Saudi Dental Journal (2019) 31, 395–416

King Saud University

Saudi Dental Journal

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REVIEW ARTICLE

Head and neck cancer management and cancer stem cells implication

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Received 20 May 2019; accepted 27 May 2019
Available online 10 June 2019

KEYWORDS

Head and neck cancer;
Carcinoma;
Squamous cell;
Cancer stem cells;
Cancer treatment;
Antineoplastic agents

Abstract Head and neck squamous cell carcinomas (HNSCCs) arise in the mucosal linings of the upper aerodigestive tract and are heterogeneous in nature. Risk factors for HNSCCs are smoking, excessive alcohol consumption, and the human papilloma virus. Conventional treatments are surgery, radiotherapy, chemotherapy, or a combined modality; however, no international standard mode of therapy exists. In contrast to the conventional model of clonal evolution in tumor development, there is a newly proposed theory based on the activity of cancer stem cells (CSCs) as the model for carcinogenesis. This "CSC hypothesis" may explain the high mortality rate, low response to treatments, and tendency to develop multiple tumors for HNSCC patients. We review current knowledge on HNSCC etiology and treatment, with a focus on CSCs, including their origins, identifications, and effects on therapeutic options.

Contents

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sdentj.2019.05.010
1013-9052

1. Introduction and epidemiology of head and neck cancer

Head and neck cancers (HNC) are a group of cancers that arise in the oral cavity, pharynx, larynx, paranasal sinuses, nasal cavity, salivary glands, or head and neck lymph nodes (Daraei and Moore, 2015). HNC is the seventh most common cancer worldwide with around 600,000 new cases annually (Ferlay et al., 2015; Jou and Hess, 2017) and unacceptably high rates of mortality, especially in developing countries, reaching 300,000 deaths each year (Chaturvedi et al., 2013). More than 90% of the HNC is head and neck squamous cell carcinoma (HNSCC), variant that originates from the mucosal lining epithelium of the upper aerodigestive tract (Ferlay et al., 2015). Of interest, it was reported that around 20% of oral squamous cell carcinoma patients will develop an upper aerodigestive tract secondary tumor (Sankaranarayanan, 1990).

The estimate is that about two-thirds of the HNSCC cases occur in developing areas such as south and south-east Asia (Marur and Forastiere, 2008). This great variation in the global prevalence of HNSCC can be seen with the prevalence rate of 5–8% of total cancer cases in Europe and America (Tobias, 1994; Vigneswaran and Williams, 2014) compared to over 30% in India (Shah et al., 2016). Historically, black HNSCC patients had poorer prognosis, higher recurrence, and mortality rates when compared to non-black patients (Ragin et al., 2011). This might be due to their lower socioeconomic status, difficulties for health care access, delayed diagnosis, and lower rates of surgical intervention (Dilling et al., 2011). Such a difference in the rate of incidence was reversed in the USA with less black HNSCC patients when compared to non-black ones starting in 1990. This, in part, can be explained by the fast-rising incidence of Human papillomavirus (HPV)-HNSCC which also have a high incidence in whites in the USA (Chaturvedi et al., 2011).

HNC, and specifically oral cancer, was always described as a disease of old age with most epidemiological studies describing higher incidence in the age group of fifty to seventy years old (Fan et al., 2014). There were reports that only 5% of HNC patients are in the age group from twenty-five to forty years old. However recently, there is an increase in HNC incidence in younger age groups (Al-Amad et al., 2014). This is partially related to the increase in smoking and usage of other drugs in young age (Gawecki et al., 2007), as well as the recently common sexually-transmitted HPV (Al-Amad et al., 2014).

Generally, HNC is more common in men by 2–5 folds compared to women in most countries (Simard et al., 2014), because of likely higher tobacco usage among men (Thun et al., 2012). However, since the 1950s there was an increase in the incidence of HNC in females associated with the increased smoking among them (Muscat et al., 1996). In the USA, oral squamous cell carcinoma (OSCC) and oropharyngeal squamous cell carcinoma (OPSCC) ratios between men to women are currently about 1.5:1 and 2.8:1, respectively (“Human papillomavirus-associated cancers - United States, 2004–2008,” 2012). In Canada, OSCC and laryngeal squamous cell carcinoma (LSCC) ratios between men to women are currently about 2.2:1 and 5.3:1, respectively (Canadian-Cancer-Statistics-Advisory-Committee, 2018).

We review in this paper the etiological factors behind this cancer and the current and future directions of treatment with special attention to the cancer stem cells hypothesis, its relation to head and neck cancer, and how it affects the line of treatment.

1.1. Etiology and pathogenesis

Although tobacco, alcohol, and HPV are the primary HNC risk factors, the etiology of such neoplasm is multifactorial,

and many additional causes have been recognized (Rettig and D'Souza, 2015).

1.1.1. Tobacco

Tobacco usage is the main etiological factor behind HNC as about 90% of the diagnosed HNC patients reported a history of tobacco consumption (Hashibe et al., 2007). It is reported that tobacco users have a 5-fold increased risk of developing oral cavity, oropharynx and hypopharynx cancers and a 10-fold increase in developing laryngeal cancers when compared to non-users (Vineis et al., 2004). There is a close correlation between cigarette smoking duration, intensity and frequency and HNC rate of development in patients (Hashibe et al., 2007). In the same context, the risk of HNC development greatly decreases with increasing the duration of cigarette smoking cessation (Schlecht et al., 1999).

Another primary HNC risk factor, in particular for oral cavity cancers, is smokeless tobacco, such as snuff or chewing tobacco (Secretan et al., 2009). Individuals, who have used smokeless tobacco, have an estimated 80% increase in the risk of developing oral cavity cancer. Countries in which there is a popular use of smokeless tobacco (including betel quid or areca nut with added tobacco) have an attributable fraction of oral cavity cancer which is as high as 53% in India and 68% in Sudan, compared to 7% in the USA (Boffetta et al., 2008). The frequent use of Shamma, Zarda, and Khat has assorted the HNC to be one of the commonest malignancies in Yemen (Abdul-Hamid et al., 2010).

1.1.2. Alcohol

Between 1% and 4% of HNC cases are attributable solely to alcohol consumption (Anantharaman et al., 2011). Hypopharynx cancer is the most common type of HNC types that is related to alcohol consumption (Menvielle et al., 2004). Alcohol drinking works synergistically with tobacco use, imposing a remarkable multiplicative impact in increasing the risk of HNC, (Hashibe et al., 2009)to a level greater than 35-fold for individuals who daily consume two or more cigarettes packs along with more than four alcoholic drinks (Blot et al., 1988).

1.1.3. Occupation

Some epidemiological studies have drawn a link between industrial employment and increasing the risk to develop HNC. Industrial jobs such involving occupational exposures to wood dust, acid mists, asbestos or solvents and jobs related to textiles and leather manufacturing have higher incidence HNC rates (Blot et al., 1988). Sinonasal undifferentiated carcinomas, a rare cancer of the nasal cavity and/or paranasal sinuses could be related to occupational exposures to chromium, nickel, and radium (Marur and Forastiere, 2008).

1.1.4. Solar exposure

Prolonged sunlight exposure is considered as a major risk factor of potentially premalignant disorder such as actinic cheilitis and lip squamous cell carcinomas that arise in the epithelial layer of the lower vermillion border (Khalesi, 2016). There is a marked resemblance of the risk factors of lip cancer to those of skin cancer. However, the risk for cancer of the lower vermillion border was reported positively correlated with increased exposure to solar ultraviolet radiation and not related to skin cancer (van Leeuwen et al., 2009).

1.1.5. Immunologic diseases

Tumor immune surveillance is the process through which the immune system can specifically identify cancerous or precancerous cells, depending on their expression of tumor-specific antigens or cellular stress inducing molecules, and eliminate them before they can develop or progress (Swann and Smyth, 2007). An increased risk of HNC might be attributed to suppression of the immunity secondary to solid organ transplantation or Human immunodeficiency virus (HIV) infection. There is roughly 10 folds rise of lip cancer incidence, and a more modest 2–5 folds increase of HNC incidence at other sites, after solid organ transplantation (Piselli et al., 2013). In a retrospective study from Switzerland, there was a 3-fold increase in the development of carcinomas of the lip, mouth, pharynx, and lung in HIV-positive patients (Clifford et al., 2005).

1.1.6. Viral infection

Chronic viral infections in human cells could encourage the mounting of multiple mutagenic onslaughts, initiating the cells transformation process, and ultimately giving rise to malignant disease. Transformed cells often exhibit chromosomal aberrations which may result from the integration of the viral genome into chromosomes of the host cell (Chang et al., 2017). HPV is a very important risk factor for HNC as up to 15–20% of all HNC are closely related to high-risk HPV infection (Kreimer et al., 2005). Furthermore, HPV-DNA can be found in up to 70% of OPSCC especially that is located at the tonsils (Jelihovschi et al., 2015). It has been suggested that there is a possible interaction between tobacco consumption, alcohol use or HPV16 and Herpes simplex virus type 1 (HSV1) in OSCC development (Acharya et al., 2015). The most acceptable method to assess HPV tumor status is the surrogate marker p16 immunohistochemistry (Fakhry et al., 2018; Lewis et al., 2018). Overexpression of this surrogate marker is strongly associated with transcriptionally active high-risk HPV. Positive cases show a threshold of at least 70 percent nuclear and cytoplasmic expression with moderate to strong intensity.

Another oncogenic double-stranded DNA virus, besides HPV, is the Epstein-Barr virus (EBV) which is one of the human herpesvirus family capable to persist lifelong in the human body (Acharya et al., 2015). The oncogenic potential of EBV has been reviewed in a wide variety of benign and malignant tumors development, however, it was less correlated to HNC except for the strong association with nasopharyngeal squamous cell carcinomas (NPSCC) (Maeda et al., 2009). Interestingly, a study showed that nearly 60% of OSCCs were EBV genome positive (Horiuchi et al., 1995), and another study correlated the poorer OSCC prognosis to the increased expression of EBV (Gonzalez-Moles et al., 1998).

1.1.7. Premalignant lesions

Oral squamous cell carcinoma (OSCC) can arise de novo or arise from pre-existing potentially malignant disorders such as oral leukoplakia, erythroplakia, oral submucous fibrosis, and lichenoid dysplastic lesions (van der Waal, 2009). Oral lichen planus has a malignant transformation rate ranging

from 1 to 5.8%, in particular the erosive form (Gonzalez-Moles et al., 2008, 2017; Kaplan et al., 2012). Other authors reported a strong association between OSCC and the erosive form of the lichen planus (Barnard et al., 1993; Silverman et al., 1991). It has been reported that OSCCs originating from leukoplakic lesions have indeed a more favorable prognosis than those evolving de novo (Bouquot et al., 1988); however, a more recent study reported that the prognosis of these two groups of OSCCs is insignificantly different (Weijers et al., 2008).

1.1.8. Genetic and familial factors

The high susceptibility of cancer development is closely related to various human genetic mutations and genetic polymorphisms (Brunotto et al., 2014). A proto-oncogene is a normal gene that, due to mutations or increased expression, can become a tumor-inducing agent, i.e. an oncogene which encodes for an oncoprotein. Proteins that are encoded by proto-oncogenes, help to regulate cell growth and differentiation; as they are often involved in signal transduction and execution of mitogenic signals (Todd and Wong, 1999). A study in India reported the mutation in Rat sarcoma (Ras) gene is related to the development and progression of OSCC (Saranath et al., 1991). A more recent study reported CT120A gene as possible oncogene for HNSCC and its overexpression is associated with high tumor grades (Baltaci et al., 2015).

A tumor suppressor gene (anti-oncogene) is a gene that protects a cell from cancerous transformation. Usually, in combination with other genetic changes, when the tumor suppressor gene mutates leading to a loss or reduction in its function, the cell might progress to cancer. The loss of these genes may be even more important than the activation of proto-oncogene/oncogene for the formation of many types of human cancer cells (Mader, 2007). Researchers had indicated that oral cancers may evolve through a series of mutations in tumor suppressor genes, especially p53 (Gonzalez et al., 1995; Poeta et al., 2007; Shin et al., 1994).

1.1.9. Other factors

Free radicals such as reactive oxygen species (ROS) are naturally formed in the body and play a crucial role in many normal cellular processes. However, at high concentrations, ROS can cause oxidative stress and be hazardous to the body damaging all major cellular components, including DNA, proteins, and cell membranes, and thus they may play a role in the development of cancer and other impaired health conditions (Valko et al., 2007). ROS produced by tobacco consumption has have been correlated to HNC initiation and progression by either inducing genotoxicity and mutation, altering the salivary proteins and normal oral mucosa, or inducing inflammatory cells infiltration (Jeng et al., 2001). An epidemiological study conducted in Papua New Guinea strongly correlated the ROS to HNC development (Thomas and MacLennan, 1992).

Antioxidants "free radical scavengers" are chemicals which interact with and neutralize these free radicals, thus preventing them from causing damage. The body capable of forming some of the antioxidants (endogenous) which it uses to neutralize free radicals. However, most of the antioxidants used by the body come from external (exogenous) sources, primarily the diet. Fruits, vegetables, and grains are rich sources of dietary antioxidants, and some dietary antioxidants are also available now as dietary supplements (Bouayed and Bohn, 2010). A study reported elevated oxidative stress and decreased antioxidant defense in patients with HNC (Singh et al., 2016).

1.2. Clinical presentation for HNSCC

Numerous signs and symptoms may be encountered depending on the location of the HNSCC. Tongue SCC usually presents as a deeply infiltrating ulcer with indurated growth, reducing its mobility. SCCs of buccal mucosa and floor of the mouth may present as either ulcers with raised indurated margins or exophytic lesions. SCC of the hard palate often presents a papillary exophytic growth rather than a flat or even an ulcerated one. On the other hand, soft palate and uvula SCC could appear as an ulcer with raised margins or as a fungating mass. Generally, the most common presenting features are ulceration, bleeding, localized pain plus referred ear pain, difficulty with speech, opening of the mouth or chewing, and neck swelling due to occasionally enlarged cervical lymph nodes (El-Naggar, 2017; Thompson and Bishop, 2019).

Haemoptysis, dysphagia, odynophagia and quality change of voice are well-known signs and symptoms of the hypopharyngeal and supraglottic tumors. Voice hoarseness characterizes the glottic SCC. For the subglottic tumor, dyspnea and stridor frequently occur. Trachea SCC may bring about dyspnea, hoarseness, wheezing, cough and haemoptysis. SCC of the nasal or paranasal sinuses may give rise to nasal fullness, nasal obstruction, epistaxis, paresthesia, rhinorrhea, and palatal bulge. Persistent non-healing nasal sore or ulcer, or in advanced cases, proptosis, diplopia, and lacrimation may evolve. The NPSCC patients are commonly presented with painless enlargement of upper cervical lymph nodes, blood-stained post-nasal drip, and serous otitis media due to Eustachian tube obstruction (El-Naggar, 2017; Thompson and Bishop, 2019).

1.3. Treatment of HNC

Tumor sub-site and tumor stage are the main factors affecting the choice of treatment modality for HNC patients. The performance status of each patient is another important aspect to take into consideration as treatment is often very intense with multiple side effects. Co-morbidity state in the HNC patients leads to poorer survival, irrespective of the choice of treatment (Gourin et al., 2009). HNC patients conventionally treated by either surgery, radiotherapy (RT), chemotherapy (CT), or combinations of these modalities. However, no worldwide standard mode of therapy exists (Argiris et al., 2008). The combined treatments can be delivered concurrently or in different temporal sequences. Recently, new targeted molecular therapies have shown very promising results (Bonner et al., 2010; Dorsey and Agulnik, 2013).

A multidisciplinary approach is needed to decide the best treatment planning, and to assess posttreatment response. Surgeons, medical oncologists, and radiation oncologists, as well as dentists, speech/swallowing pathologists, dieticians, psychosocial oncology, prosthodontists, and rehabilitation therapists should be included in the decision team. A study reported that multidisciplinary tumor board affects diagnostic and

treatment decisions in a significant number of patients specially with newly diagnosed head and neck tumors (Wheless et al., 2010).

Furthermore, complex cases of head and neck cancer have better chances to be treated at high-volume centers, where expertise in each of previously mentioned disciplines can be found (Boero et al., 2016; Corry et al., 2015). An analysis of outcomes from a large randomized trial (Radiation Therapy Oncology Group [RTOG] 0129) found that centers with high accrual to head and neck clinical trials reported significantly better five-year overall survival rate for their treated patients when compared with centers with historically low accrual (69 versus 51 percent) (Wuthrick et al., 2015).

1.3.1. Surgical intervention

1.3.1.1. Surgical removal oh HNSCC. Before radiotherapy introduction, as an onco-treatment, surgery was the only treatment modality for HNC patients, then RT was suggested as a replacement (Colledge, 1938). However, this was not the case and the two treatment modalities were used together as combined treatment (Gibson and Forastiere, 2004). Over time, surgeons shifted their concerns from only removal of the lesion and promoted improved prognosis to also considering the preservation of organ function and cosmetic appearance, resulting in a continuous emerging of new techniques (Hernández-Vila, 2016; Liu and Shah, 2010). Surgical intervention in primary cancer treatment has changed, and it is rare now to perform surgical treatments for pharyngeal cancer as it can have an excellent prognosis with less invasive treatment modalities. However, in cases of treatment resistance or cancer recurrence, salvage surgery becomes mandatory (Wong and Shah, 2010) with, if possible, reconstructions with free flaps (Burke et al., 2013; Patel et al., 2010).

In the case of oral cavity primary cancers, surgery is still the main treatment option, and usually require a free-flap reconstruction with soft tissue if there are mandibular and bone resections (de Bree et al., 2008). Lower-stage OSCC is often treated with surgery alone while patients with higher stages and poorer prognosis are treated with combined modalities (Ettinger et al., 2019). In laryngeal cancers, small tumors which are only in the right or left vocal cords, are often treated with surgery while tumors that are in both vocal cords or spread beyond the vocal cords but still confined in the larynx are treated with External Beam Radiation Therapy (EBRT) alone, and tumors with spread beyond the larynx are treated with a laryngectomy followed by EBRT (Cognetti et al., 2008; Devlin and Langer, 2007; Haigentz et al., 2010; PDQ-Adult-Treatment-Editorial-Board, 2018; Pfister et al., 2006). One of the landmarks in the development of new methods for larynx cancer treatment and surrounding organs preservation is the work done by the Department of Veterans Affairs Laryngeal Cancer Study Group (Wolf et al., 1991). They reported that induction CT and definitive RT can be effective in preserving the larynx compared to laryngectomy. There are, however, new forms of surgery which provide better organ-preserving capability such as; transoral laser microsurgery, transoral robotic surgery, and open partial laryngectomy which might increase the usage of surgery in primary laryngeal tumors (Obid et al., 2019).

