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# A radiobiological perspective on radioresistance or/and radiosensitivity of head and neck squamous cell carcinoma

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## ABSTRACT

**Background:** This article aimed to compile and summarize clinically relevant literature in radiation therapy, and to discuss the potential in radioresistant and radiosensitive head and neck cancer.

**Study Design:** Narrative review.

**Materials and methods:** Google Scholar, PubMed and the Cochrane Library were retrieved using combined key words such as "radiotherapy" and "head and neck cancer". Search strings additionally queried were "radioresistant", "radiosensitive", "head and neck region", "squamous cell carcinoma", in combination with Boolean Operators 'AND' and 'OR'. Subsequently, the resulting publications were included for review of the full text.

**Results:** Radiotherapeutic response currently in clinical observation referred to HNSCC scoping were selected into this review. The compiled mechanisms were then detailed concerning on the clinical significance, biological characteristics, and molecular function.

**Conclusions:** Brachytherapy or/and external-beam radiotherapy are crucial for treating HNSCC, especially the early stage patients, but in patients with locally advanced tumors, their outcome with radiation therapy is poor due to obvious radioresistance. The curative effects mainly depend on the response of radiation therapy, so an updated review is needed to optimize further applications in HNSCC radiotherapy.

**Key words:** head and neck; squamous cell carcinoma; radiation therapy; radioresistance; radiosensitivity

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## Introduction

Head and neck cancer is a major public health issue, ranking the seventh most common in the world [1]. Among the 890,000 new cases of head and neck cancer worldwide in 2020, squamous cell carcinoma (HNSCC) encompasses around 90% of the tumors [2]. It is difficult to make an accurate census of the remaining 10% cases since they are not collected systematically at present. HNSCCs are divided into cancers of the oral cavity, oropharynx, hypopharynx, larynx and rhinopharynx (Fig. 1). Around 40% of these cancers are diagnosed when they are locally advanced. The incidence of HNSCC has fallen slightly in men but has increased in women over the last several years [1, 2]. The ethiopathogenesis is associated, on the one hand, with alcohol consumption and tobacco smoking; as well as, on the other hand, with viral superinfection by human papillomavirus (HPV) in cancers of the oropharynx and larynx [1, 3].

The management of HNSCC is multidisciplinary, and knowledge of the natural history is vital if patients are to be offered the best possible treatment. Radiation therapy is a cornerstone of HNSCC management both as an adjuvant and curative modality that may be given to an existing tumor or postoperatively, with or without chemotherapy or targeted therapy such as cetuximab, nivolumab and pembrolizumab. In recent years, the radiotherapy modality that has emerged as the new standard for the irradiation of HNSCC is intensity-modulated technique, which allows better sparing of healthy tissue, particularly the salivary glands [3, 4]. However, treatment of HNSCC patients is still burdened by a not yet satisfactory clinical outcome with a relatively high rate of severe radiotherapy-related toxicity (*e.g.*, radiodermatitis, mucositis, xerostomia, jaws osteoradionecrosis, dysphagia) and approximately 50% local recurrence at 3 years or metastatic recurrence [3, 5]. Given a poor prognosis and treatment regimen that is not very effective in this situation, radiobiology is therefore essential to enhance cancer radiosensitivity without increasing radioresistant profile.

Tumors of the same size and stage may respond differently to radiotherapy. Understanding the factors that influence the HNSCC radioresistance means that patients can be better cured. Radioresistance is a broad concept that includes numerous parameters. Previous studies have proved that these parameters that affect tumor response to radiation therapy in HNSCC cases are linked

