ESMO POCKET GUIDELINES

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ESMO CLINICAL PRACTICE GUIDELINES

Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Grégoire V, Lefebvre J-L, Licitra L and Felip E, on behalf of the EHNS-ESMO-ESTRO Guidelines Working Group
Ann Oncol 2010;21(Suppl 5):v184–6
http://annonc.oxfordjournals.org/content/21/suppl_5/v184.full.pdf+html

Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Chan ATC, Grégoire V, Lefebvre J-L, Licitra L, Hui EP, Leung SF and Felip E, on behalf of the EHNS-ESMO-ESTRO Guidelines Working Group
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ESMO GUIDE TO EVALUATION OF DATA

ESMO POCKET GUIDELINES PROVIDE YOU WITH A CONCISE SUMMARY OF THE FUNDAMENTAL RECOMMENDATIONS MADE IN THE PARENT GUIDELINES IN AN EASILY ACCESSIBLE FORMAT.

This quick reference booklet provides you with the most important content of the full ESMO Clinical Practice Guidelines (CPG) on the management of squamous cell carcinoma of the head and neck (HNSCC) and nasopharyngeal cancer. Key content includes diagnostic criteria, staging of disease, treatment plans and follow-up for HNSCC and nasopharyngeal cancer. The ESMO CPG on HNSCC and nasopharyngeal cancer are intended to provide you with a set of recommendations for the best standards of care for HNSCC and nasopharyngeal cancer, using evidence-based medicine. Implementation of ESMO CPG facilitates knowledge uptake and helps you to deliver an appropriate quality of focussed care to your patients.

The approval and licensed indication of drugs mentioned in this pocket guideline may vary in different countries. Please consult your local prescribing information.

This booklet can be used as a quick reference guide to access key content on evidence-based management of patients with HNSCC and nasopharyngeal cancer.

Please visit **http://www.esmo.org** or **http://oncologypro.esmo.org** to view the full guidelines.

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SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (HNSCC)

DIAGNOSIS

- Pathological diagnosis should be made according to the World Health Organization (WHO) classification from a surgical biopsy sample

STAGING

- Routine staging includes:
  - Physical examination
  - Chest X-ray
  - Head and neck endoscopy
  - Head and neck computed tomography (CT) scan or magnetic resonance imaging (MRI)
    - MRI is preferred for every tumour subsite except laryngeal and hypopharyngeal cancers
- A thoracic CT scan may be performed to rule out metastases and/or second lung primary tumours
- The role of 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is under investigation
- Squamous cell carcinoma of the head and neck (HNSCC) should be staged according to the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) tumour node metastasis (TNM) staging classification system (7th edition) and grouped into categories (see table)
- Risk assessment should also include that for oropharyngeal tumour, whether the disease is human papilloma virus (HPV)-related and smoking habits

AJCC/UICC TNM STAGING CLASSIFICATION SYSTEM FOR HNSCC (7TH EDITION)

STAGE	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY.: Springer, 2010
Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com

TREATMENT

- A multidisciplinary treatment schedule should be established for all patients
- The nutritional status of the patient must be corrected and maintained
- Dental rehabilitation is indicated before the administration of radiotherapy
- As rare HNSCC originating from paranasal sinuses and nasopharynx are usually excluded from clinical trials supporting evidence-based recommendations for HNSCC, the clinical recommendations provided here do not apply to these rare tumour types

Early (stage I–II) disease

- Surgery or radiotherapy (external or brachytherapy) provides similar locoregional control (based on data from retrospective studies only)
  - Radiotherapy should include 3D conformal radiation therapy or intensity modulated radiotherapy (IMRT)

Locally advanced (stage III and IV) disease

- Standard treatment options are:
  - Surgery (including reconstruction) and post-operative radiotherapy

- Surgery (including reconstruction) and post-operative chemoradiotherapy (CRT) with single-agent platinum for patients with high-risk features (nodal extracapsular extension and/or resection with microscopic residual disease [R1 resection])