1.3.1.2. Neck dissection. Prophylactic neck dissection is performed in some cases to remove any metastasized residual cancerous tissues in the cervical lymph nodes (Argiris et al., 2008). The original use of neck dissection was for a palliative treatment for HNC patients, but G.W. Crile at the beginning of the twentieth century (Crile, 1906) reidentified this procedure as a treatment for HNC, aiming to reduce the risk of regional lymph nodes recurrence (Rinaldo et al., 2008). Later on, H. Martin introduced the more modern form of neck dissection (Martin et al., 1951). Starting from the 1960s, neck dissection became an integral part of surgical treatment in combination with RT, especially for patients with regional nodal metastasis (Barkley et al., 1972).

With the preservation of organ functions becoming more of an issue, there was a definitive change towards chemoradiotherapy (CRT) without neck dissection even with evidence of nodal metastasis. This debate about whether to use neck dissection or not in these patients and the possible effect on the prognosis, with or without RT, continued all through the 1990s (Mendenhall et al., 2002; Pellitteri et al., 2006). During the last two decades, however, most studies have shown that there is no need to perform a planned neck dissection in patients with nodal metastasis who achieve a complete response after RT or CRT (Brown et al., 2008; Ferlito et al., 2010; Hamoir et al., 2014), and even if a neck dissection is deemed mandatory, a modified technique is recommended (Givi and Andersen, 2008). Parallel to this, neck dissection also has a new role as a diagnostic tool to detect micro-metastasis in the neck, considered as a prophylactic treatment preventing regional recurrence. This is usually used with OSCC due to its high incidence for micro-metastasis (Okura et al., 2009) and is commonly referred to as a staging, selective, or elective neck surgery (Coughlin and Resto, 2010; D'Cruz et al., 2015).

According to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), neck surgery has three major types: radical, modified radical, and selective (Robbins et al., 2002), and there are ongoing attempts to further develop this classification (Hamoir et al., 2010). As an effort toward less extensive surgery, a new technique was introduced that only removes the regions of the neck that are most likely to be the site of metastasis. The sentinel node technique is regarded as an extremely selective neck dissection as it only dissects the gateway nodes (de Bree and Leemans, 2010; Demir, 2016). This is a very promising technology and it may replace the conventional elective neck dissection in the near future (Sharma et al., 2017).

Recently, new techniques have evolved to decrease the morbidity of the HNC patients after surgical treatment and to reconstruct the removed area. Techniques such as navigational systems during surgery, stereolithographic models, robotic surgery, allotransplants, and tissue engineering are the future of reconstruction and soon will replace the conventional full thickness normal flaps (Yadav, 2014).

1.3.2. Non-surgical treatment

The non-surgical treatment of HNC includes radiotherapy, either external or internal (brachytherapy), chemotherapy given for induction and/or concurrently, and pharmacological treatment.

1.3.2.1. External radiotherapy. About 40% of HNC patients undergo RT during their treatments. 60% of those patients will be receiving radiation as a definitive treatment, often in combination with surgery and CT (Fraass et al., 1998). External-beam radiotherapy or external radiotherapy is the conventional method for radiating HNC (Zackrisson et al., 2003). The usual method for EBRT is to deliver a photon beam from a linear accelerator. The ultimate goal is to deliver therapeutic radiation dosage to the tumor without affecting the surrounding tissues, especially tissues in the organ known for its vulnerability to radiation damage such as the spinal cord, the inner ear, and the salivary glands, also known as organs at risk (OARs). (Dirix and Nuyts, 2010). To help protect these organs at risk, a careful planning for the RT using 3-dimensional computed tomography-based imaging must be done (Castadot et al., 2010; Mallick and Waldron, 2009). RT is conventionally given in the form of fractions of 1.8–2.0 Gray (Gy), once daily, 5 days a week for a period of 6 or 7 weeks (making the total up to 70 Gy). In HNC patients' treatment, an accelerated schedule can be used, using six fractions per week, which appear to give improved results compared to the five visits per week (Mortensen et al., 2012; Overgaard et al., 2010). This accelerated schedule delivers the same radiation dosage in a shorter period, allowing less time for the tumor to recover (Bourhis et al., 2006; Johansson et al., 2008).

To deliver adequate target volume coverage and to decrease the risk of RT-induced toxicity, there is a need for accurate delineation of the OARs in the treatment plan. To avoid subjective contouring variations between radiation oncologists in the definition of OARs anatomical sites and limits, contouring consensus guidelines have been developed and followed (Brouwer et al., 2015; De Felice et al., 2016; Sun et al., 2014). There is a risk of small changes in positioning the patient during RT due to weight loss, tumor volume changes, and changes in OARs, especially that the RT takes several weeks. Along with the fact that the patient is not fully immobilized during treatment might lead to high radiation doses to surrounding tissues. The new adaptive radiation treatment technique reduces this risk greatly when compared to the conventional radiation methods (Surucu et al., 2017). Another rapidly developing method to target HNC while preserving OARs is the use of proton beam radiation (Leeman et al., 2017). A well-known method for rescuing OARs is the use of intensity-modulated radiotherapy (IMRT) and image-guided radiation therapy (IGRT), which reduces the irradiation to the surrounding tissues while delivering curative high radiation dosage to cancer (Dirix and Nuyts, 2010; Wang and Eisbruch, 2016).

There is a strong debate on whether there should be pre- or postoperative EBRT in the last decades. One study showed that preoperative EBRT might be negative for surgery, particularly free-flap reconstructions, and this negative effect increased by increasing the time delay between the end of EBRT and surgery (Halle et al., 2009). Another study reported that postoperative EBRT was associated with a higher risk of local recurrence (Gonzalez-Garcia et al., 2009). Even though some authors supported preoperative EBRT, especially for the OSCC (Luukkaa et al., 2003), most institutions use primary surgery for small tumors, smaller than 6 mm, with postoperative EBRT considering the tumor stage, radicality, and histopathology (Genden et al., 2010).

While surgery may alter form and function, RT or chemoradiation treatment may cause acute effects such as mucositis, function alteration and dysphagia, fatigue, and airway edema. Long-term side effects may include severe dysphagia, osteoradionecrosis, aspiration pneumonia, or radiation fibrosis syndrome, which are directly related to radiation dose (Stubblefield, 2017; Taberna et al., 2015).

1.3.2.2. Brachytherapy. Brachytherapy, or internal radiation, means delivering the therapeutic radiation dose from encapsulated radionuclides within or close to a tumor (Skowronek, 2017). This is done by using plastic tube catheters that release photon radiation and is implanted around the tumor, helping in delivering a high dose of radiation directly to the tumor without any beams passing through normal tissue. One important limitation of brachytherapy is that it is best suited for tumors with high accessibility for implantation of catheters. Some studies showed that smaller tumors could be fully treated with brachytherapy alone, while larger tumors, especially at the base of tongue, were better treated using a combination of EBRT and brachytherapy (Kovacs et al., 2017; Mazeron et al., 2009; Shibuya, 2009). Innovative technologies in imaging and analysis, such as intensity modulated brachytherapy (IMBT), Magnetic resonance imaging (MRI), Computed tomography, and Positron emission tomography (PET) make brachytherapy more efficient and a safer method when compared to the conventional technique (Kovács, 2015; Kovacs et al., 2017).

1.3.2.3. Chemotherapy and pharmacological treatment. Chemotherapy can be used as a palliative treatment alone, however, as a curative treatment it is always combined with RT which may be given before RT (as induction or neoadjuvant), alongside RT (as concomitant or concurrent), or in some cases after surgery (as adjuvant) (Choong and Vokes, 2008). The combination of RT and CT has been reported to decrease regional metastasis and improve survival rates while maintaining relatively low toxicity, especially in patients with advanced disease (Argiris et al., 2003; Iqbal et al., 2017; Mehanna et al., 2010). There is increasing use of a combined induction and concurrent chemoradiotherapy (CCRT) to reduce distant metastasis (Brizel and Vokes, 2009; Haddad et al., 2018). The current standard treatment of NPSCC is concurrent *cis*-Diammineplatinum(II) dichloride (Cisplatin) and RT followed by adjuvant CIS and 5-FU following the recommendation from the Intergroup 0099 study (Al-Sarraf et al., 1998; Marur and Forastiere, 2008). HNC patients with locally advanced, unresectable tumor are treated by CRT as a standard as long as the addition of CT is not indicated due to poor performance status or comorbid illnesses (Adelstein et al., 2003).

Acute side effects are the most important limitation for CT, but recently there is growing evidence of higher rates of late toxicity side effects as well (Bentzen and Trotti, 2007; Günen Yılmaz et al., 2018; O'Neill et al., 2015). More research is needed into patient satisfaction and quality of life after receiving CRT for HNC (Furness et al., 2010; McQuestion and Fitch, 2016). CIS has been reported to cause multiple tissue and organ toxicity due to its unspecificity along with the decrease in antioxidant defense system. CIS related toxic side effects include nephrotoxicity, hepatotoxicity, and cardiotoxicity (Dasari and Tchounwou, 2014). 5-Fluorouracil, another

gold standard CT for HNC, also have been reported to cause early and late side effects. These effects range from the common less severe diarrhea, nausea, vomiting, mouth sores, neutropenia and thrombocytopenia to the less common but life-threatening neurotoxicity and cardiotoxicity (Focaccetti et al., 2015).

Since Bonner et al. (2006) reported an improved loco-regional control in advanced HNC patients treated with a concomitant combination of high-dose RT and cetuximab as compared to RT alone, there has been increasing awareness about the possible role of monoclonal antibodies in treatment (Bonner et al., 2006; Sundvall et al., 2010). Epidermal growth factor receptor (EGFR) is highly expressed in HNC and its overexpression is related to a poorer prognosis (Ang et al., 2002). Cetuximab, an EGFR-targeting monoclonal antibody and the only targeted therapy to be routinely used in clinical practice for HNC, has been shown to significantly improve survival for HNC patients, especially with advanced and recurrent diseases (Vermorken et al., 2008). Some of the side effects of cetuximab are the classic acneiform skin rash, hypomagnesemia, a risk for infusion reactions, and the less common anaphylactic reaction (Price and Cohen, 2012). Another group of agents that have emerged recently are tyrosine kinase inhibitors (TKIs). These are a class of chemotherapeutics that act by blocking specific tyrosine kinases which are essential in cellular pathways promoting tumor growth, invasion, and metastasis (Bell et al., 2016). The two most commonly studied TKIs are gefitinib and erlotinib (Blaszczak et al., 2017). These types of immune-related drugs are aimed at more specific treatments due to different responses in different patients (Blaszczak et al., 2017; Sharafinski et al., 2010).

2. Models of tumor heterogeneity

Mostly, the evolution of HNC occurs through the accumulation of several genetic mutations, which may be induced by environmental factors such as tobacco and alcohol abuse or persistent HPV infection (Albers et al., 2012). However, it is not well understood how the alterations of multiple molecular and cellular pathways could yield the development and especially the recurrence of HNC. In general, there are two models aiming to clarify the development and maintenance of tumor growth and heterogeneity (Fig. 1).

2.1. The stochastic model

The stochastic model also known as clonal evolution or clonal genetic model of cancer, is the traditional idea of carcinogenesis, where mutant tumor cells with a growth advantage when compared to the other cells are selected and expanded, considering that cells in the dominant population have a similar potential for recapitulating tumor growth (Nowell, 1976). In other words, malignant transformation originates from a randomized genetic mutation that might affect any cell. The mutant cell progeny, which attains a proliferative advantage

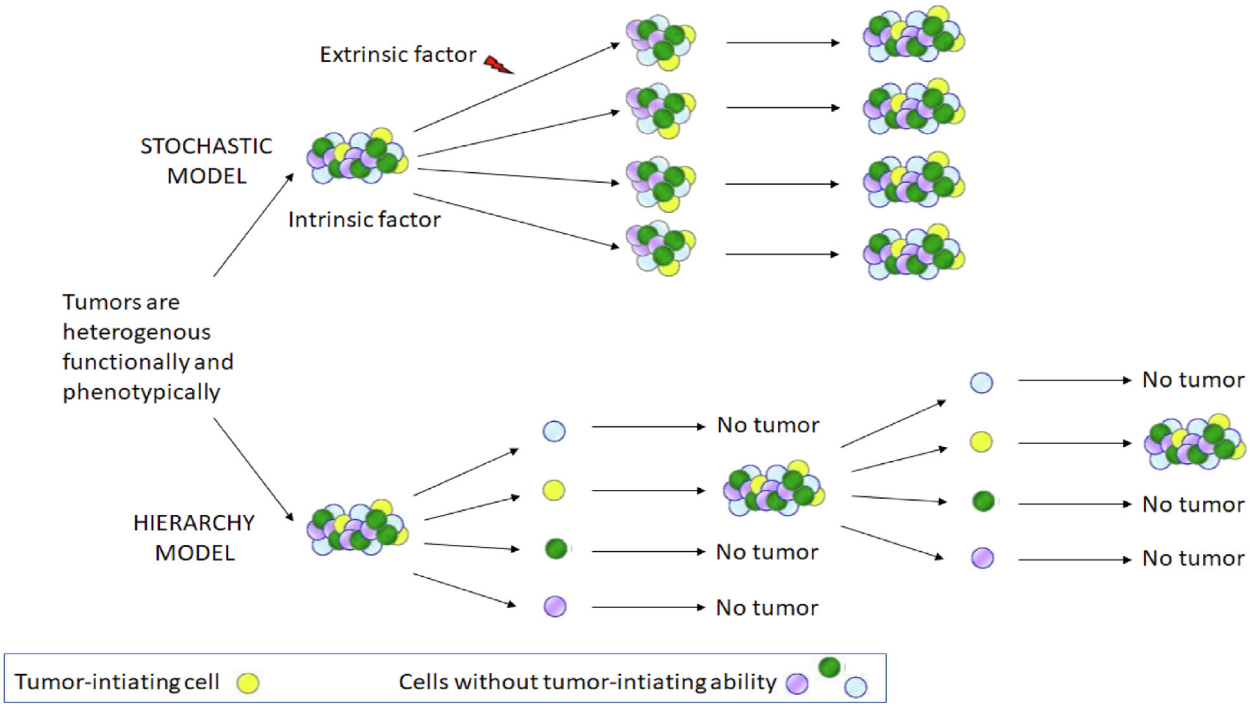

Fig. 1 Models of tumor heterogeneity. Tumors are formed from cells that are heterogenous phenotypically and functionally. There are 2 most acceptable theories as to how this heterogeneity occur. According to the stochastic model, all tumor cells are biologically equal, however, intrinsic and extrinsic factors affect their behavior causing this variability. This means tumor-initiating activity cannot be enriched by isolating cells based on intrinsic features. In contrast, the hierarchy model (Cancer stem cell model) hypothesize the existence of biologically different classes of cells each has its own function and behavior. Only a subset of cells can start the tumorgenicity; these cancer stem cells possess two main criteria, self-renewal and multilineage differentiation, giving them the ability to form the bulk of the tumor. This model speculate that tumor-initiating cells can be identified and sorted based on intrinsic characteristics.

with consequential genomic instability, accumulates more epigenetic and genetic events, causing selection of the more aggressive sub-clones with subsequent tumor evolution (Campbell and Polyak, 2007). Different phenotypic and proliferative features of these sub-clones are responsible for the tumor heterogeneity. Such model proposes cancer as a disease of proliferation (Shakib and Soskic, 2011). The major of the currently available therapeutic strategies is still based on this traditional model of carcinogenesis (Al-Hajj et al., 2003).

Due to conventional treatment resistance and tumor recurrence, researchers have focused on understanding the genetic changes directing a cell towards a malignancy and tumor behavior, without keeping an eye on the nature of cells that are affected by these mutations. Therefore, it is presently believed that a scant group of tumor cells, defined as cancer stem cells (CSCs), harbor the self-renewal potential and can give rise to a phenocopy of the genuine tumor (Sampieri and Fodde, 2012).

2.2. The cancer stem cell model (The hierarchy model)

The cancer stem cell model (The hierarchy model) is a cancer model suggesting that tumorigenesis is exclusively attributed to CSCs (Wicha et al., 2006). Such hypothesis is validated by the experimental findings that only a small number of tumor cells (i.e. CSCs) are capable of generating tumors upon serial transplantation in animal models (Dalerba et al., 2007; Prince et al., 2007; Yang et al., 2008).

2.2.1. Cancer stem cells history

Other than the well established two types of stem cells, adult and embryonic stem cells, the presence of a third type, termed as cancer stem cell (CSCs) was recently recognized (Lapidot et al., 1994). There is increasing support for the concept that the majority of cells in bulk tumors are non-tumorigenic; having limited self-renewal ability (i.e. only a small subpopulation of cancer cells is long-living with extensive self-renewal and tumor formation abilities). Other common names for CSCs are tumor stem cells (TSCs) or cancer-initiating cells (CICs) (X. (Wu et al., 2012). The consensus definition of a CSCs, being approved by the American Association of Cancer Research (AACR) workshop on cancer stem cell, is a cell within a tumor that has the capacity to self-renew and to deliver the heterogeneous lineages of cancer cells comprising the tumor, which would explain how CSCs could be responsible for driving tumorigenesis and tumor growth (Clarke et al., 2006).