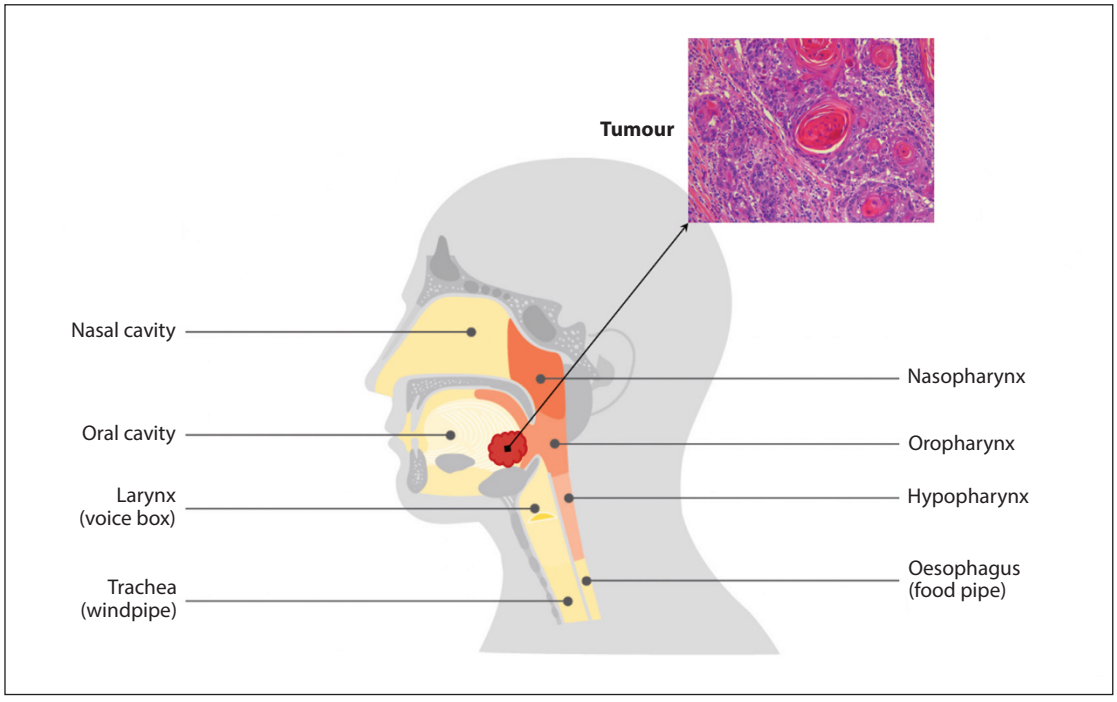


**Figure 1.** Major anatomical sites of head and neck squamous cell carcinoma (HNSCC)

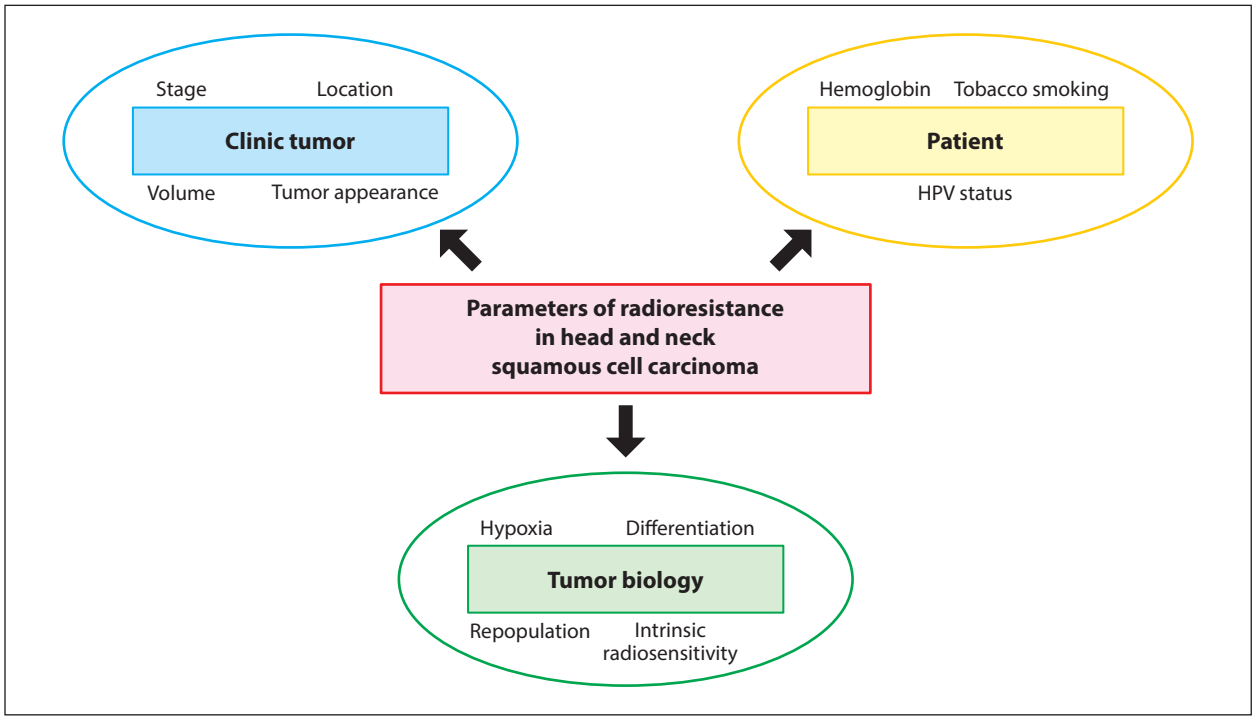


**Figure 2.** Graphic abstract of radioresistance parameters for head and neck squamous cell carcinoma (HNSCC). HPV — human papilloma virus

to the tumor clinical practice, patients themselves, and tumor biology (Fig. 2) [6, 7]. The purpose of this article is to review and summarize the potential avenues for overcoming HNSCC-related radioresistance and to describe the main mechanisms of radiosensitization involved in the HNSCC treatment by radiation therapy. Considering their gradually growing impact regarding surveillance and management of patients with HNSCC, periodic investigation is necessary for junior radiologist/oncologist education and to guide further progress of HNSCC radiotherapy.

## Materials and methods

The databanks of Google Scholar, PubMed and the Cochrane Library were retrieved using combined key words such as "radiation therapy" and "head and neck cancer". Search strings additionally queried were "radioresistant", "radiosensitive", "head and neck region", "squamous cell carcinoma", "radiotherapy", "radiosensitivity/radiosensitization", "radioresistance" in combination with Boolean Operators 'AND' and 'OR' to maximize yield of relevant topics. Subsequently, the resulting publications were included for review of the full text.

The authors did not perform a systematic literature search for this review. Most papers were selected manually at the discretion of the authors from a review of the contents of high-impact radiation oncology and cancer journals that had been published in past 20 years. Only publications released in English were considered.

Accordingly, a total of 269 research papers were identified in this scholarly review. Their titles were reviewed and selected for abstract screening. Applicable abstracts were then chosen for review of the full text. Eligible articles with respect to the topic were selected for subsequent analysis and discussion.

## Tumor size and location

Tumors that are larger and/or more locally invasive have a poorer prognosis [8]. This is partly due to worse sensitivity to treatment such as radiotherapy. Since radiation-induced cell death is a random event, as tumor volume increases, the probability of damaging all tumor cells decreases, despite a high total dose [9]. The dose-effect relationship is well established in HNSCCs; the higher the total dose, the higher the local control rate. However,

the total dose is limited by acute and late toxicity. Larger tumours are also more hypoxic, which may also partly explain their poorer radiosensitivity (Section *Hypoxia in tumors*). The location of the tumor also plays a role, for example, cancers of the oral cavity respond less well to radiotherapy than laryngeal cancers [10, 11]. Highly infiltrative tumors, which certainly have a greater potential for malignancy, are also less radiosensitive than general tumors. This may mean that surgery is preferred to radiotherapy in this type of tumor whenever possible.

## Intrinsic radiosensitivity, and the alpha/beta importance of fractionation

Description focuses here on the radiobiological parameters of squamous cell carcinomas, which represent the majority of anatomopathology in this location. The literature is abundant with data on the alpha/beta ratio of the linear-quadratic model, differences in radiation-dose fractionation and changes in therapeutic sequences [12-14]. The "intrinsic" radiobiology of each tumor is correlated with therapeutic response in a study using the survival fraction after 2-Gy irradiation [15].

The major parameter is tumor repopulation which is extremely rapid in HNSCCs. It has now been proven that interrupting treatment or unplanned re-treatment is deleterious for patients, and it is vital to maintain the fractionated therapeutic sequence. An interruption in treatment has now been shown to be a cause of therapeutic failure, particularly in terms of overall survival, with this effect being most marked in laryngeal cancers [16]. These parameters are also closely linked to tumor grade, and accelerated tumor repopulation can be also seen in well-differentiated tumors [17].

The alpha and beta parameters are difficult to assess in HNSCCs, hence their values vary from one study to another. The alpha/beta ratio is most frequently found to be 10 for tumor tissue [18]. For adjacent healthy tissue, it is most often about 3, which determines the importance of fractionation to maintain therapeutic efficacy, taking into account the therapeutic index between tumor control and limiting early toxicity. At the moment, intensity-modulated radiotherapy, a recommended irradiation technique for HNSCCs by the International Agency for Research on Cancer/National Comprehensive Cancer Network/American Academy of Otolaryngology–Head and Neck Surgery Foundation (IARC/NCCN/AAO–HNSF), allows organs at risk to be spared while maintaining satisfied therapeutic efficacy, similar to three-dimensional conformal techniques.

## Biological factors related to HNSCC patients

### Human papillomavirus (HPV)

Infection with human papillomavirus (HPV), particularly type 16, has been identified to be a risk factor for the development of HNSCC, particularly in the oropharynx [1, 19]. When $HPV^+$ HNSCC exists, its response to ionizing radiation is totally different from $HPV^-$ tumors. Roman and Aragones investigated the prognostic impact of this infection in a study of patients with squamous cell carcinoma of the oropharynx treated with irradiation, and the HPV infection was found in 60% of patients with an even distribution between men and women [20]. But in another study that performed rigorous testing for HPV, the proportion attributable to HPV by subsite of HNSCC was 3% for oral cavity cancers, 18% for oropharyngeal cancers, and 1% for laryngeal cancers [21]. In a retrospective study, Ang et al. discovered that the patients with $HPV^+$ oropharyngeal cancer had a better 3-year rate of overall survival (82.4%) compared with 57.1% in $HPV^-$ patients ($p < 0.001$) [22]. They found the probability of progression-free survival at 3 years was better in patients with HPV infection (73.7% *vs.* 43.4%, $p < 0.001$) [22]. These results were used to establish a recursive partitioning analysis (RPA) classification taking into account this infection, smoking and tumor and lymph node stage. Some scholar concluded that a substantial increase in radiation responsiveness in HPV(–) HNSCC in an autophagic adaptor p62-dependent manner; in contrast, the same treatment had a minimal effect on HPV(+) cells [23]. The degree of radioresistance and tumor progression of HPV-negative HNSCC, respectively correlated with autophagic activity and cytosolic levels of p62. The self-polymerizing activity of p62 was identified as the essential mechanism by which ubiquitinated caspase-8 was sequestered into aggresome-like

structures, without which irradiation fails to induce apoptosis in HNSCC [24].

