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Original Article

Target Volume Definition for Intensity-modulated Radiotherapy after Induction Chemotherapy and Patterns of Treatment Failure after Sequential Chemoradiotherapy in Locoregionally Advanced Oropharyngeal Squamous Cell Carcinoma

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Abstract

Aims: To validate our approach to target volume definition for intensity-modulated radiotherapy (IMRT) after induction chemotherapy and to analyse the pattern of treatment failure in patients with locoregionally advanced oropharyngeal squamous cell carcinoma (SCC) after sequential chemoradiotherapy (SCRT).

Materials and methods: We studied all patients with locoregionally advanced oropharyngeal SCC treated with SCRT, definitive IMRT and no prior surgery between December 2004 and February 2010. SCRT consisted of three cycles of induction chemotherapy followed by IMRT with concurrent weekly chemotherapy. Our approach to IMRT tumour volume definition after induction chemotherapy was similar to recommendations from published clinical practice guidelines. Volumetric expansion was used to create the high-dose clinical target volume with a margin of 10 mm. The high-dose planning target volume (PTV) was treated to 65 Gy, whereas the prophylactic-dose PTV received 54 Gy over 30 fractions using the simultaneous integrated boost technique. The location and extent of each treatment failure was recorded, reconstructed on the planning computed tomography images and analysed using the dose distribution of the IMRT plan.

Results: Fifty-two patients were included. The median follow-up was 32.2 months (range 5.0–67.1 months). There were seven local failures, no regional recurrences and one with distant disease. None of the patients required post-treatment neck dissection. All local failures were in-field and occurred within the high-dose PTV. There were no marginal recurrences. Actuarial recurrence-free, disease-specific and overall survival rates at 3 years were 83.9, 85.9 and 79.7%, respectively.

Conclusions: The absence of marginal recurrences validated the approach to IMRT target volume definition after induction chemotherapy proposed by clinical practice guidelines and practised at our institution. It suggested a lack of benefit with the use of larger geometric margins and additional anatomical expansion for the high-dose clinical target volume. SCRT resulted in excellent regional and distant disease control in patients with locoregionally advanced oropharyngeal SCC.

Key words: Intensity-modulated radiotherapy; locoregionally advanced oropharyngeal squamous cell carcinoma; patterns of treatment failure; sequential chemoradiotherapy; target volume definition

Introduction

Intensity-modulated radiotherapy (IMRT) is commonly used in the non-surgical management of locoregionally advanced squamous cell carcinoma (SCC) of the oropharynx. It produces a more conformal dose distribution than other radiation techniques and offers the potential for improved target volume coverage with better sparing of adjacent uninvolved tissues such as the major salivary glands. The steep dose gradient between the target volume and organs at risk inherent in IMRT means that any uncertainty in target volume definition can potentially lead to an increased risk of marginal tumour recurrence and reduced locoregional tumour control by under-dosing the tumour edge. Precise delineation of the target volume and accurate treatment delivery are thus essential.

Recent encouraging results from the TAX 324 study, showing a survival benefit with the addition of docetaxel to cisplatin and 5-fluorouracil, have generated renewed interest

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in the use of induction chemotherapy in locoregionally advanced SCC of the head and neck (SCCHN) [1]. Induction chemotherapy produces high response rates of 60–90% in SCCHN, including complete responses [2]. It may eradicate micrometastatic disease at distant sites and reduce tumour volume before chemoradiation (CRT) [2]. Tumour regression with induction chemotherapy can result in changes to the patient anatomy and tumour extension and dimension. This makes IMRT target volume delineation after induction chemotherapy difficult and challenging. To the best of our knowledge, there have been no published studies on gross tumour volume (GTV) definition for IMRT after induction chemotherapy in SCCHN.

The objectives of this study were to validate the approach to IMRT target volume definition after induction chemotherapy proposed by recently released clinical practice guidelines [3] and practised at our institution and to analyse the pattern of treatment failure in patients with locoregionally advanced oropharyngeal SCC managed with sequential chemoradiotherapy (SCRT) and IMRT.

