

Advances in the management of squamous cell carcinoma of the head and neck

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Abstract

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common cancer worldwide. The main risk factors for cancers of the oral cavity, larynx, oropharynx, and hypopharynx are alcohol and tobacco use. In addition, the human papillomavirus (HPV) is an established cause of oropharyngeal cancer. An experienced multidisciplinary team is necessary for adequate management and optimal outcome. The treatment of locally advanced disease generally requires various combinations of radiotherapy, surgery, and systemic therapy, but despite this aggressive multimodal treatment, 40% to 60% of the patients will relapse. In this report, we will discuss recent advances in the management of SCCHN, including new developments in molecular biology, imaging, and treatment.

Introduction

SCCHN is the sixth most common cancer worldwide; approximately 600,000 new cases are diagnosed per year worldwide [1]. SCCHN generally begins in the mucosal surfaces of the head and neck. The most frequent tumor sites of SCCHN are the larynx, the pharynx, and the oral cavity. Head and neck cancers also include salivary gland tumors as well as nasopharyngeal cancer and paranasal and nasal sinus cancer. These tumors are less frequent and will not be discussed in this report.

Consumption of alcohol or tobacco is the main risk factor for cancers of the oral cavity, larynx, oropharynx, and hypopharynx and accounts for 75% of SCCHN. The oncogenic HPV infection, mainly HPV-16, is an established cause of oropharyngeal cancer (predominantly tonsils and base of tongue) [2,3]. Globally, the incidence of HPV-induced oropharyngeal cancer increases each year, but varies from less than 10% to 70% of all oropharyngeal cancers, depending on the geographic area, being more frequent in industrialized countries [4-6]. The etiologic role of HPV in SCCHN sites other than oropharynx is unclear.

The treatment choice depends on the location of the primary tumor, the stage of the disease, and the expected oncological and functional outcomes. American Joint Committee on Cancer (AJCC) early-stage (I/II) SCCHN is usually treated with single-modality therapy (i.e. surgery or radiotherapy [RT]). The management of locally advanced disease (AJCC stage III/IV) generally requires various combinations of RT, surgery, and chemotherapy or cetuximab. The survival rates for all patients with SCCHN are approximately 40% to 60% at 5 years [7]. In this report, we review recent advances in the management of SCCHN, including new developments in molecular biology, imaging, and treatment.

1. Clinical relevance of SCCHN molecular biology

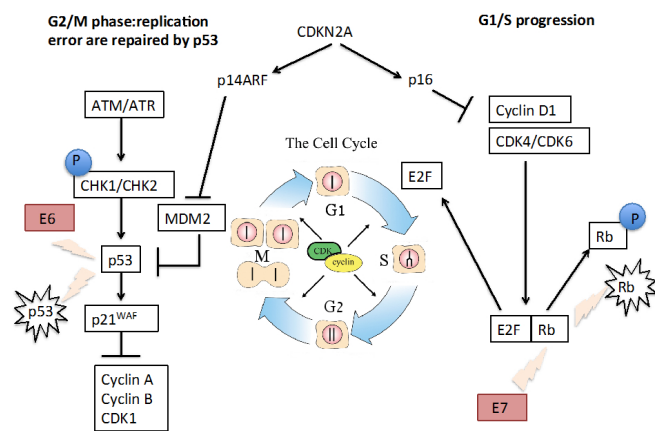
The epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor belonging to the HER/erbB family and is overexpressed in up to 90% of SCCHN [8]. High *EGFR* gene copy number has been reported in 10% to 58% of SCCHN [9-12]. In SCCHN, in contrast to lung cancer, activating *EGFR*

mutations are rare. Overexpression of EGFR and high *EGFR* gene copy number are associated with poor prognosis and radioresistance [9-17]. The EGFR is a relevant target in SCCHN since cetuximab, an immunoglobulin G1 (IgG1) monoclonal antibody targeting the EGFR, improves overall survival (OS) when combined with RT or chemotherapy [18,19]. However, only a minority of patients will benefit from anti-EGFR monoclonal antibodies, and the objective response rate in monotherapy is between 6% and 13% [20,21].

