# Head and neck oncology – 2010, part I

Nowotwory głowy I szyi – 2010, część I

Eugene N. Myers, MD, FACS, FRCS Edin (Hon)

SUMMARY

This article reviewed the current state of the art in head and neck oncology. These include very important and stimulating new areas of interest including the marked acceptance of chemoradiation in favor of surgery in patients with cancer of the head and neck. The concept of HPV as a cause of cancer of the oropharynx is relatively new and very important in the epidemiology of these tumors. New modalities such as PET CT scanning and robotic surgery are discussed and appear to be very important in management of cancer of the head and neck. Endoscopic endonasal skull base surgery is another new high technology contribution to the field of head and neck surgery as is the use of endoscopic assisted thyroid surgery. These and other new concepts are discussed in this manuscript.

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**UPP Department of Otolaryngology, University of Pittsburgh Medical Center, Eye and Ear Institute, Pittsburgh, PA**

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**Adres do korespondencji**/
Address for correspondence:
imię i nazwisko: **Eugene N. Myers, MD, FACS, FRCS Edin (Hon)**
adres pocztowy:
**Distinguished Professor and Emeritus Chair**
**UPP Department of Otolaryngology**
**University of Pittsburgh Medical Center**
**Eye and Ear Institute; Suite 519**
**200 Lothrop Street**
**Pittsburgh, PA 15213**
tel. **412-647-2111**
fax **412-647-2080**
e-mail **myersen@upmc.edu**

## Introduction

Squamous cell carcinoma is the most common cancer arising in the head and neck and affects more than 500,000 patients each year world wide. It has been thought that these cancers arise in the mucosa after exposure to carcinogens such as tobacco and alcohol. Recently, however, the human papilloma virus (HPV) has been strongly implicated as a causative agent particularly in cancer of the oropharynx. The complex regional anatomy and vital physiological role of the structures involved dictate that the goals of treatment are not only to attempt to cure the cancer, but also to preserve function. A multidisciplinary approach is important in treating these patients given the complexity of treatment and acute and long term complications that result from chemotherapy, radiation therapy and surgery. Appropriate clinical and radiographic staging is crucial for accurate treatment planning and delivery [1].

The pendulum has swung away from primary surgery to chemoradiation with surgery left for the salvage of therapeutic failures. The development of PET CT scanning has proven invaluable, both for initial precise staging of the cancer and follow up after chemoradiation. Molecular targeting agents, particularly epidermal growth factor inhibitors, have been successfully integrated into potentially curative treatment of locally advanced squamous cell carcinoma of the head and neck [2].

Recently, major improvements in technology including microvascular reconstruction, technical advances in radiation therapy delivery, such as IMRT and cyber knife, transoral laser therapy for cancer of the base of the tongue and larynx,and robotic surgery for cancer of the oropharynx and larynx have lead to improvement in patient care.

HPV has been shown to cause virtually all cancers of the female cervix. Molecular evidence also suggests a role for HPV particularly HPV 16 in the pathogenesis of a subgroup of squamous cell carcinomas in the head and neck. HPV DNA was detected in 72% of 100 oropharynx tumor specimens and 64% of the patients in the study were sero-positive for HPV 16 E6, HPV16 E7 or both [3]. Furthermore, exposure to HPV increased the association with cancer of the oropharyngeal regardless of the use of tobacco or alcohol and without evidence of synergy between exposure to HPV and the use of tobacco and alcohol. These data suggest that two distinct pathways may be involved in the development of cancer of the oropharynx. One may be driven by tobacco and alcohol and the other by HPV induced genetic instability.

Among young patients, widespread use of oral sexual practices and a trend towards multiple sexual partners may be contributing to an increased incidence of HPV related head and neck cancer particularly

those in the tonsil and base of the tongue. In fact, in Stockholm a recent report disclosed that between 1970 and 2002 there was a threefold parallel increase in the incidence of squamous cell carcinoma of the oropharynx and the proportion of HPV positive squamous cell carcinoma. The authors stated that "the incidence of HPV positive tonsil cancer is still increasing in the county of Stockholm suggesting an epidemic of virus induced cancer with soon almost all tonsil cancer being HPV positive, as in cervical cancer [4]. Since HPV vaccination is an important strategy to prevent cervical cancer, so it would seem logical that HPV vaccination trials may be tested as a potential means of preventing HPV induced cancer of the head and neck.

