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Pre-treatment anaemia alters outcome in early squamous cell carcinoma of the larynx treated by radical radiotherapy

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Abstract

The purpose of this study was to examine the effect of pre-treatment anaemia on tumour recurrence and survival in patients treated with primary radiotherapy for early squamous cell carcinoma of the larynx. A retrospective analysis of 117 patients with previously untreated $T_1N_0M_0$ and $T_2N_0M_0$ squamous cell carcinoma of the larynx was carried out. Patients were considered anaemic if their pre-treatment haemoglobin levels were below 13 g/dl in males and 11.5 g/dl in females. The influence of pre-treatment haemoglobin levels on local control and survival were evaluated using Cox proportional hazards regression models.

Two- and five-year local-regional control estimates for anaemic patients were 58 per cent and 53 per cent respectively while patients with normal haemoglobin levels had two and five-year local-regional control rates of 90 per cent and 81 per cent respectively ($p = 0.002$). Multivariate Cox regression analysis showed pre-treatment haemoglobin significantly influencing recurrence-free survival ($p = 0.0094$).

Patients with a low haemoglobin level prior to radiation therapy suffered higher levels of local-regional failure.

Key words: Larynx; Carcinoma, squamous cell; Radiotherapy; Anaemia; Outcome assessment

Introduction

Radiotherapy and surgery provide comparable control rates for early (T_1–T_2) squamous carcinoma of the larynx (Mendenhall *et al.*, 1988; Rothfield *et al.*, 1989; Danilidis *et al.*, 1990; Rudoltz *et al.*, 1993; Johnson, 1994; Fein *et al.*, 1995; Lesnicar *et al.*, 1996). Loco-regional control and survival following primary radiotherapy is influenced by a variety of factors including patient, tumour, pathological differentiation and radiotherapy techniques. (Pradier *et al.*, 1992; Small *et al.*, 1992; Fein *et al.*, 1993; Sakata *et al.*, 1994; Barton *et al.*, 1997). Studies have demonstrated an association between haemoglobin levels and outcome in the treatment of squamous cell carcinoma of the head and neck (Blitzer *et al.*, 1984; Freedman *et al.*, 1987; Bentzen *et al.*, 1991; van Acht *et al.*, 1992; Fein *et al.*, 1995; Dubray *et al.*, 1996) but the link between haemoglobin levels and tumour recurrence is not fully understood. One hypothesis is that low levels of haemoglobin render tumour cells hypoxic and resistant to the effects of radiotherapy. Clinical trials aimed at improving oxygen supply to tumours have supported this view (Bush, 1986; Dische, 1991; Sealy, 1991; Lartigau *et al.*, 1993). More recently, recombinant human erythropoietin has become available as an alternative therapy for the correction of anaemia in cancer patients (Sweeney *et al.*, 1998). The purpose of this study is to examine the effect of pre-treatment anaemia on tumour recurrence and survival in 117 patients treated with primary radiotherapy for early squamous cell carcinoma of the larynx.

Patients and Methods

A retrospective analysis of 117 patients with previously untreated $T_1N_0M_0$ and $T_2N_0M_0$ squamous cell carcinoma of the larynx was carried out. All patients were treated with curative intent using primary radiation therapy at the Department of Radiotherapy and Oncology, Aberdeen Royal Infirmary, Aberdeen between January 1980 and November 1996.

Ninety-nine (84.6 per cent) of the patients wee men and 18 (15.4 per cent) women. The median age of the patients at diagnosis was 65 years with a range of 34–87 years. Follow-up times measured from the first day of radiation therapy ranged from four to 300 months (mean 70.5, median 60). Patients were considered anaemic if their pre-treatment haemoglobin levels were below 13 g/dl in males and 11.5 g/dl in females. Twenty-four (20.3 per cent) patients had reduced haemoglobin levels prior to

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radiation therapy of whom 20 (83 per cent) were men and four (17 per cent) were women. Only 18 of our patients (15.4 per cent) were non-smokers while 99 (84.6 per cent) smoked before diagnosis. Data concerning continued smoking habits during treatment was incomplete and therefore invalid. We considered alcohol consumption of more than 21 units per week in males and 14 units per week in females to put patients at risk of ill-health. Thirty-one patients (26.5 per cent) admitted to consuming consistently high levels of alcohol prior to diagnosis. The duration of patients' symptoms prior to presentation varied between one and 96 months (mean 5.5, median 3.)