The concept that tumor growth depends on a subpopulation of stem cells, like in normal tissues, was suggested by Hamburger when he reported that only 1:1000 to 1:5000 cells isolated from a solid tumor was capable of forming colonies in-vitro (Hamburger and Salmon, 1977). Similarly, other published papers showed that only 1 to 4% of transplanted murine lymphoma cells were able to form colonies in the recipient mice (Bruce and Van Der Gaag, 1963; Park et al., 1971). There are two possible explanations for this observation. First, the tumor cells have a low potential for proliferation, making all cancer cells behave as CSCs. Second, there is only a small and identifiable subset of cells possess great proliferation capacity. Aiming to support the second hypothesis, Dick and co-workers successfully showed that human acute myeloid leukemia (AML) stem cells can be identified and isolated as CD34 + CD38- cells from patient tissue samples (Bonnet and Dick, 1997). According to this study, only CD34 + CD38- cells were able to transfer AML from human patients to non-obese diabetic with severe combined immunodeficiency disease (NOD/SCID) mice while all others cellular phenotypes failed to do so.

After the identification of CSCs in AML, Al-Hajj and colleagues reported the presence of CSCs in solid tumors (Al-Hajj et al., 2003). In this study, they found that only CD44 + CD24-/low cells have the ability to form a tumor in immunocompromised mice while cells with other phenotypes were unable to form a tumor. In the past decade, other types of solid tumors have been reported to contain CSCs such as in lung, colonic, prostatic, and pancreatic cancer (Collins et al., 2005; Eramo et al., 2008; Li et al., 2007; Ricci-Vitiani et al., 2007). In a landmark publication, Prince and collaborators reported the presence of highly tumorigenic, stem-like, cells in HNC (Prince et al., 2007).

Such model of tumorigenesis, which is exclusively based on the aberrant activity of CSCs, has been introduced to successfully explain the heterogeneous nature of many tumors in a more efficient way when compared to the stochastic model. According to the CSC theory, tumors are heterogeneous at the histological level (i.e. exhibiting areas of various differentiation degrees), at the genetic level (i.e. with areas showing different gene expression, yielding diverse immunohistochemical protein expression profiles), and at the proliferation level. Conclusively, tumor cells are heterogeneous, including HNC, at the functional level in terms of their capability of new tumors generation (Gonzalez-Moles et al., 2013), as it has been postulated that the new tumor growth can only be initiated by a small tumor cells subpopulation harboring a distinctive phenotype and not by the tumor cells comprising the tumor bulk (Margaritescu et al., 2011). The proof of CSCs existence in HNC has also been validated by the similarity in the structure between well-differentiated tumors and their epithelium of origin. A well-differentiated OSCC can recapitulate the oral epithelium histological appearance and proliferation pattern. Well-differentiated tumor nests are usually arranged in three compartments of close resemblance to the normal epithelium: CSC basal compartment, amplifying transitory cell (ATC) compartment, and the innermost differentiated cell compartment. Such replica of the hierarchical proliferation pattern of non-tumor oral epithelia postulates the tumor growth maintenance by a single type of tumor cell, designated the CSC (Gonzalez-Moles et al., 2013).

The frequency of CSCs varies from one cancer type to another and between different samples in the same tumor type. A previous study on AML reported that 1 in 10^6 cells can be called CSCs as it has self-renewal and tumor-forming capacity in nude mice (Hope et al., 2004). In colon cancer, CSCs frequency has been reported ~2% (Todaro et al., 2007). In melanoma, there was great variation between the CSCs reported frequencies as it ranged between 0.1 and 41% (Boiko et al., 2010; dos Santos and da Silva, 2013). There are multiple theories explaining this difference in CSC frequencies such as; cancer stage dependent, phenotypic switching between different tumor cells (Gupta et al., 2009), or a consequence of the different definitions used by different researchers (Zapperi and La Porta, 2012). Since the gold standard method to detect CSCs is the in-vitro isolation followed by in-vivo formation of the tumor, this method may not detect cells with the ability to

form the tumor in the original host but fail to do so in xenotransplantation.

In conclusion, CSCs are characterized by two main exclusive features in order to allow tumor formation, propagation, and maintenance. These features are: [A] differentiation, yielding heterogeneous progeny; and [B] self-renewal, maintaining an expanding a pool of stem cells (Bhaijee et al., 2012).

2.2.2. Cellular origin of the cancer stem cell

Different CSCs origins have been proposed wherein a subpopulation of self-renewing tumor cells is formed, giving rise to tumorigenesis. Normally, stem cells give rise to progenitor cells that can further divide into specialized or differentiated cells carrying out the specific body functions. It is controversial as to whether CSCs evolve from stem cells, progenitor cells, or differentiated cells in adult tissues, so this issue is currently under debate (Clarke et al., 2006) (Fig. 2).

1. The First Hypothesis: Cancer stem cells arise from normal somatic stem cells (SCs), and it is the most accepted theory (Costea et al., 2006).

A close relationship between the build-up of genetic alterations and the malignant phenotypic progression of OSCC has been proposed (Califano et al., 2000). As normal oral epithelial cells have a renewal rate of about 14–24 days, most of them do not exist long enough to accumulate the genetic changes necessary for OSCC development. It is estimated that three to six oncogenic events are needed for malignant transformation of the normal cell (Hahn and Weinberg, 2002). The hierarchical SCs structure present in human oral epithelia dictates that only long-time residents of oral epithelia are the only cells capable of accumulating the necessary number of genetic changes needed for malignant transformation; for example, micro-environment control escape mutations (Calabrese et al., 2007).

Another reason supporting the origin of CSCs to be SCs is the fact that CSCs and normal SCs are endowed with self-renewal capabilities, and dysregulation of the self-renewal process is an early and indispensable step in carcinogenesis. Generally, the long-term survival of either normal or neoplastic tissue is dependent on its self-renewal capacity, whereas its overall size is maintained by the balance between the rates of cell proliferation and cell death across its various components (Hanahan and Weinberg, 2011). In normal tissues, the number of SCs is kept under tight genetic regulation, yielding long-term maintenance of a constant tissue size (Morrison et al., 2002). In contrast, tumor tissues have escaped this homeostatic regulation, where the number of cells with the self-renewal capacity is constantly expanding, resulting in progressive tissue growth. Normal SCs already have self-renewal machinery that is known to be ready and activated, which means maintaining its activation is undoubtedly far simpler than de novo activation, through mutations, in the more differentiated cells that lack this self-renewal ability (Reya et al., 2001).

Because the size of neoplastic tissues is dependent on the number of cells able to self-renew, it is logic that a specific subset of oncogenes and/or tumor-suppressor genes affecting the self-renewal ability might be activated and/or disabled respectively in the oncogenesis process (Taipale and Beachy, 2001). The best example, among cancer genes with direct control over self-renewal functions, is probably the B cell-specific Moloney murine leukemia virus integration site 1 (BMI-1) oncogene (Allegra et al., 2014). The Wnt, Notch, and Sonic hedgehog (SHH) pathways are classic examples among multiple signaling pathways that control BMI-1 function and implicated in oncogenesis. The findings that such pathways are pivotal self-renewal regulators in normal SCs and, at the same time, frequent targets of activating mutations in cancer cells, propose that SCs and CSCs depend on a common set of signaling pathways controlling their numbers and stimulating their growth (Dalerba et al., 2014). Henceforth, continued

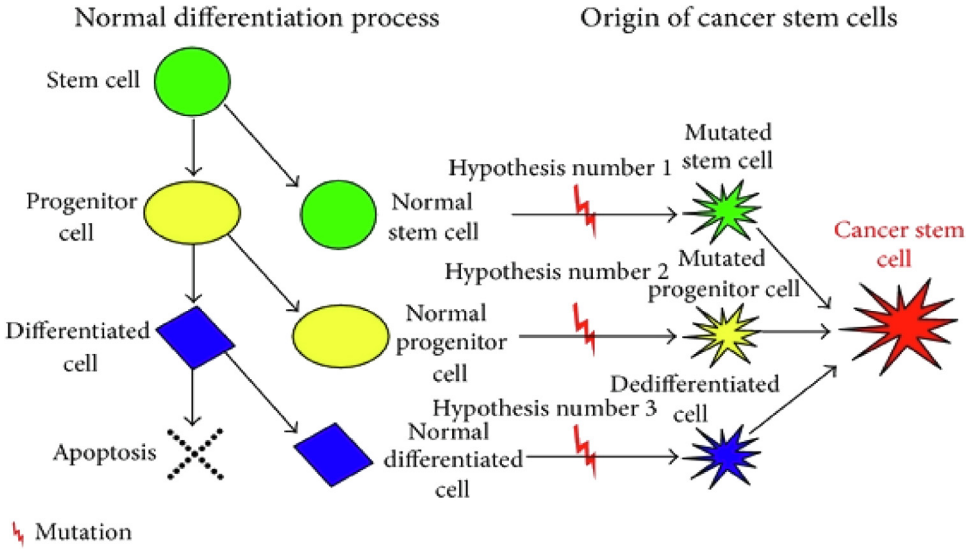

Fig. 2 Hypothesis suggesting origin of cancer stem cells. In the process of normal differentiation, a cell differentiates to form two cells, differentiated and primitive. A terminally differentiated cell is formed from precursor progenitor cell and finally undergoes apoptosis. CSC may originate from a normal stem cell (Hypothesis number 1), a normal progenitor cell (Hypothesis number 2), or a normal differentiated cell (Hypothesis number 3) by genetic mutation which will activate self-renewal genes. This figure and figure legend were originally published in (Shah et al., 2014) under a Creative Commons *license*.

activation of proliferation pathways is not sufficient enough to endow cancer cells with unlimited growth potential (Hanahan and Weinberg, 2011). It is also necessary to ensure activation of self-renewal pathways and/or inactivation of pathways that prevent self-renewal (Dalerba et al., 2014).

2. The second hypothesis: cancer stem cells arise from normal progenitor cells.

Normal progenitor cells, being more abundant in adult tissues than SCs plus having a partial self-renewal capacity, can be a potential source of CSCs (Li et al., 2007). The tumor can sometimes originate from amplifying transitory cells (ATCs) in which their high proliferative rates may boost the risk of genetic mutations, and not exclusively in normal basal SCs. Through a reprogramming process, ATCs could attain remarkable self-renewal potentials, while preserving high proliferation rates without a complete loss of their differentiation capabilities (Gonzalez-Moles et al., 2013).

It is proposed that the first set of early transforming mutations could accumulate in the SC compartment, and that the second set of late mutations, which might constitute the ultimate transforming event giving rise to cancer, might accumulate in more mature, downstream progenitors that originated as the progeny of mutated SCs (Rossi et al., 2008). In other words, mutated SCs might represent a reservoir population of pre-cancerous cells, whereas fully transformed progenitors might sustain the growth of the full-blown neoplastic mass (Jan et al., 2012).

3. The third hypothesis: cancer stem cells arise from normally differentiated cells.

CSCs could originate from mature, differentiated cells through de-differentiation to become more stem cell-like. In this hypothesis, the de-differentiation process, as well as the subsequent self-renewal of the proliferating cells, could be driven through the essential oncogenic genetic mutations (Shah et al., 2014). The virtual lack of proliferative cells in the superficial strata of normal epithelium would assure the reprogramming hurdles for differentiated cells, requiring major molecular changes (Gonzalez-Moles et al., 2013). Given that identity maintenance is an indispensable requirement for a differentiated cell, its reprogramming can exclusively be accomplished by powerful modulators of the transcriptional and/or epigenetic machinery. In oncogenesis, more than one transcription factor (TF) participate in the reprogramming process. The downregulation of somatic genes involved in the conservation of a differentiated phenotype by c-Myc has been reported to be vital at an early stage, whereas other TFs such as octamer-binding transcription factor 4 (Oct4) and SRY (sex determining region Y)-box 2 (SOX2) are implicated in reprogramming at a later stage (Abollo-Jimenez et al., 2010).

Differentiated cancer cells can acquire a CSC-like state through epithelial-mesenchymal transition (EMT) which is the liability of epithelial cells to attain polar, adhesive phenotype mesenchymal characteristics in response to specific environmental stimuli, in order to locally invade surrounding tissues and systemically disseminate to distant organs (Gonzalez-Moles et al., 2013; Smith et al., 2013). The activity of TFs such as Zinc finger protein SNAI1 (Snail) and Twist Basic Helix-Loop-Helix Transcription Factor 1 (Twist1) can promote EMT (Sanchez-Tillo et al., 2010), where the polarity of epithelial cell is altered and E-cadherin protein expression is suppressed, among other actions (Cano et al., 2000). As reported in breast, nasopharyngeal cancers, and HNSCC, EMT is engaged in the acquisition by differentiated cells of the SCs' properties, where Twist1 triggered BMI-1, another TF involved in SC self-renewal, and repressed E-cadherin expression (Morel et al., 2008; Widschwendter et al., 2007; Xia et al., 2010). Recently, researchers have immortalized epithelial cells in an effort to mimic the process of cancer development. They have reported that immortalized epithelial cells showed signs of transformation from an epithelial phenotype to a spindle-shaped, more mesenchymal-like phenotype. In addition, these transformed cells expressed a higher capability to undergo self-renewal. These findings support the hypothesis that EMT could be a potential mechanism for epithelial cells de-differentiation (Zhao et al., 2016).

2.2.3. Cancer stem cells in head and neck cancers

To date, flow cytometry/fluorescence-activated cell sorting (FACS) is the most commonly used technique to identify and isolate CSCs from different tumor types. Using cell surface antigens on HNC stem cells and tag them by fluorochrome-conjugated antibodies, Oncogenic researchers were able to identify these cells based on individual or a combination of markers. Generally, a variety of researches have stated cluster of differentiation 44 (CD44) as a CSC biomarker in breast, CNS, colon, prostate, and pancreas tumors (Collins et al., 2005; Li et al., 2007; Singh et al., 2004). Reategui et al. (2006) first discovered high levels of CD44 variant isoform 3 (CD44v3) expression in HNC tissues in comparison to normal ones. Despite the increased expression level of CD44v3 did not alter cell proliferation rate, a significant increase in cell migration was recorded. Defining CSCs in HNC was first based on CD44 expression (via flow cytometric analysis) as CD44bright and CD44dim populations. Prince et al. (2007) revealed the big difference between both populations to be so remarkable that only 5×10^3 CD44bright cells were capable of regenerating the tumor heterogeneity and demonstrating self-renewal function when transplanted into immunocompromised mice, whereas 5×10^5 CD44dim cells failed to form tumors.

A very interesting study, conducted by Wang et al. (2009) proved the intimate correlation between CD44v3, CD44v6, and CD44v10 isoforms and HNC lymph node metastasis with advanced tumor volume status, perineural invasion plus decreased survival, and distant metastasis with the failure of RT, respectively. In-vivo studies utilized CD44 to assess the metastatic potential of CSCs in HNC, as they have shown that CD44high cells, rather than CD44low cells, resulted in lung lesions when injected in tails of NOD/SCID mice (Davis et al., 2010). Since then, several studies have claimed that CD44 positive subpopulations, emanating from either HNC primary tissues or cell lines, exhibit a higher potential for proliferation, differentiation, migration, invasion, tumor-sphere formation, and resistance to chemotherapeutics (Joshua et al., 2012; Sterz et al., 2010; Su et al., 2011).

CSCs have been shown to acquire a defense mechanism against ROS, enhanced by the CD44v9 isoform. Interaction of CD44v9 with xCT (a functional subunit of the cystine-glutamate transporter) promotes cystine uptake for the synthesis of reduced glutathione (GSH), which is the primary

intracellular antioxidant. Therefore, tumor cells can avoid exposure to high levels of ROS, thus driving tumor growth and chemoresistance (Nagano et al., 2013). Patients with favorable responses to induction CCRT did not have a significant CD44v9 expression level in their HNC biopsy specimens, in comparison to CCRT non-responding patients, where CD44v9 positivity was considerably associated with poor prognosis along with advanced lymph nodal metastasis (Aso et al., 2015). Recently, it has been suggested that a combination of CD44 with other markers, such as the cell adhesion molecule CD24, was more reliable in isolating HNC cancer stem cells when compared to using CD44 alone (Han et al., 2014).

Several new cell surface antigens have recently been reported as potential markers for HNC stem cells. A study reported an increase in the expression of CD10 on HNC cells after RT or CT treatment (Fukusumi et al., 2014). In this study, CD10 used peptidase activation to generates peptides supporting the proliferation of stem and progenitor cells. CD10+ cells isolated from HNC possess enhanced sphere formation in-vitro and tumor formation in-vivo, as well as showing a higher expression of the stem cell marker Oct3/4. Moreover, resistant HNC tumors show elevated CD10 expression that has been associated with local recurrence, distant metastases, and a higher histologic tumor grade (Piattelli et al., 2006). Another recent study used sphere culture to enrich HNC stem cells for examining plasma membrane proteomics (Yan et al., 2013). This group reported that CD166 (a transmembrane glycoprotein that mediates cell-cell adhesion) expressed significantly higher in spheroid cells compared with matched adherent cells. They also showed that, at low cell density, CD166hi HNC cells formed larger tumors than CD166lo cells after implantation in nude mice and were able to reproduce the heterogeneous tumor population, suggesting CSC behavior. Interestingly, CD166hi cells were localized at the tumor invasive front in HNC, which is a typical locale for CSCs.

CD133, also called prominin 1 (PROM1), is a surface cellular transmembrane, which was discovered as a normal hematopoietic SCs marker and later it has been identified as a putative CSC marker in brain, prostate, liver, lung, skin, and colorectal cancers (Wu and Wu, 2009). Mizrak et al defined prominin as "molecule of the moment" in 2008 due to its importance in haematopoietic and CSCs identification and targeting (Mizrak et al., 2008). In the HEp-2 laryngeal cancer cell line, a minor subpopulation of CD133+ expression demonstrated sphere formation and self-renewal criteria of CSCs, plus the capacity to differentiate to phenotypically unique tumor daughter cells (Zhou et al., 2007). More recent studies have supported these findings, as CD133+ cells isolated from HNC cell lines have been suggested to display increased clonogenicity, proliferation, EMT phenotype, tumor-sphere formation, self-renewal, multilinear differentiation, and in-vivo tumorigenicity (Sun et al., 2012).

