HEAD AND NECK CANCER TREATMENT REGIMENS (Part 1 of 5)

Clinical Trials: The National Comprehensive Cancer Network (NCCN) recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Squamous Cell Cancers[1,a]

Principle of Systemic Therapy

Systemic therapy should be individualized based on patient characteristics (performance status, goals of therapy).

Note: All recommendations are category 2A unless otherwise indicated.

Primary Systemic Therapy + Concurrent Radiotherapy[1]

REGIMEN	DOSING
High-dose cisplatin (preferred; Category 1)[2,3]	**Days 1, 22, and 43:** Cisplatin 100mg/m² IV + concurrent radiotherapy 2Gy/day to a total of 70Gy.
Cetuximab (Category 1 for oropharynx, hypopharynx, or larynx; Category 2B for lip, oral cavity, ethmoid sinus, maxillary sinus, occult primary)[4]	**Day 1:** Cetuximab 400mg/m² loading dose over 2 hours, 1 week before radiotherapy, **plus** **Day 7:** Begin radiotherapy with 7 weekly infusions of cetuximab 250mg/m².
Carboplatin + infusional 5-FU (Category 1)[5,6]	**Days 1–4:** 5-FU 600mg/m²/day as continuous IV infusion for 4 days + carboplatin 70mg/m²/day IV bolus. Repeat every 3 weeks for 3 cycles (given concurrently with radiotherapy).
5-FU + hydroxyurea[7]	**Day 1:** Hydroxyurea 1,000mg orally every 12 hours (11 doses/cycle) + 5-FU 800mg/m²/day continuous IV infusion, **plus** radiotherapy: 70Gy, delivered in 35 fractions; 1 fraction delivered daily Monday–Friday. Concurrent radiotherapy and chemotherapy every other week for total treatment duration of 13 weeks.
Cisplatin + paclitaxel[7]	**Day 1:** Paclitaxel 30mg/m² IV (every Monday), plus **Day 2:** Cisplatin 20mg/m² IV (every Tuesday). Repeat cycle every week for 7 cycles, **plus** radiotherapy: 70Gy, delivered in 35 fractions; 1 fraction delivered daily Monday–Friday.
Cisplatin + infusional 5-FU[8]	**Day 1:** Cisplatin 60mg/m² over 15 minutes; **plus** **Days 1–5:** 5-FU 800mg/m²/day by continuous infusion for 5 days; **plus** **Days 1–5:** Radiotherapy: 2Gy repeated every other week for 7 cycles.
Carboplatin + paclitaxel (Category 2B)[9]	**Day 1:** Paclitaxel 40–45mg/m²/week and carboplatin 100mg/m²/week; **prior to** radiotherapy: 70.2Gy at 1.8Gy/fraction/day for 5 days/week.
Weekly cisplatin (Category 2B)[10,11]	**Day 1–28:** Cisplatin 40mg/mg² IV over 30 minutes weekly; **plus** **Days 1–38:** Radiotherapy (5 fractions/week): 1.8Gy single dose (up to total dose of 50.4Gy); **plus** **Days 22–38:** Boost radiotherapy: 1.5Gy/day (up to 19.5Gy) in addition to regular dose. Booster doses to be given at least 6-hours after regular dose (total tumor dose of 69.9Gy). **OR** **Day 1–28:** Cisplatin 40mg/mg² IV weekly; **plus** **Days 1–40:** Radiotherapy: five fractions of 1.8Gy/week (up to total dose of 54Gy); **plus** **Days 25–40:** Boost radiotherapy: 1.5Gy/day (up to 19.5Gy) in addition to regular dose. Booster doses to be given at least 6-hours after regular dose.

Primary Chemotherapy With Postoperative Chemoradiation[1]

Cisplatin (Category 1 for high-risk non-oropharyngeal cancers)[12–16]	**Days 1, 22, and 43:** Cisplatin 100mg/m² IV + radiotherapy.

