Clinical Oncology 26 (2014) 643–647

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

T-category Remains an Important Prognostic Factor for Oropharyngeal Carcinoma in the Era of Human Papillomavirus

P. Mackenzie *†, D. Pryor *†, E. Burmeister ‡§, M. Foote *†, B. Panizza †¶, B. Burmeister *†, S. Porceddu *†

* Department of Radiation Oncology, Princess Alexandra Hospital, Brisbane, Queensland, Australia
† School of Medicine, University of Queensland, St Lucia, Brisbane, Queensland, Australia
‡ Nursing Practice Development Unit, Princess Alexandra Hospital, Brisbane, Queensland, Australia
§ Centre for Health Practice Innovation, Griffith University, Nathan, Queensland, Australia
¶ Head and Neck Surgical Service, Princess Alexandra Hospital, Brisbane, Queensland, Australia

Received 7 November 2013; received in revised form 31 March 2014; accepted 7 May 2014

Abstract

Aims: To determine prognostic factors for locoregional relapse (LRR), distant relapse and all-cause death in a contemporary cohort of locoregionally advanced oropharyngeal squamous cell carcinoma (OSCC) treated with definitive chemoradiotherapy or radiotherapy alone.
Materials and methods: OSCC patients treated with definitive radiotherapy between 2005 and 2010 were identified from a prospective head and neck database. Patient age, gender, smoking history, human papillomavirus (HPV) status, T- and N-category, lowest involved nodal level and gross tumour volume of the primary (GTV-p) and nodal (GTV-n) disease were analysed in relation to LRR, distant relapse and death by way of univariate and multivariate analysis.
Results: In total, 130 patients were identified, 88 HPV positive, with a median follow-up of 42 months. On multivariate analysis HPV status was a significant predictor of LRR (hazard ratio 0.15; 95% confidence interval 0.05–0.51) and death (hazard ratio 0.29; 95% confidence interval 0.14–0.59) but not distant relapse (hazard ratio 0.53, 95% confidence interval 0.22–1.27). Increasing T-category was associated with a higher risk of LRR (hazard ratio 1.80 for T3/4 versus T1/2; 95% confidence interval 1.08–2.99), death (hazard ratio 1.37, 95% confidence interval 1.06–1.77) and distant relapse (hazard ratio 1.35; 95% confidence interval 1.00–1.83). Increasing GTV-p was associated with increased risk of distant relapse and death. N3 disease and low neck nodes were significant for LRR, distant relapse and death on univariate analysis only.
Conclusion: Tumour HPV status was the strongest predictor of LRR and death. T-category is more predictive of distant relapse and may provide additional prognostic value for LRR and death when accounting for HPV status.

Key words: Human papillomavirus; oropharyngeal squamous cell carcinoma; p16; prognosis; radiotherapy; staging

Introduction

The incidence of human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OSCC) is increasing [1–3]. Tumour HPV status has been shown to be the strongest predictor of locoregional control and overall survival in a number of large chemoradiotherapy (CRT) trials, but does not form part of the current American Joint Committee on Cancer (AJCC) staging system [4–6].

Using a recursive partitioning analysis of data from the Radiation Therapy Oncology Group (RTOG) trial 0129, Ang and colleagues [5] stratified patients as having a low, intermediate or high risk of death on the basis of HPV status, pack-years of tobacco smoking and AJCC T- and N-category [5].

A number of recent reports have also found volumetric assessment of primary and/or nodal volumes to be of additional prognostic value in OSCC, but these studies did not include HPV status as a prognostic variable [7,8].

