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Original Article

Feasibility of Dose-escalated Hypofractionated Chemoradiation in Human Papilloma Virus-negative or Smoking-associated Oropharyngeal Cancer

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Abstract

Aims: Oropharyngeal squamous cell carcinoma (OPSCC) can be divided into favourable and poor prognostic groups by association with human papilloma virus (HPV) and smoking. This study prospectively investigated a dose-intensified schedule in poor/intermediate prognosis OPSCC.
Materials and methods: Patients with p16/HPV-negative or p16-positive N2b OPSCC with a greater than 10 pack-year smoking history were eligible. Patients were planned to receive 64 Gy in 25 fractions with cisplatin. The primary end point was absence of grade 3 mucositis at 3 months.
Results: Fifteen patients were recruited over 14 months. All patients completed a minimum of 2 years of follow-up. All patients completed full-dose radiotherapy within a median treatment time of 32 days (31–35). Grade 3 mucositis was absent in all patients at 3 months. There was one grade 4 toxicity event due to cisplatin (hypokalaemia). Complete response rates at 3 months were 100% and 93% for local disease and lymph nodes, respectively. One patient developed metastatic disease and subsequently died. Overall survival at 2 years was 93% (95% confidence interval 61–99%).
Conclusions: The schedule of 64 Gy in 25 fractions with concomitant chemotherapy is tolerable in patients with poor and intermediate prognosis OPSCC.

Key words: Accelerated hypofractionation; human papilloma virus; oropharyngeal cancer; smoking

Introduction

Outcomes for oropharyngeal squamous cell carcinoma (OPSCC) are divided into favourable and poor prognostic groups by association with human papilloma virus (HPV). Within the pivotal Radiation Therapy Oncology Group (RTOG) study by Ang *et al.* [1], the 3 year overall survival for HPV-negative tumours treated with chemoradiation was 57.1% compared with 82.4% ($P < 0.001$) for HPV-positive tumours. Although there is interest in reducing the intensity of treatment in patients with HPV-positive OPSCC [2,3], HPV-negative OPSCC patients, and HPV-positive heavy smokers, warrant investigation of treatment intensification to improve survival.

Platinum-based chemoradiotherapy remains standard practice for locally advanced OPSCC [4]. A meta-analysis of 15 randomised trials with over 5000 participants showed that altered fractionation radiotherapy yielded an absolute 5 year survival benefit of 3.4% [5]. Historically, 2 Gy per fraction was the standard daily dose and interest in intensification or acceleration was restricted to standard or hyperfractionated schedules based upon sound radiobiological models [6]. Hypofractionation can also be used to accelerate. However, concerns with late toxicity have restricted use to small volume head and neck cancers or cancers with a low α/β ratio, e.g. prostate, where fractionation practice has changed rapidly [7]. With intensity-

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modulated radiotherapy (IMRT), a synchronous integrated boost (SIB) technique is standard practice and modest hypofractionation has emerged as a standard approach. Using radiobiological parameters developed by Fowler *et al.* [8,9] it was possible to develop a dose-escalated hypofractionated schedule to improve local control and survival within acceptable toxicity limits (Table 1). Using this approach, the schedule of 64 Gy over 25 daily fractions and synchronous chemotherapy was selected.

This paper reports the primary toxicity end points and 2 year local control to explore the feasibility of 64 Gy in 25 fractions with concurrent chemotherapy in patients with poor and intermediate prognosis OPSCC.

Materials and Methods

Study Design and Eligibility

This was a single-arm, feasibility study. Patients with OPSCC were identified and screening included a central review to confirm p16 and HPV status. HPV DNA was assessed using high-risk HPV *in situ* hybridisation and p16 immunohistochemistry using a proprietary kit. Follow-up was planned for 5 years. The study received ethical approval from the National Health Service Health Research Authority.

Patients with histologically proven HPV and p16-negative OPSCC, or patients with stage N2b-3 p16-positive tumours and a greater than 10 pack-year history of smoking, deemed suitable for radical primary chemoradiotherapy with curative intent requiring bilateral neck radiotherapy were eligible. Study inclusion criteria stipulated that all patients had: age $\geq$18 and $<$70 years; World Health Organisation (WHO) performance status 0 or 1; adequate bone marrow reserve (absolute neutrophil count $>$1800 cells/mm^3, platelets $>$100 000 cells/mm^3, haemoglobin $>$ 8.0 g/dl); creatinine clearance $>$50 ml/min; and gave full written informed consent.

Exclusion criteria included any prior invasive malignancy (except basal cell carcinoma and cervical intraepithelial neoplasia) within the last 3 years; prior radiotherapy to the head and neck region; pregnancy and/or lactation; reproductive capability and unwillingness to avoid conception; contraindications to cisplatin and carboplatin chemotherapy including active vascular disease (e.g. myocardial infarction within the last 6 months, angina and symptomatic peripheral vascular disease); treatment with palliative intent; non-squamous carcinoma histology; nasopharynx, larynx, hypopharynx, salivary gland or sino-nasal primary site; other physical or psychiatric disorder that could interfere with compliance or consent.

Treatment

The prescribed radiotherapy dose was 64 Gy in 25 fractions to the primary tumour and involved nodes, with elective irradiation to clinically uninvolved nodes to a dose of 50 Gy in 25 fractions. An intermediate dose of 56 Gy in 25 fractions to regions deemed at high risk of microscopic disease was permitted. Treatment was delivered using one daily fraction with an intended overall treatment time within 32 days.

All patients were immobilised supine with a Fibreplast™ thermoplastic mask of the head, neck and shoulders in combination with either a vacuum bag or Mould Care cushion under the neck. A planning computed tomography scan with intravenous contrast was taken in the treatment position with 2 mm computed tomography slices. Where indicated, bolus was applied. The gross tumour volume (GTV) was defined as the primary tumour and involved lymph nodes determined by clinical and radiological findings. GTVp was the primary tumour delineated based on

Table 1
Radiobiological basis for selection of the trial regimen

Total dose (Gy)	Fraction number	Overall treatment time (days)	Time corrected BED tumour† (Gy_{10})	Log_{10} cell kill	Time corrected BED mucosa‡ (Gy_{10})	BED late§ (Gy_3)	BED late‖ (Gy_2)
70	35	46	68	10.3	53	117	140
65	30	39	67	10.2	54	112	135
60	30	39	60	9.1	47	100	120
54	30	39	52	7.9	38	86	103
64.5	25	32	74	11.2	61	120	148
64*	25	32	73	11.1	61	119	146
63	25	32	72	10.9	59	116	142
62.5	25	32	71	10.8	58	115	141
56*	25	32	61	9.3	49	98	119
50*	25	32	53	8.0	40	83	100

BED, biologically effective dose; t_k, kick-off time or time of onset of accelerated repopulation; t_p, average doubling time during accelerated repopulation.

* Dose levels used in the study.

† $\alpha/\beta = 10$ Gy, $\alpha = 0.35$ Gy^{-1}, $t_k = 21$ days, $t_p = 3$ days.

‡ $\alpha/\beta = 10$ Gy, $\alpha = 0.35$ Gy^{-1}, $t_k = 7$ days, $t_p = 2.5$ days.

§ $\alpha/\beta = 3$ Gy.

‖ $\alpha/\beta = 2$ Gy.

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