Future challenges in head and neck cancer: From the bench to the bedside?

Luca Calabrese a, b, *, Angelo Ostuni a, Mohssen Ansarin a, Gioacchino Giugliano a, Fausto Maffini c, Daniela Alterio d, Maria Cossu Rocca e, Giuseppe Petralia f, Roberto Bruschini a, Fausto Chiesa a, on behalf of AROME 1

a Division of Head & Neck Surgery, Head & Neck Multi-Disciplinary Task Force, European Institute of Oncology, Milan, Italy
b AROME (Association of Radiotherapy and Oncology of the Mediterranean Area), Head & Neck Multi-Disciplinary Task Force, European Institute of Oncology, Milan, Italy
c Division of Pathology & Laboratory Medicine, Head & Neck Multi-Disciplinary Task Force, European Institute of Oncology, Milan, Italy
d Division of Radiotherapy, Head & Neck Multi-Disciplinary Task Force, European Institute of Oncology, Milan, Italy
e Division of Medical Oncology, Head & Neck Multi-Disciplinary Task Force, European Institute of Oncology, Milan, Italy
f Division of Radiology, Head & Neck Multi-Disciplinary Task Force, European Institute of Oncology, Milan, Italy

Accepted 3 November 2010

Contents

1. Introduction ............................................................................................................. e91
2. Diagnostic challenges: from morphology to functional and molecular biology .................................................. e91
3. Challenges in chemoprevention ................................................................................. e91
   3.1. Prognostic biomolecular markers ........................................................................... e91
   3.2. New trends in chemoprevention ............................................................................ e92
4. Challenges in surgery: surgical margins and organ preservation .............................. e92
   4.1. What constitutes adequate margins in oncologic surgery? .................................. e92
   4.2. Compartmental resection of tongue tumors ......................................................... e92
   4.3. Endoscopic laryngeal laser surgery ....................................................................... e92
   4.4. Trans-oral-robotic-surgery (TORS) ....................................................................... e92
5. Challenges in chemo-radiotherapy ............................................................................ e93
   5.1. New modalities of treatment delivery in radiotherapy ......................................... e93
   5.2. Next generation chemotherapeutic agents ......................................................... e93
   Reviewer .................................................................................................................. e93
   References ............................................................................................................... e93
   Biography ............................................................................................................... e96

Abstract

HNC is the 11th most frequent carcinoma with a world-wide yearly incidence exceeding over half a million cases [1], a 10:1 male gender predilection and country specific variability [2]. The principal risk factors are tobacco and alcohol use and, in a growing population without these exposures, HPV infection.

© This work was presented at the AROME International Oncology Meeting in Monaco, 22–23 January 2010.
* Corresponding author at: Istituto Europeo di Oncologia, Via Ripamonti 435, 20141 Milan, Italy. Tel.: +39 02 57489490; fax: +39 02 94379216.
E-mail addresses: luca.calabrese@ieo.it, mariaangela.massaro@ieo.it (L. Calabrese).
1 Association of Radiotherapy and Oncology of the Mediterranean arEa (www.aromecancer.org).

1040-8428/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.critrevonc.2010.11.001
While much progress has been made in understanding the molecular basis of cancer, the 5-year mortality of head and neck cancer has remained approximately 50%. To this date we have not been able to translate as much of our basic science knowledge into significant disease altering therapeutic strategies in terms of local, loco-regional, functional and overall survival. Challenges remain in all aspects of head and neck cancer management: prevention, diagnosis, surgical and non-surgical treatment.

© 2010 Elsevier Ireland Ltd. All rights reserved.