- For patients with resectable disease whose anticipated functional outcome and/or prognosis is so poor that mutilating surgery is not justified, combined concomitant CRT is preferred
- Combined concomitant CRT is also preferred for patients with unresectable disease
- Treatment with radiotherapy + concomitant cetuximab has demonstrated a higher response rate and longer progression-free survival (PFS) and overall survival (OS) compared with radiotherapy alone. However:
  - No formal comparison between radiotherapy + concomitant cetuximab and radiotherapy + concomitant cisplatin has been undertaken
  - Treatment with radiotherapy + concomitant cisplatin is associated with significant toxicity and its efficacy in elderly patients is questioned
  - Treatment with radiotherapy + concomitant cetuximab is associated with a greater magnitude of effect compared with RT alone and lower toxicity than concomitant CRT but its efficacy in elderly patients is also questioned
  - Data for radiotherapy + concomitant cisplatin is based on thousands of patients versus 200 patients for radiotherapy + concomitant cetuximab
  - The therapeutic decision between radiotherapy + concomitant cisplatin and radiotherapy + concomitant cetuximab remains difficult
- Induction chemotherapy (ICT) is not considered standard treatment for advanced disease (except for organ preservation protocols)
- ICT followed by CRT is still under evaluation

Organ preservation treatment protocols

- Not all patients are suitable for an organ preservation protocol (e.g. those with massive larynx cartilage invasion)
- Taxane-platinum-based ICT followed by radiotherapy in responsive patients is an option for patients with advanced larynx and hypopharynx cancer who would otherwise require total laryngectomy
  - CRT is another option for these patients
- ICT- and CRT-based organ preservation protocols have no negative impact on disease-free survival (DFS) or OS due to successful salvage treatment with surgery
- In general, patients receiving ICT- or CRT-based organ preservation protocols have a reduction in the incidence of distant metastases

- The choice between an ICT- or CRT-based organ preservation protocol depends on various factors, including:
  - Anatomical subsite
  - Foreseeable compliance/tolerance to treatment
  - Performance status (PS)

Local, regional and metastatic recurrence

- Surgery (if operable) or re-irradiation can be considered in selected cases of localised recurrence
- For most patients, palliative chemotherapy is the standard treatment
- First-line treatment options for fit patients include:
  - Cetuximab + cisplatin/5-fluorouracil (5-FU)
  - Cetuximab + carboplatin/5-FU
- Single-agent chemotherapy should be used in patients anticipated to have a poor tolerability to polychemotherapy
  - Weekly methotrexate is the accepted treatment
  - Cetuximab has a favourable toxicity profile and comparable efficacy to methotrexate
  - The role of taxanes in this setting is unclear

FOLLOW-UP

- Treatment response should be evaluated by clinical examination and CT or MRI of the head and neck, depending on the initial procedure
- FDG-PET (or PET-CT) may be used to evaluate response to radiotherapy or concomitant CRT at the neck level and to decide upon the usefulness of a neck node dissection
- The aim of follow-up is early detection of potentially curable locoregional recurrence and/or secondary tumours
- Follow-up protocols should include physical examination and radiological imaging in cases where recurrence is suspected
  - FDG-PET may be useful in the presence of doubtful findings, particularly after combined CRT
- Special attention should be paid to the treatment sequelae that include swallowing and respiratory impairment
- Chest X-ray may be performed on a yearly basis
- Evaluation of thyroid function (serum thyroid-stimulating hormone [TSH] levels) in patients with irradiation to the neck is recommended at 1, 2 and 5 years

SUMMARY RECOMMENDATIONS FOR SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (HNSCC)

DIAGNOSIS

Pathological diagnosis should be made according to the WHO classification from a surgical biopsy sample

STAGING

Routine staging includes: Physical examination, chest X-ray, head and neck endoscopy and head and neck CT or MRI (MRI preferred for all except laryngeal and hypopharyngeal cancers)

