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Original Article

Induction Chemotherapy Followed by Chemo-intensity-modulated Radiotherapy for Locally Advanced Nasopharyngeal Cancer

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Abstract

Aims: To determine the toxicity and tumour control rates after chemo-intensity-modulated radiotherapy (chemo-IMRT) for locally advanced nasopharyngeal cancers (LA-NPC).

Materials and methods: Patients with LA-NPC were enrolled in a trial to receive induction chemotherapy followed by parotid-sparing chemo-IMRT. The primary site and involved nodal levels received 65 Gy in 30 fractions and at risk nodal levels received 54 Gy in 30 fractions. Incidence of ≥grade 2 subjective xerostomia was the primary end point. Secondary end points included incidences of acute and late toxicities and survival outcomes.

Results: Forty-two patients with American Joint Committee on Cancer stages II (12%), III (26%) and IV (62%) (World Health Organization subtype: I [5%]; II [40%]; III [55%]) completed treatment between January 2006 and April 2010 with a median follow-up of 32 months. Incidences of ≥grade 2 acute toxicities were: dysphagia 83%; xerostomia 76%; mucositis 97%; pain 76%; fatigue 99% and ototoxicity 12%. At 12 months, ≥grade 2 subjective xerostomia was observed in 31%, ototoxicitiy in 13% and dysphagia in 4%. Two year locoregional control was 86.2% (95% confidence interval: 70.0–94.0) with 2 year progression-free survival at 78.4% (61.4–88.6) and 2 year overall survival at 85.9% (69.3–93.9).

Conclusions: Chemo-IMRT for LA-NPC is feasible with good survival outcomes. At 1 year, 31% experience ≥grade 2 subjective xerostomia.

Key words: Chemoradiotherapy; IMRT; nasopharyngeal cancer; radiotherapy; sequential

Introduction

In Europe, the incidence of nasopharyngeal cancers (NPC) is 1.1 per 100 000 [1] and in the UK 0.39 per 100 000 [2]. Treatment with radiotherapy is technically challenging. Clinical target volumes (CTVs) lie in close proximity to the optic apparatus and brainstem, which make optimal dose delivery difficult. Additionally, the parotid glands have commonly been irradiated to a high dose, resulting in long-term xerostomia. Two phase III studies have reported on parotid gland-sparing intensity-modulated radiotherapy (IMRT) versus conventional radiotherapy. Pow *et al.* [3] randomised 50 patients between the two radiotherapy techniques. Recovery of parotid function at 1 year was superior with IMRT compared with conventional radiotherapy (83% versus 9.5%). Global quality of life was significantly superior with IMRT when compared with the conventional group. Kam *et al.* [4] randomised 60 patients between IMRT and conventional radiotherapy. The primary end point of Radiation Therapy Oncology Group (RTOG) xerostomia score was significantly better with IMRT (39.3% versus 82.1%, $P = 0.001$), as were the secondary end points of parotid and floor of mouth salivary flow rates. However, both these studies reported patients with early stage NPCs who received radiotherapy alone.

It is reasonable to expect a higher degree of xerostomia in more advanced cases of NPC. Treatment includes irradiation of the bilateral parapharyngeal spaces, which can result in a high dose to the deep lobe of the parotid glands. In the UK, NPC is very rare and no clinical experience with

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outcomes of modern treatment with IMRT has been published. The purpose of this study was to determine the toxicity and tumour control rates after chemo-IMRT for locally advanced NPC (LA-NPC) and in particular to determine the incidence of high grade (≥grade 2) subjective xerostomia at 1 year.

Materials and Methods

Study Objectives/Patient Eligibility

Patients diagnosed with histologically confirmed NPC were eligible for the study. Patients <16 years old or with a previous malignancy other than non-melanomatous skin cancer were excluded. Pre-treatment evaluations comprised history and examination, examination under anaesthesia, biopsy, dental assessment, haematological and biochemical parameters, computed tomography scan of the head, neck and chest and magnetic resonance imaging of the head and neck. Disease was staged according to the 1997 American Joint Committee on Cancer (AJCC) criteria [5]. Patients were eligible for the trial if they had started induction chemotherapy at another institution. All patients signed written informed consent and the study was approved by the institutional research and ethics committee (Royal Marsden Hospital CCR 2608, clinical trials registration number: NCT02149641).