All patients underwent direct laryngoscopy and biopsy for staging and histological diagnosis prior to the commencement of treatment. As the study period straddled two editions of the UICC TNM staging classification, one in 1978 (International Union Again Cancer, 1978) and one in 1987 (International Union Against Cancer, 1987), tumours diagnosed prior to 1987 were re-staged according to the revised 1987 classification. Seventy-nine patients (67.5 per cent) had T_1 tumours while 38 (32.5 per cent) had T_2 tumours. Ninety-four (80.3 per cent) of the tumours were glottic in origin while 23 (19.7 per cent) were supraglottic. There were no subglottic tumours. There was no correlation between haemoglobin levels and tumour stage or location. Forty-nine patients (41.9 per cent) had moderately differentiated tumours, 39 (33.3 per cent) had well-differentiated and 29 (24.8 per cent) had poorly differentiated lesions.

During the study period radiotherapy techniques remained unaltered. Lateral wedged parallel opposed pair radiation fields were given with megavoltage equipment using Cobalt 60 or 6 MV linear accelerator beams. Those patients with T_1 tumours were treated with daily fractions between 2.0–3.33 Gy (mean 2.73 Gy, median 2.75 Gy) while patients with T_2 lesions were treated with daily fractions between 2.20 and 2.89 Gy (mean 2.66 Gy, median 2.75 Gy). All patients received one fraction per day Monday to Friday, patients with T_1 tumours received between 15 and 25 fractions in total (mean, 20; median, 20) while those with T_2 tumours received between 19 and 25 fractions (mean 21, median 20). Patients with T_1 tumours received a total dosage of between 50.00 and 57.90 Gy (mean, 54.71 Gy; median, 55.00 Gy) while total dosage for patients with T_2 tumours was between 50.00 and 55.00 Gy (mean 54.61 Gy, median 55.00 Gy).

Statistical analysis

The outcome measures for this study were recurrence of disease (local-regional control), death from any cause (crude survival) and death from carcinoma-related disease (adjusted survival). These were measured from the commencement of the patients' radiation therapy. Survival curves were calculated using the Kaplan-Meier method (Kaplan and Meier, 1958) with statistical significance between patient groups measured using the logrank test. Following primary radiotherapy, patients with no signs of disease recurrence were censored from the analysis at the time of their last follow-up appointment or at their death.

The influence of pre-treatment haemoglobin levels and other clinical and patient variables on local control and survival were evaluated using Cox proportional hazards regression models (Cox, 1972). Statistical analysis was performed using SPSS ver 8.0 with the assistance of D. Baird, medical statistician.

Results

Loco-regional control

Failure of loco-regional control occurred in 28 out of 117 patients (23.9 per cent). The time interval between the start of therapy and diagnosis of tumour recurrence was between three and 225 months (mean 27, median 11.5). The total two- and five-year loco-regional control estimates for all patients were 82 per cent and 75 per cent respectively (Figure 1). Pre-treatment haemoglobin and tumour stage significantly influenced recurrence-free survival (Figure 2). Patients with a low haemoglobin level prior to radiation therapy suffered higher levels of loco-regional failure. Two- and five-year local-regional control for anaemic patients was 58 per cent and 53 per cent respectively while patients with normal pre-treatment haemoglobin levels had two- and five-year loco-regional control of 90 per cent and 81 per cent respectively ($p = 0.002$). Survival analysis showed that tumour recurrence varied significantly with tumour histology ($p = 0.002$) and tumour location ($p = 0.001$) (Table I). Gender, smoking, alcohol consumption, fraction dose or total radiation dose did not significantly influence disease recurrence (all $p>0.01$). Twelve patients were successfully salvaged following tumour recurrence resulting in a two-year ultimate local control rate of 88 per cent (Figure 1).

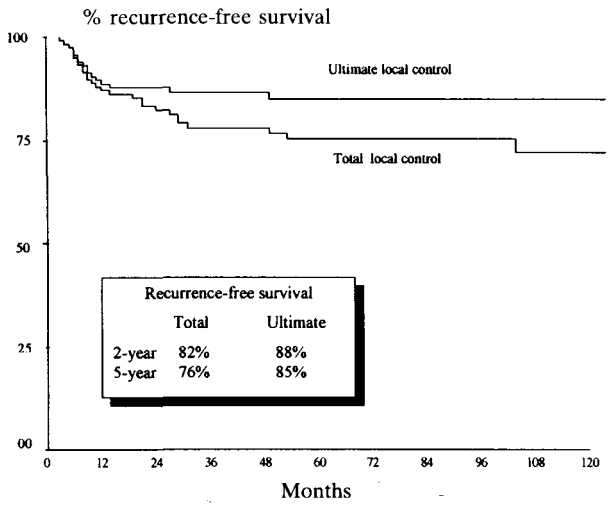

FIG. 1

Survival analysis of local-regional control. Total local control includes all cases of disease recurrence. Ultimate local control excludes cases of recurrence successfully salvaged.