A thoracic CT may be performed to rule out metastases and/or second lung primary tumours

HNSCC should be staged according to the AJCC/UICC TNM system (7th edition)

TREATMENT

Treatment schedules should be established by a multidisciplinary team (MDT)

Early (stage I–II) disease:

- Surgery or radiotherapy provides similar locoregional control
- Locally advanced (stage III–IV) disease:
- Surgery + post-operative radiotherapy or surgery + post-operative CRT (for patients with high-risk features) are standard treatment options
- Combined concomitant CRT is preferred for patients with unresectable disease and those with an anticipated poor functional outcome and/or prognosis
- ICT is not a standard treatment for advanced disease
- Organ preservation treatment protocols are an option for some patients
- ICT- and CRT-based organ preservation protocols have no negative impact on DFS or OS (due to successful salvage surgery) and are associated with a reduction in the incidence of distant metastases
- Local, regional and metastatic recurrence:
- Surgery or re-irradiation can be considered in selected cases of localised recurrence
- For most patients, palliative chemotherapy is the standard treatment
- Polychemotherapy (cetuximab + cisplatin/5-FU or cetuximab + carboplatin/5-FU) is the first-line treatment for fit patients; single-agent chemotherapy (methotrexate or cetuximab) should be used in patients anticipated to have a poor tolerability to polychemotherapy

SUMMARY RECOMMENDATIONS (CON'T)

FOLLOW-UP

Treatment response should be evaluated by clinical examination and CT/MRI of the head and neck (depending on the initial procedure)

The aim of follow-up is early detection of potentially curable locoregional recurrence and/or secondary tumours

Follow-up protocols should include:

- Physical examination and radiological imaging (in cases where recurrence is suspected)
- Assessment of treatment effects on swallowing and respiratory impairment
- Chest X-ray on a yearly basis
- Evaluation of thyroid function at 1, 2 and 5 years (in patients who have received irradiation to the neck)

NASOPHARYNGEAL CANCER

DIAGNOSIS

- Definitive diagnosis of cancer of the nasopharynx (NPC) should be made by endoscopic-guided biopsy of the primary nasopharyngeal tumour
- Histological type should be determined according to the World Health Organization (WHO) classification
- Neck biopsy and/or neck nodal dissection is not recommended since it may reduce the likelihood of cure and have an impact on late treatment sequelae

STAGING

- NPC should be clinically staged according to the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) tumor node metastasis (TNM) staging classification system (7th edition) (see table on next page)
- Routine staging procedures include:
  - History
  - Physical examination (including cranial nerve examination)
  - Complete blood cell count
  - Serum biochemistry (including liver function test)
  - Chest X-ray
  - Nasopharyngoscopy
  - Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the nasopharynx and base of the skull and neck
    - MRI is generally preferred, if available
- Imaging for distant metastases, including isotope bone scan and CT scan of the chest and upper abdomen, may be considered for at-risk patients (e.g. those with node positive disease, especially N3 stage) and those with clinical or biochemical abnormalities
  - Positron emission tomography (PET)-CT scan can replace the traditional work-up for detection of distant metastases since it has proven to be the most sensitive, specific and accurate diagnostic method
- Pre- and post-treatment plasma/serum load of Epstein-Barr viral deoxyribonucleic acid (DNA) has prognostic value

AJCC/UICC TNM STAGING CLASSIFICATION SYSTEM (7TH EDITION) FOR NPC

PRIMARY TUMOUR (T)	
T1	Tumour confined to the nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal extension
T2	Tumour with parapharyngeal extension
T3	Tumour involves bony structures of skull base and/or paranasal sinuses
T4	Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space

REGIONAL LYMPH NODES (N)	
N1	Unilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, ≤6 cm, in greatest dimension
N2	Bilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa
N3	Metastasis in a lymph node(s) >6 cm and/or to supraclavicular fossa
N3a	>6 cm in dimension
N3b	Extension to the supraclavicular fossa