### Cigarette smoking

While tobacco smoking as a major risk factor that is strongly associated with HNSCC initiation and progression, its role during radiotherapy also conditions the therapeutic response. Studies into the influence of smoking during radiotherapy indicated that local control of disease and overall survival rate were reduced in patients who smoked compared with non-smokers during treatment of HNSCC [25]. The biological explanation is related to the greater quantity of carboxyhemoglobin and the relevant tumor hypoxia [26]. In a prospective study of 178 patients with HNSCC tumors of current and former smokers showed perineural invasion significantly more often than tumors of never smokers [27]. This study warranted further research on perineural invasion in HNSCC with special emphasis on the impact of tobacco consumption to identify suitable candidates for therapeutic interventions. Moreover, perineural invasion as a marker for aggressive tumor growth, strongly linked with local recurrence and metastatic occurrence in advanced HNSCC because of attenuated responsiveness in radiotherapy. There is growing evidence of an association between neurotrophic factors and smoking. Current smoking and higher number of smoking years were associated with higher serum levels of brain-derived neurotrophic factor (BDNF), suggesting BDNF influences nicotine dependence [28]. Few existent radiobiological research studies concentrate on smoker affected by HNSCC with a radioresistant profile, therefore the mechanisms involved in the radiobiological response to smoking history are still poorly understood.

### Hemoglobin

Hemoglobin concentration in cancer patients have always been at the center of debate, especially in HNSCC, following the studies on erythropoietin and its association with the risk of thromboembolic events [29, 30]. Some studies have viewed the response to radiotherapy as a function of hemoglobin level, despite the thromboembolic risk established in 2003 for patients undergoing radiochemotherapy being in fact linked to an excessively high hemoglobin level [31–33]. Anemia was thus a recognized factor in worse response to radiotherapy in terms of lower local-regional control and overall survival reported by Maahs et al. [34] The interpretation is related to hypoxia, the mechanisms which are described in the dedicated paragraph. But a recent publication of long-term analysis of a study confirmed that erythropoietin treatment caused no improvement on response to radiotherapy, even though erythropoietin could raise the hemoglobin level in anemic patients with HNSCC [35]. In fact, in this phase III randomized clinical trial conducted by Radiation Therapy Oncology Group (RTOG) comparing a radiotherapy arm with erythropoietin and a radiotherapy arm alone, progression-free survival and overall survival were equivalent in both groups and the possibility of a detrimental effect of EPO could not be ruled out. However, the relationship between hemoglobin concentration, tumor oxygenation status and radioresistance is complex. Most anemic patients have tumors that are hypoxic, but the absence of anemia does not mean that the tumor is well oxygenated.

## The epidermal growth factor receptor (EGFR)

The epidermal growth factor receptor (EGFR/ Erb-B1/HER1) belongs to the human epidermal growth factor receptor (HER) family, and it is among the first tumor-associated antigens identified [36]. EGFR has been validated as a clinical target for several passive, non-immune therapeutics presently approved for the treatment of epithelial malignancies [37]. From molecular biological perspective, EGFR has three homologs: HER2 (Erb-B2/NEU), HER3 (Erb-B3), and HER4 (Erb-B4). These receptors share a high degree of homology in terms of primary structure. They are transmembrane receptors with an extracellular N-terminal domain carrying the ligand binding site, a transmembrane domain and an intracellular C-terminal domain carrying tyrosine kinase activity [38]. EGFR plays a major physiological role in the development of epithelial tissues and is present in a monomeric state on the cell surface. Activation of the receptor requires dimerization, either by homodimerization or heterodimerization (with HER2 in particular). This dimerization leads to phosphorylation of the intracellular kinase domain, activating various intracellular signalling pathways, resulting

in increased cell proliferation, invasion and migration, and reduced apoptosis [39].

In HNSCCs, the overexpression of EGFR has been observed in 80~100% of cases, depending on the series [40]. EGFR-mediated signalling pathways are a hot spot of cancer research in the field of targeted therapies. For treating HNSCC, the monoclonal antibody cetuximab has marketing authorization in combination with radiation therapy for locoregionally advanced forms [41]. Cetuximab is a chimeric monoclonal antibody directed against the extracellular domain of EGFR. Cetuximab blocks ligand binding, receptor dimerization and phosphorylation. The EGFR is then internalized and degraded in the lysosomes [42]. It is administered intravenously on a weekly basis, with prophylaxis using H1-antagonists and corticosteroids due to the risk of allergy (e.g., acneiform rash) [41, 43]. More than ever, EGFR is at the heart of the radioresistance process. Its overexpression is associated with a poor prognosis and, in particular, with recurrence after treatment, both *in vitro* and *in vivo* [44]. It should also be noted that EGFR can be activated by irradiation in the absence of ligand; and this effect has been found not only *in vitro*, but also *in vivo* in circulating tumor cells [45]. Irradiation acts as a phenomenon of cellular stress and activates EGFR even in the absence of ligand. The survival among cell proliferation-related pathways in HNSCC is therefore activated by irradiation, which reinforces the dominant idea of maintaining an uninterrupted therapeutic rhythm and sequence in this type of tumor.

## The sub-population of cancer stem cells

First described in leukemia in 1994, the presence of cancer stem cells (CSCs) has been demonstrated in many solid tumors, including glioblastoma, prostate, breast, colorectum, as well as head and neck cancer [46]. There are two hypotheses as to the origin of these CSCs: derived from healthy stem cells or produced by dedifferentiation of tumor cells. The specific characteristics of CSC, especially in terms of phenotype, vary according to each primary tumor site. They are defined as cells with the capacity to initiate tumorigenesis and proliferate in an unrestricted manner, the ability to preserve and renew themselves, and the potential to give rise to numerous parental progenitor cells [47]. A hierarchical model is accordingly established on the basis of this theory of CSCs, according to which tumors derive from adult stem cells that have acquired genetic and epigenetic variations that give them tumorigenic power while maintaining their capability for self-renewal [48]. Remarkably, this hierarchical model is now opposed to the stochastic model described historically [49].

Recently, the studies regarding CSC phenotype, plasticity, and oncogenic metabolism under ionizing radiation are booming [49]. Indeed, CSCs defy the commonly accepted rules of radiobiology. CSCs have a radioresistant profile, characterized with over-activated repair systems of DNA damage, redistribution of the cell cycle that towards a radioresistant phase (S to G0 phase), a strong capacity for tumor repopulation and cellular oxygenation independence [50]. These cells also have the capacity to invade and migrate, particularly in HNSCC [51]. The quality of the radiation is another crucial element. The relative biological effectiveness (RBE) of photon-based radiotherapy is low on CSCs [52]. Recent work by Oonishi et al. [53] unraveled that the use of carbon ions makes it possible to avoid the oxygen effect and thus to recover radiosensitivity.

## Invasion-migration and epithelial-mesenchymal transition

One of the major mechanisms of resistance to radiotherapy, and of distant metastatic recurrence, can be explained by the phenomenon of cell invasion-migration. Epithelial-mesenchymal transition (EMT) as well as its reversed process (i.e. mesenchymal-epithelial transition) are fundamental processes in embryonic development and tissue repair but confer malignant properties to carcinoma cells, being explained as CSC activity which have greater resistance to immunotherapy and radiochemotherapy [54]. CSCs are capable of adhering to the extracellular matrix, degrading it under the effect of proteases, and invading and migrating, within the organ itself or at a distance, thus creating metastases [55]. The initial process enabling cell migration is described as "a cell with an epithelial phenotype is transformed into a mesenchymal phenotype and acquires the ability to migrate", known in other words as epithelial-to-mesenchy-

mal transition. The membrane markers most frequently studied to characterize this transition are E-cadherin, epithelial phenotype, and the loss of its expression when the mesenchymal phenotype is acquired, N-cadherin and vimentin. Nuclear transcription factors such as Twist and Snail have also been examined using immune assays in the HNSCC subpopulation and are found in many malignant tumors [56, 57]. Invasion-migration is a process that can be activated through photon irradiation. There is activation of the EMT behavior, once again via the altered EGFR signaling pathway (*EGFR* tertiary mutations and amplification) [58]. In a study investigated by Zuo et al. [59], the loss of E-cadherin expression was found after radiotherapy, as was the modulation of matrix metalloproteinase secretion induced by irradiation. Carbon ion irradiation actually decreases the migration/invasion of CSCs, although the conventional radiotherapy promotes these processes under normoxia. The uniform distribution of reactive oxygen species (ROS) after X-rays regulates the mechanisms causing invasion/migration, which ROS concentrated in carbon ion tracks are unable to trigger [60].

