**NEW TRENDS IN THE MANAGEMENT OF HEAD AND NECK CANCERS**


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**INTRODUCTION**

More than half a million people per year worldwide are newly diagnosed with head and neck cancer (HNCA). In Lebanon, the Ministry of Public Health reported 230 new cases in 2005, 286 in 2006 and 268 in 2007 [http://www.moph.gov.lb/Prevention/Surveillance/Pages/Cancer.aspx].

Head and neck cancer represents around 7% of all malignant tumors according to the National Cancer Database report. These malignancies can be located in the paranasal sinuses and nasal cavity, nasopharynx, oropharynx, oral cavity, hypopharynx, and larynx. Over 90% of HNCAs are squamous cell carcinomas [1-2].

Fifty-eight percent are diagnosed at an early stage (carcinoma in situ, stage I, stage II), however 42% are diagnosed at advanced stages (stage III, stage IV) and 20% of advanced cases have distant metastases [2]. Patients who have vascular or lymphatic invasion, extracapsular spread in lymph node metastases and positive margins after surgical resection have particularly high rates of local recurrence and distant metastases, with a significantly higher risk of death [3]. Head and neck tumors have a major effect on the quality of life, social interactions and self-image because many of the structures affected are essential for mastication, swallowing, breathing, and communication. Treatments aim to cure the underlying malignancy with as limited functional and cosmetic morbidity as possible.

Despite the recent advances in therapeutic approaches with minimally invasive surgery and organ preservation strategies, there is only a modest improvement of overall survival. Statistically significant improvements in survival are seen in carcinomas of the oral cavity, oropharynx, and nasopharynx, however, there is a small but significant decrease in survival in carcinomas of the larynx [4-5] (Figure 1).

Are available diagnostic procedures more precise? Are minimally invasive surgeries as good as open-neck surgeries? Are organ preservation protocols adequate treatment options? Do they induce more toxicity? Is there a better understanding of the disease with more targeted therapy options? … What are the new trends in the management of head and neck cancer in 2011?

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**TRANSORAL SURGERY REPLACES OPEN-NECK SURGERIES IN SELECTED CASES**

In the era of organ preservation, minimally invasive transoral surgery is replacing open-neck surgeries for an increasing number of tumors, in different sites and more and more advanced stages, allowing improvements in functional results with lower morbidity and without compro-
mising oncologic safety. The American Society of Clinical Oncology recommends endoscopic resection for T1a and T1b glottic cancers and places it as an option for selected patients for T2 of the glottis or supraglottis [6]. The European Laryngological Society reserves more indications to transoral surgery [7-9].

Two transoral modalities are now available: transoral laser microsurgery (TLM) and transoral robotic surgery (TORS).

In 1972, the carbon dioxide (CO₂) laser was introduced for transoral resection of early laryngeal tumors. It has produced cure rates equivalent to those achieved with open surgical approaches and radiotherapy (RT), precluding the need for tracheotomy and maintaining the laryngeal framework [10-13]. TLM has been extended since then to include larger tumors (T2 and selected T3). The European Laryngological Society proposed classifications for cordectomies and endoscopic supraglottic laryngectomies to allow a standardization of the description of the procedures [7-9]. However, TLM is limited by the difficulty of exposure in some patients, massive involvement of the anterior commissure, management of the neck, and previous radiation therapy. Like most other minimally invasive procedures, it needs a learning curve. Because TLM minimizes the extent of resection, one of the concerns is the lack of generous margins, knowing that the positive surgical margins induce a high rate of recurrence [14]. That is why the pathology examination for margins, although very important, is still controversial. Some teams rely on the margins status as seen through the operating microscope [10-11], others perform a systematic second look [15], and others rely on peroperative frozen sections [16].

More recently, TORS has been introduced to the field of head and neck surgery. It is mostly used for tumors of the pharynx (tonsils, base of tongue, hypopharynx) and the supraglottis with good functional outcomes [17-20]. Short-term results are encouraging, however long-term results will only be available in a few years.

### Increasing Role of Concomitant Chemoradiation Therapy

The management of locoregionally advanced resectable tumors of the larynx, hypopharynx, and oropharynx, has also undergone a shift during the past decades.

Organ-preserving strategies have been replacing surgical approaches because total laryngectomy is recognized as one of the most feared surgical procedures by patients. Chemoradiation therapy (CRT) became the standard of care for such cases [6, 21]. However, Hoffman et al. identified a trend toward diminished survival among patients treated for laryngeal cancer from the mid-1980s to mid-1990s, a period during which initial treatment evolved from surgery to concomitant chemoradiation [5, 22].

Meanwhile, many randomized controlled trials have been conducted providing some answers to the place of chemoradiation therapy in HNCAs.