DISTANT METASTASIS (M)	
M0	No distant metastasis
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Tis, Carcinoma *in situ*

Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY.: Springer, 2010

TREATMENT

- The optimal treatment strategy for patients with advanced NPC should be discussed in a multidisciplinary team (MDT)
- Radiotherapy is the mainstay of treatment
- Stage I disease should be treated with radiotherapy alone whereas stage II, III, IVA and IVB disease should be treated with radiotherapy and concurrent chemotherapy
- Patients should receive intensity modulated radiotherapy (IMRT), with radiotherapy targeted to the primary tumour, adjacent regions considered at risk of microscopic spread and to both sides of the neck

- The supraclavicular fossa should also be included in patients with lower neck nodes
- Elective nodal irradiation is recommended for N0 stage disease

- A total radiotherapy dose of 70 Gy is recommended for eradication of gross tumour and either 50–60 or 40–60 Gy for elective treatment of potential risk sites
  - Dose fractions of >2 Gy/day and excessive acceleration with multiple fractions of >1.9 Gy/fraction should be avoided to minimise the risk of late toxicity
- The standard agent used in concurrent chemoradiotherapy regimens is cisplatin
- Although three cycles of adjuvant cisplatin/5-fluorouracil (5-FU) has been a standard component of many concurrent chemoradiotherapy regimens, its benefit is uncertain and its toxicity is substantial
- Cisplatin-based induction chemotherapy (ICT) may be considered in locally advanced NPC but it is not considered a standard treatment
  - If used, ICT should not negatively affect the optimal administration of concurrent chemoradiotherapy

SUMMARY OF TREATMENT RECOMMENDATIONS FOR NPC

Early stage	Stage I	Radiation alone
Intermediate stage	Stage II	Concurrent chemoradiotherapy
Advanced stage	Stage III, IVA, IVB	Concurrent chemoradiotherapy ± adjuvant chemo-therapy
Problematic radiation therapy planning (e.g. tumour abutting chiasm)	Stage IVA, IVB	Induction chemotherapy followed by concurrent chemoradiotherapy

Treatment of recurrent or metastatic disease

- Treatment options for small, local recurrence include:
  - Nasopharyngectomy
  - Brachytherapy
  - Radiosurgery
  - Stereotactic radiotherapy
  - IMRT
  - A combination of surgery and radiotherapy, with or without concurrent chemotherapy

- The treatment decision should be tailored to each patient and should consider tumour volume, location and extent of the recurrence
- Regional recurrence should be managed by radical neck resection, if resectable
- Palliative chemotherapy should be considered for patients with metastatic NPC and an adequate performance status (PS)
  - Platinum-based combinations are most commonly used as first-line therapy
  - Other active agents include paclitaxel, docetaxel, gemcitabine, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin and oxaliplatin (as single agents or in combination)
  - Polychemotherapy is more active than monotherapy
  - Treatment choice should be based on prior treatment and anticipated toxicity

FOLLOW-UP

- Complete remission in the nasopharynx and neck by clinical and endoscopic examination and/or imaging should be documented
  - MRI is often used to evaluate response to radiotherapy or chemoradiotherapy, especially for T3 and T4 tumours, although distinction between post-irradiation changes and recurrent tumours may be difficult
- Follow-up protocols should include:
  - Periodic examination of the nasopharynx and neck
  - Assessment of cranial nerve function
  - Evaluation of any systemic complaints to identify distant metastasis
  - MRI assessment of the nasopharynx and base of the skull every 6–12 months for at least the first few years post-treatment (T3 and T4 tumours)
  - Evaluation of thyroid function at 1, 2 and 5 years in patients who have received irradiation to the neck