CD271 is known also as the low-affinity nerve growth factor receptor (NGFR) or p75 neurotrophin receptor. It plays a major rule in the nervous system as it controls functions such as cell survival (Casaccia-Bonnefil et al., 1999), differentiation (Yan et al., 1991), and migration (Sailer et al., 2013) of neuronal cells. Earlier, CD271 was reported as a squamous epithelial SCs marker in the larynx (Li et al., 2012), oral cavity (Nakamura et al., 2007), and esophagus (Okumura et al., 2003). Recent studies reported CD271 as a CSCs marker in melanoma (Boiko et al., 2010; Civenni et al., 2011), esophageal carcinoma (Huang et al., 2009), and hypopharyngeal cancer (Imai et al., 2013). Imai et al. were the first to speculate that CD271 is a marker of CSCs in HNC (Imai et al., 2013). They reported high tumorigenicity in-vivo for CD271+ cells compared to the negative one and localization in the invasive front. Murillo-Sauca et al. also reported that CD271+ in HNC is more invasive with an enhanced capacity for metastasis to regional lymph nodes due to upregulation of Snai2/Slug (Chung et al., 2018). In another study, they showed that CD271 a functional and targetable marker in HNC through monoclonal antibody (Murillo-Sauca et al., 2014).

Apart from cell surface antigens, functional activities of aldehyde dehydrogenase (ALDH) and ATP-binding cassette transporters (ABC transporters) have been used to identify and isolate HNC stem cells. ALDH is a large family of enzymes that control the transformation of aldehydes to carboxylic acids through oxidation and involved in converting retinol to retinoic acid (Marcato et al., 2011; Sobreira et al., 2011). Studies have reported that ALDH enriches for CSCs and is involved in EMT, self-renewal abilities, tumor formation, and resistance to chemotherapeutics (Marcato et al., 2011; Yu et al., 2011). The ALDH1A1 isoform is the most commonly reported to be responsible for enhanced ALDH activity in different types of CSCs, including HNC (Yang et al., 2014). One study reported that as low as 500 ALDH + cells were able to create tumors, unlike the ALDH- cells (Clay et al., 2010). Side population (SP) is a term describing a subset of cancer cells, that is considered CSCs, which possess the ability to efflux Hoechst DNA binding dye and chemotherapeutic drugs using ABC transporters (Dou and Gu, 2010). SP cells isolated from HNC are more tumorigenic, chemoresistant and demonstrate self-renewal ability in-vivo (Tabor et al., 2011; Yanamoto et al., 2011; Zhang et al., 2009). Interestingly, a study reported an increase in the SP cells in HNC by the activation of EGFR, a receptor tyrosine kinase often overexpressed in HNC, and this phenotype was reversed by addition of EGFR inhibitor (Chen et al., 2006). In another study, SP isolated form HNC metastatic cell lines had abnormal activation of Wnt/beta-catenin signaling as compared to non-SP cells (Song et al., 2010).

2.2.4. Therapeutic implication of CSCs in HNC

The CSC hypothesis has important implications regarding cancer therapy and may lead to new treatment strategies along with reviewing the conventional treatment paradigm. According to what we discussed earlier, within the diverse and heterogeneous cell population comprising the HNC mass, the small subpopulation of CSCs may be responsible for tumor recurrence, the initiation of metastasis because of high migration capacity, as well as resistance to both radio- and chemotherapy. Intrinsic characteristics of CSCs such as an elevated level in ABC transmembrane proteins, a semi-quiescent state, and transformed apoptotic mechanisms limit susceptibility to cell death (Clarke and Fuller, 2006; Zhang et al., 2009).

It is frequently suggested that CT resistance is related to accelerated drug transport and to drug metabolism (Morrison et al., 2011; Ogawa et al., 2013). Permeability glycoprotein (P-gp), a product of the gene ATP Binding Cassette Subfamily B Member 1 (ABCB1) or Multidrug Resistance

Protein 1 (MDR1), is an ABC transporter associated with multidrug resistance, and it has been shown to induce the ability of resistance to multiple chemotherapeutic drugs (Becker and Levy, 2017). The MDR1 gene encodes a P-gp transmembrane segment which function is the excretion of different drugs. Previous studies have demonstrated that P-gp expression is correlated with the MDR of HNC (Chen et al., 1994; Ng et al., 1998; Rabkin et al., 1995). Knocking down BMI-1 and CD44 have led to an enhanced chemo-sensitivity of CSCs in HNC.

Yaromina et al reported that therapeutic success after radiotherapy of human squamous cell carcinomas is inversely proportional to the percentage of CSCs within the tumor mass (Yaromina et al., 2007). CSCs that survive the radiation are potentially responsible for recurrence, as they have the capacity for self-renewal and differentiate into the heterogeneous constituents of the tumor (Wicha et al., 2006). CSCs are inherently more radioresistant, by employing mechanisms which increase checkpoint activation and enhanced DNA damage repair responses (Eyler and Rich, 2008). However, increasing the radiation dose in HNC treatment will cause intolerable side effects that worsen the patients' life quality such as xerostomia (Toledano et al., 2012). This was explained by the effect of radiation on micro-niches of normal salivary SCs, often in close proximity to blood vessels in the salivary glands (Vissink et al., 2010).

Central tumor hypoxia, which is found in the center of larger masses, may also provide a survival advantage to CSCs against chemotherapeutics or radiation (Heddleston et al., 2010). Poor perfusion of larger tumor masses might help the enrichment of CSC phenotype by creating specific CSC niches in the same way the hypoxia maintains the pluripotency of embryonic SCs. Suboptimal blood flow will decrease the optimal distribution of chemotherapeutic agents to cancer cells as well as lowers the oxygen tension needed for free radical formation in response to radio- or chemo-therapy (Satpute et al., 2013). Overexpression of hypoxia-inducible factors (HIFs) in CSCs was correlated to radio-resistance in HNC (Vlashi et al., 2009). Yang et al correlated the overexpression of HIF-1-α in CSCs with the induction of EMT which in turn increased mobility, as well as maintained their pluripotency (Yang et al., 2010).

During the surgical treatment of HNC, residual cancer cells may remain in the incisal margin, in the vicinity of the tumor, and in the adjacent tissues surrounding the tumor; those will be dealt with post-operatively or primarily with combined or primary radiotherapy. The CSCs model further emphasizes the great implication of safe margins during surgical intervention and demonstrates that the objective of revolutionary therapies must be the development of specific drugs against the CSCs of a tumor, which survive after the removal of the tumor bulk via conventional therapy modalities.

Because of what we discussed earlier, new strategies targeting CSCs are being under development to be used in combination with the traditional therapeutic means to prevent tumor relapse and to ensure a highly efficient and less toxic treatment for cancer (Fig. 3). New techniques of targeting specific cell membrane growth factor receptors or downstream signaling pathway mutations are currently under investigation, especially in patients with metastatic tumors (Marur and Forastiere, 2016). One of the most promising strategies for cancer treatment is inhibiting the key self-renewal signaling pathways (e.g. Wnt, SHH, Notch signaling pathways) that are aberrantly active in CSCs (Takebe et al., 2011), introducing novel therapeutic approaches for HNSCC (Keysar et al., 2013; Stransky et al., 2011; Takahashi-Yanaga and Kahn, 2010).

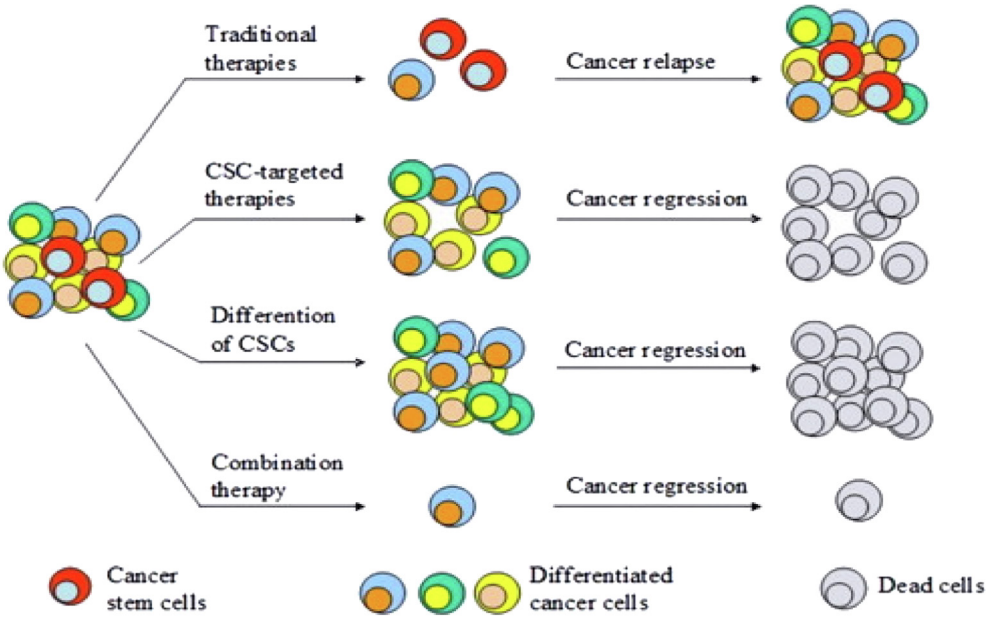

Fig. 3 Therapeutic targeting strategies for CSCs. The traditional cancer therapies kill differentiated cancer cells but fail to target CSCs, resulting in cancer relapse. However, CSC-targeted therapies can eliminate or differentiate the CSCs, and the remaining and resulting differentiated cancer cells will die thereafter. But it is promising to combine CSC-targeted therapies and traditional therapies for depleting CSCs as well as killing differentiated cancer cells, this combination therapy may have the benefits of increased efficacy and quick action. This figure and figure legend were originally published in (Han et al., 2013) under a Creative Commons *license*.

These new therapeutic techniques have a significant reduction in the CSCs, reducing its tumorigenicity, apoptotic resistance, and enhanced the sensitivity to CT (Lim et al., 2012; Zhao et al., 2016).

The markers used to isolate, identify and enrich CSCs are also ideal targets for cancer therapy (Han et al., 2013). DNA damage, caused by treatment with chemotherapeutic drugs, generates pro-apoptotic signals that are known to be suppressed by increased protein kinase B (Akt) phosphorylation, a mediator of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway (Fayard et al., 2010; Igarashi et al., 2003). In HNC, PI3k and Rho kinase (ROCK) have been suggested to mediate HA-CD44 promotion of CIS resistance; as simultaneous inhibition of both kinases reduced CIS resistance to a substantially greater degree than what was observed with inhibition of either enzyme alone. Also, the capacity of hyaluronic acid and CD44 to promote malignant tumor phenotypes (such as abnormal proliferation, migration, and invasion) could be diminished in HNC cell line through the inhibition of these enzymes. Therefore, CD44 and its associated signaling molecules (i.e., ROCK and PI3K) have been introduced as innovated targets for the future development of novel therapies against HNC (Torre et al., 2010). In another study, they reported that knockdown of CD44 increased the sensitivity of HNC cells to CIS (Chen et al., 2010).

Another approach favored targeting the drug-detoxify enzyme ALDH1A1 in HNC, Kulsum and his colleagues reported correlation between CIS resistance and elevated ALDH1A1 expression in HNC, which can be reversed by application of ALDH1A1 inhibitors (Kulsum et al., 2017; Visus et al., 2011). Targeting ABC drug transporters, which in combination with other chemotherapeutic drugs, also offers a very powerful and selective strategy to eliminate CSCs (Lou and Dean, 2007). Recent therapeutic strategies exploited the interdependence of CSCs and vascular endothelial cells (perivascular niche) in HNC to decrease the rate of tumor recurrence and distant metastasis (Bhaijee et al., 2012).

Dysregulated apoptotic mechanisms (including impaired apoptotic machinery, increased DNA damage repair after CRT, and altered cell cycle checkpoint control) contribute to cancer development, progression, and CSCs resistance (Signore et al., 2013). Therefore, induction of CSCs apoptosis through manipulating the apoptotic machinery reveals a great potential to eradicate CSCs for tumor therapy (Han et al., 2013). Several compounds have been introduced to induce apoptosis through targeting the intrinsic and extrinsic apoptosis pathways. For example, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a transcription factor that inhibits apoptosis by elevating the expression of survival factor (García et al., 2012). Hexum et al. synthesized several bicyclic cyclohexenones capable for inhibiting NF-κB signaling by inhibiting NF-κB-induced interleukin-8 (IL-8) expression, thus exerting antiproliferative activity against lung adenocarcinoma epithelial cell line, T cell lymphoblast-like cell line, and prostate carcinoma cell line (Hexum et al., 2012). Another interesting way to manage tumor progression is inducing the terminal differentiation of CSCs (Fig. 3) to lose their self-renewal property (Soltanian and Matin, 2011), by the means of either retinoic acids or drugs targeting tumor epigenetic changes (Massard et al., 2006).

Recently, phytochemicals and herbs have been suggested to be potential sources of therapeutics for CSC elimination, for example; resveratrol, curcumin, sulforaphane, and so forth (Efferth, 2012).

3. Conclusion

Head and neck cancers remain a frequent occurring disease associated with a high mortality rate. The etiology behind such cancer is multifactorial, however, temperance from smocking and alcohol remains the best way to prevent HNC. Aggressive surgical resection is the cornerstone of treatment, with increasing roles for both radiation and chemotherapy, especially for organ preservation. Cancer stem cells are a subpopulation of cells inside the tumor that cause treatment resistance and tumor recurrence which has special implications on the cancer treatment and progression.

Funding

This work was partly funded by: Canadian Institutes of Health Research (CIHR grant 159577), Natural Sciences and Engineering Research Council of Canada (NSERC grant 05247), MJW Kim research fund and the Ministry of Higher Education in Egypt (MOHE post graduate studies funding).

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of Competing Interest

All authors declare that they have no conflict of interest.

References

Abdul-Hamid, G., Saeed, N.M., Al-Kahiry, W., Shukry, S., 2010. Pattern of head and neck cancer in Yemen. Gulf J.Oncolog. (7), 21–24.

Abollo-Jimenez, F., Jimenez, R., Cobaleda, C., 2010. Physiological cellular reprogramming and cancer. Semin. Cancer Biol. 20 (2), 98–106. https://doi.org/10.1016/j.semcancer.2010.02.002.

Acharya, S., Ekalaksananan, T., Vatanasapt, P., Loyha, K., Phusingha, P., Promthet, S., et al, 2015. Association of Epstein-Barr virus infection with oral squamous cell carcinoma in a case-control study. J. Oral Pathol. Med. 44 (4), 252–257. https://doi.org/10.1111/jop.12231.

El-Naggar, Adel K., Chan, John K.C., Grandis, Jennifer R., Takata, Takashi, Slootweg, Pieter J., 2017. WHO Classification of Head and Neck Tumours. International Agency for Research on Cancer.

Adelstein, D.J., Li, Y., Adams, G.L., Wagner Jr., H., Kish, J.A., Ensley, J.F., et al, 2003. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J. Clin. Oncol. 21 (1), 92–98. https://doi.org/10.1200/jco.2003.01.008.

Al-Amad, S.H., Awad, M.A., Nimri, O., 2014. Oral cancer in young Jordanians: potential association with frequency of narghile smoking. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 118 (5), 560–565. https://doi.org/10.1016/j.oooo.2014.08.002.

Al-Hajj, M., Wicha, M.S., Benito-Hernandez, A., Morrison, S.J., Clarke, M.F., 2003. Prospective identification of tumorigenic breast cancer cells. Proc. Natl. Acad. Sci. USA 100 (7), 3983–3988. https://doi.org/10.1073/pnas.0530291100.

Al-Sarraf, M., LeBlanc, M., Giri, P.G., Fu, K.K., Cooper, J., Vuong, T., et al, 1998. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J. Clin. Oncol. 16 (4), 1310–1317. https://doi.org/10.1200/jco.1998.16.4.1310.

Albers, A.E., Chen, C., Koberle, B., Qian, X., Klussmann, J.P., Wollenberg, B., Kaufmann, A.M., 2012. Stem cells in squamous head and neck cancer. Crit. Rev. Oncol. Hematol. 81 (3), 224–240. https://doi.org/10.1016/j.critrevonc.2011.03.004.

Allegra, E., Trapasso, S., Pisani, D., Puzzo, L., 2014. The role of BMI1 as a biomarker of cancer stem cells in head and neck cancer: a review. Oncology 86 (4), 199–205. https://doi.org/10.1159/000358598.

Anantharaman, D., Marron, M., Lagiou, P., Samoli, E., Ahrens, W., Pohlabeln, H., et al, 2011. Population attributable risk of tobacco and alcohol for upper aerodigestive tract cancer. Oral Oncol. 47 (8), 725–731. https://doi.org/10.1016/j.oraloncology.2011.05.004.

Ang, K.K., Berkey, B.A., Tu, X., Zhang, H.Z., Katz, R., Hammond, E.H., et al, 2002. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res. 62 (24), 7350–7356.

Argiris, A., Haraf, D.J., Kies, M.S., Vokes, E.E., 2003. Intensive concurrent chemoradiotherapy for head and neck cancer with 5-Fluorouracil- and hydroxyurea-based regimens: reversing a pattern of failure. Oncologist 8 (4), 350–360.

Argiris, A., Karamouzis, M.V., Raben, D., Ferris, R.L., 2008. Head and neck cancer. Lancet 371 (9625), 1695–1709. https://doi.org/10.1016/s0140-6736(08)60728-x.

Aso, T., Matsuo, M., Kiyohara, H., Taguchi, K., Rikimaru, F., Shimokawa, M., et al, 2015. Induction of CD44 variant 9-expressing cancer stem cells might attenuate the efficacy of chemoradioselection and Worsens the prognosis of patients with advanced head and neck cancer. PLoS ONE 10 (3), e0116596. https://doi.org/10.1371/journal.pone.0116596.

Baltaci, E., Ekizoglu, S., Sari, E., Karaman, E., Ulutin, T., Buyru, N., 2015. CT120A acts as an oncogene in head and neck squamous cell carcinoma. J. Cancer 6 (12), 1255–1259. https://doi.org/10.7150/jca.12969.

Barkley Jr., H.T., Fletcher, G.H., Jesse, R.H., Lindberg, R.D., 1972. Management of cervical lymph node metastases in squamous cell carcinoma of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx. Am. J. Surg. 124 (4), 462–467.