Advances in treatment strategies have affected all the approaches used in head and neck cancer: radiation therapy, chemotherapy, and targeted agents: radiation therapy is now the mainstay of curative therapy for oropharyngeal cancer and advanced hypopharyngeal and laryngeal cancer. Recent advances have focused primarily on variations in fractionation schedule and intensity modulated radiation therapy (IMRT) a form of high precision conformal radiotherapy that delivers radiation more precisely to the tumor while relatively sparing the surrounding normal tissue in particular the salivary glands to try to prevent xerostomia. In our Department and others, the cyberknife has come into common practice for use in patients with recurrent cancer in the head and neck.

Chemotherapy is an integral part of treating locally advanced head and neck cancer. It may be administered either before radiotherapy as induction (neoadjuvant) therapy or concurrently with radiotherapy. Postoperative adjunctive chemoradiation continues to play an important role in treating locally advanced, but operable, cancer of the head and neck [5, 6].

Targeting agents such as Cetuximab appear to have promise both in combination with chemo/radiotherapy as primary treatment, or as single agents in patients with recurrent or metastatic cancer [7, 8].

## Nonsurgical treatment

Concurrent chemotherapy has a long record of improving local and regional control in squamous cell carcinoma of the head and neck, however, its affect on distant metastases is controversial. Conversely induction chemotherapy appears to reduce distant metastases. Induction chemotherapy may be ideally used in patients with good performance status and advanced primary and nodal presentations, such as T3, T4, and N2A or N3. It is also reasonable to offer induction chemotherapy to symptomatic patients in need of immediate therapy.

Many retrospective analyses have shown poor outcome for patients with squamous cell carcinoma of the head and neck which express high levels of EGFR. Targeting this receptor with a monoclonal antibody has been successfully exploited for therapeutic purposes, an example of which previousy mentioned is cetuximab. Cetuximab is a monoclonal antibody approved by the FDA for treating cancer of the head and neck. Its use as a single agent in patients with platinum resistant cancer has been approved for use in combination with radiation in previously untreated patients. Bonner et al [7], in a recent Phase III trial, demonstrated that cetuximab in combination with radiotherapy improved local regional control and progression free and overall survival in locally advanced cancer. Treatment with a combination regimen decreased the risk of local regional progression by 32% and the risk of death by 26%. However, the rates of distant metastasis in one and two years were similar in the two study groups. Cetuximab has also been tested as a single agent in 103 patients with recurrent or metastatic head and neck cancer resistant to platinum based therapy. The response rate was 13% and the rate of cancer control was 46% [8].

Angiogenesis is also fundamental to cancer growth and metastasis and is regulated by many endogenous pro-angiogenic and anti-angiogenic factors, the most important being the vascular endothelial growth factor (VEGF) and its receptors [9]. VEGF can be upregulated and has prognostic significance in squamous cell carcinoma of the head and neck. Anti-angiogenesis therapeutic strategies have been extensively studied in other solid tumors and are currently being evaluated in the treatment of squamous cell carcinoma of the head and neck.

Definitive chemoradiation for cancer of the oropharynx, larynx, and hypopharynx has replaced surgery in many cases. A meta-analysis involving patients with head and neck cancer showed an absolute benefit of 8% associated with concurrent chemoradiation compared to radiation therapy alone [10]. Unfortunately the side effects of many of the chemotherapy approaches include neuropathy, hearing loss, marked nausea and vomiting, renal dysfunction and long term sequela such as dysphagia.

Postoperative concurrent chemoradiation has been tested in two Phase III studies conducted by the Radiation Therapy Oncology Group (RTOG) [5] and the European Organization for Research and Treatment of Cancer (EORTC) [6]. Both trials aimed to determine whether the addition of cisplatinum to radiotherapy improved the outcome as compared with radiotherapy alone. In both studies, patients with high risk pathological features after surgery were randomly assigned to receive either radiotherapy alone or radiotherapy plus cisplatinum. High risk features were defined as the presence of positive margins, extracapsular spread, lymphovascular invasion, perineural invasion, and