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Radiotherapy Controversies and Prospective in Head and Neck Cancer: A Literature-Based Critical Review

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Abstract

In treating head and neck cancer (HNC), the objectives are provided for best functional results and minimal risk of serious complications. The choice of appropriate management depends primarily on specific site and stage of primary tumor at diagnosis. Radiation therapy (RT) with or without concomitant chemotherapy represents a classical treatment option. In this review, we provide an update of recent research strategies to counteract the existing damage caused by RT and highlight clinical trials currently in progress. We discuss the challenges in the evaluation of new stage system and RT-related toxicity onset. We mainly address the deficiencies and the advantages noted in the current treatment era.

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Introduction

Head and neck cancer (HNC) accounts for approximately 5% of all malignancies and squamous cell carcinoma represents the main histological type [1]. The vast majority of patients are diagnosed with locally advanced disease at the time of presentation, and treatment options have traditionally included surgery, radiation therapy (RT) and chemotherapy (C), or combinations of these therapeutic modalities, depending on primary location [2]. In fact, HNC is a heterogeneous group of malignancies, consisting of various anatomic sites, including nasopharynx, paranasal sinuses, oral cavity, oropharynx, hypopharynx and larynx. Worldwide, more than 650,000 new cases of HNC are reported annually and more than 350,000 deaths from HNC occurred yearly, with 9,300 new cases and 2,820 deaths described in Italy per year [3,4]. Due to its rarity, as well as its complexity in optimal strategy plan and patients support care through treatment, high-volume centers including the presence of multidisciplinary tumor board should be prioritize in HNC management [5]. It has been demonstrated that received treatment at centers with expertise affects both overall survival (OS) and progression-free survival (PFS) in patients with locally advanced HNC (5-year OS: 51.0% versus 69.1%, $P = 0.002$; 5-year PFS: 42.7% versus 61.8%, $P < 0.001$) [5]. Similarly, survival outcomes are improved in those centers in which HNC patients are managed by a multidisciplinary team meeting (hazard ratio, HR: 0.79, $P = 0.024$) [6]. However, even with this evidence-based recommendation, outcomes remain poor, especially in locally advanced disease.

The aim of this review is to discuss the current optimal management of these patients, especially supporting RT treatment. We provide an overview of HNC landscape, focusing on the new risk stratification, the main changes and pitfalls of recent RT technique and the challenges of the next generation clinical trials.

Search Strategy

We performed a search of the electronic databases (PubMed and Scopus), using the following combinations of keywords: "head neck cancer", "human papilloma virus", "radiotherapy", "surgery", "chemotherapy", "proton therapy", "immunotherapy", "alpha radiation", "Ra-224". We provided a comprehensive picture of RT

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perspectives in HNC using hand searching (meeting proceedings of European SocieTy for Radiotherapy & Oncology and American Society of Clinical Oncology) and clinicaltrials.gov. Literature search strategy was performed up to August 2017. Only English written publications were selected. Titles and abstracts of search results were screened to determine eligibility in the manuscript. Additional references were selected from relevant articles. Abstract from international meetings were included only if with appropriate and sufficiently powered statistical data.

Risk Stratification

An important paradigm shift in HNC in the past several years has been the identification of human papilloma virus (HPV) infection as a risk factor, especially for the development of oropharyngeal cancer. Over the past decades, HPV-related HNC incidence rates have been essentially increased, whereas there has been a reduction in incidence rates of tobacco- and alcohol-related cancer, such as laryngeal and hypopharyngeal tumors [2]. This modification has been noticed in parallel with a decline in cigarette smoking and alcohol consumption and, on the other hand, a raise in HPV infection. Typically, HPV-related HNC presents in young individual (< 60 years) with high socioeconomic status and a history of multiple sexual partners [7]. At diagnosis, clinical presentation is characterized by a small primary tumor (T) with a massive regional nodal (N) involvement. However, HPV-related HNC has a favorable prognosis than that for tobacco-related HNC treated similarly and this evidence becomes paramount in the reorganizing of the HNC tumor, lymph node, metastasis (TNM) staging system [7,8]. In fact, recently, the American joint committee on cancer (AJCC) staging manual introduces significant modifications in the head and neck section [8].