Recently, deep sequencing technology has allowed a better characterization of the implicated genes [22-24]. Somatic mutations in *TP53* (47% to 72%), *NOTCH1* (14% to 19%), *CDKN2A* (9% to 22%), *PIK3CA* (6% to 21%), *FBXW7* (5%), *HRAS* (4% to 8%), *FAT1* (23%), and *CASP8* (8%) have been reported. Besides these mutations, some genes or their related proteins have been found to be altered by other mechanisms (amplification, deletion, epigenetic) [25-29]. Altogether, activating mutations in classic oncogenes seem relatively rare in SCCHN and most of the genetic alterations occur in tumor suppressor genes. These findings are important for the further development of novel therapies for SCCHN, although developing new compounds to restore the activity of altered tumor suppressor genes like *p53* or *CDKN2A* is extremely challenging.

Most of the genetic alterations described above have been found in HPV⁻ tumors. Biologically, HPV-induced SCCHN is different and is characterized by the inactivation of the *p53* tumor suppressor gene by the viral oncoprotein E6 and the retinoblastoma suppressor gene by the HPV oncoprotein E7 [30,31] (Figure 1). Globally, HPV⁺ tumors have fewer genetic alterations than HPV⁻ tumors [24,32]. Interestingly, activation of the phosphoinositide 3-kinase (PI3K) pathway appears quite frequent in HPV⁺ tumors [33]. Many studies have shown that patients with HPV⁺, p16⁺, or *p53* wild-type tumors have better OS and progression-free survival (PFS) rates than patients with HPV⁻, p16⁻, or *p53* altered SCCHN [34-36]. Ang and colleagues classified patients with SCCHN as having a low, intermediate, or high risk of death on the basis on four factors: HPV status, pack-years of tobacco smoking, tumor stage, and nodal stage [2]. Therefore, it is crucial that future clinical trials select or at least stratify patients according to their HPV and risk status. Since the prognosis for patients with HPV⁺ is better, specific trials investigating treatment de-intensification in this population are ongoing. However, today without the results of these trials, HPV⁺ tumors must be treated with the same regimens as HPV⁻ tumors.

Figure 1. Molecular biology of human papillomavirus (HPV)-positive squamous cell carcinoma of the head and neck (SCCHN)



HPV-induced SCCHN is characterized by the inactivation of the *p53* tumor suppressor gene by the viral oncoprotein E6 and the retinoblastoma (Rb) suppressor gene by the HPV oncoprotein E7. Inactivation of the Rb gene induces the release of the E2F transcriptional factor that leads to cell cycle progression (G₁ to S phase). Inactivation of *p53* removes the break of p21 on cyclin-dependent kinase (CDK) activity. All together, these molecular alterations lead to cell cycle progression and cell division.

2. Challenges and perspectives in imaging work-up

2.1. Positron emission tomography

Positron emission tomography (PET) is a non-invasive procedure using tracers labeled with positron emitters such as fluorine-18. The most frequently used tracer in clinical practice is ¹⁸F-fluorodeoxyglucose (FDG), an analog of glucose, allowing metabolic mapping of the entire body in one procedure. In the last decade, all manufacturers have developed PET cameras coupled with conventional computerized tomography (CT) scanners (PET-CT), allowing instant fusion of anatomical and metabolic images, leading to better anatomic localization of lesions and increasing accuracy [37].

In head and neck cancers, some controversies have arisen about some specific indications [38]. There is a large consensus for the role of PET in the detection of occult primary SCCHN, staging and restaging of patients with high-risk of disseminated disease, and the assessment of lesions of unknown origin [39-41].

In addition, PET has an increasing role in therapy response assessment after chemoradiotherapy (CRT) in SCCHN, showing a high negative predictive value in neck evaluation when performed 12-weeks after completion of treatment [42-44]. This post-therapy evaluation to identify which patient will benefit from neck dissection is

considered an indication by National Comprehensive Cancer Network and Society of Nuclear Medicine guidelines [40,41]. However, some data suggested no added value of PET compared with conventional imaging in this purpose, but these data were acquired on a PET-alone camera (not PET-CT) and performed as early as 7-weeks after completion of treatment [45]. Residual inflammation is known to increase the rate of false-positive uptake in these delays. Ongoing studies such as PET-NECK and GETTEC (Groupe d'Etude des Tumeurs de la Tete et du Cou) studies should further clarify the precise role of PET-CT in this indication.