## Hypoxia in tumors

Tumor oxygenation status appears to be a principal parameter in the response to ionizing radiation. Under hypoxic conditions, the effect of photon radiation (indirectly ionizing radiation that passes through the radical cascade) is much less because of the reduced production of ROS. The radical cascade can be potentiated or enhanced by the presence of oxygen. Hence, generally speaking, well-oxygenated tumors are more radiosensitive than hypoxic tumors. The high-energy photons used in radiotherapy exert their biological effects on the DNA molecule either directly or indirectly. The indirect effects, which are predominant, involve the formation of highly reactive free radicals which interact with the DNA and damage it. The presence of oxygen increases these indirect effects by prolonging the life of the free radicals. In addition, oxygen reduces the capacity of cells to repair sublethal radiation-induced DNA damage [61]. Other biological mechanisms also modulate the link between hypoxia and radiosensitivity, many signalling pathways are affected by hypoxia, for example those involved in angiogenesis or glucose transport [8, 61]. Tumor hypoxia may be chronic, developing as the tumor grows and limiting access to blood vessels, or acute in the event of localized interruption of blood flow [62].

The radiotherapy of HNSCC is affected in the absence of oxygen, or in hypoxic conditions, the production of radicals is significantly decreased, leading to fewer DNA breaks [63, 64]. On the basis of this radiobiological observation, a number of trials have focused on the modification of hypoxic parameters in HNSCC patients during irradiation via hyperbaric chambers, drugs modifying hypoxic parameters (e.g., nitromidazoles) [64]. A recent clinical study conducted by Hassan Metwally et al. [65] suggested that an improvement in loco-regional tumor control and overall survival in patients with advanced HNSCC who had been given the hypoxic radiosensitizer (nimorazole) in addition to accelerated fractionation radiotherapy; however, the results were incomplete and this study suffered from a small number of patients. The change in hypoxic parameters was most apparent in loco-regional control [odd ratio (OR) = 0.71, 95% CI: 0.63–0.80; $p < 0.001$]. More importantly, HPV infection does not alter the role of hypoxia microenvironment, because HPV-positive and HPV-positive HNSCC proliferating cells have the same response to radiotherapy. In addition, a decreasing hypoxic fraction following irradiation in the HPV-positive tumors could explain the lack of benefit from hypoxic modifiers observed in patients [66]. Meanwhile, linear energy transfer (LET) is also of major importance. As the LET of the particle used increases, the effect of hypoxia decreases. So, with high LTE particles such as carbon ions, irradiation under hypoxic and normoxic conditions is comparable. CSCs clustering in "hypoxic niches" with a dedicated microenvironment are closely linked to hypoxic conditions. They are therefore highly radioresistant tumor zones and, finally, the invasion-migration phenomenon may also be relevant to hypoxia, which favors EMT and therefore promotes invasion-migration.

## Hadrontherapy as a major therapeutic weapon for head and neck cancer

Hadrontherapy is defined as the application of particles of electromagnetic radiation for treatment. It is often referred to as carbon-ion radio-

therapy, proton radiotherapy or even particle beam radiotherapy, depending on the particle accelerated and used in the therapy. Hadrontherapy was originated in 1946 by Dr Robert R. Wilson, who first used protons to treat cancer [67]. The advantage of this technique is that it uses the specific ballistic and biological properties of heavy charged particles. When they travel through matter, these particles deposit very little energy at the beginning of their track. As they slow down, the energy deposited becomes maximum (Bragg peak) at the desired location, enabling maximum energy to be released in the target volume while sparing neighboring organs at risk [68]. Many particles have been studied in therapeutics. Given protons with a collimated heavy-ion microbeam have now been validated in clinical practice for targeted indications, carbon ions are promising and are the subject in HNSCC studies [69]. They have the advantage of having an RBE two to three times higher than photons or protons. This is determined by the ratio of the doses of reference radiation (photons) and the radiation under study (hadrons) producing the same biological effect. RBE values are plotted as a function of LET, and the RBE-LET relationship is used to evaluate different types of damage contributing to mammalian cell reproductive death. For carbon ion hadrontherapy, with an equivalent physical dose, irradiation induces two to three times more cell death than photons [70]. Biologically, carbon ion irradiation can achieve significant radiosensitization in HNSCC, based on clonogenicity data that survival fractions at 2 Gy (SF2) increasing from SF2 = 0.45 with photon irradiation to SF2 = 0.85 with carbon ion irradiation [71]. The effect of hadrontherapy is all the more interesting in that it enables radiosensitization of CSCs in a model derived from radioresistant laryngeal carcinoma. The work carried out by Oonishi et al. [53] showed that this type of irradiation eliminated the oxygen effect and thence maintained therapeutic efficacy in hypoxic areas. Since the charged particles are directly ionizing, the radical cascade which is normally potentiated by oxygen is no longer necessary. At the same time, hadrontherapy, unlike photon radiotherapy, inhibits chemotaxis and cell invasion. Furthermore, several series have reported the inhibition of the invasion and migration of radioresistant cancer cells in the larynx after carbon ion irradiation [72, 73]. In clinical terms, a study of carbon ion radiotherapy in Japan provides us with the most reliable data on its practical use. Based on a large-scale retrospective series, Kamada et al. [74] reported that this procedure is feasible in practice, with toxicities that remain entirely acceptable. The study published by Mizoe et al. [69] demonstrated good efficacy in local control as the therapeutic effectiveness for adenoid cystic carcinoma and malignant melanoma without severe morbidity of the normal tissues; and it remains for the moment the only prospective clinical study published on the use of hadrontherapy in cancers occurring in the head and neck region. Radiosensitization strategies for HNSCC are summarized in Tab. 1.

## Radiation-sensitizing nanoparticles

Nanoparticles are defined as particles < 100 nm in diameter, with chemical, magnetic and structural properties specific to their composition. Their utility in the medical field is vast and currently expanding rapidly, with applications in imaging, therapeutics (cardiovascular and degenerative diseases, infectious pathologies, cancer) and theranostics. This technique looks very promising and is the subject of both radiobiological and clinical studies in the field of head and neck cancer. More than ever, it combines physical and biological knowledge, which are truly inseparable in the radiosensitization strategy for head and neck cancer cells.

In radiation therapy, the use of nanoparticles with high electron density makes it possible to accentuate the physical phenomena of the photo-electric effects and Compton and Rayleigh scattering, and thus the consequences on a radiobiological scale. Nanoparticles can be guided to the tumor using a variety of strategies. Nanoparticles can be connected to a pharmacological vector (labelled nanoparticles) that recognizes a membranous target to facilitate their internalization. The "enhanced permeability ratio (EPR)" effect also enables them to penetrate the tumor more easily due to a difference in vascular permeability between healthy and tumor tissues, conferring much better diffusion of particles in tumor tissues [83].