The main changes include the HPV-status evaluation, the addition of extracapsular extension to N category in all but the HPV-related cancers and the update to the T categories for oral cavity cancer, including the depth of tumor invasion. These modifications better discriminate the higher risk cancers – HPV-negative tumors, extranodal cancer extension and/or deeply invasive tumors – from those with HPV-related cancers and/or less invasive disease that have an excellent prognosis. The inclusion of these new criteria in combining T and N into stage grouping definitively improves discrimination in the risk stratification data, between stage I, II and III, in case of HPV/non HPV-associated tumors and depth of invasion/extranodal extension alike [8].

General Management

In general, the appropriate strategy is based on both stage of disease and primary location.

The mainstay of treatment for oral cavity cancer is surgery followed by adjuvant (C)RT in case of pathological T3-4, N2-3 nodal disease, positive surgical margins, extracapsular nodal spread, perineural invasion and lymphovascular invasion [9]. Whereas RT is usually considered as definitive treatment in the remainder HNC cancer sites, especially in locally advanced stage disease to propose an organ preservation strategy [9]. The update meta-analysis of 87 randomized trials including 16,485 patients showed that the addition of concomitant C to RT improved OS in HNC treated by surgery and/or RT (HR: 0.81, 95% confidence interval, CI 0.78–0.86) with an overall 6.5% benefit at 5 years, from 27.2% to 33.7% [10]. The observed benefit of CRT was greater than the absolute benefit of 2.4% at 5 years of induction C (HR: 0.96, 95% CI 0.90–1.02). Therefore, at present, CRT represents the standard treatment for HNC, when appropriate. Radiation total dose ranges from 50 to 70 Gy, depending on tumor type and target volumes. In order to effectively eliminate tumor cells and minimize side effects to normal tissue, conventional RT regimens deliver the prescribed radiation dose in multiple daily fractions (usually 2 Gy/fraction), given over several weeks. The therapeutic use of local ionizing radiation is mainly based on the rational foundation provided by the 5 traditional Rs of radiobiology (repair, repopulation, redistribution, reoxygenation and radiosensitivity) and the normal tissues proper architecture and reserve capacity (parallel and/or serial organ) [11,12]. In order to assure adequate target volume coverage and minimize the risk of RT-induced toxicity, an accurate definition of the organs at risk (OARs) in the treatment plan is paramount. To reduce subjective contouring variations among radiation oncologists in the delineation of OARs anatomic boundaries, contouring consensus guidelines have been developed [13–15]. Similarly, specific dose constrains have been proposed to every single OAR [16]. Considering that, in the head and neck region, OARs are numerous (more than 25), it is often not possible to respect all dose constraints, especially in case of advanced disease. Ideally all OARs should receive a dose exposure as low as possible without compromising coverage of tumor targets. Top priority should be given to critical neurological structures, including brainstem, spinal cord, optic chiasm, optic nerve and temporal lobes. Generally, doses to other OARs should be reduced as much as achievable, but without resulting in inadequate coverage of primary target volume, that represents a key issue for local control disease [17].

Controversies – Radiation Therapy and Toxicity

Altered Fractionation

Over the past few decades, survival rates in HNC have not really improved, emphasizing the need for novel investigation into multi-modality therapies. Various modalities, including altered fractionation RT regimens and multi-agent CRT, have been tested to improve tumor control while maintain a relative low toxicity rate. The updated Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) confirmed that altered fractionation RT is associated with improved OS and PFS when compared with conventional RT [18]. Actually, the survival benefit was slight and restricted to the hyperfractionation subgroup (HR: 0.83, 95% CI 0.74–0.92), with absolute differences at 5 years of 8.1% (95% CI 3.4–12.8) and at 10 years of 3.9% (-0.6 –8.4). However, the comparison between altered fractionation RT and CRT showed significantly worse OS with altered fractionation (HR: 1.22, 95% CI 1.05–1.42). Interestingly, patients treated with altered fractionation RT presented a significantly increased prevalence of acute mucositis (odds ratio, OR:2.02, 95% CI 1.81–2.26) and need for a feeding tube placement (OR: 1.75, 95% CI 1.49–2.05). This toxicity analysis was also in agreement with the safety data evaluation of different HNC treatments proposed by Trotti et al [19]. Authors provided a concise method to compare relative risk among treatment options. Results revealed that toxicity values were higher in the more aggressive approaches that used multiple concomitant drugs or altered RT fractionation with or without C. At present, conventional CRT remains the standard of care in HNC.