Intense research is ongoing in radiation oncology to evaluate the role of molecular imaging for target volume delineation. In particular, FDG (glucose uptake) or other tracers such as [¹⁸F]-fluorothymidine (FLT, proliferation tracer) and [¹⁸F]-fluoroazomycin-araboside (FAZA, hypoxia tracer) are currently studied for their potential ability to identify subzones of the tumor with more hypoxia (FAZA) or tumor proliferation (FLT) [46,47]. This information could lead radiation oncologists to target small areas of the tumor with higher radiation doses ('dose painting') to reach better local control [48].

2.2. Computed tomography and magnetic resonance

Tumor imaging

Both CT scanner and magnetic resonance imaging (MRI) are giving highly relevant information about location, size, shape, and contours of the primary tumor [49]. The two modalities have specific advantages but also suffer from significant limitations: 'fast' CT is able to freeze motion artefacts and has the unsurpassed advantage in yielding information about electron density, useful for RT planning. 'Slow' MRI has the major advantage of enhancing soft tissue contrast, including the bone marrow, whereas CT detects the mineralized tissues. Main limitations of both modalities are the overestimation of the gross tumor volume by 30% to 60% when compared with FDG-PET because of their inability to separate the tumor from the adjacent reactive changes [50].

Nodal imaging

Morphological CT or MRI images have insufficient diagnostic accuracy because nodal size is not a robust predictor of the presence of metastases. CT and MRI perform similarly in nodal staging. Enlarged nodes can be benign (inflammatory changes), and small-sized nodes can host micro-metastases. When a cutoff value at 10 mm (short axis diameter) is used, an overall diagnostic accuracy of only 80% is achieved by both modalities [51]. Twenty-five percent of clinically and radiologically N0 necks are positive at histopathology. Other criteria

such as heterogeneity (central necrosis), round shape, differential enhancement, irregular margins (suggesting extra-nodal spreading), and clustering of more than three nodes are being considered as ancillary criteria for malignancy but require validation [52].

Distant metastases imaging

Newly available multi-row CT systems are used for metastatic work-up. Emerging 'whole-body' MRI techniques combining morphological imaging and diffusion-weighted imaging (DWI) hold major promise in the field [53].

2.3. Diffusion- and perfusion-weighted imaging

DWI gives a quantitative index of the free-water diffusion restriction as encountered in tissues with high cellular density. For tumor imaging, the DWI technique allows tumor characterization at initial work-up (benign versus malignant), pre-treatment prognosis, early treatment response evaluation, and recurrence detection [54]. For nodal imaging, DWI seems extremely useful to differentiate tumoral and non-tumoral nodes but with the limitation that the DWI technique is uneasy to standardize and requires expertise in pulse sequence programming, image processing, and quantitative data interpretation [55].

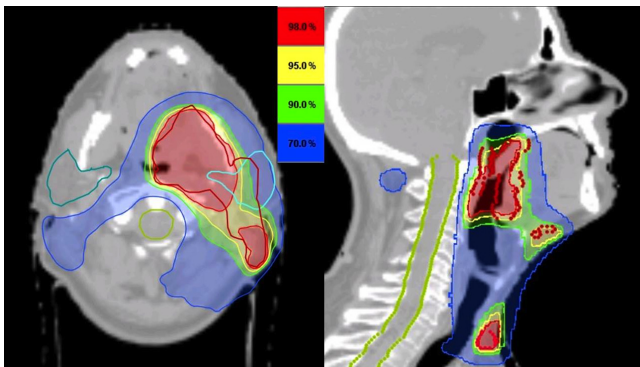
Perfusion-weighted imaging (PWI) has shown the ability to predict patient outcome [56]. Multiparametric approaches combining PET metabolic information and MRI 'functional' DWI or PWI data (or both) are currently being investigated [57,58].