Nowadays, gold and gadolinium nanoparticles are the most widely used. Gold particles can be associated with carrier molecules because of their high affinity. Simultaneously, gadolinium particles have the advantage of being able to be chelating agents

**Table 1.** Principal radiosensitization strategies for head and neck cancers

| Reference | Type of study | Strategy | Number of studies | Sample size | Local control | Overall survival | Metastases | Comments |
|---|---|---|---|---|---|---|---|---|
| Bonner et al. [41, 43] | RCT phase 3 | With or without anti-EGFR (cetuximab) | 2 | 424 | +13%* over 3 years | +9%* over 5 years | NS | Correlated response with skin rash |
| Haddad et al. [75] | RCT phase 3 | Sequential chemoradiotherapy | 1 | 145 | NS | NS | NM | No difference in local control and overall survival |
| Cohen et al. [76] | RCT phase 3 | Chemoradiotherapy alone | 1 | 285 | NS | NS | Positive for induction | Cancer-related deaths > concomitant arm; non-cancer-related deaths > induction arm |
| Gu et al. [77] | Meta-analysis of published data | Effect of amifostine in HNSCC patients treated with radiation | 17 | 1167 | NS | NM | NM | Reduced toxicity if radiotherapy alone (three-dimensional radiotherapy without intensity modulation) |
| Overgaard et al. [64] | Meta-analysis of published data | With or without hypoxia-sensitising agents | 18 | 3255 | Positive: OR: 0.71 (95% CI: 0.63–0.80)* | NS | NS | Long-term peripheral neuropathy (misonidazole) |
| Lambin et al. [78] | Meta-analysis of published data | With or without erythropoietin | 5 | 1397 | NS | Negative: OR: 0.73 (95% CI: 0.58-0.91)* | NM | Lower overall and progression-free survival with erythropoietin. Not recommended in clinical practice |
| Bourhis et al. [79] | Meta-analysis of individual data | With or without radioprotector (amifostine) | 12 | 1119 | NS | NS | NM | No negative impact on overall and progression-free survival |
| Bourhis et al. [80] | Meta-analysis of individual data | Modifications to fractionation versus normofractionation | 15 | 6515 | +6.4%* over 5 years | +3.4%* over 5 years | NS | Hyperfractionation > accelerated radiotherapy |
| Pignon et al. [81] | Meta-analysis of individual data | With or without concomitant chemotherapy | 87 | 16485 | +9.3%* over 5 years | +4.5%* over 5 years | –2.5%* over 5 years | Concomitant > induction *in situ* and postoperative cisplatin monotherapy |
| Blanchard et al. [82] | Meta-analysis of individual data | Induction chemotherapy TPF versus PF | 5 | 1772 | +7.4%* over 5 years | +7.4%* over 5 years | –6.4%* over 5 years | Poorly defined role in relation to concomitant chemoradiotherapy |

*Statistically significant ($p < 0.05$). CI — confidence intervals; EGFR — epidermal growth factor receptor; NM — not mentioned; NS — not significant; OR — odds ratio; PF — cisplatin plus fluorouracil; RCT — randomized controlled trial; TPF — taxane (docetaxel or paclitaxel), cisplatin, and fluorouracil

for molecular imaging in nuclear medicine [84]. In addition to DNA breaks, the biological effects discovered are membrane alterations and functions on the cell cycle, mitochondria and tumor vascularization. Few toxicities are associated with this type of treatment, apart from high concentrations of nanoparticles [85]. More often than not, they are captured by the phagocytic system.

Direct intratumoral injection of nanoparticles is possible, particularly in accessible areas such as head and neck. The utility of these nanoparticles remains an area of research, but benefits from firm preclinical data (*vitro*, *vivo*) and phase I trials are underway.

## Conclusion and also opening remarks

HNSCCs are the cancers where the parameters influencing radiosensitivity/radioresistance have been studied most extensively. Some parameters are linked to the clinic properties of tumor (embracing volume, stage, location, tumor appearance, etc.), others to the patient (hemoglobin concentration, tobacco smoking, HPV-infection status, etc.) and others to the tumor biology (stemness, differentiation, hypoxia, repopulation, intrinsic radiosensitivity, etc.).

Concomitant chemoradiotherapy is one of the reference treatments for improving clinical outcomes in patients with locally advanced HNSCC, and this technique has to contend with the radioresistance of this population of cancer cells. While the technological development of this treatment over the last ten years has made it possible to enhance therapeutic efficacy and improve tolerance, this cannot be achieved without detailed knowledge of the biological parameters involved. The combination of radiotherapy and cetuximab (anti-EGFR) is another validated option, but with only a few RCTs, it is less robust. Modifications to fractionation are another validated approach, notably hyperfractionation.

From the cell itself, through its microenvironment extending to the patient and his or her biological parameters, many factors participate in the response of these cells to radiation. Taken together, these parameters represent a range of possible therapeutic approaches for circumventing the radioresistance. Hadrontherapy plays a central role in these therapeutic approaches. On the molecular side, the study of resistance mechanisms involving the EGFR pathway is also vital, in particular via the pathways of the same HER family (HER2 and 3) but also IGF-1R. Eventually, cancer stem cells are the key element in these radioresistance phenomena, at the kernel of multitudinous parameters such as hypoxia and invasion-migration.

Head and neck malignancies are challenging for surgical and radiotherapy treatment due to the density of sensitive tissues. We concluded that apoptosis is associated with radiosensitivity in HPV-positive HNSCC, whereas autophagy is associated with radiation resistant HPV-negative HNSCC. Further basic studies could pay more attention chiefly to the aforementioned two angles in the future.

### Ethics approval

Not required.

### Consent for publication

Not applicable.

### Availability of data and materials

Not applicable.

### Conflicts of interest

The authors declare no competing interests with respect to the research, authorship, and/or publication of this article.

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### Authorship contributions

Conceptualization: Ch.L. and Zh.G. Data curation: Ch.L. Formal analysis: Ch.L. Funding acquisition: Ch.L. and Zh.G. Investigation: Ch.L. Methodology: Ch.L. and X.T., W.Z. and Y.Z. Project administration: Zh.G. and H.Z. Resources: X.T, W.Z. and Y.Z. Software: Ch.L. Supervision: Zh.G. and Ch.L. Validation: H.Z. Visualization: Ch.L. Writing — origi-