Intensity Modulated Radiotherapy

The preferred technique is intensity modulated RT (IMRT), due to its ability to deliver non-uniform and optimized radiation beam

intensities to conform highly complex shape of the target. The main advantage of IMRT is to confine the higher radiation doses to the target volumes and, therefore, offer a better protection of surrounding OARs. The PARSPORT phase III trial represents a convincing example to highlight improvements for IMRT over conventional RT [20]. The most common and challenging late toxicity of RT to the head and neck is historically connected with the impaired functioning of the salivary glands, especially parotid glands. The PARSPORT trial recorded a significant reduction of RT-induced xerostomia for patients treated with IMRT compared with conventional RT (38% versus 74%, $P = 0.0027$) [20]. When considering the mean doses for the parotid glands, the doses for the IMRT plans were significantly lower than for the conventional RT, in both controlateral and ipsilateral parotid glands (22.2 Gy versus 60.0 Gy and 50.1 Gy versus 61.9 Gy, respectively) [21]. Parotid-sparing IMRT achieved recovery of saliva secretion, but, at the same time, to preserve function of a specific OAR, a larger amount of other tissues and structures in the head and neck region are irradiated to a lower dose when IMRT is used. It results in additional toxicities that were uncommon before IMRT treatment strategy [22]. For instance, the mandible can be at highest risk of developing osteoradionecrosis (ORN). In fact, because of multiplicity of beam paths, it could be possible that non target segments of mandible may receive higher doses than previous less conformal RT technique. Surely ORN represents a multifactorial late complication, influenced by both RT-induced factors (total dose, fractionation scheme, type of energy, treatment field size) and patient-related parameters (old age, bad habits, poor oral hygiene, general health) [23]. But the direct irradiation of non-target bone areas can contribute to its development. Consequently, it remains unclear which dosimetric parameters should be considered to minimize the ORN risk [24]. A recent case-matched comparison of only IMRT treated patients, showed that all doses in the intermediate and high range were more likely to be elevated in the ORN patients compared to asymptomatic controls [25]. These findings suggested that, to reduce ORN incidence, in IMRT treatment planning, whenever feasible, several volumetric constraints should be utilized, rather than a single point-dose maximum as in the pre-IMRT era. Furthermore, IMRT beam path exposures large volumes of normal tissues to lower doses of radiation and, therefore, delivers a higher integral dose to the patient. This would suggest an increase in the future incidence of second primary malignancy following RT treatment [26]. Usually the latent period for the development of second tumor ranges between 5 to 10 years. Generally, HNC presents modest number of long-term survivors. But if we considered specific clinical conditions – such as nasopharynx carcinoma or the increasing oral cavity carcinoma incidence in young adults – patients life expectancy once the HNC is cured is expected to be long and patients may have decades of risk to develop RT-related effects [27,28]. Therefore, radiation exposure becomes of paramount importance in order to balance the risk of long-term RT sequelae.

Prospective

Radiation De-Intensification

Efforts to minimize acute and late toxicity among HNC patients are warranted. Considering that patients with HPV-associated HNC are comparatively more curable and, thus, may carry RT sequelae for decades, novel treatment paradigm has been proposed in this setting of patients. A radiation de-intensification could decrease acute and late sequelae, particularly xerostomia and dysphagia, while maintaining excellent cure rates. The ECOG-ACRIN Cancer Research Group has recently presented encouraging results, but validations in phase III studies are required [29]. HPV-related oropharyngeal cancer patients, who achieved complete clinical response to induction C with cisplatin, paclitaxel, and cetuximab, received reduced-dose IMRT (54 Gy) with concurrent weekly cetuximab. Radiation dose reduction resulted in higher rate of disease control (2-year PFS: 80% versus 67%; 2-year OS: 94% versus 87%) and significantly reduced difficulty in swallowing solids (40% versus 89%, $P = 0.011$) and prejudiced nutritional status (10% versus 44%, $P = 0.025$) compared with patients with less than complete clinical response at the primary site after induction C.

Actually, the effect of dose reduction on HNC patients has been studied as a phase III trial in the late 1980s [30]. A sequential program of induction C followed by 65-75 Gy RT was compared with an alternation of C and RT (three courses of 20 Gy, 2 Gy/fraction). In the radiation de-intensification patients, a significant improvement in complete response (49.2% versus 25.5%, $P = 0.03$) and PFS ($P = 0.046$) were recorded. Whereas, results were similar for OS. The toxicity analysis showed a significantly increased prevalence of mucositis compared with sequential treatment. However, this trial was performed before the HPV era and used outdated RT technique. Thus, the association between dose de-intensification and both toxicity and treatment efficacy shown in this study should be careful interpret, because nowadays both HPV-status and IMRT are the standard of care in HNC. Ongoing trials will elucidate the best management in HPV-related HNC patients [31].