3. Challenges and perspectives in (chemo) radiation

The head and neck region contains numerous intricately organized organs essential for basic physiological functions and critical for physical appearance, expression, and social interactions. Therefore, minimizing radiation-related toxicities is the main challenge.

Technological innovations have greatly changed the way the dose is delivered. The use of three-dimensional treatment planning and the ability to modulate the beams during treatment allowed a more accurate dose delivery with steeper dose gradients around the target volume, allowing a decrease of the dose to the surrounding organs at risk while maintaining target coverage (Figure 2) [59]. This so-called intensity-modulated radiotherapy (IMRT) was rapidly implemented in SCCHN as it allowed a significant sparing of the contralateral parotid, effectively reducing the rate of severe late xerostomia in these patients without compromising outcome [60-62]. The role of IMRT in reducing other toxicities such as late dysphagia is

Figure 2. The potential of intensity-modulated radiotherapy (IMRT)



A squamous cell carcinoma of the left tonsil from a 58-year-old patient was classified as cT4aN2c. IMRT allows steep dose gradients to be generated, ensuring an adequate target coverage while sparing surrounding at-risk organs such as the contralateral parotid gland (dark green) and the spinal cord (light green).

currently being investigated [63-65]. On the other hand, the effect of IMRT on tumor control is much debated. As poorly implemented, it harbors an increased risk of missing the target volume [66,67]. Internationally endorsed delineation guidelines are of paramount importance to reduce inter-observer and inter-patient treatment variations and have proven essential in the conduction of multi-institutional clinical trials [68-70]. A recent analysis of the Surveillance, Epidemiology, and End Results (SEER) database demonstrated that the use of IMRT was associated with a significant improvement in cause-specific survival compared with non-IMRT techniques [71]. There is growing interest in using IMRT in strategies to increase tumor control by escalating the dose to the target volume. For example, the information provided by imaging techniques such as FDG-PET and functional MRI could improve target volume delineation and might even identify regions of increased radioresistance within the tumor [50,72,73]. Therefore, we have both the rationale and the means to target these subvolumes selectively with a higher radiation dose without increasing the doses to the surrounding organs at risk. Theoretically, such a so-called 'dose-painting' approach could increase tumor control while maintaining the same toxicity levels. Other approaches have already been investigated. In an attempt to exploit the differential sensitivity between tumor cells and normal tissue, the idea arose to deviate from conventional fractionation schedules [74]. In a large meta-analysis, Bourhis *et al.* found that altered fractionation schedules improve survival compared with conventional fractionation [75].

The combination of RT with chemotherapy and other radiosensitizers has been investigated. The updated meta-analysis of chemotherapy in combination with radiation for SCCHN (Meta-Analyses of Chemotherapy in Head and Neck Cancer, or MACH-NC) showed that the addition of chemotherapy concomitantly to radiation improves the absolute 5-year survival by 6.5% [76,77]. Concomitant platinum-based CRT is the standard of care in locally advanced SCCHN.

The exact role of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (TPF) remains controversial and investigational. So far, several randomized trials testing sequential approaches with TPF induction followed by concurrent CRT versus concurrent CRT alone have been reported [78-80]. They failed to demonstrate a statistically significant difference in OS and PFS. Cetuximab combined with RT improves locoregional control and OS rate compared with RT alone, apparently without increasing the radiation-induced side effects [81]. Cetuximab-RT is therefore considered an alternative to CRT; however, so far there are no data comparing CRT with cetuximab-RT.

In an attempt to improve outcome, several studies have attempted to combine the above-mentioned treatment strategies. In both the RTOG (Radiation Therapy Oncology Group) 0129 and the GORTEC (Groupe Oncologie Radiothérapie Tête et Cou) 99-02 trials, accelerated CRT failed to demonstrate a benefit compared with conventionally fractionated CRT [2,82]. Both trials concluded that acceleration seemed unable to compensate for the absence of concurrent chemotherapy. Similarly, the combination of EGFR targeting drugs with CRT has failed to demonstrate any benefit so far [83,84].

