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Original Article

Hypofractionated Accelerated Radiotherapy with Concurrent Carboplatin for Locally Advanced Squamous Cell Carcinoma of the Head and Neck

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Abstract

Aims: Hypofractionated accelerated radiotherapy with concurrent carboplatin utilises both advantages of altered fractionation and synchronous chemotherapy to maximise local control in locally advanced head and neck cancer. Such fractionation schedules are increasingly used in the intensity-modulated radiotherapy era and the aim of this study was to determine the outcome of hypofractionated accelerated radiotherapy with carboplatin.
Materials and methods: One hundred and fifty consecutive patients with squamous cell carcinoma of the larynx, oropharynx, oral cavity and hypopharynx (International Union Against Cancer [IUAC] stage II–IV) treated with 55 Gy in 20 fractions over 25 days with concurrent carboplatin were analysed. Outcome measures were 2 year overall survival, local control and disease-free survival.
Results: The median follow-up in surviving patients was 25 months. IUAC stages: II $n = 15$; III $n = 42$; IV $n = 93$. Two year overall survival for all patients was 74.9% (95% confidence interval 66.0–81.7%). Two year local control was 78.3% (95% confidence interval 69.6–84.8%). Two year disease-free survival was 67.2% (95% confidence interval 58.3–74.7%). There were 135 patients with stage III and IV disease. For these patients, the 2 year overall survival, local control and disease-free survival were 74.3% (95% confidence interval 64.7–81.6%), 79.1% (95% confidence interval 69.8–85.9%) and 67.6% (95% confidence interval 58.0–75.4%), respectively. Prolonged grade 3 and 4 mucositis seen at $\geq$4 weeks were present in 9 and 0.7%, respectively. Late feeding dysfunction (determined by dependence on a feeding tube at 1 year) was seen in 13% of the surviving patients at 1 year.
Conclusion: Hypofractionated accelerated radiotherapy with concurrent carboplatin achieves a high local control. This regimen should be considered for a radiotherapy dose-escalation study using intensity-modulated radiotherapy.

Key words: Acceleration; carboplatin; head and neck carcinoma; hypofractionation; radiotherapy

Introduction

Meta-analyses in locally advanced squamous cell carcinoma of the head and neck (SCCHN) have shown that the same benefit in overall survival can be achieved using dose-escalated hyperfractionated radiotherapy or synchronous chemotherapy [1,2]. Hyperfractionation has received considerable attention [3], but many departments have not been able to implement such resource-intense schedules [4].

Simultaneous integrated boost intensity-modulated radiotherapy (IMRT) has led to increased interest in the use of hypofractionated schedules [5]. The principle reason is the ability to deliver high doses per fraction to macroscopic disease while simultaneously delivering smaller doses per fraction to nodes and volumes at risk of microscopic spread requiring a prophylactic dose, thereby reducing late normal tissue damage. There have been concerns that large fraction sizes may lead to greater toxicity in late-responding tissues, but the total dose must be taken into account. Fowler [6] recently reported radiobiological modelling predicting a lower rate of late toxicity with a hypofractionated accelerated regimen (55 Gy in 20 fractions over 25 days) when compared with standard fractionation (70 Gy over 35

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fractions over 46 days), yet with a comparable rate of local control as a result of reduced overall treatment time obviating tumour repopulation [6,7]. Additional advantages of this regimen are that it ensures an efficient use of radiotherapy resources and minimises poor compliance in this particular group of patients.

Although some centres are now investigating the use of hypofractionation, there are limited data before the use of IMRT. The Queen Elizabeth Hospital Cancer Centre, Birmingham, UK has been using a hypofractionated accelerated radiotherapy schedule (55 Gy in 20 daily fractions over 25 days) with concurrent carboplatin since 2002. The safety of the schedule was demonstrated in a phase I trial [8]. A previous analysis of 81 patients treated with either synchronous methotrexate or carboplatin showed local control in line with published studies [9]. In this report we include only patients receiving concurrent carboplatin, updating the follow-up on 39 previously reported patients and including 111 new patients. This constitutes the largest series of platinum-based hypofractionated accelerated radiochemotherapy for locally advanced SCCHN.