Proton Therapy

HNC patients treated with proton therapy is increasing in the last year

Year by year, proton therapy is becoming more accessible in Europe [32]. In Italy, two centers deliver protons. Treatment recommendations are currently restricted to cranial or extra-cranial chordomas/chondrosarcomas, brain tumors including meningiomas, soft tissue sarcomas, ocular tumors, pediatric cases and patients with an history of genetic or collagen disease. Concerning head and neck region, recurrence after previous RT, adenoid cystic carcinoma of salivary glands, sarcomas and cancer of paranasal sinuses are accepted for protons [33]. In contrast to photon therapy, proton therapy allows optimal dose distributions, with essentially no exit dose. Due to its physical properties, the energy is essentially deposited at a specific depth (Bragg peak) within tissues and, therefore, highly OARs-sparing treatment plans can be created. The theoretical advantages of proton therapy in HNC are to decrease the probability of late RT-induced side effects, including but not limited to secondary cancers.

Currently, proton therapy high-level evidence is lacking. A recent dosimetric study has demonstrated a consistent lower doses to the mandible compared with IMRT treatment plan (minimum 0.8 Gy versus 7.3 Gy; mean 25.6 Gy versus 41.2 Gy; $P < 0.001$) and a subsequent reduction in ORN development (2% versus 7.7%) [34]. These results strongly suggest that the potential benefits of proton therapy translated into clinical benefits. Further prospective studies are necessary to better clarify the role of proton therapy in HNC management.

Immunotherapy

In 2015, nivolumab and pembrolizumab, classified as immunomodulatory monoclonal antibodies, were the first immunotherapeutic agents approved for the HNC treatment. Nivolumab and

Table 1. Key Points Summary

Controversies	
Alterated fractionation	Hyperfractionation allows the repair of RT-induced damage in normal tissue, but tumor tissue. It has the potential to reduce late side effects, delivering a higher total dose than CRT. Hyperfractionated RT should be considered in the treatment of locally advanced HNC.
"New" toxicity	IMRT can expose head and neck structures to significant doses of radiation. New dose-volume parameters should be considered.
Prospective	
Dose de-intensification	Due to proven improved outcomes, HPV-related HNC should receive less-intense RT treatment.
Proton therapy	A promising alternative to IMRT. Due to its physical properties, proton therapy assures high doses to target volume and largely spare surrounding tissues.
Immunotherapy	RT with immunotherapy can improve tumor control and reduce toxicity. Further clinical trials are needed.
DaRT	A novel method that use the decay of Radium-224 to release alpha particles into the tumor. No firm conclusions can be made because of the lack of human data.

RT, radiation therapy; CRT, chemoradiotherapy; HNC, head and neck cancer; HPV, human papilloma virus; IMRT, intensity modulated radiation therapy; DaRT, diffusing alpha emitters radiation therapy.

pembrolizumab are recommended as a category 1 and 2a, respectively, in recurrent and/or metastatic HNC (non-nasopharyngeal cancer) if disease progression on or after platinum-based C [9]. Food and Drug Administration (FDA) approval was based on recently published results of the randomized phase III CheckMate 141 trial (nivolumab) and nonrandomized phase Ib KEYNOTE-012 trial (pembrolizumab). The CheckMate 141 results showed, in patients with platinum-refractory recurrent/metastatic HNC, an high-quality evidence of nivolumab efficacy (median OS: 7.5 months versus 5.1 months; 1-year OS: 36.0% versus 16.6%) and safety (grade ≥3 toxicity: 13.1% versus 35.1%) compared to standard second-line single-agent therapy [35]. The KEYNOTE-012 data supported pembrolizumab safety (grade ≥ 3 toxicity: 9%) and efficacy (overall response rate: 18%; in the treatment of recurrent/metastatic HNC patients [36]. Interestingly, the overall response was 32% among patients with HPV-associated HNC and 14% among those with non–HPV-associated disease.