This study aimed to determine prognostic factors associated with locoregional relapse (LRR), distant relapse and death in a contemporary cohort of locoregionally advanced OSCC treated with a uniform management protocol of

Author for correspondence: D. Pryor, Department of Radiation Oncology, The Princess Alexandra Hospital, Ipswich Rd, Woolloongabba, QLD 4120, Brisbane, Australia. Tel: +61-7-3176-7853; Fax: +61-7-3176-1983.
E-mail address: david_pryor@health.qld.gov.au (D. Pryor).

http://dx.doi.org/10.1016/j.clon.2014.06.007
0936-6555/

definitive CRT, reserving surgery for salvage. Data on HPV status, smoking history, age, gender, TNM staging, tumour volumetrics [gross tumour volume primary disease (GTV-p) and gross tumour volume nodal disease (GTV-n)] and lowest involved nodal level were available. We hypothesised that HPV status would be the strongest predictor of locoregional failure and overall survival and that nodal size and nodal extension below level III would predict for distant failure and overall survival.

Materials and Methods

Patient Population

Node-positive OSCC patients treated between 2005 and 2010 with definitive radiotherapy with or without systemic therapies were identified from our institutional ethics board-approved prospective head and neck database. Patients were required to have histologically confirmed OSCC and were staged according to the sixth AJCC staging system. Tumour HPV status was assessed by immunohistochemical analysis of the surrogate biomarker, p16. P16 positivity was defined as strong and diffuse nuclear and cytoplasmic staining in >70% of tumour cells.

Patient Management

All patients underwent an initial work-up with pan-endoscopy, biopsy and computed tomography-positron emission tomography. Treatment consisted of definitive radiotherapy with gross disease treated to a dose intensity equivalent to 70 Gy in conventional 2 Gy fractions over 7 weeks. The standard systemic therapy was concurrent high dose cisplatin chemotherapy (100 mg/m^2 days 1, 22 and 43), but concurrent cetuximab or radiotherapy alone was used for patients where cisplatin was contraindicated. The management policy post-CRT treatment has been previously described by Porceddu *et al.* [9]. Management of the neck in patients achieving a complete response at the primary site was guided by the 12 week post-treatment positron emission tomography. Patients underwent routine 3 monthly review for the first 2 years, 4 monthly to year 3 and 6 monthly to year 5, with repeat imaging guided by symptoms and clinical findings.

Statistical Analysis

Descriptive statistics were computed with differences between HPV status groups compared using Pearson chi-squared or Fisher's exact tests. LRR-free survival, distant

Table 1
Baseline characteristics according to human papillomavirus (HPV) status ($n = 130$)

Clinical characteristics	Number of patients (%)			*P* value
	HPV positive ($n = 88$)	HPV negative ($n = 29$)	HPV unknown ($n = 13$)	
Median age at presentation years (range)	54 (33–76)	60 (40–86)	56 (47–82)	0.45
Gender				
Male	78 (89)	22 (76)	10 (77)	0.18
Female	10 (11)	7 (24)	3 (23)	
Smoking status in pack-years				
≤10 pack-year history	34 (39)	1 (3)	5(38)	<0.01
>10 pack-year history	39 (44)	22 (76)	5 (38)	
Unknown	15 (17)	6 (21)	3 (23)	
T-category				
T1	13(15)	4 (14)	4 (31)	0.41
T2	31 (35)	8 (28)	6 (46)	
T3	31 (35)	12 (41)	1 (8)	
T4	13 (15)	5 (17)	2 (15)	
N-category				
N1 or N2	79 (90)	26 (90)	11 (85)	0.74
N3	9 (10)	3 (10)	2 (15)	
AJCC stage				
Stage III	7 (8)	1 (3)	1 (8)	0.75
Stage IVA/B	81 (92)	28 (97)	12 (92)	
GTV-primary (cm^3)				
Median (interquartile range)	19.4 (11–31)	27.5 (21–46)	8.8 (5–19)	<0.01
GTV-nodal (cm^3)				
Median (interquartile range)	19.1 (10–30)	11.3 (3–24)	21.9 (8–44)	0.68
Treatment				
Concurrent cisplatin	71 (80%)	19 (66%)	11 (84%)	0.56
Concurrent cetuximab	9 (10%)	7 (24%)	1 (8%)	
Concurrent chemotherapy other	4 (5%)	1 (3%)	0 (0%)	
Radiotherapy alone	4 (5%)	2 (7%)	1 (8%)	

AJCC, American Joint Committee on Cancer; GTV, gross tumour volume.