Barnard, N.A., Scully, C., Eveson, J.W., Cunningham, S., Porter, S. R., 1993. Oral cancer development in patients with oral lichen planus. J. Oral Pathol. Med. 22 (9), 421–424.

Becker, M., Levy, D., 2017. Modeling the transfer of drug resistance in solid tumors. Bull. Math. Biol. 79 (10), 2394–2412. https://doi.org/10.1007/s11538-017-0334-x.

Bell, R.B., Leidner, R.S., Crittenden, M.R., Curti, B.D., Feng, Z., Montler, R., et al, 2016. OX40 signaling in head and neck squamous cell carcinoma: Overcoming immunosuppression in the tumor microenvironment. Oral Oncol. 52, 1–10. https://doi.org/10.1016/j.oraloncology.2015.11.009.

Bentzen, S.M., Trotti, A., 2007. Evaluation of early and late toxicities in chemoradiation trials. J. Clin. Oncol. 25 (26), 4096–4103. https://doi.org/10.1200/JCO.2007.13.3983.

Bhaijee, F., Pepper, D.J., Pitman, K.T., Bell, D., 2012. Cancer stem cells in head and neck squamous cell carcinoma: a review of current knowledge and future applications. Head Neck 34 (6), 894–899. https://doi.org/10.1002/hed.21801.

Blaszczak, W., Barczak, W., Wegner, A., Golusinski, W., Suchorska, W.M., 2017. Clinical value of monoclonal antibodies and tyrosine kinase inhibitors in the treatment of head and neck squamous cell carcinoma 60 60 Med. Oncol. 34 (4). https://doi.org/10.1007/s12032-017-0918-1.

Blot, W.J., McLaughlin, J.K., Winn, D.M., Austin, D.F., Greenberg, R.S., Preston-Martin, S., et al, 1988. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res. 48 (11), 3282–3287.

Boero, I.J., Paravati, A.J., Xu, B., Cohen, E.E., Mell, L.K., Le, Q.T., Murphy, J.D., 2016. Importance of radiation oncologist experience among patients with head-and-neck cancer treated with intensity-modulated radiation therapy. J. Clin. Oncol. 34 (7), 684–690. https://doi.org/10.1200/jco.2015.63.9898.

Boffetta, P., Hecht, S., Gray, N., Gupta, P., Straif, K., 2008. Smokeless tobacco and cancer. Lancet Oncol. 9 (7), 667–675. https://doi.org/10.1016/s1470-2045(08)70173-6.

Boiko, A.D., Razorenova, O.V., van de Rijn, M., Swetter, S.M., Johnson, D.L., Ly, D.P., et al, 2010. Human melanoma-initiating cells express neural crest nerve growth factor receptor CD271. Nature 466 (7302), 133–137. https://doi.org/10.1038/nature09161.

Bonner, J.A., Harari, P.M., Giralt, J., Azarnia, N., Shin, D.M., Cohen, R.B., et al, 2006. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N. Engl. J. Med. 354 (6), 567–578. https://doi.org/10.1056/NEJMoa053422.

Bonner, J.A., Harari, P.M., Giralt, J., Cohen, R.B., Jones, C.U., Sur, R.K., et al, 2010. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 11 (1), 21–28. https://doi.org/10.1016/s1470-2045(09)70311-0.

Bonnet, D., Dick, J.E., 1997. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat. Med. 3 (7), 730–737.

Bouayed, J., Bohn, T., 2010. Exogenous antioxidants–Double-edged swords in cellular redox state: health beneficial effects at physiologic doses versus deleterious effects at high doses. Oxid. Med. Cell. Longevity 3 (4), 228–237. https://doi.org/10.4161/oxim.3.4.12858.

Bouquot, J.E., Weiland, L.H., Kurland, L.T., 1988. Leukoplakia and carcinoma in situ synchronously associated with invasive oral/oropharyngeal carcinoma in Rochester, Minn., 1935–1984. Oral Surg. Oral Med. Oral Pathol. 65 (2), 199–207.

Bourhis, J., Overgaard, J., Audry, H., Ang, K.K., Saunders, M., Bernier, J., et al, 2006. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 368 (9538), 843–854. https://doi.org/10.1016/s0140-6736(06)69121-6.

Brizel, D.M., Vokes, E.E., 2009. Induction chemotherapy: to use or not to use? That is the question. Semin. Radiat. Oncol. 19 (1), 11–16. https://doi.org/10.1016/j.semradonc.2008.09.003.

Brouwer, C.L., Steenbakkers, R.J., Bourhis, J., Budach, W., Grau, C., Gregoire, V., et al, 2015. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother. Oncol. 117 (1), 83–90. https://doi.org/10.1016/j.radonc.2015.07.041.

Brown, K.M., Lango, M., Ridge, J.A., 2008. The role of neck dissection in the combined modality therapy setting. Semin. Oncol. 35 (3), 229–235. https://doi.org/10.1053/j.seminoncol.2008.03.006.

Bruce, W.R., Van Der Gaag, H., 1963. A quantitative assay for the number of murine lymphoma cells capable of proliferation in vivo. Nature 199, 79–80.

Brunotto, M., Zarate, A.M., Bono, A., Barra, J.L., Berra, S., 2014. Risk genes in head and neck cancer: a systematic review and meta-analysis of last 5 years. Oral Oncol. 50 (3), 178–188. https://doi.org/10.1016/j.oraloncology.2013.12.007.

Burke, M.S., Kaplan, S.E., Kaplowitz, L.J., Lotempio, M.M., Hicks Jr., W.L., Rigual, N.R., et al, 2013. Pectoralis major myocutaneous flap for reconstruction of circumferential pharyngeal defects. Ann. Plast. Surg. 71 (6), 649–651. https://doi.org/10.1097/SAP.0b013e3182583e80.

Calabrese, C., Poppleton, H., Kocak, M., Hogg, T.L., Fuller, C., Hamner, B., et al, 2007. A perivascular niche for brain tumor stem cells. Cancer Cell 11 (1), 69–82. https://doi.org/10.1016/j.ccr.2006.11.020.

Califano, J., Westra, W.H., Meininger, G., Corio, R., Koch, W.M., Sidransky, D., 2000. Genetic progression and clonal relationship of recurrent premalignant head and neck lesions. Clin. Cancer Res. 6 (2), 347–352.

Campbell, L.L., Polyak, K., 2007. Breast tumor heterogeneity: cancer stem cells or clonal evolution? Cell Cycle 6 (19), 2332–2338. https://doi.org/10.4161/cc.6.19.4914.

Canadian-Cancer-Statistics-Advisory-Committee, 2018. Canadian Cancer Statistics 2018. Toronto, ON: Canadian Cancer Society; 2018. Available at: cancer.ca/Canadian-Cancer-Statistics-2018-EN (accessed 21-11-2018). Retrieved from <http://www.cancer.ca/en/cancer-information/cancer-101/canadian-cancer-statistics-publication/?region=on#ixzz5XXikeMEh>.

Cano, A., Perez-Moreno, M.A., Rodrigo, I., Locascio, A., Blanco, M.J., del Barrio, M.G., et al, 2000. The transcription factor snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression. Nat. Cell Biol. 2 (2), 76–83. https://doi.org/10.1038/35000025.

Casaccia-Bonnefil, P., Gu, C., Chao, M.V., 1999. Neurotrophins in cell survival/death decisions. Adv. Exp. Med. Biol. 468, 275–282.

Castadot, P., Lee, J.A., Geets, X., Gregoire, V., 2010. Adaptive radiotherapy of head and neck cancer. Semin. Radiat. Oncol. 20 (2), 84–93. https://doi.org/10.1016/j.semradonc.2009.11.002.

Chang, Y., Moore, P.S., Weiss, R.A., 2017. Human oncogenic viruses: nature and discovery. Philos. Trans. R. Soc. Lond. B Biol. Sci. 372 (1732). https://doi.org/10.1098/rstb.2016.0264.

Chaturvedi, A.K., Anderson, W.F., Lortet-Tieulent, J., Curado, M. P., Ferlay, J., Franceschi, S., et al, 2013. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J. Clin. Oncol. 31 (36), 4550–4559. https://doi.org/10.1200/jco.2013.50.3870.

Chaturvedi, A.K., Engels, E.A., Pfeiffer, R.M., Hernandez, B.Y., Xiao, W., Kim, E., et al, 2011. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J. Clin. Oncol. 29 (32), 4294–4301. https://doi.org/10.1200/JCO.2011.36.4596.

Chen, J.S., Pardo, F.S., Wang-Rodriguez, J., Chu, T.S., Lopez, J.P., Aguilera, J., et al, 2006. EGFR regulates the side population in head and neck squamous cell carcinoma. Laryngoscope 116 (3), 401–406. https://doi.org/10.1097/01.mlg.0000195075.14093.fb.

Chen, K.G., Jaffrezou, J.P., Fleming, W.H., Duran, G.E., Sikic, B.I., 1994. Prevalence of multidrug resistance related to activation of the mdr1 gene in human sarcoma mutants derived by single-step doxorubicin selection. Cancer Res. 54 (18), 4980–4987.

Chen, Y.C., Chang, C.J., Hsu, H.S., Chen, Y.W., Tai, L.K., Tseng, L. M., et al, 2010. Inhibition of tumorigenicity and enhancement of radiochemosensitivity in head and neck squamous cell cancer-derived ALDH1-positive cells by knockdown of Bmi-1. Oral Oncol. 46 (3), 158–165. https://doi.org/10.1016/j.oraloncology.2009.11.007.

Choong, N., Vokes, E., 2008. Expanding role of the medical oncologist in the management of head and neck cancer. CA Cancer J. Clin. 58 (1), 32–53. https://doi.org/10.3322/ca.2007.0004.

Chung, M.K., Jung, Y.H., Lee, J.K., Cho, S.Y., Murillo-Sauca, O., Uppaluri, R., et al, 2018. CD271 confers an invasive and metastatic phenotype of head and neck squamous cell carcinoma through the upregulation of slug. Clin. Cancer Res. 24 (3), 674–683. https://doi.org/10.1158/1078-0432.Ccr-17-0866.

Civenni, G., Walter, A., Kobert, N., Mihic-Probst, D., Zipser, M., Belloni, B., et al, 2011. Human CD271-positive melanoma stem cells associated with metastasis establish tumor heterogeneity and long-term growth. Cancer Res. 71 (8), 3098–3109. https://doi.org/10.1158/0008-5472.Can-10-3997.

Clarke, M.F., Dick, J.E., Dirks, P.B., Eaves, C.J., Jamieson, C.H.M., Jones, D.L., et al, 2006. Cancer stem cells—perspectives on current status and future directions: AACR workshop on cancer stem cells. Cancer Res. 66 (19), 9339–9344. https://doi.org/10.1158/0008-5472.Can-06-3126.

Clarke, M.F., Fuller, M., 2006. Stem cells and cancer: two faces of eve. Cell 124 (6), 1111–1115. https://doi.org/10.1016/j.cell.2006.03.011.

Clay, M.R., Tabor, M., Owen, J.H., Carey, T.E., Bradford, C.R., Wolf, G.T., et al, 2010. Single-marker identification of head and neck squamous cell carcinoma cancer stem cells with aldehyde dehydrogenase. Head Neck 32 (9), 1195–1201. https://doi.org/10.1002/hed.21315.

Clifford, G.M., Polesel, J., Rickenbach, M., Dal Maso, L., Keiser, O., Kofler, A., et al, 2005. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J. Natl Cancer Inst. 97 (6), 425–432. https://doi.org/10.1093/jnci/dji072.

Cognetti, D.M., Weber, R.S., Lai, S.Y., 2008. Head and neck cancer: an evolving treatment paradigm. Cancer 113 (7 Suppl), 1911–1932. https://doi.org/10.1002/cncr.23654.

Colledge, L., 1938. Treatment of cancer of pharynx and larynx. Br. Med. J. 2 (4046), 167–168.

Collins, A.T., Berry, P.A., Hyde, C., Stower, M.J., Maitland, N.J., 2005. Prospective identification of tumorigenic prostate cancer stem cells. Cancer Res. 65 (23), 10946–10951. https://doi.org/10.1158/0008-5472.Can-05-2018.

Corry, J., Peters, L.J., Rischin, D., 2015. Impact of center size and experience on outcomes in head and neck cancer. J. Clin. Oncol. 33 (2), 138–140. https://doi.org/10.1200/jco.2014.58.2239.

Costea, D.E., Tsinkalovsky, O., Vintermyr, O.K., Johannessen, A.C., Mackenzie, I.C., 2006. Cancer stem cells – new and potentially important targets for the therapy of oral squamous cell carcinoma. Oral Dis. 12 (5), 443–454. https://doi.org/10.1111/j.1601-0825.2006.01264.x.

Coughlin, A., Resto, V.A., 2010. Oral cavity squamous cell carcinoma and the clinically n0 neck: the past, present, and future of sentinel lymph node biopsy. Curr. Oncol. Rep. 12 (2), 129–135. https://doi.org/10.1007/s11912-010-0090-7.

Crile, G., 1906. III. On the technique of operations upon the head and neck. Ann. Surg. 44 (6), 842–850.

D'Cruz, A.K., Vaish, R., Kapre, N., Dandekar, M., Gupta, S., Hawaldar, R., et al, 2015. Elective versus therapeutic neck dissection in node-negative oral cancer. N. Engl. J. Med. 373 (6), 521–529. https://doi.org/10.1056/NEJMoa1506007.

Dalerba, P., Clarke, M.F., Weissman, I.L., Diehn, M., 2014. 7 - Stem cells, cell differentiation, and cancer. In: Niederhuber, J.E., Armitage, J.O., Doroshow, J.H., Kastan, M.B., Tepper, J.E. (Eds.), Abeloff's Clinical Oncology (Fifth Edition). Content Repository Only!, Philadelphia, pp. 98–107.e103.

Dalerba, P., Dylla, S.J., Park, I.K., Liu, R., Wang, X., Cho, R.W., et al, 2007. Phenotypic characterization of human colorectal cancer stem cells. Proc. Natl. Acad. Sci. USA 104 (24), 10158–10163. https://doi.org/10.1073/pnas.0703478104.

Daraei, P., Moore, C.E., 2015. Racial disparity among the head and neck cancer population. J. Cancer Educ. 30 (3), 546–551. https://doi.org/10.1007/s13187-014-0753-4.

Dasari, S., Tchounwou, P.B., 2014. Cisplatin in cancer therapy: molecular mechanisms of action. Eur. J. Pharmacol. 740, 364–378. https://doi.org/10.1016/j.ejphar.2014.07.025.

Davis, S.J., Divi, V., Owen, J.H., et al, 2010. Metastatic potential of cancer stem cells in head and neck squamous cell carcinoma. Arch. Otolaryngol.-Head Neck Surg. 136 (12), 1260–1266. https://doi.org/10.1001/archoto.2010.219.

de Bree, R., Leemans, C.R., 2010. Recent advances in surgery for head and neck cancer. Curr. Opin. Oncol. 22 (3), 186–193. https://doi.org/10.1097/CCO.0b013e3283380009.

de Bree, R., Rinaldo, A., Genden, E.M., Suarez, C., Rodrigo, J.P., Fagan, J.J., et al, 2008. Modern reconstruction techniques for oral and pharyngeal defects after tumor resection. Eur. Arch. Otorhinolaryngol. 265 (1), 1–9. https://doi.org/10.1007/s00405-007-0413-y.

De Felice, F., Musio, D., Tombolini, V., 2016. Mastication structures definition in head and neck cancer. Radiother. Oncol. 118 (2), 419. https://doi.org/10.1016/j.radonc.2015.12.016.

Demir, D., 2016. The role of sentinel lymph node biopsy in head and neck cancers and its application areas. Turk. Arch. Otorhinolaryngol. 54 (1), 35–38. https://doi.org/10.5152/tao.2016.1129.

Devlin, J.G., Langer, C.J., 2007. Combined modality treatment of laryngeal squamous cell carcinoma. Expert Rev. Anticancer Ther. 7 (3), 331–350. https://doi.org/10.1586/14737140.7.3.331.

Dilling, T.J., Bae, K., Paulus, R., Watkins-Bruner, D., Garden, A.S., Forastiere, A., et al, 2011. Impact of gender, partner status, and race on locoregional failure and overall survival in head and neck cancer patients in three radiation therapy oncology group trials. Int. J. Radiat. Oncol. Biol. Phys. 81 (3), e101–e109. https://doi.org/10.1016/j.ijrobp.2011.01.013.

Dirix, P., Nuyts, S., 2010. Evidence-based organ-sparing radiotherapy in head and neck cancer. Lancet Oncol. 11 (1), 85–91. https://doi.org/10.1016/s1470-2045(09)70231-1.

Dorsey, K., Agulnik, M., 2013. Promising new molecular targeted therapies in head and neck cancer. Drugs 73 (4), 315–325. https://doi.org/10.1007/s40265-013-0025-3.

dos Santos, R.V., da Silva, L.M., 2013. A possible explanation for the variable frequencies of cancer stem cells in tumors e69131-e69131 PLoS ONE 8 (8). https://doi.org/10.1371/journal.pone.0069131.

Dou, J., Gu, N., 2010. Emerging strategies for the identification and targeting of cancer stem cells. Tumour Biol. 31 (4), 243–253. https://doi.org/10.1007/s13277-010-0023-y.

Efferth, T., 2012. Stem cells, cancer stem-like cells, and natural products. Planta Med. 78 (10), 935–942. https://doi.org/10.1055/s-0031-1298540.

Eramo, A., Lotti, F., Sette, G., Pilozzi, E., Biffoni, M., Di Virgilio, A., et al, 2008. Identification and expansion of the tumorigenic lung cancer stem cell population. Cell Death Differ. 15 (3), 504–514. https://doi.org/10.1038/sj.cdd.4402283.

Ettinger, K.S., Ganry, L., Fernandes, R.P., 2019. Oral cavity cancer. Oral Maxillofac. Surg. Clin. North Am. 31 (1), 13–29. https://doi.org/10.1016/j.coms.2018.08.002.

Eyler, C.E., Rich, J.N., 2008. Survival of the fittest: cancer stem cells in therapeutic resistance and angiogenesis. J. Clin. Oncol. 26 (17), 2839–2845. https://doi.org/10.1200/jco.2007.15.1829.