Keywords: Head neck oncology; Challenges; Prevention; Diagnosis; Surgery; Radiation oncology; Medical oncology

1. Introduction

HNC is the 11th most frequent carcinoma with a worldwide yearly incidence exceeding over half a million cases [1], a 10:1 male gender predilection and country specific variability [2]. The principal risk factors are tobacco, alcohol use and HPV infection [1–7]. Carcinogenesis can develop over 10–20 years from genetic, progressive, though not necessarily sequential, multi-step mutations that generate morphologically similar lesions with different molecular fingerprints [8–16]. Important cellular events that participate in carcinogenesis are the loss of heterozygosity (LOH) of 9p21 and 17p13, highly expressed in dysplastic lesions, and found respectively in 20% and 11% of hyperplastic lesions. The resulting loss of p16INK4a and p53 activity [17] affects the inhibition of cyclin dependent kinases (Cdk), allows crossing of the restriction point with phosphorylation of the pRb-E2F complex promoting DNA synthesis [17–19].

The 5-year mortality rate has remained approximately 50% in spite of recent therapeutic advances [20–25]. We have not been able to fully translate new knowledge of basic molecular and cellular processes at the heart of tumor biology into clinically successful strategies. Therein resides the challenge facing head & neck oncology in the next century.

2. Diagnostic challenges: from morphology to functional and molecular biology

Conventional imaging techniques, including computed tomography (CT) and magnetic resonance imaging (MRI), are excellent for imaging of the head and neck tumors, but provide only morphological information. The development of functional imaging techniques that can depict non-invasively the patho-physiological processes is highly desirable. The integration of positron emission tomography (PET) with CT scan was a great step forward in this direction, as the information on tumor metabolism is routinely used for the work-up of head and neck tumors [26]. Diffusion-weighted magnetic resonance imaging (DW-MRI) measures microscopic mobility of water molecules across tissues that is highly influenced by the cellular environment and can reflect biologic abnormalities of the underlying tissues. In malignant head and neck tumors a significantly more impeded microscopic mobility of water molecules than in benign lesions and normal tissues has been observed [27,28]. DW-MRI can be used as a surrogate biomarker for early treatment response in head and neck tumors, with an increase in microscopic mobility of water molecules after non surgical treatment [29,30]. This imaging technique has shown promise in addressing one of the major challenges for clinicians and radiologists: the differentiation between post-therapeutic changes and tumor recurrence in patients with laryngeal and hypo-pharyngeal tumors previously treated by radiation therapy and chemo-radiotherapy [31,32].

Perfusion imaging, whether performed with CT or MRI, quantifies the exchange of contrast agent between the vascular compartment and the extravascular/extracellular compartment. This exchange between compartments is altered in tumors as a result of neo-angiogenesis, since the newly formed vessels are dilated, hyper-permeable and offer low resistance to flow. Perfusion imaging is useful for the characterization of head and neck tumors and for monitoring non-surgical therapy [33,34] and could be particularly useful for predicting therapeutic response and outcomes. Patients with low perfusion parameters at baseline are generally less sensitive to chemotherapy [33–35] and have a higher local failure rate after radiation therapy [36], most likely a result of inadequate drug delivery and a low radio-sensitivity.

Molecular imaging is an emerging field that provides information on biological processes in non-invasive fashion and characterization of diseases based on molecular markers [37]. Targeted gold nano-particles have been used to selectively visualize cancer cells by CT imaging in experiments performed on SCC human head and neck cancer cell lines [37]. A range of new PET tracers are becoming available for tumor characterization on a molecular level. [18F]-fluorothymidine (FLT) can be used for quantification of tumor cell proliferation and [18F]-fluorothyryosine (FET) for measurement of protein synthesis related to tumor growth. Other PET radio-tracers can be specifically designed for imaging of apoptosis and epidermal growth factor receptor (EGFR) [38].

3. Challenges in chemoprevention

3.1. Prognostic biomolecular markers

A biomarker is a parameter objectively measured and evaluated as an indicator of normal biological and pathogenic processes, gauging the response to therapeutic interventions [39]. The search for reliable biomarkers focuses on identification of indicators of malignant transformation in clinically
suspect lesions, those linked to second primary tumors and/or identification of individuals at greatest risk for neoplasias [40]. Currently the body of evidence available is not strong enough to advocate in clinical practice the use of biomarkers as prognostic indicators for HNC [40,41]. Research in the field continues particularly with gene expression and salivary proteomics studies [42,43]. Recent reports have identified podoplanin [44,45] and the genotype CD1 AA and AG [46] as promising new markers however their validity has yet to be established.

