or without cetuximab) and eligible for immunotherapy pembrolizumab or nivolumab are the treatment of choice (EL 1; Grade A).

Pembrolizumab is recommended as a single agent in patients with CPS ≥20, and in combination with or without platinum plus FU in patients with CPS ≥1 and <20 (EL 1; Grade A)\(^{[5,6]}\)

Nivolumab is recommended as a single agent if disease has progressed during or within 6 months of platinum-based therapy (EL 1; Grade A)\(^{[7]}\)

Patients who are not eligible for immunotherapy, single agent, or combination therapy of platinum plus taxane are recommended or 5-FU or methotrexate can also be considered.

**Treatment of resectable recurrent/persistent disease**

Choice of adjuvant treatment should be based on the findings of the surgery/neck dissection. In case of no adverse features, observation should be done. In case of recurrent disease extranodal extension/positive margin, adjuvant CT/RT and in case of other adverse events like pT3 or pT4, primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular
embolism, and lymphatic invasion, CT/RT should be considered,[9–11]

Other treatment options for resectable recurrent/persistent disease are concurrent CT/RT or induction CT followed by CT or CT/RT.

Adjuvant CTRT schedules include:

- **CT:** 100 mg/m² three weekly cisplatin/30 or 40 mg/m² weekly cisplatin or 5-FU and hydroxyurea
- **RT:** For high-risk patients, typically, 70 Gy (2.0 Gy/fraction) and for low-to-intermediate risk patients 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction) of radiation doses can be considered.

**Adjuvant RT schedule**

For high-risk patients, 60–66 Gy (2.0 Gy/fraction), daily Monday–Friday in 6–6.5 weeks and for low-to-intermediate risk patients 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction) should be considered.

Unresectable recurrent and persistent head and neck cancer should be treated as the other unresectable very advanced disease. Single-agent pembrolizumab/nivolumab is recommended. Re-irradiation should be limited to highly selected subset of patients. Standard dosing is 59.4–60 Gy at 1.8–2 Gy/fraction or hyperfractionated schedule is 60 Gy at 1.2–1.5 Gy/fraction. The decision to treat with re-irradiation should be based on the comorbidity, the toxicity of previous treatment methods, and the amount of time that has passed since previous treatment.[12–14]

Algorithm for management of very advanced disease is given in Figure 1. Appendix 3 and 4 give the summary of clinical evidences in locally advanced and recurrent and/or metastatic disease.

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![Figure 1: Algorithm for management of very advanced disease](image-url)
Conflicts of interest
Oral Cancer Task Force (OCTF) members and authors do not have any conflicts of interest

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