Induction Chemotherapy[b]/Sequential chemotherapy[1,c]

Docetaxel + cisplatin + 5-FU (Category 1 if induction is chosen)[17–19]	**Day 1:** Docetaxel 75mg/m² IV + cisplatin 75mg/m² IV, **plus** **Days 1–5:** 5-FU 750mg/m²/day continuous IV infusion for 5 days. Repeat every 3 weeks for up to 4 cycles.
Paclitaxel + cisplatin+ infusional 5-FU[20,d]	**Day 1:** Paclitaxel 175mg/m² over 3 hours **Day 2:** Cisplatin 100mg/m²; **plus** **Day 2–6:** 5-FU 500mg/m²/day continuous IV infusion for 5 days. Repeat every 3 weeks for 3 cycles.

continued

HEAD AND NECK CANCER TREATMENT REGIMENS (Part 2 of 5)

Nasopharynx Cancer[1]

Chemoradiation Followed by Adjuvant Chemotherapy[1]

REGIMEN	DOSING
Cisplatin + radiotherapy + cisplatin + 5-FU[21,22]	**Cycles 1–3** **Day 1:** Cisplatin 100mg/m² IV; **plus** radiotherapy. Repeat cycle every 3 weeks; **followed by** **Cycles 4–6** **Days 1:** Cisplatin 80mg/m² IV over 1 hour **plus** **Days 1-4:** 5-FU 1,000mg/m² continuous IV infusion daily. Repeat cycle every 4 weeks for 3 cycles.
Carboplatin + radiotherapy + carboplatin + 5-FU (Category 2B)[23]	**Cycles 1–3** **Day 1:** Carboplatin AUC 6mg·min/mL IV over 1 hour; **plus** radiotherapy: 200cGy/fraction with 5 daily fractions/week (to a total dose of 6600–7000cGy). Repeat cycle every 3 weeks for 3 cycles; **followed by** **Cycles 4–6** **Day 1:** Carboplatin AUC 5mg·min/mL IV over 1 hour **Days 1–4:** 5-FU 1,000mg/m²/day continuous IV infusion over 24 hours Repeat cycle every 3 weeks for 2 cycles.
Cisplatin + radiotherapy without adjuvant chemotherapy (Category 2B)[24]	Cisplatin 40mg/m² weekly for up to 7 weeks, concurrently with radiotherapy at a dose of 2.0 to 2.27Gy per fraction with 5 daily fractions per week for 6 to 7 weeks to a total dose of 66Gy or greater to the primary tumor and 60 to 66Gy to the involved neck area.

Induction Chemotherapy[b]/Sequential Chemotherapy[1,e]

Docetaxel + cisplatin + 5-FU (Category 1 if induction is chosen)[25]	**Day 1:** Docetaxel 70mg/m² IV over 1 hour and cisplatin 75mg/m² IV over 3 hours; **followed by** **Days 1–4:** 5-FU 1,000mg/m²/day continuous IV infusion for 4 days. Repeat every week for 3 cycles; **followed by** Cisplatin 100mg/m²; **plus** radiotherapy: 5 daily fractions of 1.8 or 2Gy/day (total dose of 68.4Gy) Repeat every 3 weeks.
Docetaxel + cisplatin (Category 2B)[26]	**Day 1:** Docetaxel 75mg/m² IV + cisplatin 75mg/m² IV every 3 weeks for two cycles, **followed by** Cisplatin 40mg/m² IV weekly concurrent with radiotherapy.
Cisplatin + 5-FU[18]	**Day 1:** Cisplatin 100mg/m²/day IV. **Days 1–4:** 5-FU 1,000mg/m²/day continuous IV infusion for 4 days. Repeat cycle every 3 weeks for a minimum of 6 cycles.
Cisplatin + epirubicin + paclitaxel	This regimen was included in the NCCN guidelines but no reference was provided to indicate appropriate dosage.