The primary objective was to determine the incidence of ≥grade 2 xerostomia at 1 year using the subjective component of LENTSOMA [6]. Secondary objectives included: acute and other late radiation toxicities, locoregional disease-free survival, progression-free survival and overall survival.

Trial Design

This trial was a prospective longitudinal cohort study to determine the incidence of ≥grade 2 subjective xerostomia (LENTSOMA) in patients treated with chemo-IMRT for LA-NPC. A sample size of 42 patients was selected so as to compare the incidence of ≥grade 2 subjective xerostomia with an equivalent number of patients with oropharyngeal and hypopharyngeal squamous cell cancers who received IMRT in the PARSPORT trial [7].

Treatment

Chemotherapy schedule

Patients treated at the Royal Marsden Hospital received induction chemotherapy with two cycles of cisplatin (75 mg/m^2) day 1 and 5-fluorouracil (1000 mg/m^2) days 1–4 on a 21 day cycle. Patients received concomitant cisplatin 100 mg/m^2 on days 1 and 29 of IMRT. Where cisplatin was contraindicated, carboplatin (AUC5) or cetuximab (initial dose 400 mg/m^2 then 250 mg/m^2 weekly during radiotherapy) was given. Patients could be recruited to the study if they had received other induction chemotherapy schedules in other institutions.

Radiotherapy technique

Patients were recruited to the study during their induction chemotherapy schedule. Patients were immobilised and contrast-enhanced computed tomography scans were taken at 2 mm intervals through the head and neck region. Target volumes and organs at risk (optic apparatus, brainstem and spinal cord) were delineated following ICRU-50 and ICRU-62 guidelines. Ipsilateral and contralateral parotid glands (reference to the location of the primary site) were outlined. In addition, combined superficial lobes of both parotid glands were outlined as a separate volume. Both cochleas were outlined retrospectively. The gross tumour volume (GTV) comprised residual disease in the nasopharynx and lymph nodes after induction chemotherapy. The CTV for primary site and involved nodal groups (CTV1) comprised the GTV with a 1 cm margin, including the entire nasopharynx, bilateral parapharyngeal spaces, the posterior half of the nasal cavity, inferior half of sphenoid sinus (or entire sphenoid if involved), retropharyngeal nodes and lymph node groups with macroscopic disease. Pre-treatment diagnostic imaging was reviewed to confirm that sites of macroscopic disease reported at presentation were encompassed within CTV1. CTV2 comprised the superior half of the sphenoid sinus (if uninvolved at presentation) and lymph node groups at risk of harbouring microscopic disease. Planning target volumes (PTVs) were constructed from CTVs with a 3 mm margin.

Radiotherapy was delivered using a five- or seven-beam simultaneous integrated boost IMRT technique. Doses were prescribed to the median dose-volume point of the PTV1 dose volume histogram at 65 Gy in 30 daily fractions; 54 Gy in 30 daily fractions were prescribed to PTV2. Maximum dose constraints applied to the spinal cord and brainstem were 46 Gy and 54Gy, respectively; the optic chiasm, 54 Gy, optic nerves and eyes 55 Gy. A dose constraint was applied to the contralateral parotid gland and the optimisation was weighted to particularly spare the superficial lobes of both parotid glands, to a mean dose of less than 26 Gy. No dose constraint was applied to the cochleas.

Outcome Assessment

A complete response was defined as complete disappearance of disease as evaluated clinically including nasendoscopy and computed tomography and magnetic resonance imaging at up to 3 months after completing treatment. RECIST criteria were used to record the radiological response. Where residual lesions were present in the nasopharynx or neck, biopsies or fine needle aspirations were carried out to determine the presence of persistent disease. A neck dissection was undertaken if patients showed a clinical or radiological partial response, stable disease or progressive disease after radiotherapy. Recurrence was defined as clinical, radiological and/or histopathological evidence of disease presenting 3 months after completing radiotherapy. Where possible, patients proceeded to salvage surgery for persistent or recurrent disease.

Acute toxicity scores were recorded using NCI-CTCAE v3.0 [8] weekly during chemo-IMRT, for 4 weeks of

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