3.2. New trends in chemoprevention

As of October 2010 the National Institute of Health [47] reports five recruiting chemoprevention clinical trials using molecular agents (kinase or serin protease inhibitors) and anti-inflammatory drugs (COX-2 inhibitors, sulindac or ASA) as single agents or in combination. Twelve other primary or adjuvant chemoprevention trials are currently active, though not in the recruiting phase, testing the effectiveness of natural and synthetic retinoids (4 trials), dietary supplements (1 study), anti-inflammatory (5 studies) and anti-diabetic drugs (2 studies). The ultimate challenge in HNC chemoprevention remains the identification and validation of suitable biomarkers with well designed and adequately funded long term studies to create accurate molecular risk stratification models that translate into advances in clinical practice [48–52].

4. Challenges in surgery: surgical margins and organ preservation

4.1. What constitutes adequate margins in oncologic surgery?

The aim of curative surgical oncology of the HN is to remove the primary tumor with a wide margin of normal tissue. The current standard is to remove the primary lesion macroscopically with a 1.5–2 cm circumferential margin [53] and microscopically with at least a 5 mm margin [54]. The rational bases of what constitutes a sufficient margin of resection in oral, oro-pharyngeal and laryngeal cancer are unclear [55–57], complicated by geographical and surgon-dependent variability [58]. This approach does not take into consideration embryological, anatomical and histological differences in the specific organs affected by a primary tumor (oral cavity & oropharynx vs. larynx) [57] and the anatomical pathways of disease progression. Local disease control remains one of the most significant challenges [59,60] however there is no definitive and acceptable guideline that establishes site-specific resection margins in head and neck cancer (HNC). Until recently there have been few studies in the literature that challenged the notion of what is an oncologically radical surgical margin and addressed the impact on local and loco-regional control as well as disease specific survival. Molecular analysis of surgical margin status, in particular the presence of p53 and p16 mutation is thought to be an important predictor of local and loco-regional recurrence [61,62], however recent reports confirm this data has not led to significant therapeutic modifications [62–64]. The challenges for the surgical oncologist remain: the ability to remain oncologically radical while minimizing the impact on aesthetics, function and the psycho-social balance of the patient.

4.2. Compartmental resection of tongue tumors

Compartmental tongue surgery (CTS) [65] is an anatomically based surgical technique that introduces a paradigm shift in ablative oral surgery with improvements akin to those achieved in the treatment of musculoskeletal sarcomas [66]. Anatomical considerations and histo-pathological correlation of the pathways of tumor progression allowed redefinition of surgical margins not as an arbitrary measure of tissue to be removed but as individual functional musculoskeletal units whose resection eliminates the primary and all of its potential pathways of spread and recurrence (muscular, vascular and lymphatic). The oncologic and functional impact of this technique is currently being evaluated.

4.3. Endoscopic laryngeal laser surgery

Adequacy of surgical margins in laryngeal tumors depends on the histologic subtype, the primary site of growth, anatomical limitations, and the ability to perform conservative surgery. Until recently several studies in the literature addressing the impact of resection margins in laryngeal cancer treated with endoscopic laser surgery were contradicting at best [67–71]. Ansarin [72] was one of the first investigators to study and challenge disease specific criteria for oncologically radical surgical margins in early laryngeal cancer. Unlike tumors of the other HN districts laser removal of early glottis cancer can be adequately radical and maximally conservative with margins of 1 mm.