Materials and Methods

Study Population

Patients with American Joint Committee on Cancer stage III-IVB SCC of the oropharynx were eligible for this study if they had received induction chemotherapy and definitive IMRT at our institution between December 2004 and February 2010. During this period, IMRT was used in all patients who required bilateral neck irradiation to facilitate sparing of the contralateral parotid gland to reduce the risk of long-term xerostomia. Exclusion criteria were radical surgery, including neck dissection, before IMRT and a follow-up of less than 12 months in the absence of persistent or recurrent disease or death. Patients with well-lateralised, T0-T2 N0-N2b M0 SCC of the tonsil (no tongue base invasion or greater than 1 cm extension into the soft palate) were managed with unilateral three-dimensional conformal radiotherapy and were also excluded from the study.

Treatment Approach

SCRT consisted of up to three cycles of induction chemotherapy with cisplatin 100 mg/m^2 on day 1 and continuous infusion 5-fluorouracil 1000 mg/m^2/day days 1–5 administered every 3 weeks. Those with no clinical or radiological evidence of disease progression (as defined by the Response Evaluation Criteria In Solid Tumours) on induction chemotherapy proceeded to IMRT with once-weekly concurrent carboplatin 100 mg/m^2. The GTV consisted of the primary tumour and involved lymph nodes. The primary tumour GTV was defined based on the disease extension pre-induction chemotherapy rather than dimension and included all regions involved by tumour at presentation. It was thus delineated using information from the pre-treatment clinical evaluation and diagnostic imaging studies. In some cases, tumour regression with induction chemotherapy resulted in significant alteration in patient anatomy such that direct mapping of the original tumour dimension from the diagnostic images on to the planning computed tomography (CT) led to the inclusion of adjacent uninvolved structures. In these cases, the GTV was modified to take the post-induction chemotherapy patient anatomy into account while reflecting the initial pattern of disease. Lymph nodes were presumed to be involved if they measured more than 10 mm in short axis diameter on pre-therapeutic imaging (5 mm in the case of retropharyngeal nodes), contained necrotic centres, showed extracapsular extension or showed increased uptake on staging fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT). The lymph node dimension after induction chemotherapy was used to delineate the nodal GTV. However, this was expanded to include regions involved by extracapsular extension pre-treatment. An example of our approach to primary tumour and nodal GTV definition after induction chemotherapy is shown in Figure 1.

We used volumetric expansion and a two dose level technique when defining the clinical target volumes (CTVs). Both the primary tumour and the nodal GTV were expanded by a margin of 10 mm to create a high-dose CTV that took into account microscopic extension and extracapsular spread. This was then edited off natural barriers to tumour spread (such as bone and air) and expanded to include the involved nodal levels and structures at high risk of harbouring microscopic disease, such as the entire sternocleidomastoid muscle at the involved nodal level in the presence of extracapsular extension. In N0 cases, the high-dose CTV would encompass the first echelon nodes (level II) adjacent to the primary tumour CTV. The prophylactic-dose CTV included the high-dose CTV and nodal sites at lower risk of metastasis. The nodal CTVs were contoured using consensus guidelines [4,5]. Figure 2 shows an example of our approach to the delineation of the high-dose and prophylactic-dose CTV. Each CTV was expanded by an isotropic margin of 3 mm to obtain the corresponding planning target volume (PTV) based on local data on systematic and random errors. The high-dose PTV was treated to 65 Gy, whereas the prophylactic-dose PTV received 54 Gy over 30 fractions using the simultaneous integrated boost technique. IMRT treatment was delivered once daily, 5 days per week over 6 weeks with five or seven equally spaced coplanar, non-opposed beams and 6 MV photons. Whole-field IMRT was used if the high-dose PTV extended below the inferior border of the cricoid cartilage. Otherwise, a matched anterior neck beam was used to treat the lower cervical nodes.

FDG PET/CT was obtained in patients with N2-3 disease 12 weeks after IMRT completion to assess the need for post-treatment neck dissection. This was carried out in those with residual neck nodes after SCRT showing focal increased FDG uptake [6]. Salvage surgery was also carried out in patients with biopsy-proven resectable persistent or recurrent disease at the primary site and/or neck in the absence of distant metastases.