

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

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## incidence

In 2002, the crude incidence rates of carcinoma of the head and neck (ICD, 10th revision C00–C10, C12–C14, C32) in Europe were 36/100 000/year in the male population and 7/100 000/year for females, while the corresponding mortality rates were 18 and 3/100 000/year. On the European scale, head and neck cancer accounts for 139 000 new cases per year. More than 90% of head and neck malignancies are squamous cell carcinomas.

In Europe the relative survival rate for head and neck cancer patients was 72% at 1 year and 42% at 5 years in adults. Five-year survival was higher in women (51%) than men (39%). The effect of age on survival is marked. Survival at 5 years was 54% for the youngest age group (15–45 years) and 35% in the oldest group of patients (≥75 years old).

## diagnosis

Pathological diagnosis should be made according to the World Health Organization classification from a surgical biopsy sample.

Routine staging includes physical examination, chest X-ray, head and neck endoscopy, and head and neck computed tomography (CT) scan or magnetic resonance imaging (MRI). MRI is the preferable staging procedure for every tumour subsite except laryngeal and hypopharyngeal cancers. A thoracic CT scan may be performed to rule out metastatic disease and/or second lung primaries. The role of 2-[<sup>18</sup>F]fluoro-

2-deoxy-D-glucose positron emission tomography (FDG-PET or PET-CT) at staging is under investigation. In this context it can be stated that in general PET has a lower specificity than sensitivity, and that it may be more useful for staging the metastasis or synchronous tumours than the neck node. Squamous cell head and neck cancer should be staged according to the TNM system and grouped into categories shown in Table 1. According to the seventh AJCC classification T4 tumours are subdivided into T4a moderately advanced and T4b very advanced. Stage IV is subdivided into stages IVa and IVb accordingly, and stage IVc for metastatic disease.

Modern risk assessment should also include that for oropharyngeal tumour, whether the disease is HPV related, together with the smoking habits.

## treatment plan

A multidisciplinary treatment schedule should be established in all cases. The patient's nutritional status must be corrected and maintained. Dental rehabilitation is indicated before radiotherapy. Treatment depends on primary tumour location and extension. Rare squamous head and neck cancer originating from paranasal sinuses and nasopharynx are usually excluded from trial treatment series supporting evidence-based recommendations, so they are excluded from these clinical recommendations. In early stage (I–II), either conservative surgery or radiotherapy (external radiotherapy or brachytherapy) gives similar loco-regional control. However, this is based only on retrospective studies as there are no randomized trials available for reference. Modern radiotherapy treatment should include 3D conformal radiation therapy or intensity-modulated radiation therapy (IMRT).

Standard options for locally advanced stage III and IV tumours are: surgery including reconstruction plus postoperative radiotherapy and, for those patients found at surgery to have high-risk features (nodal extracapsular extension and/or R1 resection), post-operative chemoradiotherapy (CRT) with single-agent platinum [I, A]. However, in resectable patients, when the anticipated functional outcome and/or the prognosis is so poor that mutilating surgery is not justified, combined concomitant

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**Table 1.** TNM categories for squamous cell head and neck cancer (TNM seventh edition 2009)

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	Tb	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

chemoradiation is preferred. Combined concomitant chemoradiation is also the standard treatment in non-resectable patients [I, A]. Radiotherapy given concomitantly with cetuximab has demonstrated a higher response rate, longer disease-free progression and longer overall survival versus radiotherapy alone [II, B]. There is no formal comparison between the combination of radiotherapy with cisplatin or cetuximab. In this context the therapeutic decision is difficult to take. However, it should be considered that results of concomitant chemoradiation are based on thousands of patients, that this combination is associated with significant toxicity and that its efficacy in the elderly population is questioned. On the other hand results of cetuximab + radiation are based on 200 patients, the magnitude in effect was similar or even better than that achieved by concomitant chemoradiation, it proved to be less toxic and the benefit in the elderly subgroup is also questioned.

The role of induction chemotherapy (ICT) has been reconsidered since the introduction of taxane–platinum-based (TPF) combinations that have proved to be superior to platinum–fluorouracil PF schedule in loco-regionally advanced disease [I, A]. However, at present, induction chemotherapy is not considered standard treatment in advanced disease. ICT followed by RT-CT (so-called sequential CT-RT) is still under evaluation. The overall toxicity of this approach can be substantial thus compromising the final result.

TPF induction chemotherapy followed by radiotherapy in responsive patients is an option for organ preservation in advanced larynx and hypopharynx cancer in patients otherwise requiring total laryngectomy [II, A]. CRT is another option. In one randomized trial, concurrent CRT achieved higher larynx preservation rates in the first 2 years after treatment completion but this was not associated with improved survival over either ICT followed by radiation in responsive patients or radiotherapy alone [II A]. The choice between either an ICT-based or a CRT-based organ-preserving protocol depends on various factors (anatomical subsite, foreseeable compliance/tolerance to treatment, performance status, etc.). In addition, not every patient and tumour presentation is suitable for organ preservation. Patients with massive larynx cartilage invasion should be excluded from this approach. Whether based on ICT or CRT, these treatment options have no negative impact on disease-free or overall survival, due to the successful salvage

treatment with surgery [II, A], although in general those patients undergoing such treatments tend to have a reduction in distant metastasis.

## local, regional and metastatic recurrence

In selected cases of localized recurrence, surgery (if operable) or re-irradiation can be considered. For most patients palliative chemotherapy is the standard option. First-line option for fit patients should include the combination of cetuximab with cisplatin or carboplatin plus 5-fluorouracil (PF). It resulted in longer survival than PF alone [II, A]. In patients for which polychemotherapy tolerability is anticipated to be poor monochemotherapy should be used. Weekly methotrexate may be considered as the accepted treatment [I, A]. Since there is no comparison between taxanes and methotrexate as monotherapy it is difficult to state whether taxanes are useful in this context. Cetuximab alone has a favourable toxicity profile with activity that is comparable to methotrexate alone.

## follow-up

Treatment response should be evaluated by clinical examination and CT scan or MRI of head and neck depending on the initial procedure. FDG-PET (or PET-CT) may be used to evaluate the response to radiotherapy or concomitant CRT at the neck level and decide upon the usefulness of a neck node dissection. The aim of follow-up is the early detection of potentially curable loco-regional recurrence and second tumours. Physical examination along with radiological imaging in the case of suspicion of recurrence should be included in the follow-up. FDG-PET scanning may be useful in the presence of doubtful findings, particularly after combined chemoradiation. In such situations its negative predictive value is superior to the positive one. At this time, special attention should be paid to the treatment sequelae that include swallowing and respiratory impairment. Chest X-ray may be included 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.

## note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts.

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