Fakhry, C., Lacchetti, C., Rooper, L.M., Jordan, R.C., Rischin, D., Sturgis, E.M., et al, 2018. Human papillomavirus testing in head and neck carcinomas: ASCO clinical practice guideline endorsement of the college of American pathologists guideline. J. Clin. Oncol. 36 (31), 3152–3161. https://doi.org/10.1200/jco.18.00684.

Fan, Y., Zheng, L., Mao, M.H., Huang, M.W., Liu, S.M., Zhang, J., et al, 2014. Survival analysis of oral squamous cell carcinoma in a subgroup of young patients. Asian Pac. J. Cancer Prev. 15 (20), 8887–8891.

Fayard, E., Xue, G., Parcellier, A., Bozulic, L., Hemmings, B.A., 2010. Protein kinase B (PKB/Akt), a key mediator of the PI3K signaling pathway. Curr. Top. Microbiol. Immunol. 346, 31–56. https://doi.org/10.1007/82_2010_58.

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., et al, 2015. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer 136 (5), E359–E386. https://doi.org/10.1002/ijc.29210.

Ferlito, A., Corry, J., Silver, C.E., Shaha, A.R., Thomas Robbins, K., Rinaldo, A., 2010. Planned neck dissection for patients with complete response to chemoradiotherapy: a concept approaching obsolescence. Head Neck 32 (2), 253–261. https://doi.org/10.1002/hed.21173.

Focaccetti, C., Bruno, A., Magnani, E., Bartolini, D., Principi, E., Dallaglio, K., et al, 2015. Effects of 5-fluorouracil on morphology, cell cycle, proliferation, apoptosis, autophagy and ROS production in endothelial cells and cardiomyocytes e0115686-e115686 PLoS ONE 10 (2). https://doi.org/10.1371/journal.pone.0115686.

Fraass, B., Doppke, K., Hunt, M., Kutcher, G., Starkschall, G., Stern, R., Van Dyke, J., 1998. American Association of Physicists in Medicine Radiation Therapy Committee Task Group 53: quality assurance for clinical radiotherapy treatment planning. Med. Phys. 25 (10), 1773–1829. https://doi.org/10.1118/1.598373.

Fukusumi, T., Ishii, H., Konno, M., Yasui, T., Nakahara, S., Takenaka, Y., et al, 2014. CD10 as a novel marker of therapeutic resistance and cancer stem cells in head and neck squamous cell carcinoma. Br. J. Cancer 111 (3), 506–514. https://doi.org/10.1038/bjc.2014.289.

Furness, S., Glenny, A.M., Worthington, H.V., Pavitt, S., Oliver, R., Clarkson, J.E., et al, 2010. Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. Cochrane Database Syst.Rev (9), Cd006386. https://doi.org/10.1002/14651858.CD006386.pub2.

García, M.A., Carrasco, E., Ramírez, A., Jiménez, G., López-Ruiz, E., Perán, M., et al, 2012. Apoptosis as a therapeutic target in cancer and cancer stem cells: novel strategies and futures perspectives. Apoptosis and Medicine.

Gawecki, W., Kostrzewska-Poczekaj, M., Gajecka, M., Milecki, P., Szyfter, K., Szyfter, W., 2007. The role of genetic factor in etiopathogenesis of squamous cell carcinoma of the head and neck in young adults. Eur. Arch. Otorhinolaryngol. 264 (12), 1459–1465. https://doi.org/10.1007/s00405-007-0386-x.

Genden, E.M., Ferlito, A., Silver, C.E., Takes, R.P., Suárez, C., Owen, R.P., et al, 2010. Contemporary management of cancer of the oral cavity. Eur. Arch. Otorhinolaryngol. 267 (7), 1001–1017. https://doi.org/10.1007/s00405-010-1206-2.

Gibson, M.K., Forastiere, A.A., 2004. Multidisciplinary approaches in the management of advanced head and neck tumors: state of the art. Curr. Opin. Oncol. 16 (3), 220–224.

Givi, B., Andersen, P.E., 2008. Rationale for modifying neck dissection. J. Surg. Oncol. 97 (8), 674–682. https://doi.org/10.1002/jso.21016.

Gonzalez-Garcia, R., Naval-Gias, L., Roman-Romero, L., Sastre-Perez, J., Rodriguez-Campo, F.J., 2009. Local recurrences and second primary tumors from squamous cell carcinoma of the oral cavity: a retrospective analytic study of 500 patients. Head Neck 31 (9), 1168–1180. https://doi.org/10.1002/hed.21088.

Gonzalez-Moles, M., Gutierrez, J., Ruiz, I., Fernandez, J.A., Rodriguez, M., Aneiros, J., 1998. Epstein-Barr virus and oral squamous cell carcinoma in patients without HIV infection: viral detection by polymerase chain reaction. Microbios 96 (383), 23–31.

Gonzalez-Moles, M.A., Gil-Montoya, J.A., Ruiz-Avila, I., Bravo, M., 2017. Is oral cancer incidence among patients with oral lichen planus/oral lichenoid lesions underestimated? J. Oral Pathol. Med. 46 (2), 148–153. https://doi.org/10.1111/jop.12480.

Gonzalez-Moles, M.A., Scully, C., Gil-Montoya, J.A., 2008. Oral lichen planus: controversies surrounding malignant transformation. Oral Dis. 14 (3), 229–243. https://doi.org/10.1111/j.1601-0825.2008.01441.x.

Gonzalez-Moles, M.A., Scully, C., Ruiz-Avila, I., Plaza-Campillo, J. J., 2013. The cancer stem cell hypothesis applied to oral carcinoma. Oral Oncol. 49 (8), 738–746. https://doi.org/10.1016/j.oraloncology.2013.04.002.

Gonzalez, M.V., Pello, M.F., Lopez-Larrea, C., Suarez, C., Menendez, M.J., Coto, E., 1995. Loss of heterozygosity and mutation analysis of the p16 (9p21) and p53 (17p13) genes in squamous cell carcinoma of the head and neck. Clin. Cancer Res. 1 (9), 1043–1049.

Gourin, C.G., Boyce, B.J., Vaught, C.C., Burkhead, L.M., Podolsky, R.H., 2009. Effect of comorbidity on post-treatment quality of life scores in patients with head and neck squamous cell carcinoma. Laryngoscope 119 (5), 907–914. https://doi.org/10.1002/lary.20199.

Günen Yılmaz, S., Bayrakdar, İ.Ş., Bayrak, S., Yaşa, Y., 2018. Late Side Effects of Chemotherapy and Radiotherapy in Early Childhood on the Teeth: Two Case ReportsErken Çocukluk Döneminde Alınan Radyoterapi ve Kemoterapinin Dişler Üzerine Geç Dönem

Etkileri: İki Olgu Sunumu. Turk. J. Haematol.: Off. J. Turk. Soc. Haematol. 35 (1), 87–88. https://doi.org/10.4274/tjh.2017.0216.
Gupta, P.B., Chaffer, C.L., Weinberg, R.A., 2009. Cancer stem cells: mirage or reality? Nat. Med. 15 (9), 1010–1012. https://doi.org/10.1038/nm0909-1010.
Haddad, R.I., Posner, M., Hitt, R., Cohen, E.E.W., Schulten, J., Lefebvre, J.L., Vermorken, J.B., 2018. Induction chemotherapy in locally advanced squamous cell carcinoma of the head and neck: role, controversy, and future directions. Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol. 29 (5), 1130–1140. https://doi.org/10.1093/annonc/mdy102.
Hahn, W.C., Weinberg, R.A., 2002. Rules for making human tumor cells. N. Engl. J. Med. 347 (20), 1593–1603. https://doi.org/10.1056/NEJMra021902.
Haigentz Jr., M., Silver, C.E., Hartl, D.M., Takes, R.P., Rodrigo, J. P., Robbins, K.T., et al, 2010. Chemotherapy regimens and treatment protocols for laryngeal cancer. Expert Opin. Pharmacother. 11 (8), 1305–1316. https://doi.org/10.1517/14656561003749256.
Halle, M., Bodin, I., Tornvall, P., Wickman, M., Farnebo, F., Arnander, C., 2009. Timing of radiotherapy in head and neck free flap reconstruction–a study of postoperative complications. J. Plast. Reconstr. Aesthet. Surg. 62 (7), 889–895. https://doi.org/10.1016/j.bjps.2008.01.005.
Hamburger, A.W., Salmon, S.E., 1977. Primary bioassay of human tumor stem cells. Science 197 (4302), 461–463.
Hamoir, M., Leemans, C.R., Dolivet, G., Schmitz, S., Gregoire, V., Andry, G., 2010. Selective neck dissection in the management of the neck after (chemo)radiotherapy for advanced head and neck cancer. Proposal for a classification update. Head Neck 32 (6), 816–819. https://doi.org/10.1002/hed.21386.
Hamoir, M., Schmitz, S., Gregoire, V., 2014. The role of neck dissection in squamous cell carcinoma of the head and neck. Curr. Treat. Options Oncol. 15 (4), 611–624. https://doi.org/10.1007/s11864-014-0311-7.
Han, J., Fujisawa, T., Husain, S.R., Puri, R.K., 2014. Identification and characterization of cancer stem cells in human head and neck squamous cell carcinoma 173 173 BMC Cancer 14. https://doi.org/10.1186/1471-2407-14-173.
Han, L., Shi, S., Gong, T., Zhang, Z., Sun, X., 2013. Cancer stem cells: therapeutic implications and perspectives in cancer therapy. Acta Pharmaceutica Sinica B 3 (2), 65–75. https://doi.org/10.1016/j.apsb.2013.02.006.
Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. Cell 144 (5), 646–674. https://doi.org/10.1016/j.cell.2011.02.013.
Hashibe, M., Brennan, P., Benhamou, S., Castellsague, X., Chen, C., Curado, M.P., et al, 2007. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J. Natl Cancer Inst. 99 (10), 777–789. https://doi.org/10.1093/jnci/djk179.
Hashibe, M., Brennan, P., Chuang, S.C., Boccia, S., Castellsague, X., Chen, C., et al, 2009. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol. Biomarkers Prev. 18 (2), 541–550. https://doi.org/10.1158/1055-9965.Epi-08-0347.
Heddleston, J.M., Li, Z., Lathia, J.D., Bao, S., Hjelmeland, A.B., Rich, J.N., 2010. Hypoxia inducible factors in cancer stem cells. Br. J. Cancer 102, 789. https://doi.org/10.1038/sj.bjc.6605551.
Hernández-Vila, C., 2016. Current prognosis and quality of life following surgical treatment for head and neck squamous cell carcinoma. Plastic Aesthetic Res. 3 (6), 203–210.
Hexum, J.K., Tello-Aburto, R., Struntz, N.B., Harned, A.M., Harki, D.A., 2012. Bicyclic cyclohexenones as inhibitors of NF-κB signaling. ACS Med. Chem. Lett. 3 (6), 459–464. https://doi.org/10.1021/ml300034a.
Hope, K.J., Jin, L., Dick, J.E., 2004. Acute myeloid leukemia originates from a hierarchy of leukemic stem cell classes that differ in self-renewal capacity. Nat. Immunol. 5 (7), 738–743. https://doi.org/10.1038/ni1080.
Horiuchi, K., Mishima, K., Ichijima, K., Sugimura, M., Ishida, T., Kirita, T., 1995. Epstein-Barr virus in the proliferative diseases of squamous epithelium in the oral cavity. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 79 (1), 57–63.
Huang, S.D., Yuan, Y., Liu, X.H., Gong, D.J., Bai, C.G., Wang, F., et al, 2009. Self-renewal and chemotherapy resistance of p75NTR positive cells in esophageal squamous cell carcinomas. BMC Cancer 9, 9. https://doi.org/10.1186/1471-2407-9-9.
Human papillomavirus-associated cancers - United States, 2004-2008, 2012. MMWR Morb. Mortal. Wkly. Rep. 61, 258–261.
Igarashi, M., Irwin, C.R., Locke, M., Mackenzie, I.C., 2003. Construction of large area organotypical cultures of oral mucosa and skin. J. Oral Pathol. Med. 32 (7), 422–430. https://doi.org/10.1034/j.1600-0714.2003.00090.x.
Imai, T., Tamai, K., Oizumi, S., Oyama, K., Yamaguchi, K., Sato, I., et al, 2013. CD271 defines a stem cell-like population in hypopharyngeal cancer. PLoS ONE 8 (4), e62002. https://doi.org/10.1371/journal.pone.0062002.
Iqbal, M.S., Chaw, C., Kovarik, J., Aslam, S., Jackson, A., Kelly, J., et al, 2017. Primary concurrent chemoradiation in head and neck cancers with weekly cisplatin chemotherapy: analysis of compliance, toxicity and survival. Int. Arch. Otorhinolaryngol. 21 (2), 171–177. https://doi.org/10.1055/s-0036-1594020.
Jan, M., Snyder, T.M., Corces-Zimmerman, M.R., Vyas, P., Weissman, I.L., Quake, S.R., Majeti, R., 2012. Clonal evolution of preleukemic hematopoietic stem cells precedes human acute myeloid leukemia. Sci. Transl. Med. 4 (149), 149ra118. https://doi.org/10.1126/scitranslmed.3004315.
Jelihovschi, I., Bidescu, A.C., Tucaliuc, S.E., Iancu, L.S., 2015. Detection of human papilloma virus in head and neck squamous cell carcinomas: a literature review. Rev. Med. Chir. Soc. Med. Nat. Iasi 119 (2), 502–509.
Jeng, J.H., Chang, M.C., Hahn, L.J., 2001. Role of areca nut in betel quid-associated chemical carcinogenesis: current awareness and future perspectives. Oral Oncol. 37 (6), 477–492.
Johansson, K.A., Nilsson, P., Zackrisson, B., Ohlson, B., Kjellen, E., Mercke, C., et al, 2008. The quality assurance process for the ARTSCAN head and neck study – a practical interactive approach for QA in 3DCRT and IMRT. Radiother. Oncol. 87 (2), 290–299. https://doi.org/10.1016/j.radonc.2007.12.005.
Joshua, B., Kaplan, M.J., Doweck, I., Pai, R., Weissman, I.L., Prince, M.E., Ailles, L.E., 2012. Frequency of cells expressing CD44, a head and neck cancer stem cell marker: correlation with tumor aggressiveness. Head Neck 34 (1), 42–49. https://doi.org/10.1002/hed.21699.
Jou, A., Hess, J., 2017. Epidemiology and molecular biology of head and neck cancer. Oncol. Res. Treat. 40 (6), 328–332. https://doi.org/10.1159/000477127.
Kaplan, I., Ventura-Sharabi, Y., Gal, G., Calderon, S., Anavi, Y., 2012. The dynamics of oral lichen planus: a retrospective clinicopathological study. Head Neck Pathol. 6 (2), 178–183. https://doi.org/10.1007/s12105-011-0318-3.
Keysar, S.B., Le, P.N., Anderson, R.T., Morton, J.J., Bowles, D.W., Paylor, J.J., et al, 2013. Hedgehog signaling alters reliance on EGF receptor signaling and mediates anti-EGFR therapeutic resistance in head and neck cancer. Cancer Res. 73 (11), 3381–3392. https://doi.org/10.1158/0008-5472.CAN-12-4047.
Khalesi, S., 2016. A review of head and neck squamous cell carcinoma risk factors with more focus on oral cancer. J. Dent. Oral Disord. 2 (6), 1032.
Kovács, G., 2015. Modern head and neck brachytherapy: from radium towards intensity modulated interventional brachytherapy. J. Contemp. Brachytherapy 6 (4), 404–416. https://doi.org/10.5114/jcb.2014.47813.

Kovacs, G., Martinez-Monge, R., Budrukkar, A., Guinot, J.L., Johansson, B., Strnad, V., et al, 2017. GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update – improvement by cross sectional imaging based treatment planning and stepping source technology. Radiother. Oncol. 122 (2), 248–254. https://doi.org/10.1016/j.radonc.2016.10.008.

Kreimer, A.R., Clifford, G.M., Boyle, P., Franceschi, S., 2005. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol. Biomarkers Prev. 14 (2), 467–475. https://doi.org/10.1158/1055-9965.Epi-04-0551.

Kulsum, S., Sudheendra, H.V., Pandian, R., Ravindra, D.R., Siddappa, G., et al, 2017. Cancer stem cell mediated acquired chemoresistance in head and neck cancer can be abrogated by aldehyde dehydrogenase 1 A1 inhibition. Mol. Carcinog. 56 (2), 694–711. https://doi.org/10.1002/mc.22526.

Lapidot, T., Sirard, C., Vormoor, J., Murdoch, B., Hoang, T., Caceres-Cortes, J., et al, 1994. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature 367 (6464), 645–648. https://doi.org/10.1038/367645a0.

Leeman, J.E., Romesser, P.B., Zhou, Y., McBride, S., Riaz, N., Sherman, E., et al, 2017. Proton therapy for head and neck cancer: expanding the therapeutic window. Lancet Oncol. 18 (5), e254–e265. https://doi.org/10.1016/s1470-2045(17)30179-1.

Lewis Jr., J.S., Beadle, B., Bishop, J.A., Chernock, R.D., Colasacco, C., Lacchetti, C., et al, 2018. Human papillomavirus testing in head and neck carcinomas: guideline from the college of American pathologists. Arch. Pathol. Lab. Med. 142 (5), 559–597. https://doi.org/10.5858/arpa.2017-0286-CP.

Li, C., Heidt, D.G., Dalerba, P., Burant, C.F., Zhang, L., Adsay, V., et al, 2007. Identification of pancreatic cancer stem cells. Cancer Res. 67 (3), 1030–1037. https://doi.org/10.1158/0008-5472.Can-06-2030.

Li, X., Shen, Y., Di, B., Li, J., Geng, J., Lu, X., He, Z., 2012. Biological and clinical significance of p75NTR expression in laryngeal squamous epithelia and laryngocarcinoma. Acta Otolaryngol. 132 (3), 314–324. https://doi.org/10.3109/00016489.2011.639086.