### Definitive Chemoradiation Therapy in Advanced Head and Neck Cancer

With the current available data, chemotherapy does not have a role neither in early cancers nor in patients with T4 diseases. In clinical practice, patients with early cancers are treated with radiation therapy or partial surgery, and patients with T4 laryngeal disease, particularly when the tumor extends massively through the cartilage into neck soft tissue, undergo initial surgery and are not considered candidates for an organ preservation approach.

Many trials have shown that chemoradiation therapy is a viable treatment alternative to surgical excision for locally advanced HNCA (T3). The Veterans Affairs Laryngeal Cancer study showed that induction chemotherapy followed by radiation resulted in equivalent survival and good organ preservation compared with radical open surgery followed by radiotherapy for advanced laryngeal cancer [23]. The EORTC pyriform sinus cancer trial showed similar results for the hypopharynx subsite [24]. The Radiation Therapy Oncology Group (RTOG) study 91-11 demonstrated that patients with advanced...
laryngeal cancer receiving concurrent cisplatin and radiation had a better larynx preservation rate (84%) at a median follow-up of 3.8 years compared to that obtained either with radiation alone or with induction cisplatin/fluorouracil followed by radiation (rates of 67% and 72%, respectively), however, concurrent chemotherapy did not improve survival [25].

The recent update of the meta-analysis by Pignon et al. of chemotherapy in head and neck cancer (MACH-NC) [26], including a total of 93 randomized trials and 17,346 patients, confirmed the benefit of concurrent chemoradiation therapy with an absolute survival benefit of 6.5% at 5 years.

**Definitive chemoradiation therapy**

**Future trials**

The problem with the currently available data is the fact that many of the studies have different end points and even different methodologies. More studies are required to better define the eligibility and the outcomes and benefits of definitive chemoradiation in HNCA. With these limitations in mind, Lefebvre et al. [27], set the standards required for future trials: more specific inclusion criteria, better defined exclusion criteria, and better recording of vocal cord fixation and partial response to treatment.

**Postoperative concurrent radiotherapy and chemotherapy**

The place of concurrent radiotherapy and chemotherapy after surgery for high risk patients is better established. Adding chemotherapy to radiotherapy in the postoperative setting has been shown to improve locoregional control and progression-free survival for patients with advanced disease and adverse features such as histologic evidence of invasion of two or more regional lymph nodes, extracapsular extension of nodal disease, and microscopically involved mucosal margins of resection. In a study by Cooper et al. [28], after total resection of visible and palpable disease, 231 patients were randomly assigned to receive radiotherapy alone (60 to 66 Gy in 30 to 33 fractions over a period of 6 to 6.6 weeks) and 228 patients to receive the identical treatment plus concurrent cisplatin (100 mg per square meter of body-surface area intravenously on days 1, 22, and 43). After a median follow-up of 45.9 months, the rate of local and regional control was significantly higher in the combined-therapy group than in the group given radiotherapy alone. Disease-free survival was significantly longer in the combined-therapy group than in the radiotherapy group, but overall survival was not. However, the combined treatment was associated with a substantial increase in adverse effects.

Bernier et al. [29] conducted the same study with a variation in inclusion criteria. After a median follow-up of 60 months, the rate of progression-free survival and overall survival was significantly higher in the combined-therapy group than in the group given radiotherapy alone. The cumulative incidence of local or regional relapses was significantly lower in the combined-therapy group.

Severe (grade 3 or higher) adverse effects were more frequent after combined therapy than after radiotherapy.

**Chemoradiation or bioradiation: Should cetuximab replace conventional chemotherapy?**

Due to the high toxicity of conventional chemotherapy drugs, new molecules have been introduced. Epidermal growth factor receptor antagonist, cetuximab, has been shown to have biologic activity against HNCA. The epidermal growth factor receptor (EGFR), a member of the ErbB family of receptor tyrosine kinases, is abnormally activated in epithelial cancers. The cells of almost all such neoplasms express high levels of EGFR, a feature associated with a poor clinical outcome. Radiation increases the expression of EGFR in cancer cells, and blockade of EGFR signaling sensitizes cells to the effects of radiation.

Vermorken et al. [30] investigated the efficacy of cetuximab plus platinum-based chemotherapy as first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck. 220 of 442 eligible patients with untreated recurrent or metastatic squamous-cell carcinoma of the head and neck were randomly assigned to receive cisplatin or carboplatin plus fluorouracil every three weeks for a maximum of six cycles and 222 patients to receive the same chemotherapy plus cetuximab for a maximum of six cycles. Adding cetuximab to platinum-based chemotherapy with fluorouracil (platinum-fluorouracil) significantly prolonged the median overall survival, the median progression-free survival time, and increased the response rate. There were no cetuximab-related deaths.