SUMMARY RECOMMENDATIONS FOR NASOPHARYNGEAL CANCER

DIAGNOSIS

Definitive diagnosis of NPC should be made by endoscopic-guided biopsy of the primary nasopharyngeal tumour

Histological type should be determined according to the WHO classification

Neck biopsy and/or neck nodal dissection is not recommended

STAGING

NPC should be clinically staged according to the AJCC/UICC TNM staging classification system (7th edition)

Routine staging procedures include: History, physical examination (including cranial nerve examination), complete blood cell count, serum biochemistry (including liver function test), chest X-ray, nasopharyngoscopy, CT or MRI of the nasopharynx and base of the skull and neck (MRI preferred)

Imaging for distant metastases may be considered for at-risk patients (PET-CT scan can replace the traditional work-up)

Pre- and post-treatment plasma/serum load of Epstein-Barr viral DNA has prognostic value

TREATMENT

Treatment should be discussed in an MDT

Radiotherapy

- Radiotherapy is the mainstay of treatment
- Stage I: Radiotherapy alone
- Stage II, III, IVA and IVB: Radiotherapy and concurrent chemotherapy
- Patients should receive IMRT, with radiotherapy targeted to the primary tumour, adjacent regions considered at risk of microscopic spread and to both sides of the neck (the supraclavicular fossa should be included in patients with lower neck nodes)
- Elective nodal irradiation is recommended for N0 stage disease
- Radiotherapy dose: 70 Gy for eradication of gross tumour and 50–60 or 40–60 Gy for treatment of potential risk sites
- Radiotherapy dose fractionation schedule: >2 Gy/day and excessive acceleration with multiple fractions of >1.9 Gy/fraction should be avoided

- The standard agent used in concurrent chemoradiotherapy regimens is cisplatin
- Cisplatin-based ICT may be considered in locally advanced NPC but is not considered standard and should not negatively affect the optimal administration of concurrent chemoradiotherapy

Treatment of recurrent or metastatic disease

- Treatment options for small, local recurrence: Nasopharyngectomy, brachytherapy, radiosurgery, stereotactic radiotherapy, IMRT or a combination of surgery and radiotherapy ± concurrent chemotherapy
- Treatment of regional recurrence: Radical neck resection (if resectable)
- Treatment of metastatic NPC: Palliative chemotherapy for patients with a good PS
  - Platinum-based combinations are most commonly used as first-line therapy
  - Other active agents include paclitaxel, docetaxel, gemcitabine, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin and oxaliplatin
  - Polychemotherapy is more active than monotherapy

FOLLOW-UP

Complete remission in the nasopharynx and neck by clinical and endoscopic examination and/or imaging should be documented

Follow-up protocols should include: Periodic examination of the nasopharynx and neck, assessment of cranial nerve function, evaluation of any systemic complaints to identify distant metastasis, MRI assessment of the nasopharynx and base of the skull every 6–12 months for at least the first few years post-treatment (T3 and T4 tumours), and evaluation of thyroid function at 1, 2 and 5 years (in patients who have received irradiation to the neck)

GLOSSARY

5-FU, 5-fluorouracil
AJCC, American Joint Committee on Cancer
CPG, Clinical Practice Guidelines
CRT, chemoradiotherapy
CT, computed tomography
DFS, disease-free survival
DNA, deoxyribonucleic acid
ESMO, European Society for Medical Oncology
FDG-PET, 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography
HNSCC, squamous cell carcinoma of the head and neck
HPV, human papilloma virus
ICT, induction chemotherapy
IMRT, intensity modulated radiotherapy
MDT, multidisciplinary team
MRI, magnetic resonance imaging
NPC, cancer of the nasopharynx
OS, overall survival
PFS, progression-free survival
PS, performance status
R1, resection with microscopic residual disease
TIS, Carcinoma *in situ*
TNM, tumour node metastasis
TSH, thyroid-stimulating hormone
UICC, Union for International Cancer Control
WHO, World Health Organization

NOTES