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## References

1. Chow LQM. Head and Neck Cancer. N Engl J Med. 2020; 382(1): 60–72, doi: 10.1056/NEJMra1715715, indexed in Pubmed: 31893516.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209–249, doi: 10.3322/caac.21660, indexed in Pubmed: 33538338.
3. Alterio D, Marvaso G, Ferrari A, et al. Modern radiotherapy for head and neck cancer. Semin Oncol. 2019; 46(3): 233–245, doi: 10.1053/j.seminoncol.2019.07.002, indexed in Pubmed: 31378376.
4. Yang Z, Zhang X, Wang X, et al. Multiple-CT optimization: An adaptive optimization method to account for anatomical changes in intensity-modulated proton therapy for head and neck cancers. Radiother Oncol. 2020; 142: 124–132, doi: 10.1016/j.radonc.2019.09.010, indexed in Pubmed: 31564553.
5. Li CX, Sun JL, Gong ZC, et al. An umbrella review exploring the effect of radiotherapy for head and neck cancer patients on the frequency of jaws osteoradionecrosis. Cancer Radiother. 2023; 27(5): 434–446, doi: 10.1016/j.canrad.2023.01.009, indexed in Pubmed: 37268457.
6. Gensheimer MF, Le QT. Adaptive radiotherapy for head and neck cancer: Are we ready to put it into routine clinical practice? Oral Oncol. 2018; 86: 19–24, doi: 10.1016/j.oraloncology.2018.08.010, indexed in Pubmed: 30409300.
7. Spencer S. Head and Neck Cancers: Advantages of Advanced Radiation Therapy and Importance of Supportive Care. J Natl Compr Canc Netw. 2018; 16(5S): 666–669, doi: 10.6004/jnccn.2018.0049, indexed in Pubmed: 29784752.
8. Silva P, Homer JJ, Slevin NJ, et al. Clinical and biological factors affecting response to radiotherapy in patients with head and neck cancer: a review. Clin Otolaryngol. 2007; 32(5): 337–345, doi: 10.1111/j.1749-4486.2007.01544.x, indexed in Pubmed: 17883552.
9. Liu T, Pei P, Shen W, et al. Radiation-Induced Immunogenic Cell Death for Cancer Radioimmunotherapy. Small Methods. 2023; 7(5): e2201401, doi: 10.1002/smtd.202201401, indexed in Pubmed: 36811166.
10. Beadle BM, Chan AW. The Potential of Adaptive Radiotherapy for Patients With Head and Neck Cancer-Too Much or Not Enough? JAMA Oncol. 2023; 9(8): 1064–1065, doi: 10.1001/jamaoncol.2023.1306, indexed in Pubmed: 37261837.
11. Lohynska R, Jirkovska M, Malinova B, et al. Tumour volume and radiotherapy prolongation in locally advanced head and neck cancer patients treated with radical IMRT. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2022; 166(4): 405–411, doi: 10.5507/bp.2021.047, indexed in Pubmed: 34498610.
12. Caudell JJ, Torres-Roca JF, Gillies RJ, et al. The future of personalised radiotherapy for head and neck cancer. Lancet Oncol. 2017; 18(5): e266–e273, doi: 10.1016/S1470-2045(17)30252-8, indexed in Pubmed: 28456586.
13. Marzec J, Marzec L, Martus P, et al. MATLAB®-based fitting method to evaluate survival fractions after multimodal treatment. Clin Transl Radiat Oncol. 2018; 10: 36–41, doi: 10.1016/j.ctro.2018.03.003, indexed in Pubmed: 29928704.
14. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet. 2019; 394(10196): 385–395, doi: 10.1016/S0140-6736(19)31131-6, indexed in Pubmed: 31227373.
15. Björk-Eriksson T, West C, Karlsson E, et al. Tumor radiosensitivity (SF2) is a prognostic factor for local control in head and neck cancers. Int J Radiat Oncol Biol Phys. 2000; 46(1): 13–19, doi: 10.1016/s0360-3016(99)00373-9, indexed in Pubmed: 10656366.
16. Overgaard J, Mohanti BK, Begum N, et al. 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. 2010; 11(6): 553–560, doi: 10.1016/S1470-2045(10)70072-3, indexed in Pubmed: 20382075.
17. Lazarev S, Gupta V, Ghiassi-Nejad Z, et al. Premature discontinuation of curative radiation therapy: Insights from head and neck irradiation. Adv Radiat Oncol. 2018; 3(1): 62–69, doi: 10.1016/j.adro.2017.10.006, indexed in Pubmed: 29556582.
18. Pedicini P, Caivano R, Fiorentino A, et al. Clinical radiobiology of head and neck cancer: the hypothesis of stem cell activation. Clin Transl Oncol. 2015; 17(6): 469–476, doi: 10.1007/s12094-014-1261-z, indexed in Pubmed: 25487602.
19. Caudell JJ, Gillison ML, Maghami E, et al. NCCN Guidelines® Insights: Head and Neck Cancers, Version 1.2022. J Natl Compr Canc Netw. 2022; 20(3): 224–234, doi: 10.6004/jnccn.2022.0016, indexed in Pubmed: 35276673.
20. Roman BR, Aragones A. Epidemiology and incidence of HPV-related cancers of the head and neck. J Surg Oncol.

2021; 124(6): 920–922, doi: 10.1002/jso.26687, indexed in Pubmed: 34558067.
21. Castellsagué X, Alemany L, Quer M, et al. ICO International HPV in Head and Neck Cancer Study Group. HPV Involvement in Head and Neck Cancers: Comprehensive Assessment of Biomarkers in 3680 Patients. J Natl Cancer Inst. 2016; 108(6): djv403, doi: 10.1093/jnci/djv403, indexed in Pubmed: 26823521.
22. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010; 363(1): 24–35, doi: 10.1056/NEJMoa0912217, indexed in Pubmed: 20530316.
23. Cho WJ, Kessel D, Rakowski J, et al. Photodynamic Therapy as a Potent Radiosensitizer in Head and Neck Squamous Cell Carcinoma. Cancers (Basel). 2021; 13(6), doi: 10.3390/cancers13061193, indexed in Pubmed: 33801879.
24. Lee SuH, Cho WJ, Najy AJ, et al. p62/SQSTM1-induced caspase-8 aggresomes are essential for ionizing radiation-mediated apoptosis. Cell Death Dis. 2021; 12(11): 997, doi: 10.1038/s41419-021-04301-7, indexed in Pubmed: 34697296.
25. Browman GP, Mohide EA, Willan A, et al. Association between smoking during radiotherapy and prognosis in head and neck cancer: a follow-up study. Head Neck. 2002; 24(12): 1031–1037, doi: 10.1002/hed.10168, indexed in Pubmed: 12454940.
26. Fortin A, Wang CS, Vigneault E. Influence of smoking and alcohol drinking behaviors on treatment outcomes of patients with squamous cell carcinomas of the head and neck. Int J Radiat Oncol Biol Phys. 2009; 74(4): 1062–1069, doi: 10.1016/j.ijrobp.2008.09.021, indexed in Pubmed: 19036528.
27. Baumeister P, Welz C, Jacobi C, et al. Is Perineural Invasion of Head and Neck Squamous Cell Carcinomas Linked to Tobacco Consumption? Otolaryngol Head Neck Surg. 2018; 158(5): 878–881, doi: 10.1177/0194599817750354, indexed in Pubmed: 29293403.
28. Jamal M, Van der Does W, Elzinga BM, et al. Association between smoking, nicotine dependence, and BDNF Val66Met polymorphism with BDNF concentrations in serum. Nicotine Tob Res. 2015; 17(3): 323–329, doi: 10.1093/ntr/ntu151, indexed in Pubmed: 25183693.
29. Wun T, Law L, Harvey D, et al. Increased incidence of symptomatic venous thrombosis in patients with cervical carcinoma treated with concurrent chemotherapy, radiation, and erythropoietin. Cancer. 2003; 98(7): 1514–1520, doi: 10.1002/cncr.11700, indexed in Pubmed: 14508840.
30. Li CX, He Qi, Wang ZY, et al. Risk assessment of venous thromboembolism in head and neck cancer patients and its establishment of a prediction model. Head Neck. 2023; 45(10): 2515–2524, doi: 10.1002/hed.27475, indexed in Pubmed: 37548087.
31. Tham T, Olson C, Wotman M, et al. Evaluation of the prognostic utility of the hemoglobin-to-red cell distribution width ratio in head and neck cancer. Eur Arch Otorhinolaryngol. 2018; 275(11): 2869–2878, doi: 10.1007/s00405-018-5144-8, indexed in Pubmed: 30251123.
32. Tham T, Rahman L, Persaud C, et al. Venous Thromboembolism Risk in Head and Neck Cancer: Significance of the Preoperative Platelet-to-Lymphocyte Ratio. Otolaryngol Head Neck Surg. 2018; 159(1): 85–91, doi: 10.1177/0194599818756851, indexed in Pubmed: 29406795.
33. Clayburgh DR, Stott W, Cordiero T, et al. Prospective study of venous thromboembolism in patients with head and neck cancer after surgery. JAMA Otolaryngol Head Neck Surg. 2013; 139(11): 1143–1150, doi: 10.1001/jamaoto.2013.4911, indexed in Pubmed: 24076972.
34. Maahs L, Ghanem AI, Gutta R, et al. Cetuximab and anemia prevention in head and neck cancer patients undergoing radiotherapy. BMC Cancer. 2022; 22(1): 626, doi: 10.1186/s12885-022-09708-9, indexed in Pubmed: 35672745.
35. Shenouda G, Zhang Q, Ang KK, et al. Long-term results of radiation therapy oncology group 9903: a randomized phase 3 trial to assess the effect of erythropoietin on local-regional control in anemic patients treated with radiation therapy for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 2015; 91(5): 907–915, doi: 10.1016/j.ijrobp.2014.12.018, indexed in Pubmed: 25670542.
36. Talukdar S, Emdad L, Das SK, et al. EGFR: An essential receptor tyrosine kinase-regulator of cancer stem cells. Adv Cancer Res. 2020; 147: 161–188, doi: 10.1016/bs.acr.2020.04.003, indexed in Pubmed: 32593400.
37. Fasano M, Della Corte CM, Viscardi G, et al. Head and neck cancer: the role of anti-EGFR agents in the era of immunotherapy. Ther Adv Med Oncol. 2021; 13: 1758835920949418, doi: 10.1177/1758835920949418, indexed in Pubmed: 33767760.
38. Kumar R, George B, Campbell MR, et al. HER family in cancer progression: From discovery to 2020 and beyond. Adv Cancer Res. 2020; 147: 109–160, doi: 10.1016/bs.acr.2020.04.001, indexed in Pubmed: 32593399.
39. Liu Q, Yu S, Zhao W, et al. EGFR-TKIs resistance via EGFR-independent signaling pathways. Mol Cancer. 2018; 17(1): 53, doi: 10.1186/s12943-018-0793-1, indexed in Pubmed: 29455669.
40. Gröbe A, Eichhorn W, Fraederich M, et al. Immunohistochemical and FISH analysis of EGFR and its prognostic value in patients with oral squamous cell carcinoma. J Oral Pathol Med. 2014; 43(3): 205–210, doi: 10.1111/jop.12111, indexed in Pubmed: 24020871.
41. Bonner JA, Harari PM, Giralt J, et al. 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. 2010; 11(1): 21–28, doi: 10.1016/S1470-2045(09)70311-0, indexed in Pubmed: 19897418.
42. Goldberg RM. Cetuximab. Nat Rev Drug Discov. 2005; Suppl: S10–S11, doi: 10.1038/nrd1728, indexed in Pubmed: 15962524.
43. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006; 354(6): 567–578, doi: 10.1056/NEJMoa053422, indexed in Pubmed: 16467544.
44. Ang KK, Berkey BA, Tu X, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res. 2002; 62(24): 7350–7356, indexed in Pubmed: 12499279..
45. Tinhofer I, Hristozova T, Stromberger C, et al. Monitoring of circulating tumor cells and their expression of EGFR/phospho-EGFR during combined radiotherapy regimens in locally advanced squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 2012; 83(5):