Bonner et al. [31] reported on the phase 3 study of cetuximab plus radiotherapy for locoregionally advanced squamous-cell carcinoma of the head and neck. They found an improvement in locoregional control, progression-free survival, and overall survival among patients treated with cetuximab plus radiotherapy, as compared with radiotherapy alone. Furthermore, the addition of cetuximab did not increase the incidence of severe mucositis.

However, these studies do not allow oncologists to replace platinum-based chemoradiation therapy with cetuximab and radiotherapy in all HNCA patients. An article by Posner [21] emphasizes the fact that Bonner et al. did not compare the combination of cetuximab plus radiotherapy with the current standard of care – platinum-based chemoradiation therapy – and did not administer the radiotherapy uniformly among all patients. The benefit of cetuximab in terms of survival was evident for the subgroup of oropharyngeal cancer but not among patients with hypopharyngeal or laryngeal cancer. In the study by Bonner et al., cetuximab appeared to be effective when added to hyperfractionated radiotherapy and in patients younger than 65 years.

Whether cetuximab plus radiotherapy is a better therapy than platinum-based chemoradiation therapy and whether cetuximab can be added to platinum-based chemoradiation therapy are important questions, the answers to which are
not currently available and require randomized studies that are being performed. Until future data is available, for patients who can tolerate it, chemoradiation therapy with cisplatin remains the standard of care. Patients who cannot tolerate platinum-based chemotherapy for a variety of reasons should be expected to benefit from the addition of cetuximab to radiotherapy, in particular the elderly patients who seem to suffer higher toxicity and less efficacy with chemotherapy [26].

INTERNITY-MODULATED RADIATION THERAPY (IMRT)

Radiation therapy has improved significantly over the past decades in an effort to minimize toxicity to normal tissue. IMRT is a new technology that was designed to increase the conformity of the radiation dose. It uses inverse planning to define specific target doses for the tumor and maximum acceptable doses to surrounding normal tissue [32]. On the basis of these values, a computer optimization algorithm determines beam parameters that will lead to the desired volumetrically conformed dose distribution, and allow for tumor dose escalation. IMRT allows for the delivery of a simultaneous, integrated boost without treatment field modifications. Most of the current data on IMRT focuses on nasopharyngeal cancer (NPC) and oropharyngeal cancer at single institutions, with an excellent locoregional control. Several multi-institutional randomized trials investigating IMRT are in progress, including two RTOG studies: One investigating IMRT versus conventional RT in early-stage oropharyngeal cancer and another examining IMRT with and without chemotherapy in NPC. The Groupe d’oncologie radiothérapie tête et cou (GORTEC) is evaluating IMRT with concomitant cisplatin versus conventional RT and cisplatin in patients with stage III and IV HNCA. RTOG 0522 is designed to define the effect of cetuximab added to concurrent CRT by comparing concurrent cisplatin and accelerated RT with and without cetuximab [33-34].

Neck management after chemoradiation therapy

According to the American Society of Clinical Oncology Clinical Practice Guideline [6], patients with clinically involved regional cervical nodes (N1) who are treated with definitive radiation therapy or chemoradiation therapy and who have a complete clinical response do not require elective neck dissection. Neck dissection should be performed for patients who do not have a complete clinical response to radiation therapy. Surgical treatment of the neck is recommended for patients with N2 or N3 disease who are treated with definitive radiation therapy or chemoradiation therapy, regardless of response. However, some surgeons and patients are reluctant to risk the morbidity of neck dissection, given the prospect of a negative pathologic diagnosis in most cases [35-36]. Until now, the problem of the N2-N3 neck has not been resolved [27]. With the aim to study the extent of neck dissection after definitive treatment with chemoradiation therapy, Goguen et al. [37] showed that negative computed tomography (CT) accurately predicted pathologic complete response at neck dissection. Neck dissection can be avoided in patients who have a complete neck response on CT. Additionally, computed tomography reliably identified low-risk neck levels that do not require dissection, permitting selective neck dissection or superselective neck dissection in partial response patients with limited residual disease.

PET SCAN IN THE ASSESSMENT AND FOLLOW-UP OF HEAD AND NECK CANCER

The place of functional imaging in HNCA is widening, whether alone (PET scan) or in combination with anatom imaging (PET/CT). PET scanning relies on differential levels of radiolabeled glucose uptake in various tissues, with metabolically active tumors showing increased uptake. In HNCA, PET scan is essential in the initial assessment of stage III and IV tumors, and whenever remote dissemination or a second tumor is suspected, contraindicating heavy surgery [38-39]. However, it does not have a role in the systematic workup of early stage HNCA of known origin.