4.4. Trans-oral-robotic-surgery (TORS)

The recent introduction of the “da Vinci” robotic system has revolutionized surgical approaches in various fields such as cardiac and urologic surgery. Current applications in HN surgery include tonsillectomy [73], base of the skull surgery [74–76], free flap harvest and reconstruction [77,78], oral, oro- and naso-pharyngeal and laryngeal cancer [79–89]. While the promise held by this technique is great, district specific instrumentation needs to be developed and definitive studies to assess the oncologic efficacy of TORS (compared to chemo-radiotherapy or as salvage) are necessary.
5. Challenges in chemo-radiotherapy

5.1. New modalities of treatment delivery in radiotherapy

Recent advances in radiation technologies have allowed more selective dose distribution with better target coverage and sparing of surrounding normal tissue. Intensity Modulated Radiation Therapy (IMRT) currently represents the most modern external beam radiation technique for head and neck cancer patients allowing better dose conformation around irregularly shaped tumors. The main advantages of IMRT are represented by the ability to deliver a higher radiation dose to the tumor (with potential improvement in local control) and to improve sparing of surrounding normal tissues. IMRT however requires accurate target delineation with a specific radiation oncologist expertise produces a greater heterogeneity in the dose distribution within the target volume and results in a more extensive low dose irradiation of normal tissues [90]. IMRT is employed mainly for nasopharyngeal (because of the multiple surrounding critical structures like brain, optic structures, brain stems etc.) and oropharyngeal (as a parotid-sparing technique) cancer patients [91–96]. Patients with paranasal sinuses could also benefit from an IMRT treatment [97], whereas data for patients with laryngeal and hypopharyngeal tumors are scarce [98,99]. Encouraging preliminary results have also been published for patients with recurrent head and neck disease [97]. In case of radio-resistant tumors, such as salivary glands tumors, hadron-therapy (using charged protons and heavy ions) is an emerging new radiotherapy approach that holds promise but further investigation is warranted [100–105]. Ongoing studies will demonstrate if increasingly selective dose distribution and new radiation sources translate to improved disease control and better post-treatment quality of life.

5.2. Next generation chemotherapeutic agents

The primary challenge in medical oncology is to define areas of treatment where a systemic approach can improve treatment outcomes. In patients amenable to surgical treatment, the medical oncologist has a small, well-defined role in administering concomitant postoperative chemoradiotherapy (CRT) [106,107] and growing trends favor organ preservation through combined modality therapies [108]. For non-surgical patients, however, the medical oncologist plays a central role together with the radiation oncologist. The association of chemotherapy with radiotherapy remains the gold standard and has demonstrated improved patient survival if administered concomitantly (8% improvement at 5 years) [109,110] and if cis-platinum based (CT) compared to RT alone. In an effort to reduce CRT related toxicity, while maintaining local disease control, the administration of Cetuximab (a monoclonal EGFR-Ab) in association with RT has been studied and compared to therapeutic RT treatment. Cetuximab represents an effective and well tolerated treatment option for patients that are considered high risk, that are ineligible for CT and for those patients that are unlikely to complete CRT. The association of Cetuximab to RT and the efficacy of this treatment compared to CRT alone requires however further investigation [111–114].

With the introduction of the TPF regimen (taxanes in association with cis-platin and 5-fluorouracil) there has been renewed interest in induction CT and its role in organ preservation protocols for selected patients [115–120]. Current studies are trying to assess the best induction and concurrent chemotherapeutic regimens to associate to RT, the most appropriate induction protocol for patients that are ineligible for TPF regimen and finally the role of induction chemotherapy in HPV positive patients. Future challenges include the integration of molecular based therapies that are site and disease specific particularly important in patients with locally advanced and non-metastatic disease. The ultimate challenge remains the delivery of patient tailored therapies that respond to disease specific biological profiles [121].

Reviewer

David G. Pfister, M.D., Chief, Head and Neck Oncology Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, NY 10021-6007, United States.

References


Biography

Dr Calabrese received his degree in medicine from the University of Bologna and specialised in Plastic Surgery at the University of Bari and in Otolaryngology at the University of Pavia, Italy. Dr Calabrese has performed over 1500 major operations for head and neck tumors and over 500 major reconstructions with myocutaneous and free microvascular flaps. As a member of the Italian National Study Group for Head and Neck Cancer screening he is actively concerned with prevention of head and neck tumors in health centres of the Italian League Against Cancer. He has co-authored 58 publications on head and neck oncology and plastic surgery and is a lecturer on head and neck oncology at University of Pavia. Dr Calabrese is a member of the AROME (Association of Radiotherapy and Oncology of the Mediterranean Area).