Both nivolumab and pembrolizumab are anti-programmed death-1 (PD-1) antibody. Physiologically, PD-1 receptor is expressed primarily on the activated T cells surface. The interaction with its ligands, mainly programmed death-ligand 1 (PD-L1), inhibits T-cell activation and reduces the response to inflammation. In a pathological condition, tumor cells induce expression of PD-L1 on cells in the tumor environment and the PD-1 and PD-L1 interaction results in escaping from tumor-directed immunity [36,37]. Thus, block the bond between the PD-1 and PD-L1 using an anti-PD-1 antibody represents an inhibitory signal to tumor growth. Nivolumab and pembrolizumab immune-checkpoint inhibitors have changed the radiation oncologic landscape such that several of the near future clinical trials may be based primarily on immunoradiation association. Considering the mechanism of action of the anti-PD-1 antibody, immunotherapy should be administered after or concurrently to RT. Mechanistically, giving RT before the checkpoint blockade, anti-PD-1 antibody might benefit from an increase in PD-1 expression on T cells – ionizing radiation enhances dendritic cell and T-cell activation and proliferation –, promoting a superior tumor control. The potential role of RT combination with these agents has recently been proposed in patients with intermediate (HPV-related oropharynx cancer with smoking status > 10 pack-years, stage T1-2N2b-N3 or ≤ 10 pack-years, stage T4N0-N3 or T1-3N3) and high-risk (oral cavity, larynx, hypopharynx, or non HPV-related oropharynx cancer, stage T1-2N2a-N3 or T3-4N0-3) local-regionally advanced HNC patients [38]. The aim is to tested the safety of nivolumab added to several CRT regimens, including weekly cisplatin, high-dose cisplatin, cetuximab or IMRT alone. Final data collection is estimated in March 2019.

Furthermore, other promising strategy for combining RT and immunotherapy is the altered fractionation. There are two potential advantages. Firstly, hypofractionated RT to small target volume could minimize the radiation dose to circulating blood, sparing circulating lymphocytes while supporting anti-PD-1 antibody activity. Secondly, RT seems to induce immune-mediated effects in unirradiated neoplastic tissues following irradiation of a different tissue in a distant location (abscopal effect). The exact nature of the abscopal response is still unclear, but successful preclinical studies have demonstrated promise once translated to the clinic [39]. The Memorial Sloan Kettering Cancer Center is currently recruiting metastatic HNC patients to randomly receive nivolumab and hypofractionated RT (total dose 27 Gy, 9 Gy/fraction) versus nivolumab alone. The primary outcome is to determine the best overall response of non-irradiated lesions [40]. Final data collection is estimated in February 2018.

Overall, although it remains to be well-determined, combining RT with immunotherapy seems a promising strategy in HNC management.

Diffusing α-Emitters Radiation Therapy

Diffusing α-emitters Radiation Therapy (DaRT) represents a new, in a sense innovative method to treat solid tumors [41]. Alpha particles are high linear energy transfer (LET) particles, able to impart irreparable damage to the DNA, independently of the oxygenation state of the cell. The radioactive sources are directly inserted into the tumor lesion with few millimeters spacing from one another. The short range of α particles guarantees the sparing of normal tissue outside the target. The Radium 224 (^{224}Ra) decay chain is mainly utilized. The parent nuclide ^{224}Ra produces radioactive daughter atoms that disperse into the tumor, forming a cluster of alpha emissions extending over several millimeters. The efficacy of DaRT has been demonstrated in preclinical studies on murine squamous cell carcinoma tumors, as well as athymic mice bearing malignant human-derived tumors including prostate, glioblastoma, colon, squamous cell carcinoma and melanoma [42,43]. The method is now being developed toward clinical trials, in human HNC too.

Conclusions

At present, a wide range of dose and fractionation schedules, as well as new RT technique and different drugs association are tested in clinical studies, and the optimal regimen to improve HNC survival outcomes with an acceptable toxicity rates remains unknown. For sure, HNC management required an experienced multidisciplinary expert team, in order to offer the optimal treatment according to both tumor and patient risk factors.

Table 1 goes over the main controversies and prospective. With the increasing incidence of HPV-related disease, which has a significantly

better OS than non-HPV HNC, the value of tailored therapy needs to be assessed. Concrete strategies to decrease RT-induced toxicity include radiation de-intensification program and proton therapy. Selection of appropriate patients for dose reduction enrollment remains decisive. Proton therapy has the potential to transform HNC treatment, due to its properties to achieve higher dose conformity and drastically reduce dose to surrounding tissues. The number of clinical trials testing the use of RT with immunotherapy is rapidly growing, in the metastatic and primary setting alike. While evidence in support of this combination continues to accumulate, results of ongoing trials will help to determine the optimal dose, technique and sequencing of RT with immunotherapy. DaRT represents an exciting new field of research, but human data is warranted in order to determine its safety and efficacy. Surely, improvement on HNC treatments should be primarily efficacy-driven.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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