Lim, Y.C., Kang, H.J., Kim, Y.S., Choi, E.C., 2012. All-trans-retinoic acid inhibits growth of head and neck cancer stem cells by suppression of Wnt/β-catenin pathway. Eur. J. Cancer 48 (17), 3310–3318. https://doi.org/10.1016/j.ejca.2012.04.013.

Liu, J.C., Shah, J.P., 2010. Surgical technique refinements in head and neck oncologic surgery. J. Surg. Oncol. 101 (8), 661–668. https://doi.org/10.1002/jso.21454.

Lou, H., Dean, M., 2007. Targeted therapy for cancer stem cells: the patched pathway and ABC transporters. Oncogene 26, 1357. https://doi.org/10.1038/sj.onc.1210200.

Luukkaa, M., Minn, H., Aitasalo, K., Kronqvist, P., Kulmala, J., Pyrhonen, S., Grenman, R., 2003. Treatment of squamous cell carcinoma of the oral cavity, oropharynx and hypopharynx–an analysis of 174 patients in south western Finland. Acta Oncol. 42 (7), 756–762.

Mader, C., 2007. The biology of cancer. Yale J. Biol. Med. 80 (2). 91 91.

Maeda, E., Akahane, M., Kiryu, S., Kato, N., Yoshikawa, T., Hayashi, N., et al, 2009. Spectrum of Epstein-Barr virus-related diseases: a pictorial review. Jpn. J. Radiol. 27 (1), 4–19. https://doi.org/10.1007/s11604-008-0291-2.

Mallick, I., Waldron, J.N., 2009. Radiation therapy for head and neck cancers. Semin. Oncol. Nurs. 25 (3), 193–202. https://doi.org/10.1016/j.soncn.2009.05.002.

Marcato, P., Dean, C.A., Giacomantonio, C.A., Lee, P.W., 2011. Aldehyde dehydrogenase: its role as a cancer stem cell marker comes down to the specific isoform. Cell Cycle 10 (9), 1378–1384. https://doi.org/10.4161/cc.10.9.15486.

Margaritescu, C., Pirici, D., Simionescu, C., Stepan, A., 2011. The utility of CD44, CD117 and CD133 in identification of cancer stem cells (CSC) in oral squamous cell carcinomas (OSCC). Rom. J. Morphol. Embryol. 52 (3 Suppl), 985–993.

Martin, H., Del Valle, B., Ehrlich, H., Cahan, W.G., 1951. Neck dissection. Cancer 4 (3), 441–499.

Marur, S., Forastiere, A.A., 2008. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clin. Proc. 83 (4), 489–501. https://doi.org/10.4065/83.4.489.

Marur, S., Forastiere, A.A., 2016. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin. Proc. 91 (3), 386–396. https://doi.org/10.1016/j.mayocp.2015.12.017.

Massard, C., Deutsch, E., Soria, J.C., 2006. Tumour stem cell-targeted treatment: elimination or differentiation. Ann. Oncol. 17 (11), 1620–1624. https://doi.org/10.1093/annonc/mdl074.

Mazeron, J.J., Ardiet, J.M., Haie-Meder, C., Kovacs, G., Levendag, P., Peiffert, D., et al, 2009. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. Radiother. Oncol. 91 (2), 150–156. https://doi.org/10.1016/j.radonc.2009.01.005.

McQuestion, M., Fitch, M.I., 2016. Patients' experience of receiving radiation treatment for head and neck cancer: Before, during and after treatment. Can. Oncol. Nurs. J./Revue canadienne de soins infirmiers en oncologie 26 (4), 11.

Mehanna, H., West, C.M., Nutting, C., Paleri, V., 2010. Head and neck cancer–Part 2: Treatment and prognostic factors. BMJ 341, c4690. https://doi.org/10.1136/bmj.c4690.

Mendenhall, W.M., Villaret, D.B., Amdur, R.J., Hinerman, R.W., Mancuso, A.A., 2002. Planned neck dissection after definitive radiotherapy for squamous cell carcinoma of the head and neck. Head Neck 24 (11), 1012–1018. https://doi.org/10.1002/hed.10187.

Menvielle, G., Luce, D., Goldberg, P., Bugel, I., Leclerc, A., 2004. Smoking, alcohol drinking and cancer risk for various sites of the larynx and hypopharynx. A case-control study in France. Eur. J. Cancer Prev. 13 (3), 165–172.

Mizrak, D., Brittan, M., Alison, M., 2008. CD133: molecule of the moment. J. Pathol. 214 (1), 3–9. https://doi.org/10.1002/path.2283.

Morel, A.-P., Lièvre, M., Thomas, C., Hinkal, G., Ansieau, S., Puisieux, A., 2008. Generation of breast cancer stem cells through epithelial-mesenchymal transition. PLoS ONE 3 (8), e2888. https://doi.org/10.1371/journal.pone.0002888.

Morrison, R., Schleicher, S.M., Sun, Y., Niermann, K.J., Kim, S., Spratt, D.E., et al, 2011. Targeting the mechanisms of resistance to chemotherapy and radiotherapy with the cancer stem cell hypothesis. J. Oncol. 2011, 941876. https://doi.org/10.1155/2011/941876.

Morrison, S.J., Qian, D., Jerabek, L., Thiel, B.A., Park, I.K., Ford, P.S., et al, 2002. A genetic determinant that specifically regulates the frequency of hematopoietic stem cells. J. Immunol. 168 (2), 635–642.

Mortensen, H.R., Overgaard, J., Specht, L., Overgaard, M., Johansen, J., Evensen, J.F., et al, 2012. Prevalence and peak incidence of acute and late normal tissue morbidity in the DAHANCA 6&7 randomised trial with accelerated radiotherapy for head and neck cancer. Radiother. Oncol. 103 (1), 69–75. https://doi.org/10.1016/j.radonc.2012.01.002.

Murillo-Sauca, O., Chung, M.K., Shin, J.H., Karamboulas, C., Kwok, S., Jung, Y.H., et al, 2014. CD271 is a functional and targetable marker of tumor-initiating cells in head and neck squamous cell carcinoma. Oncotarget 5 (16), 6854–6866. https://doi.org/10.18632/oncotarget.2269.

Muscat, J.E., Richie Jr., J.P., Thompson, S., Wynder, E.L., 1996. Gender differences in smoking and risk for oral cancer. Cancer Res. 56 (22), 5192–5197.

Nagano, O., Okazaki, S., Saya, H., 2013. Redox regulation in stem-like cancer cells by CD44 variant isoforms. Oncogene 32 (44), 5191–5198. https://doi.org/10.1038/onc.2012.638.

Nakamura, T., Endo, K., Kinoshita, S., 2007. Identification of human oral keratinocyte stem/progenitor cells by neurotrophin receptor p75 and the role of neurotrophin/p75 signaling. Stem Cells 25 (3), 628–638. https://doi.org/10.1634/stemcells.2006-0494.

Ng, I.O.L., Lam, K.Y., Ng, M., Kwong, D.L.W., Sham, J.S.T., 1998. Expression of P-glycoprotein, a multidrug-resistance gene product, is Induced by radiotherapy in patients with oral squamous cell carcinoma. Cancer 83 (5), 851–857. doi:10.1002/(SICI)1097-0142(19980901)83:5<851::AID-CNCR8>3.0.CO;2-L.

Nowell, P.C., 1976. The clonal evolution of tumor cell populations. Science 194 (4260), 23–28.

O'Neill, C.B., Baxi, S.S., Atoria, C.L., O'Neill, J.P., Henman, M.C., Sherman, E.J., et al, 2015. Treatment-related toxicities in older adults with head and neck cancer: a population-based analysis. Cancer 121 (12), 2083–2089. https://doi.org/10.1002/cncr.29262.

Obid, R., Redlich, M., Tomeh, C., 2019. The Treatment of Laryngeal Cancer. Oral Maxillofac. Surg. Clin. North Am. 31 (1), 1–11. https://doi.org/10.1016/j.coms.2018.09.001.

Ogawa, K., Yoshioka, Y., Isohashi, F., Seo, Y., Yoshida, K., Yamazaki, H., 2013. Radiotherapy targeting cancer stem cells: current views and future perspectives. Anticancer Res. 33 (3), 747–754.

Okumura, T., Shimada, Y., Imamura, M., Yasumoto, S., 2003. Neurotrophin receptor p75(NTR) characterizes human esophageal keratinocyte stem cells in vitro. Oncogene 22 (26), 4017–4026. https://doi.org/10.1038/sj.onc.1206525.

Okura, M., Aikawa, T., Sawai, N.Y., Iida, S., Kogo, M., 2009. Decision analysis and treatment threshold in a management for the N0 neck of the oral cavity carcinoma. Oral Oncol. 45 (10), 908–911. https://doi.org/10.1016/j.oraloncology.2009.03.013.

Overgaard, J., Mohanti, B.K., Begum, N., Ali, R., Agarwal, J.P., Kuddu, M., et al, 2010. Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): a randomised, multicentre trial. Lancet Oncol. 11 (6), 553–560. https://doi.org/10.1016/s1470-2045(10)70072-3.

Park, C.H., Bergsagel, D.E., McCulloch, E.A., 1971. Mouse myeloma tumor stem cells: a primary cell culture assay. J. Natl. Cancer Inst. 46 (2), 411–422.

Patel, R.S., Goldstein, D.P., Brown, D., Irish, J., Gullane, P.J., Gilbert, R.W., 2010. Circumferential pharyngeal reconstruction: history, critical analysis of techniques, and current therapeutic recommendations. Head Neck 32 (1), 109–120. https://doi.org/10.1002/hed.21169.

PDQ-Adult-Treatment-Editorial-Board, 2018. Laryngeal Cancer Treatment (Adult) (PDQ®): Health Professional Version Retrieved from <https://www.ncbi.nlm.nih.gov/books/NBK65746/>.

Pellitteri, P.K., Ferlito, A., Rinaldo, A., Shah, J.P., Weber, R.S., Lowry, J., et al, 2006. Planned neck dissection following chemoradiotherapy for advanced head and neck cancer: is it necessary for all? Head Neck 28 (2), 166–175. https://doi.org/10.1002/hed.20302.

Pfister, D.G., Laurie, S.A., Weinstein, G.S., Mendenhall, W.M., Adelstein, D.J., Ang, K.K., et al, 2006. American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. J. Clin. Oncol. 24 (22), 3693–3704. https://doi.org/10.1200/jco.2006.07.4559.

Piattelli, A., Fioroni, M., Iezzi, G., Perrotti, V., Stellini, E., Piattelli, M., Rubini, C., 2006. CD10 expression in stromal cells of oral cavity squamous cell carcinoma: a clinic and pathologic correlation. Oral Dis. 12 (3), 301–304. https://doi.org/10.1111/j.1601-0825.2005.01196.x.

Piselli, P., Serraino, D., Segoloni, G.P., Sandrini, S., Piredda, G.B., Scolari, M.P., et al, 2013. Risk of de novo cancers after transplantation: results from a cohort of 7217 kidney transplant recipients, Italy 1997–2009. Eur. J. Cancer 49 (2), 336–344. https://doi.org/10.1016/j.ejca.2012.09.013.

Poeta, M.L., Manola, J., Goldwasser, M.A., Forastiere, A., Benoit, N., Califano, J.A., et al, 2007. TP53 mutations and survival in squamous-cell carcinoma of the head and neck. N. Engl. J. Med. 357 (25), 2552–2561. https://doi.org/10.1056/NEJMoa073770.

Price, K.A.R., Cohen, E.E., 2012. Current treatment options for metastatic head and neck cancer. Curr. Treat. Options Oncol. 13 (1), 35–46. https://doi.org/10.1007/s11864-011-0176-y.

Prince, M.E., Sivanandan, R., Kaczorowski, A., Wolf, G.T., Kaplan, M.J., Dalerba, P., et al, 2007. Identification of a subpopulation of cells with cancer stem cell properties in head and neck squamous cell carcinoma. Proc. Natl. Acad. Sci. USA 104 (3), 973–978. https://doi.org/10.1073/pnas.0610117104.

Rabkin, D., Chhieng, D.C., Miller, M.B., Jennings, T., Feustel, P., Steinisrer, J., Parnes, S.M., 1995. P-Glycoprotein expression in the squamous cell carcinoma of the tongue base. Laryngoscope 105 (12), 1294–1299. https://doi.org/10.1288/00005537-199512000-00006.

Ragin, C.C., Langevin, S.M., Marzouk, M., Grandis, J., Taioli, E., 2011. Determinants of head and neck cancer survival by race. Head Neck 33 (8), 1092–1098. https://doi.org/10.1002/hed.21584.

Reategui, E.P., de Mayolo, A.A., Das, P.M., Astor, F.C., Singal, R., Hamilton, K.L., et al, 2006. Characterization of CD44v3-containing isoforms in head and neck cancer. Cancer Biol. Ther. 5 (9), 1163–1168.

Rettig, E.M., D'Souza, G., 2015. Epidemiology of head and neck cancer. Surg. Oncol. Clin. N. Am. 24 (3), 379–396. https://doi.org/10.1016/j.soc.2015.03.001.

Reya, T., Morrison, S.J., Clarke, M.F., Weissman, I.L., 2001. Stem cells, cancer, and cancer stem cells. Nature 414, 105. https://doi.org/10.1038/35102167.

Ricci-Vitiani, L., Lombardi, D.G., Pilozzi, E., Biffoni, M., Todaro, M., Peschle, C., De Maria, R., 2007. Identification and expansion of human colon-cancer-initiating cells. Nature 445 (7123), 111–115. https://doi.org/10.1038/nature05384.

Rinaldo, A., Ferlito, A., Silver, C.E., 2008. Early history of neck dissection. Eur. Arch. Otorhinolaryngol. 265 (12), 1535–1538. https://doi.org/10.1007/s00405-008-0706-9.

Robbins, K.T., Clayman, G., Levine, P.A., Medina, J., Sessions, R., Shaha, A., et al, 2002. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch. Otolaryngol. Head Neck Surg. 128 (7), 751–758.

Rossi, D.J., Jamieson, C.H.M., Weissman, I.L., 2008. Stems cells and the pathways to aging and cancer. Cell 132 (4), 681–696. https://doi.org/10.1016/j.cell.2008.01.036.

Sailer, M.H., Gerber, A., Tostado, C., Hutter, G., Cordier, D., Mariani, L., Ritz, M.F., 2013. Non-invasive neural stem cells become invasive in vitro by combined FGF2 and BMP4 signaling. J. Cell Sci. 126 (Pt 16), 3533–3540. https://doi.org/10.1242/jcs.125757.

Sampieri, K., Fodde, R., 2012. Cancer stem cells and metastasis. Semin. Cancer Biol. 22 (3), 187–193.

Sanchez-Tillo, E., Lazaro, A., Torrent, R., Cuatrecasas, M., Vaquero, E.C., Castells, A., et al, 2010. ZEB1 represses E-cadherin and induces an EMT by recruiting the SWI/SNF chromatin-remodeling protein BRG1. Oncogene 29 (24), 3490–3500. https://doi.org/10.1038/onc.2010.102.

Sankaranarayanan, R., 1990. Oral cancer in India: an epidemiologic and clinical review. Oral Surg. Oral Med. Oral Pathol. 69 (3), 325–330.

Saranath, D., Chang, S.E., Bhoite, L.T., Panchal, R.G., Kerr, I.B., Mehta, A.R., et al, 1991. High frequency mutation in codons 12 and 61 of H-ras oncogene in chewing tobacco-related human oral carcinoma in India. Br. J. Cancer 63 (4), 573–578.

Satpute, P.S., Hazarey, V., Ahmed, R., Yadav, L., 2013. Cancer stem cells in head and neck squamous cell carcinoma: a review. Asian Pac. J. Cancer Prev. 14 (10), 5579–5587.

Schlecht, N.F., Franco, E.L., Pintos, J., Kowalski, L.P., 1999. Effect of smoking cessation and tobacco type on the risk of cancers of the upper aero-digestive tract in Brazil. Epidemiology 10 (4), 412–418.

Secretan, B., Straif, K., Baan, R., Grosse, Y., El Ghissassi, F., Bouvard, V., et al, 2009. A review of human carcinogens–Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 10 (11), 1033–1034.

Shah, A., Patel, S., Pathak, J., Swain, N., Kumar, S., 2014. The evolving concepts of cancer stem cells in head and neck squamous cell carcinoma. Sci. World J. 2014, 8. https://doi.org/10.1155/2014/842491.

Shah, S.B., Sharma, S., D'Cruz, A.K., 2016. Head and neck oncology: The Indian scenario. South Asian J Cancer 5 (3), 104–105. https://doi.org/10.4103/2278-330x.187572.

Shakib, K., Soskic, V., 2011. Stem cells in head and neck squamous cell carcinoma. Br. J. Oral Maxillofac. Surg. 49, S99. https://doi.org/10.1016/j.bjoms.2011.03.212.

Sharafinski, M.E., Ferris, R.L., Ferrone, S., Grandis, J.R., 2010. Epidermal growth factor receptor targeted therapy of squamous cell carcinoma of the head and neck. Head Neck 32 (10), 1412–1421. https://doi.org/10.1002/hed.21365.

Sharma, D., Koshy, G., Grover, S., Sharma, B., 2017. Sentinel Lymph Node Biopsy: a new approach in the management of head and neck cancers. Sultan Qaboos Univ. Med. J. 17 (1), e3–e10. https://doi.org/10.18295/squmj.2016.17.01.002.

Shibuya, H., 2009. Current status and perspectives of brachytherapy for head and neck cancer. Int. J. Clin. Oncol. 14 (1), 2–6. https://doi.org/10.1007/s10147-008-0859-y.

Shin, D.M., Kim, J., Ro, J.Y., Hittelman, J., Roth, J.A., Hong, W. K., Hittelman, W.N., 1994. Activation of p53 gene expression in premalignant lesions during head and neck tumorigenesis. Cancer Res. 54 (2), 321–326.

Signore, M., Ricci-Vitiani, L., De Maria, R., 2013. Targeting apoptosis pathways in cancer stem cells. Cancer Lett. 332 (2), 374–382. https://doi.org/10.1016/j.canlet.2011.01.013.