A meta-analysis by Xu et al. showed that whole-body PET-CT and PET have good diagnostic performance in M staging of head and neck cancer; and PET-CT tended to have higher accuracy than PET [40]. PET scan should also be performed in case of negative conventional results for isolated metastatic adenopathy from unknown origin [41]. In the study by Rusthoven et al. the PET scan detected 25% of previously undetected primaries in unknown primary patients, previously undetected regional metastases in 16% of patients, previously undetected distant metastases in 11% of patients. The sensitivity was 88% being the lowest for the base of tongue region. The specificity was 75%, being the lowest for tonsils and reactive nodes [42]. However, PET scan does not eliminate the role of a careful panendoscopy with directed biopsies that has great success in identifying primary tumors too small to show on the PET.

During follow-up of organ preservation treatments, PET scan should be performed after a 3- to 4-month interval of termination of treatment in order to optimize prognostic value because of the high false positive and false negative rates before that time [43-44].

Finally, PET scan is of interest in determining radiotherapy target volumes, but implementation still needs close cross-disciplinary teamwork [45].

HPV IN OROPHARYNGEAL CANCER

Human papillomavirus (HPV) has been recognized as an important independent risk factor in head and neck squamous cell carcinoma (HNSCC). Approximately 25% of HNSCC specimens contain HPV genomic DNA, primarily HPV type 16 and, less frequently, type 18. Expression of the E6 and E7 viral oncoproteins inactivate the tumor-
suppressor proteins p53 and Rb, respectively [46]. Certain high-risk sexual behaviors have been associated with HPV transmission and oropharyngeal carcinoma [47]. The association of HPV and HNSCC has important implications regarding prevention, treatment, and prognosis. The presence of HPV may be a favorable prognostic factor in HNSCC, especially in patients with no history of tobacco and/or alcohol use, possibly because of increased radiosensitivity [48]. A 2007 meta-analysis by Ragin and Taioli [49] indicated that patients with high-risk HPV-associated HNCA, independent of site of tumor, have an 18% reduced risk of dying and a 38% reduced risk of disease failure compared to patients with HPV-negative tumors. When broken down by head and neck subsite, this finding appeared to be limited statistically to oropharyngeal squamous cell carcinoma (OPSCC). HPV-associated OPSCC had a 28% reduced risk of death and a 49% reduced risk of disease failure compared to HPV-negative OPSCC. No differences in survival were observed between HPV-associated and HPV-negative non-OPSCC.

No recommendations are available for changing the therapeutic regimen. The role of vaccination against HPV in HNSCC remains to be explored.

**TARGETED THERAPIES OTHER THAN CETUXIMAB AND FUTURE DIRECTIONS**

Squamous cell carcinoma of the head and neck has been associated with alterations in the expression of p16, p53, pRb, and cyclin D1; as well as other oncopenes. Alterations in the p53 tumor-suppressor gene represent an early event in progression, whereas mutations in the p16 gene, an inhibitor of cyclin-dependent kinase that is important in regulating the cell cycle, are associated with later stages of tumor progression [50]. Vascular endothelial growth factor (VEGF) and its receptor are also involved in tumorigenesis and angiogenesis in HNCA, and may correlate with tumor progression [51].

Novel agents are currently under active investigation. These include other EGFR antibodies, such as the fully human panitumumab, which has demonstrated significant single-agent activity in colorectal cancer with increased progression-free survival [52]. In addition, the EGFR tyrosine kinase inhibitor erlotinib has demonstrated modest single agent activity in recurrent or metastatic HNSCC and is currently being evaluated in combination with standard CRT regimens. Activation of the Src kinase family is important in HNCA progression. Dasatinib is an oral agent with activity against Src kinase family members, and clinical trials in HNSCC are currently under development [53]. In addition, bevacizumab, a monoclonal antibody against VEGF, is being currently evaluated in combination with concurrent CRT or erlotinib in HNSCC patients. Finally, vanitibin has become an interesting candidate agent given its ability to competitively inhibit EGFR and VEGFR receptor 2. The combination of these agents with conventional CRT may be a promising strategy for novel and potentially more efficacious treatments for patients with HNSCC as more targeted therapeutic agents are developed [54].

**CONCLUSION**

Both surgical and nonsurgical therapies represent continuously evolving modalities for treating HNCA with the goal of organ preservation. Vigilance must be maintained regarding the applicability of randomized controlled clinical trial regimens to wider clinical practice. Just as resection of a structure that can be cured oncologically and preserved functionally with nonsurgical treatment does not seem reasonable, resistance to excision of resectable tumors that are likely to have poor residual function after organ-preservation CRT regimens is similarly problematic [54]. Transoral laser resection for small tumors, IMRT for nasopharyngeal tumors, as well as concomitant chemoradiation for T3 of the larynx otherwise requiring total laryngectomy, are all here to stay. Better pretreatment selection criteria are still required to optimize the selection of the treatment modality that offers every specific patient the best chance of cure with the best possible quality of life.

**CONFLICT OF INTEREST:** None.

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