Following induction, agents to be used with concurrent chemoradiation typically include weekly cisplatin or carboplatin.[22,50]

Principles of Systemic Therapy[1]

- The choice of systemic therapy should be individualized based on patient characteristics (performance status, goals of therapy).
- Unless otherwise specified, regimens listed below can be used for either nasopharyngeal or non-nasopharyngeal cancer.

Combination Therapy for Recurrent, Unresectable, or Metastatic Disease (With No Surgery or RT Option)[1]

Cisplatin or carboplatin + 5-FU + cetuximab (Category 1)[27] (non-nasopharyngeal)	**Day 1:** Cisplatin 100mg/m² IV or carboplatin AUC 5mg·min/mL 1 hour IV infusion, **plus** **Day 1:** Cetuximab 400mg/m² IV over 2 hours (initial dose), **followed by** 250mg/m² IV over 1 hour once weekly **Days 1–4:** 5-FU 1,000mg/m²/day continuous IV infusion for 4 days. Repeat cycle every 3 weeks for a maximum of 6 cycles.
Cisplatin or carboplatin + docetaxel[28]	**Day 1:** Docetaxel 75mg/m² IV over 1 hour; **followed immediately by** cisplatin 75mg/m² IV. **OR** **Day 1:** Docetaxel 65mg/m² IV over 1 hour; **followed immediately by** carboplatin AUC 6mg·min/mL IV. Repeat cycle every 3 weeks.
Cisplatin or carboplatin + paclitaxel[29]	**Day 1:** Cisplatin 75mg/m²/day IV + paclitaxel 175mg/m² IV over 3 hours. **OR** **Day 1:** Carboplatin AUC 6mg·min/mL IV + paclitaxel 200mg/m² IV over 3 hours. Repeat cycle every 3 weeks for a minimum of 6 cycles.
Cisplatin + cetuximab[30] (non-nasopharyngeal)	**Day 1:** Cetuximab 200mg/m² IV over 120 minutes for 1 cycle, then cetuximab 125mg/m²/week IV over 60 minutes for subsequent cycles Repeat once weekly, **plus** **Day 1:** Cisplatin 100mg/m² IV. Repeat every 4 weeks.

continued

HEAD AND NECK CANCER TREATMENT REGIMENS (Part 3 of 5)

Nasopharynx Cancer[1] (continued)

Combination Therapy for Recurrent, Unresectable, or Metastatic Disease (With No Surgery or RT Option)[1] (continued)

REGIMEN	DOSING
Cisplatin + 5-FU[29,31]	**Day 1:** Cisplatin 100mg/m²/day IV **Days 1–4:** 5-FU 1,000mg/m²/day continuous IV infusion for 4 days. Repeat cycle every 3 weeks for a minimum of 6 cycles.
Cisplatin or carboplatin + docetaxel + cetuximab[32] (non-nasopharyngeal)	**Day 1:** Cisplatin 75mg/m² IV or carboplatin 5mg·min/mL IV **Day 1:** Docetaxel 75mg/m² IV + cetuximab (400mg/m² on day 1 of cycle 1, then 250mg/m² weekly). Repeat cycle every 21 days for 4 cycles, followed by cetuximab 500mg/m² IV every 2 weeks as maintenance therapy until disease progression or unacceptable toxicity.
Cisplatin or carboplatin + paclitaxel + cetuximab[33,34] (non-nasopharyngeal)	**Day 1:** Cisplatin 75 or 100mg/m² IV or carboplatin AUC 6mg·min/mL IV **Day 1**: Paclitaxel 175mg/m² IV. Repeat every 3 weeks for 2 cycles, **followed by** **Day 1:** Cisplatin 75 or 100mg/m² IV or carboplatin AUC 6mg·min/mL every 3 weeks + cetuximab (400mg/m² IV on day 1, then 250mg/m² weekly) for 4 cycles.
Carboplatin + cetuximab[35] (nasopharyngeal)	**Day 1:** Cetuximab initial dose of 400mg/m² IV over 2 hours; **followed by** weekly doses of cetuximab 250mg/m² IV over 1 hour; **followed by** carboplatin AUC 5mg·min/mL IV. Repeat every 3 weeks for a maximum of 8 cycles.
Cisplatin + gemcitabine[36] (nasopharyngeal)	**Days 1 and 8:** Gemcitabine 1,000mg/m² IV **Days 1–3:** Cisplatin 80mg/m² IV in divided doses. Repeat cycle every 3 weeks.
Gemcitabine + vinorelbine[40] (nasopharyngeal)	**Day 1 and 8:** Vinorelbine 25mg/m² IV; **followed by** gemcitabine 1,000mg/m² IV over 30 minutes. Repeat every 3 weeks.