Silverman Jr., S., Gorsky, M., Lozada-Nur, F., Giannotti, K., 1991. A prospective study of findings and management in 214 patients with oral lichen planus. Oral Surg. Oral Med. Oral Pathol. 72 (6), 665–670.

Simard, E.P., Torre, L.A., Jemal, A., 2014. International trends in head and neck cancer incidence rates: differences by country, sex and anatomic site. Oral Oncol. 50 (5), 387–403. https://doi.org/10.1016/j.oraloncology.2014.01.016.

Singh, A.K., Pandey, P., Tewari, M., Pandey, H.P., Gambhir, I.S., Shukla, H.S., 2016. Free radicals hasten head and neck cancer risk: a study of total oxidant, total antioxidant, DNA damage, and histological grade. J. Postgrad. Med. 62 (2), 96–101. https://doi.org/10.4103/0022-3859.180555.

Singh, S.K., Hawkins, C., Clarke, I.D., Squire, J.A., Bayani, J., Hide, T., et al, 2004. Identification of human brain tumour initiating cells. Nature 432, 396 https://www.nature.com/articles/nature03128#supplementary-information. https://doi.org/10.1038/nature03128.

Skowronek, J., 2017. Current status of brachytherapy in cancer treatment – short overview. J. Contemp. Brachytherapy 9 (6), 581–589. https://doi.org/10.5114/jcb.2017.72607.

Smith, A., Teknos, T.N., Pan, Q., 2013. Epithelial to mesenchymal transition in head and neck squamous cell carcinoma. Oral Oncol. 49 (4), 287–292. https://doi.org/10.1016/j.oraloncology.2012.10.009.

Sobreira, T.J., Marletaz, F., Simoes-Costa, M., Schechtman, D., Pereira, A.C., Brunet, F., et al, 2011. Structural shifts of aldehyde dehydrogenase enzymes were instrumental for the early evolution of retinoid-dependent axial patterning in metazoans. Proc. Natl. Acad. Sci. USA 108 (1), 226–231. https://doi.org/10.1073/pnas.1011223108.

Soltanian, S., Matin, M.M., 2011. Cancer stem cells and cancer therapy. Tumour Biol. 32 (3), 425–440. https://doi.org/10.1007/s13277-011-0155-8.

Song, J., Chang, I., Chen, Z., Kang, M., Wang, C.Y., 2010. Characterization of side populations in HNSCC: highly invasive, chemoresistant and abnormal Wnt signaling. PLoS ONE 5 (7), e11456. https://doi.org/10.1371/journal.pone.0011456.

Sterz, C.M., Kulle, C., Dakic, B., Makarova, G., Bottcher, M.C., Bette, M., et al, 2010. A basal-cell-like compartment in head and neck squamous cell carcinomas represents the invasive front of the tumor and is expressing MMP-9. Oral Oncol. 46 (2), 116–122. https://doi.org/10.1016/j.oraloncology.2009.11.011.

Stransky, N., Egloff, A.M., Tward, A.D., Kostic, A.D., Cibulskis, K., Sivachenko, A., et al, 2011. The mutational landscape of head and neck squamous cell carcinoma. Science 333 (6046), 1157–1160. https://doi.org/10.1126/science.1208130.

Stubblefield, M.D., 2017. Clinical evaluation and management of radiation fibrosis syndrome. Phys. Med. Rehabil. Clin. N. Am. 28 (1), 89–100. https://doi.org/10.1016/j.pmr.2016.08.003.

Su, J., Xu, X.H., Huang, Q., Lu, M.Q., Li, D.J., Xue, F., et al, 2011. Identification of cancer stem-like CD44+ cells in human nasopharyngeal carcinoma cell line. Arch. Med. Res. 42 (1), 15–21. https://doi.org/10.1016/j.arcmed.2011.01.007.

Sun, Y., Han, J., Lu, Y., Yang, X., Fan, M., 2012. Biological characteristics of a cell subpopulation in tongue squamous cell carcinoma. Oral Dis. 18 (2), 169–177. https://doi.org/10.1111/j.1601-0825.2011.01860.x.

Sun, Y., Yu, X.L., Luo, W., Lee, A.W., Wee, J.T., Lee, N., et al, 2014. Recommendation for a contouring method and atlas of organs at risk in nasopharyngeal carcinoma patients receiving intensity-modulated radiotherapy. Radiother. Oncol. 110 (3), 390–397. https://doi.org/10.1016/j.radonc.2013.10.035.

Sundvall, M., Karrila, A., Nordberg, J., Grenman, R., Elenius, K., 2010. EGFR targeting drugs in the treatment of head and neck squamous cell carcinoma. Expert Opin Emerg. Drugs 15 (2), 185–201. https://doi.org/10.1517/14728211003716442.

Surucu, M., Shah, K.K., Roeske, J.C., Choi, M., Small Jr., W., Emami, B., 2017. Adaptive radiotherapy for head and neck cancer. Technol. Cancer Res. Treat. 16 (2), 218–223. https://doi.org/10.1177/1533034616662165.

Swann, J.B., Smyth, M.J., 2007. Immune surveillance of tumors. J. Clin. Invest. 117 (5), 1137–1146. https://doi.org/10.1172/jci31405.

Taberna, M., Rullan, A.J., Hierro, C., Navarro, V., Vazquez, S., Lozano, A., et al, 2015. Late toxicity after radical treatment for locally advanced head and neck cancer. Oral Oncol. 51 (8), 795–799. https://doi.org/10.1016/j.oraloncology.2015.05.002.

Tabor, M.H., Clay, M.R., Owen, J.H., Bradford, C.R., Carey, T.E., Wolf, G.T., Prince, M.E., 2011. Head and neck cancer stem cells: the side population. Laryngoscope 121 (3), 527–533. https://doi.org/10.1002/lary.21032.

Taipale, J., Beachy, P.A., 2001. The Hedgehog and Wnt signalling pathways in cancer. Nature 411 (6835), 349–354. https://doi.org/10.1038/35077219.

Takahashi-Yanaga, F., Kahn, M., 2010. Targeting Wnt signaling: can we safely eradicate cancer stem cells? Clin. Cancer Res. 16 (12), 3153–3162. https://doi.org/10.1158/1078-0432.Ccr-09-2943.

Takebe, N., Harris, P.J., Warren, R.Q., Ivy, S.P., 2011. Targeting cancer stem cells by inhibiting Wnt, Notch, and Hedgehog pathways. Nat. Rev. Clin. Oncol. 8 (2), 97–106. https://doi.org/10.1038/nrclinonc.2010.196.

Thomas, S.J., MacLennan, R., 1992. Slaked lime and betel nut cancer in Papua New Guinea. Lancet 340 (8819), 577–578.

Thompson, L.D.R., Bishop, J.A., 2019. Head and neck pathology. In: Foundations of diagnostic pathology. Retrieved from <http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=1697179>

Thun, M., Peto, R., Boreham, J., Lopez, A.D., 2012. Stages of the cigarette epidemic on entering its second century. Tob. Control 21 (2), 96–101. https://doi.org/10.1136/tobaccocontrol-2011-050294.

Tobias, J.S., 1994. Cancer of the head and neck. BMJ 308 (6934), 961–966.

Todaro, M., Alea, M.P., Di Stefano, A.B., Cammareri, P., Vermeulen, L., Iovino, F., et al, 2007. Colon cancer stem cells dictate tumor growth and resist cell death by production of interleukin-4. Cell Stem Cell 1 (4), 389–402. https://doi.org/10.1016/j.stem.2007.08.001.

Todd, R., Wong, D.T., 1999. Oncogenes. Anticancer Res. 19 (6a), 4729–4746.

Toledano, I., Graff, P., Serre, A., Boisselier, P., Bensadoun, R.-J., Ortholan, C., et al, 2012. Intensity-modulated radiotherapy in head and neck cancer: results of the prospective study GORTEC 2004–03. Radiother. Oncol. 103 (1), 57–62. https://doi.org/10.1016/j.radonc.2011.12.010.

Torre, C., Wang, S.J., Xia, W., Bourguignon, L.Y.W., 2010. Reduction of hyaluronan-CD44-mediated growth, migration, and cisplatin resistance in head and neck cancer due to inhibition of Rho kinase and PI-3 kinase signaling. Arch. Otolaryngol. Head Neck Surg. 136 (5), 493–501. https://doi.org/10.1001/archoto.2010.25.

Valko, M., Leibfritz, D., Moncol, J., Cronin, M.T., Mazur, M., Telser, J., 2007. Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol. 39 (1), 44–84. https://doi.org/10.1016/j.biocel.2006.07.001.

van der Waal, I., 2009. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. Oral Oncol. 45 (4–5), 317–323. https://doi.org/10.1016/j.oraloncology.2008.05.016.

van Leeuwen, M.T., Grulich, A.E., McDonald, S.P., McCredie, M. R., Amin, J., Stewart, J.H., et al, 2009. Immunosuppression and other risk factors for lip cancer after kidney transplantation. Cancer Epidemiol. Biomarkers Prev. 18 (2), 561–569. https://doi.org/10.1158/1055-9965.Epi-08-0919.

Vermorken, J.B., Mesia, R., Rivera, F., Remenar, E., Kawecki, A., Rottey, S., et al, 2008. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N. Engl. J. Med. 359 (11), 1116–1127. https://doi.org/10.1056/NEJMoa0802656.

Vigneswaran, N., Williams, M.D., 2014. Epidemiologic trends in head and neck cancer and aids in diagnosis. Oral Maxillofac. Surg. Clin. North Am. 26 (2), 123–141. https://doi.org/10.1016/j.coms.2014.01.001.

Vineis, P., Alavanja, M., Buffler, P., Fontham, E., Franceschi, S., Gao, Y.T., et al, 2004. Tobacco and cancer: recent epidemiological evidence. J. Natl Cancer Inst. 96 (2), 99–106.

Vissink, A., Mitchell, J.B., Baum, B.J., Limesand, K.H., Jensen, S.B., Fox, P.C., et al, 2010. Clinical management of salivary gland hypofunction and xerostomia in head-and-neck cancer patients: successes and barriers. Int. J. Radiat. Oncol. Biol. Phys. 78 (4), 983–991. https://doi.org/10.1016/j.ijrobp.2010.06.052.

Visus, C., Wang, Y., Lozano-Leon, A., Ferris, R.L., Silver, S., Szczepanski, M.J., et al, 2011. Targeting ALDH(bright) human carcinoma-initiating cells with ALDH1A1-specific $CD8^+$ T cells. Clin. Cancer Res. 17 (19), 6174–6184. https://doi.org/10.1158/1078-0432.CCR-11-1111.

Vlashi, E., McBride, W.H., Pajonk, F., 2009. Radiation responses of cancer stem cells. J. Cell. Biochem. 108 (2), 339–342. https://doi.org/10.1002/jcb.22275.

Wang, S.J., Wong, G., de Heer, A.M., Xia, W., Bourguignon, L.Y., 2009. CD44 variant isoforms in head and neck squamous cell carcinoma progression. Laryngoscope 119 (8), 1518–1530. https://doi.org/10.1002/lary.20506.

Wang, X., Eisbruch, A., 2016. IMRT for head and neck cancer: reducing xerostomia and dysphagia. J Radiat Res 57 (S1), i69–i75. https://doi.org/10.1093/jrr/rrw047.

Weijers, M., Ten Hove, I., Allard, R.H., Bezemer, D.P., van der Waal, I., 2008. Patients with oral cancer developing from pre-existing oral leukoplakia: do they do better than those with de novo oral cancer? J. Oral Pathol. Med. 37 (3), 134–136. https://doi.org/10.1111/j.1600-0714.2007.00601.x.

Wheless, S.A., McKinney, K.A., Zanation, A.M., 2010. A prospective study of the clinical impact of a multidisciplinary head and neck tumor board. Otolaryngol. Head Neck Surg. 143 (5), 650–654. https://doi.org/10.1016/j.otohns.2010.07.020.

Wicha, M.S., Liu, S., Dontu, G., 2006. Cancer stem cells: an old idea—A paradigm shift. Cancer Res. 66 (4), 1883–1890. https://doi.org/10.1158/0008-5472.CAN-05-3153.

Widschwendter, M., Fiegl, H., Egle, D., Mueller-Holzner, E., Spizzo, G., Marth, C., et al, 2007. Epigenetic stem cell signature in cancer. Nat. Genet. 39 (2), 157–158. https://doi.org/10.1038/ng1941.

Wolf, G.T., Fisher, S.G., Hong, W.K., Hillman, R., Spaulding, M., Laramore, G.E., et al, 1991. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N. Engl. J. Med. 324 (24), 1685–1690. https://doi.org/10.1056/nejm199106133242402.

Wong, R.J., Shah, J.P., 2010. The role of the head and neck surgeon in contemporary multidisciplinary treatment programs for advanced head and neck cancer. Curr. Opin. Otolaryngol. Head Neck Surg. 18 (2), 79–82. https://doi.org/10.1097/MOO.0b013e32833782f0.

Wu, X., Chen, H., Wang, X., 2012. Can lung cancer stem cells be targeted for therapies? Cancer Treat. Rev. 38 (6), 580–588. https://doi.org/10.1016/j.ctrv.2012.02.013.

Wu, Y., Wu, P.Y., 2009. CD133 as a marker for cancer stem cells: progresses and concerns. Stem Cells Dev. 18 (8), 1127–1134. https://doi.org/10.1089/scd.2008.0338.

Wuthrick, E.J., Zhang, Q., Machtay, M., Rosenthal, D.I., Nguyen-Tan, P.F., Fortin, A., et al, 2015. Institutional clinical trial accrual volume and survival of patients with head and neck cancer. J. Clin. Oncol. 33 (2), 156–164. https://doi.org/10.1200/jco.2014.56.5218.

Xia, H., Cheung, W.K., Sze, J., Lu, G., Jiang, S., Yao, H., et al, 2010. miR-200a regulates epithelial-mesenchymal to stem-like transition via ZEB2 and beta-catenin signaling. J. Biol. Chem. 285 (47), 36995–37004. https://doi.org/10.1074/jbc.M110.133744.

Yadav, P., 2014. Recent advances in head and neck cancer reconstruction. Indian J. Plastic Surg.: Off. Publ. Assoc. Plastic Surg. India 47 (2), 185–190. https://doi.org/10.4103/0970-0358.138939.

Yan, H., Schlessinger, J., Chao, M.V., 1991. Chimeric NGF-EGF receptors define domains responsible for neuronal differentiation. Science 252 (5005), 561–563.

Yan, M., Yang, X., Wang, L., Clark, D., Zuo, H., Ye, D., et al, 2013. Plasma membrane proteomics of tumor spheres identify CD166 as a novel marker for cancer stem-like cells in head and neck squamous cell carcinoma. Mol. Cell. Proteomics: MCP 12 (11), 3271–3284. https://doi.org/10.1074/mcp.M112.025460.

Yanamoto, S., Kawasaki, G., Yamada, S., Yoshitomi, I., Kawano, T., Yonezawa, H., et al, 2011. Isolation and characterization of cancer stem-like side population cells in human oral cancer cells. Oral Oncol. 47 (9), 855–860. https://doi.org/10.1016/j.oraloncology.2011.06.501.

Yang, L., Ren, Y., Yu, X., Qian, F., Bian, B.S., Xiao, H.L., et al, 2014. ALDH1A1 defines invasive cancer stem-like cells and predicts poor prognosis in patients with esophageal squamous cell carcinoma. Mod. Pathol. 27 (5), 775–783. https://doi.org/10.1038/modpathol.2013.189.

Yang, M.-H., Hsu, D.S.-S., Wang, H.-W., Wang, H.-J., Lan, H.-Y., Yang, W.-H., et al, 2010. Bmi1 is essential in Twist1-induced epithelial–mesenchymal transition. Nat. Cell Biol. 12, 982 https://www.nature.com/articles/ncb2099#supplementary-information. https://doi.org/10.1038/ncb2099.

Yang, Z.F., Ho, D.W., Ng, M.N., Lau, C.K., Yu, W.C., Ngai, P., et al, 2008. Significance of CD90+ cancer stem cells in human liver cancer. Cancer Cell 13 (2), 153–166. https://doi.org/10.1016/j.ccr.2008.01.013.

Yaromina, A., Krause, M., Thames, H., Rosner, A., Krause, M., Hessel, F., et al, 2007. Pre-treatment number of clonogenic cells and their radiosensitivity are major determinants of local tumour control after fractionated irradiation. Radiother. Oncol. 83 (3), 304–310. https://doi.org/10.1016/j.radonc.2007.04.020.

Yu, C.C., Lo, W.L., Chen, Y.W., Huang, P.I., Hsu, H.S., Tseng, L. M., et al, 2011. Bmi-1 regulates snail expression and promotes metastasis ability in head and neck squamous cancer-derived ALDH1 positive cells. J. Oncol. 2011. https://doi.org/10.1155/2011/609259.

Zackrisson, B., Mercke, C., Strander, H., Wennerberg, J., Cavallin-Stahl, E., 2003. A systematic overview of radiation therapy effects in head and neck cancer. Acta Oncol. 42 (5–6), 443–461.

Zapperi, S., La Porta, C.A., 2012. Do cancer cells undergo phenotypic switching? The case for imperfect cancer stem cell markers. Sci. Rep. 2, 441. https://doi.org/10.1038/srep00441.

Zhang, P., Zhang, Y., Mao, L., Zhang, Z., Chen, W., 2009. Side population in oral squamous cell carcinoma possesses tumor stem cell phenotypes. Cancer Lett. 277 (2), 227–234. https://doi.org/10.1016/j.canlet.2008.12.015.

Zhao, Z.-L., Zhang, L., Huang, C.-F., Ma, S.-R., Bu, L.-L., Liu, J.-F., et al, 2016. NOTCH1 inhibition enhances the efficacy of conventional chemotherapeutic agents by targeting head neck cancer stem cell. Sci. Rep. 6, 24704 https://www.nature.com/articles/srep24704#supplementary-information. https://doi.org/10.1038/srep24704.

Zhou, L., Wei, X., Cheng, L., Tian, J., Jiang, J.J., 2007. CD133, one of the markers of cancer stem cells in Hep-2 cell line. Laryngoscope 117 (3), 455–460. https://doi.org/10.1097/01.mlg.0000251586.15299.35.