4. Challenges and perspectives in surgery

In the past, advanced resectable tumors were preferentially treated by primary radical surgery followed by adjuvant RT. During the nineties, the development of CRT dramatically changed the role of surgery for locally advanced SCCHN, in particular when a voice-sparing surgical approach was not possible [85-87]. Today, primary total pharyngolaryngectomy remains indicated only in very advanced resectable cancer, when the ability to recover a functional organ after CRT is low. Open surgery remains the best primary treatment for a majority of head and neck tumors localized in the oral cavity, salivary glands, thyroid gland, nose and paranasal sinus, skull base, and skin as well as for sarcomas of the head and neck [88].

The concept of minimally invasive surgery includes laser and robotic surgery. For small transorally accessible

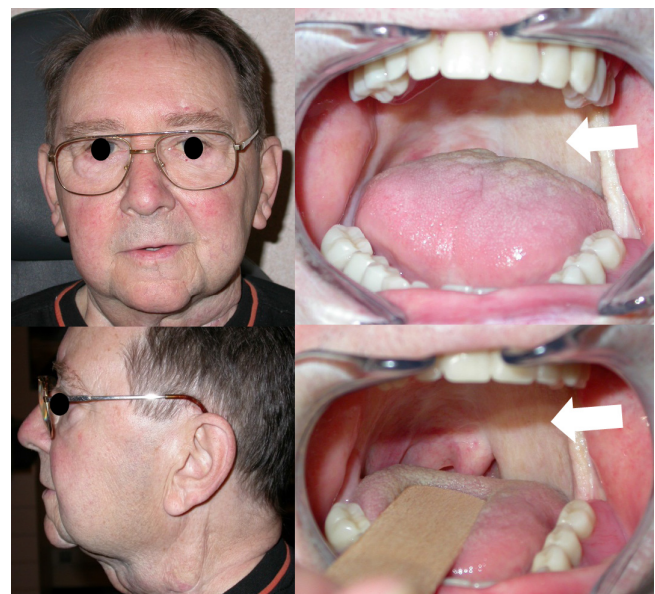
cancers of the oral cavity, pharynx, and larynx, surgical excision can be achieved with functional preservation of the involved organ and good oncological results. Transoral laser surgery is less invasive compared with many open procedures. However, oncologic and functional outcomes of early glottic cancers do not seem better with laser surgery than with radiation, despite the lack of prospective randomized trials [89,90]. For locally advanced laryngeal cancer, good long-term oncological outcome with laser microsurgery was recently reported [91,92]. Regarding oropharynx, minimally invasive approaches, including transoral laser microsurgery and recently robotic surgery, have shown improved functional outcomes and oncologic outcomes similar to primary radiation [93]. There is little doubt that transoral robotic surgery, in experienced hands, is associated with less morbidity than traditional open surgery. Resection is possible without a mandibulotomy approach. However, we should be prudent about assuming that something must be better just because it is newer: in one series, suboptimal exposure was reported in 26% and post-operative hemorrhages in 12%, leading to death in 2% [94]. Currently indicated for early oropharyngeal carcinoma, this approach has been employed in the management of supraglottic cancer. However, with the exception of base of tongue tumors, many T1-T2 oropharynx cancers can be resected transorally. Importantly, regardless of the surgical approach, elective neck dissection is recommended in patients clinically N0 because the risk of occult lymph node metastases is around 30% [95]. Typically, unilateral or bilateral dissection of levels II, III, and IV is indicated in oropharynx cancer. Robust data from a randomized trial comparing oncologic and functional outcomes of transoral surgery plus elective neck dissection versus RT including the tumor site and the lymph nodes at risk in the clinical target volume are lacking.

Regarding advanced head and neck squamous cell carcinoma, the emergence of organ preservation strategies has considerably limited the role of primary surgery in this setting. The surgeon is more frequently faced with failures of primary non-surgical therapies. Besides the expertise of the surgeon, an accurate selection of the patients who are suitable for surgery and who require a combination of large resection and well-vascularized flap reconstruction is key in salvage surgery. Although the definition of unresectability is not uniform, it is typically accepted that a tumor invading the common carotid artery, the base of the skull, or the prevertebral muscles should be considered unresectable. Advances in microvascularized free flaps have considerably expanded the possibilities of reconstruction following resection of advanced tumors. Accurate tailoring of the flap improves

the cosmetic result and the functional outcome (Figure 3). Use of these flaps has allowed voice-preservation surgery for selected patients with advanced hypopharyngeal or laryngeal cancer, even after failure of organ-sparing therapy [96].