e685–e690, doi: 10.1016/j.ijrobp.2012.02.009, indexed in Pubmed: 22583603.
46. Moncharmont C, Levy A, Gilormini M, et al. Targeting a cornerstone of radiation resistance: cancer stem cell. Cancer Lett. 2012; 322(2): 139–147, doi: 10.1016/j.canlet.2012.03.024, indexed in Pubmed: 22459349.
47. Clarke MF. Clinical and Therapeutic Implications of Cancer Stem Cells. N Engl J Med. 2019; 380(23): 2237–2245, doi: 10.1056/NEJMra1804280, indexed in Pubmed: 31167052.
48. Trumpp A, Haas S. Cancer stem cells: The adventurous journey from hematopoietic to leukemic stem cells. Cell. 2022; 185(8): 1266–1270, doi: 10.1016/j.cell.2022.03.025, indexed in Pubmed: 35385684.
49. Song Y, Wang Y, Tong C, et al. A unified model of the hierarchical and stochastic theories of gastric cancer. Br J Cancer. 2017; 116(8): 973–989, doi: 10.1038/bjc.2017.54, indexed in Pubmed: 28301871.
50. Lee SuY, Jeong EK, Ju MK, et al. Induction of metastasis, cancer stem cell phenotype, and oncogenic metabolism in cancer cells by ionizing radiation. Mol Cancer. 2017; 16(1): 10, doi: 10.1186/s12943-016-0577-4, indexed in Pubmed: 28137309.
51. Chen C, Zimmermann M, Tinhofer I, et al. Epithelial-to-mesenchymal transition and cancer stem(-like) cells in head and neck squamous cell carcinoma. Cancer Lett. 2013; 338(1): 47–56, doi: 10.1016/j.canlet.2012.06.013, indexed in Pubmed: 22771535.
52. Orlandi E, Iacovelli NA, Bonora M, et al. Salivary Gland. Photon beam and particle radiotherapy: Present and future. Oral Oncol. 2016; 60: 146–156, doi: 10.1016/j.oraloncology.2016.06.019, indexed in Pubmed: 27394087.
53. Oonishi K, Cui X, Hirakawa H, et al. Different effects of carbon ion beams and X-rays on clonogenic survival and DNA repair in human pancreatic cancer stem-like cells. Radiother Oncol. 2012; 105(2): 258–265, doi: 10.1016/j.radonc.2012.08.009, indexed in Pubmed: 23017870.
54. Zhang N, Ng AS, Cai S, et al. Novel therapeutic strategies: targeting epithelial-mesenchymal transition in colorectal cancer. Lancet Oncol. 2021; 22(8): e358–e368, doi: 10.1016/S1470-2045(21)00343-0, indexed in Pubmed: 34339656.
55. Wang H, Mei Y, Luo C, et al. Single-Cell Analyses Reveal Mechanisms of Cancer Stem Cell Maintenance and Epithelial-Mesenchymal Transition in Recurrent Bladder Cancer. Clin Cancer Res. 2021; 27(22): 6265–6278, doi: 10.1158/1078-0432.CCR-20-4796, indexed in Pubmed: 34526362.
56. Harris K, Gelberg HB, Kiupel M, et al. Immunohistochemical Features of Epithelial-Mesenchymal Transition in Feline Oral Squamous Cell Carcinoma. Vet Pathol. 2019; 56(6): 826–839, doi: 10.1177/0300985819859873, indexed in Pubmed: 31331247.
57. Moncharmont C, Levy A, Guy JB, et al. Radiation-enhanced cell migration/invasion process: a review. Crit Rev Oncol Hematol. 2014; 92(2): 133–142, doi: 10.1016/j.critrevonc.2014.05.006, indexed in Pubmed: 24908570.
58. He J, Huang Z, Han L, et al. Mechanisms and management of 3rdgeneration EGFRTKI resistance in advanced nonsmall cell lung cancer (Review). Int J Oncol. 2021; 59(5), doi: 10.3892/ijo.2021.5270, indexed in Pubmed: 34558640.
59. Zuo JH, Zhu W, Li MY, et al. Activation of EGFR promotes squamous carcinoma SCC10A cell migration and invasion via inducing EMT-like phenotype change and MMP-9-mediated degradation of E-cadherin. J Cell Biochem. 2011; 112(9): 2508–2517, doi: 10.1002/jcb.23175, indexed in Pubmed: 21557297.
60. Wozny AS, Vares G, Alphonse G, et al. ROS Production and Distribution: A New Paradigm to Explain the Differential Effects of X-ray and Carbon Ion Irradiation on Cancer Stem Cell Migration and Invasion. Cancers (Basel). 2019; 11(4), doi: 10.3390/cancers11040468, indexed in Pubmed: 30987217.
61. Liao C, Liu X, Zhang C, et al. Tumor hypoxia: From basic knowledge to therapeutic implications. Semin Cancer Biol. 2023; 88: 172–186, doi: 10.1016/j.semcancer.2022.12.011, indexed in Pubmed: 36603793.
62. Tharmalingham H, Hoskin P. Clinical trials targeting hypoxia. Br J Radiol. 2019; 92(1093): 20170966, doi: 10.1259/bjr.20170966, indexed in Pubmed: 29979089.
63. Gallez B, Neveu MA, Danhier P, et al. Manipulation of tumor oxygenation and radiosensitivity through modification of cell respiration. A critical review of approaches and imaging biomarkers for therapeutic guidance. Biochim Biophys Acta Bioenerg. 2017; 1858(8): 700–711, doi: 10.1016/j.bbabio.2017.01.002, indexed in Pubmed: 28088332.
64. Overgaard J. Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck--a systematic review and meta-analysis. Radiother Oncol. 2011; 100(1): 22–32, doi: 10.1016/j.radonc.2011.03.004, indexed in Pubmed: 21511351.
65. Hassan Metwally MA, Ali R, Kuddu M, et al. IAEA-HypoX. A randomized multicenter study of the hypoxic radiosensitizer nimorazole concomitant with accelerated radiotherapy in head and neck squamous cell carcinoma. Radiother Oncol. 2015; 116(1): 15–20, doi: 10.1016/j.radonc.2015.04.005, indexed in Pubmed: 25913070.
66. Sørensen BS, Busk M, Horsman MR, et al. Effect of radiation on cell proliferation and tumor hypoxia in HPV-positive head and neck cancer in vivo models. Anticancer Res. 2014; 34(11): 6297–6304, indexed in Pubmed: 25368228.
67. Thariat J, Moya Plana A, Vérillaud B, et al. membres REFCOR. [Diagnosis, prognosis and treatment of sinonasal carcinomas (excluding melanomas, sarcomas and lymphomas)]. Bull Cancer. 2020; 107(5): 601–611, doi: 10.1016/j.bulcan.2020.02.013, indexed in Pubmed: 32305127.
68. Merlotti A, Alterio D, Orlandi E, et al. AIRO GORTEC consensus on postoperative radiotherapy (PORT) in low-intermediate risk early stages oral squamous cell cancers (OSCC). Radiother Oncol. 2022; 177: 95–104, doi: 10.1016/j.radonc.2022.10.035, indexed in Pubmed: 36336113.
69. Mizoe JE, Hasegawa A, Jingu K, et al. Organizing Committee for the Working Group for Head Neck Cancer. Results of carbon ion radiotherapy for head and neck cancer. Radiother Oncol. 2012; 103(1): 32–37, doi: 10.1016/j.radonc.2011.12.013, indexed in Pubmed: 22321201.
70. Wozny AS, Lauret A, Battiston-Montagne P, et al. Differential pattern of HIF-1α expression in HNSCC cancer stem cells after carbon ion or photon irradiation: one molecular explanation of the oxygen effect. Br J Cancer. 2017; 116(10): 1340–1349, doi: 10.1038/bjc.2017.100, indexed in Pubmed: 28407653.
71. Bertrand G, Maalouf M, Boivin A, et al. Targeting head and neck cancer stem cells to overcome resistance to photon and carbon ion radiation. Stem Cell Rev Rep. 2014;

