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Overview

Neurocognitive Function After (Chemo)-Radiotherapy for Head and Neck Cancer

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Abstract

Radical radiotherapy has a pivotal role in the treatment of head and neck cancer (HNC) and cures a significant proportion of patients while simultaneously sparing critical normal organs. Some patients treated with radical radiotherapy for HNC receive significant radiation doses to large volumes of brain tissue. In fact, intensity-modulated radiotherapy techniques for HNC have been associated with a net increase in irradiated brain volumes. The increasing use of chemoradiotherapy for HNC has additionally exposed this patient population to potential neurotoxicity due to cytotoxic drugs. Patients with HNC may be particularly at risk for adverse late brain effects after (chemo)-radiotherapy, such as impaired neurocognitive function (NCF), as risk factors for the development of HNC, such as smoking, excess alcohol consumption and poor diet, are also associated with impaired NCF. The relatively good survival rates with modern treatment for HNC, and exposure to multiple potentially neurotoxic factors, means that it is important to understand the impact of (chemo)-radiotherapy for HNC on NCF, and to consider what measures can be taken to minimise treatment-related neurotoxicity. Here, we review evidence relating to the late neurotoxicity of radical (chemo)-radiotherapy for HNC, with a focus on studies of NCF in this patient population.

Key words: Chemotherapy; head and neck cancer; neurocognitive impairment; radiotherapy

Statement of Search Strategies Used and Sources of Information

Pubmed search for (radiotherapy OR irradiation OR chemotherapy OR radiochemotherapy) AND (neuropsychologic OR cognitive OR memory OR intelligence OR attention OR neuropsychology) AND (head and neck) AND English [Language]. Reference lists were examined and cited articles retrieved. Clinical trial information was obtained from published abstracts and clinicaltrials.gov.

Introduction

Head and neck cancer (HNC) is the fourth most common cancer worldwide [1,2] and its incidence is increasing, at least in part due to an epidemic of infection with high-risk strains of the human papillomavirus [1,3–6]. The changing epidemiology of HNC over the last three decades in Western countries has resulted in an increasing cohort of younger patients presenting with potentially curable disease [4,6]. These epidemiological changes have occurred at the same time as major technological advances in the delivery of radical treatment for HNC, which have the potential to significantly improve patient outcomes [7–10]. With an increasing number of younger patients, and with the enhanced potential for curative treatment, comes the need for an increased focus on efforts to minimise the long-term morbidities associated with radical treatment for HNC.

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About two-thirds of patients with HNC present with locally advanced disease without evidence of distant metastases and are treated with multimodality locoregional therapy [1,9,10]. A combination of surgery, radiotherapy and chemotherapy is used in an attempt to eradicate disease while preserving organ function. Radiotherapy has a pivotal role in the treatment of HNC and most patients with HNC will receive radiotherapy, with or without induction and/or concomitant chemotherapy [11]. The morbidity associated with radiotherapy to the head and neck relates to the irradiation of the normal tissues and organs surrounding the target tumour volume. As HNC primaries, and their associated cervical lymph node metastases, often lie in close proximity to the brain and other central nervous system (CNS) structures, a portion of the volume of these organs inevitably lies in the path of radiation beams used to deliver radiotherapy [12,13]. A typical radical radiotherapy plan for HNC, therefore, inevitably delivers some radiation dose to the CNS and particularly to the following brain regions: basal frontal lobes, temporal lobes, olfactory bulbs, pituitary, hypothalamus, cerebellum and brainstem (Figure 1). Depending on the location of the primary tumour, radical radiotherapy for HNC may expose these brain structures to radiation doses close to their tolerances [14–18]. The CNS radiotherapy tolerance doses used to constrain intensity-modulated radiotherapy (IMRT) planning relate to the risk of tissue necrosis rather than to any lesser, but nevertheless still potentially clinically significant, types of tissue injury [18,19]. In particular, existing CNS radiotherapy tolerance doses do not address the risk of radiotherapy-induced impairment of neurocognitive function (NCF), which is a long recognised and potentially debilitating sequela to brain irradiation [16,20–23].