Materials and Methods

Consecutive patients with biopsy-proven squamous cell carcinoma of the larynx, oropharynx, oral cavity and hypopharynx (International Union Against Cancer [IUAC] stage II–IV) who underwent hypofractionated accelerated radiotherapy with concurrent carboplatin between November 2002 and August 2008 were included in the study. Patients with distant metastases were not included. The hospital notes were examined retrospectively with additional data retrieved from dieticians, general practitioners and the cancer registry. The information obtained included: patient characteristics; tumour site and stage; total radiation dose and overall radiotherapy treatment time; number of carboplatin doses given and carboplatin doses; details of any neoadjuvant chemotherapy; toxicity; details of any planned neck dissections and salvage surgery; recurrence and survival data.

Patients were assessed weekly during treatment with a clinical examination and blood profile (full blood count and biochemistry). Toxicity was assessed using the 1995 edition of the National Cancer Institute common toxicity criteria. The acute toxicity data collected included grade of mucositis, dysphagia, skin reaction and bone marrow toxicity. The use of a feeding tube and details of any hospital admissions were also collected. The incidence of prolonged confluent mucositis (defined as grade 3 mucositis at 4 weeks after the completion of radiotherapy) and the dependence of a feeding tube at 1 year were recorded for long-term toxicity.

Radiotherapy

All patients underwent simulation and treatment in a beam directional shell using conventional or conformal planning. Two lateral fields using megavoltage photons were used to treat the primary tumour and upper neck with a matched anterior field to treat the lower neck where appropriate. Electrons were used to treat volumes overlying the spinal cord after the first 12 fractions. The intended radiation dose to the primary tumour and involved nodes was 55 Gy in 20 fractions prescribed to the isocentre; treating 5 days a week over 4 weeks. 50 Gy in 20 fractions was given to the neck after pre-radiotherapy neck dissection. 41.25 Gy in 15 fractions was given as a prophylactic dose to clinically and radiologically negative but at risk nodal areas.

Concurrent Chemotherapy

Patients received outpatient carboplatin chemotherapy in weeks 1 and 4. The study group included 19 patients participating in a previously reported dose-escalation study with an area under the curve (AUC) dose ranging from 3.5 to 6 [8]. Therefore, not all patients received the current institutional recommended dosage of two doses of carboplatin at AUC 4.5.

Statistical Analysis

The main outcomes studied were overall survival, local control and disease-free survival at 2 years. The Kaplan–Meier method was used for analysis. Two sample survival comparisons were compared using the Log-rank test and trends by stage were tested using proportional hazards models. Overall survival was defined from the start of radiotherapy until the date of death for those who died or censored at the date last seen alive. Local control was defined as recurrence either at the primary site or the locoregional nodes. Time to locoregional recurrence was calculated from the date of starting radiotherapy to the date of locoregional recurrence. For analysis of local control, patients without locoregional recurrence were censored at their last follow-up date or the date of death. Disease-free survival was defined until the date of recurrence or death, and patients who were alive without recurrence were censored at the last follow-up visit. Overall treatment time (OTT) was defined as the number of days from the initiation to the completion of radiotherapy. For example, the OTT was taken to be 25 days for a 4 week radiotherapy schedule starting on a Monday and completing on a Friday in the fourth week.

Results

In total, 150 consecutive patients meeting the study criteria were identified and included in the analysis. The median age of patients was 58 years (range 31–78 years) with 127 men and 23 women. The stage distribution of patients was: stage II in 15 patients (10%); stage III in 42 patients (28%); stage IV in 93 patients (62%). Table 1 lists the TNM stage distribution. The distribution by site of primary tumour was: oropharynx 87 patients (58%); larynx 46 patients (30.7%); hypopharynx 13 patients (8.7%); oral cavity four patients (2.6%).

Of the 150 patients, 146 received the intended radiotherapy dose. OTT was within 25 days in 113 patients