10(1): 114–126, doi: 10.1007/s12015-013-9467-y, indexed in Pubmed: 23955575.
72. Held T, Windisch P, Akbaba S, et al. Carbon Ion Reirradiation for Recurrent Head and Neck Cancer: A Single-Institutional Experience. Int J Radiat Oncol Biol Phys. 2019; 105(4): 803–811, doi: 10.1016/j.ijrobp.2019.07.021, indexed in Pubmed: 31349059.
73. Jensen AD, Krauss J, Potthoff K, et al. Phase II study of induction chemotherapy with TPF followed by radioimmunotherapy with Cetuximab and intensity-modulated radiotherapy (IMRT) in combination with a carbon ion boost for locally advanced tumours of the oro-, hypopharynx and larynx--TPF-C-HIT. BMC Cancer. 2011; 11: 182, doi: 10.1186/1471-2407-11-182, indexed in Pubmed: 21595970.
74. Kamada T, Tsujii H, Blakely EA, et al. Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience. Lancet Oncol. 2015; 16(2): e93–e9e100, doi: 10.1016/S1470-2045(14)70412-7, indexed in Pubmed: 25638685.
75. Haddad R, O'Neill A, Rabinowits G, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncol. 2013; 14(3): 257–264, doi: 10.1016/S1470-2045(13)70011-1, indexed in Pubmed: 23414589.
76. Cohen EEW, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol. 2014; 32(25): 2735–2743, doi: 10.1200/JCO.2013.54.6309, indexed in Pubmed: 25049329.
77. Gu J, Zhu S, Li X, et al. Effect of amifostine in head and neck cancer patients treated with radiotherapy: a systematic review and meta-analysis based on randomized controlled trials. PLoS One. 2014; 9(5): e95968, doi: 10.1371/journal.pone.0095968, indexed in Pubmed: 24788761.
78. Lambin P, Ramaekers BLT, van Mastrigt GA, et al. Erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer. Cochrane Database Syst Rev. 2009(3): CD006158, doi: 10.1002/14651858.CD006158.pub2, indexed in Pubmed: 19588382.
79. Bourhis J, Blanchard P, Maillard E, et al. Effect of amifostine on survival among patients treated with radiotherapy: a meta-analysis of individual patient data. J Clin Oncol. 2011; 29(18): 2590–2597, doi: 10.1200/JCO.2010.33.1454, indexed in Pubmed: 21576630.
80. Bourhis J, Overgaard J, Audry H, et al. Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet. 2006; 368(9538): 843–854, doi: 10.1016/S0140-6736(06)69121-6, indexed in Pubmed: 16950362.
81. Pignon JP, le Maître A, Maillard E, et al. MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009; 92(1): 4–14, doi: 10.1016/j.radonc.2009.04.014, indexed in Pubmed: 19446902.
82. Blanchard P, Bourhis J, Lacas B, et al. Meta-Analysis of Chemotherapy in Head and Neck Cancer, Induction Project, Collaborative Group. Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group. J Clin Oncol. 2013; 31(23): 2854–2860, doi: 10.1200/JCO.2012.47.7802, indexed in Pubmed: 23835714.
83. Goel M, Mackeyev Y, Krishnan S. Radiolabeled nanomaterial for cancer diagnostics and therapeutics: principles and concepts. Cancer Nanotechnol. 2023; 14(1): 15, doi: 10.1186/s12645-023-00165-y, indexed in Pubmed: 36865684.
84. Durand M, Chateau A, Jubréaux J, et al. Radiosensitization with Gadolinium Chelate-Coated Gold Nanoparticles Prevents Aggressiveness and Invasiveness in Glioblastoma. Int J Nanomedicine. 2023; 18: 243–261, doi: 10.2147/IJN.S375918, indexed in Pubmed: 36660336.
85. Rajaee A, Wang S, Zhao L, et al. Multifunction bismuth gadolinium oxide nanoparticles as radiosensitizer in radiation therapy and imaging. Phys Med Biol. 2019; 64(19): 195007, doi: 10.1088/1361-6560/ab2154, indexed in Pubmed: 31082811.