That radical radiotherapy for HNC can result in the delivery of clinically significant radiation doses to the brain, leading to radiation-induced brain injury (RIBI) and associated neurotoxicity, including impaired NCF, has been recognised for decades, particularly in the context of radical radiotherapy for patients with nasopharyngeal carcinoma (NPC) [16,24]. The development of IMRT has resulted in significantly improved conformality of the delivered radiotherapy dose to tumour target volumes, enabling improved dose-sparing of adjacent organs at risk, while maintaining radical radiation dose delivery to the tumour target volume [11,25,26]. However, typical IMRT plans consist of more fields with a greater number of beam entry points, while requiring two to three times more monitor units, than a conventional radiotherapy (CRT) plan, resulting in a net increase in the integral radiation dose to the patient (Figure 1). This so-called low-dose bath effect of IMRT delivery has given rise to concerns regarding the possibility of increased late normal tissue toxicity in irradiated areas not specifically spared by the IMRT plan and also regarding the possibility of increased rates of second, radiotherapy-induced, malignancies [27–29]. IMRT for HNC was associated with increased acute neurotoxicity in a prospective randomised trial of parotid-sparing IMRT versus CRT, due to increased dose to the posterior-fossa [12,25]. The acute neurotoxicity of IMRT for HNC manifests predominantly as fatigue, which occurs in more than

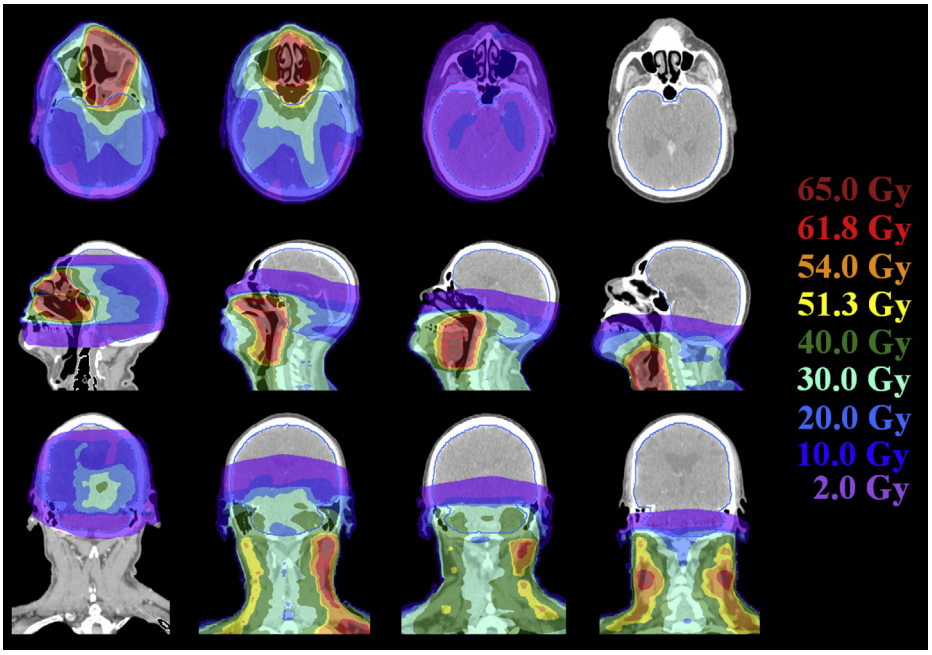

Fig 1. Brain radiotherapy doses resulting from the bath effect of intensity-modulated radiotherapy for head and neck cancer. Radiotherapy planning computed tomography scans with planned intensity-modulated radiotherapy dose distributions shown as an overlying colourwash. From left to right: ethmoid sinus primary; nasopharyngeal primary; oropharyngeal primary; laryngeal primary. Mid-sagittal slices are shown with axial and coronal slices taken through approximately equivalent levels in each case. Isodose levels are as shown by the colour bar. In each case the high-dose planning target volume prescription was 65 Gy and the elective dose planning target volume prescription was 54 Gy, both delivered in 30 fractions over 6 weeks.

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