Single Agents for Recurrent, Unresectable, or Metastatic Disease (With No Surgery or RT Option)[1]

Cisplatin[30,38]	**Day 1:** Cisplatin 100mg/m² IV over 15–20 minutes. Repeat every 3–4 weeks.
Carboplatin[39]	**Day 1:** 25mg/m² daily **followed by** radiotherapy: 5 daily fractions of 1.8 or 2Gy.
Paclitaxel[40]	**Day 1:** Paclitaxel 80mg/m² IV over 1 hour. Repeat every 6 weeks.
Docetaxel[41,42]	**Day 1:** Docetaxel 40–100mg/m² IV over 1 hour. Repeat every 3 weeks.
5-FU[38]	**Days 1–4:** 5-FU 1,000mg/m²/day continuous IV infusion for 4 days. Repeat every 3 weeks.
Methotrexate[31,43]	**Day 1:** Methotrexate 40mg/m² IV weekly, with progressive increase to 60mg/m², if tolerated.
Cetuximab[44] (non-nasopharyngeal)	**Day 1:** Cetuximab 400mg/m² over 2 hours as a loading dose (including a 20mg test dose); **followed by** cetuximab 250mg/m² IV over 1 hour weekly. Repeat for at least 6 weeks. If treatment response or stable disease, continue until progressive disease or unacceptable toxicity.
Gemcitabine[45] (nasopharyngeal)	**Days 1, 8, and 15:** Gemcitabine 1,000mg/m² IV over 30 minutes. Repeat every 4 weeks.
Capecitabine[46]	**Days 1–14:** Capecitabine 1250mg/m² orally twice daily; **followed by** a 1-week rest period. Repeat every 3 weeks for at least two cycles.
Afatinib (Category 2B)[47,f] (non-nasopharyngeal; second-line)	**Day 1:** Afatinib 40 mg orally daily until disease progression or unacceptable toxicity.
Pembrolizumab[51,52,f] (non-nasopharyngeal)	**Day 1:** Pembrolizumab 10mg/kg IV. Repeat cycle every 2 weeks.
Nivolumab (Category 1)[53,f] (non-nasopharyngeal)	**Day 1:** Nivolumab 3mg/kg IV. Repeat cycle every 2 weeks.

[a] Includes lip, oral cavity, oropharynx, hypopharynx, glottic larynx, supraglottic larynx, ethmoid sinus, maxillary sinus, occult primary.

[b] Induction chemotherapy should only be done in a tertiary setting.

[c] Following induction, agents to be used with concurrent chemoradiation typically include weekly carboplatin or cetuximab.[48-50]

[d] Patients with complete partial response of greater than 80% in primary tumor received additional chemoradiation therapy (ie, cisplatin 100mg/m² on days 1, 22, and 43 plus 70Gy). Radiotherapy was administered in 35 fractions of 2Gy each over a 7-week period.

[e] Following induction, agents to be used with concurrent chemoradiation typically include weekly cisplatin[22] or carboplatin.[48]

[f] If disease progression on or after platinum-containing chemotherapy.

continued

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