NEOPLASIA
www.neoplasia.com

Volume 20 Number xx pp. 227–232 227

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.

Neoplasia (2018) 20, 227–232

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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Received 25 September 2017; Accepted 3 January 2018

1476-5586/18
https://doi.org/10.1016/j.neo.2018.01.002

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