When surgery is the primary treatment, neck dissection is recommended in most tumors with the exception of early tumors of the vocal cord. The rationale for a selective neck dissection is based on known patterns of metastases from each site. Currently, selective neck dissection is an oncologically safe and low-morbidity surgical procedure indicated for clinically negative necks harboring a risk of micrometastasis in up to 30% and for clinically N1 disease [97,98]. In patients treated with primary CRT, neck dissection is recommended when residual disease is suspected, whereas its role remains controversial in the setting of complete response [99,100]. However, because patients achieving a complete clinical response to CRT have a very low risk of an isolated neck recurrence, the strategy of systematic neck dissection is no longer justified [101]. The next issues are to identify patients who have residual anatomic abnormalities with no viable tumor cells and to improve the outcome of patients who have pathological residual disease. Use of less morbid neck dissection after CRT was progressively proposed in patients initially staged N2-N3 with a very low rate of subsequent neck failure [102,103].

Figure 3. Oropharyngectomy through mandibular swing approach



Reconstruction of the soft palate and lateral oropharynx with a microvascularized radial forearm free flap (arrows) is shown.

Many publications support the suitability of selective neck dissection after chemoradiation in patients with initially advanced regional disease and in patients with clinically persistent disease [98,104-106].

5. Recurrent or metastatic disease or both

SCCHN that recurs after multimodal local treatment is generally considered incurable if the patient cannot be salvaged by surgery or additional RT. Platinum-based chemotherapy in combination with cetuximab is considered the standard of care in fit patients. The combination of cisplatin or carboplatin with 5-fluorouracil and cetuximab improves OS (median OS is 10.1 months) [18]. Docetaxel, paclitaxel, and methotrexate are other chemotherapy compounds sometimes used in this indication. Based on the improvement in SCCHN molecular biology knowledge, new compounds are currently being investigated (EGFR/HER-3 dual, irreversible pan-HER or PI3K inhibitors, cell cycle inhibitors) [107].

Conclusions

SCCHN is a heterogeneous disease at both the anatomical and molecular levels. An experienced multidisciplinary team is necessary for adequate management and to optimize the outcome. Despite multimodal treatment, including surgery, RT, chemotherapy, or some combination thereof, 40% to 60% of the patients with locally advanced SCCHN will relapse. Further treatment intensification with these classic treatment modalities is almost impossible since the maximal tolerable toxicity is reached, limiting further improvement in treatment.

Improvement in technology, including imaging, radiation technique, and surgery, has allowed better functional and cancer outcomes. Ongoing trials address important questions regarding treatment sequences (i.e., induction versus concomitant CRT, de-escalation in HPV⁺ cancer, induction followed by cetuximab-RT). In addition, our better understanding of the molecular biology of the disease has opened new treatment avenues that should be explored in the near future with the hope that targeted therapies may help to circumvent the toxicities of the classic modalities. However, only a minority of patients seem to benefit from molecular targeted therapies. Therefore, a major challenge in coming years will be to identify predictive biomarkers to tailor each treatment to the most appropriate population.

Abbreviations

AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; CT, computerized tomography; DWI, diffusion-weighted imaging; EGFR, epidermal growth factor receptor; FAZA, [¹⁸F]-fluoroazomycin-

arabinoside; FDG, ¹⁸F-fluorodeoxyglucose; FLT, [¹⁸F]-fluorothymidine; HPV, human papillomavirus; IMRT, intensity-modulated radiotherapy; MRI, magnetic resonance imaging; OS, overall survival; PI3K (phosphoinositide 3-kinase); PET, positron emission tomography; PFS, progression-free survival; PWI, perfusion-weighted imaging; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; TPF, docetaxel, cisplatin, and 5-fluorouracil.

Disclosures

The authors declare that they have no disclosures.

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