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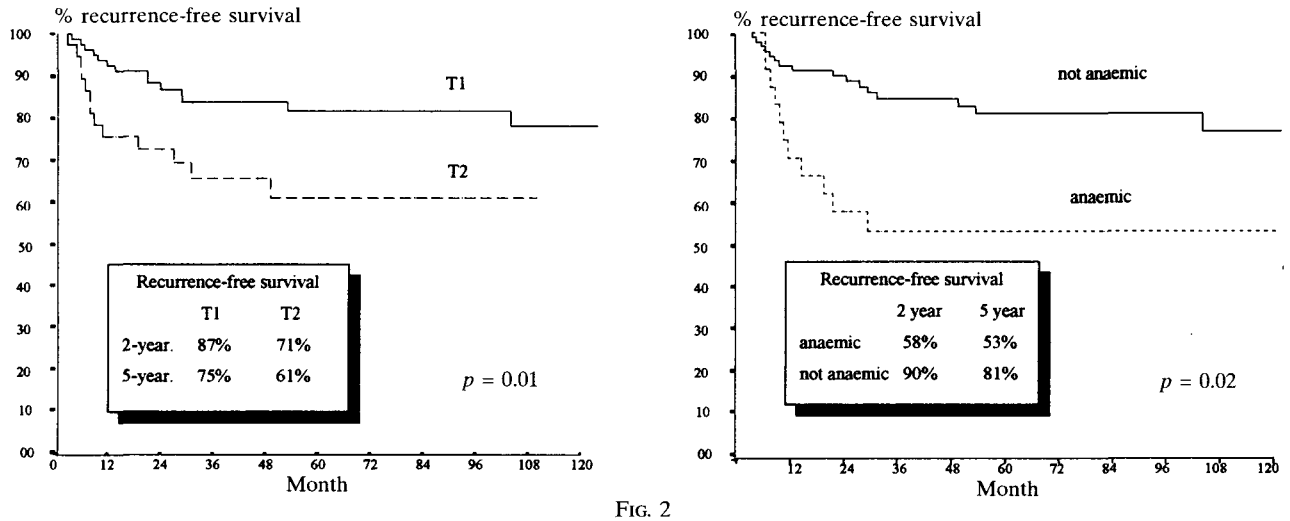

FIG. 2

Estimates of recurrence-free survival by tumour stage (a) and haemoglobin level (b).

Survival

Thirty-eight patients (32.5 per cent) died during the study period: 20 (17.1 per cent) of carcinoma-related disease and 18 (15.4 per cent) from other causes while 79 patients (67.5 per cent) were alive and disease-free at their last follow-up appointment. Two- and five-year adjusted survival was 92 per cent and 86 per cent respectively. Crude survival estimates were 91 per cent and 77 per cent at two and five years respectively. Pre-treatment haemoglobin levels showed only borderline significance in relation to adjusted survival ($p = 0.02$) and no significant influence on crude survival estimates. Adjusted patient survival was significantly influenced by tumour stage, differentiation and tumour localization (Table I). Tumour stage, tumour localization, differentiation and excess alcohol consumption significantly influenced crude survival estimates ($p<0.01$).

Multivariate analysis

Multivariate Cox regression analysis showed pre-treatment haemoglobin and tumour differentiation significantly influencing recurrence-free survival (Table II). Only tumour stage and tumour differentiation significantly influenced adjusted survival estimates in the Cox models. Only tumour location, histology and alcohol consumption significantly influenced the crude survival outcomes (Table II).

Discussion

In this current study primary radiotherapy has been shown to be an effective treatment for T_1N_0 and T_2N_0 squamous carcinoma of the larynx. Our two-year loco-regional control estimate of 87 per cent for patients with T_1 tumours compares well with the 85–95 per cent control rates published by other groups (Pradier *et al.*, 1992; Small *et al.*, 1992; Fein

TABLE I
LOCO-REGIONAL CONTROL AND SURVIVAL

		% loco-regional control		% survival	
Data	No. of patients	At two years	*p* value	At two years	*p* value
All patients	117	82		92	
Haemoglobin					
Anaemic	24	58		88	
Not anaemic	93	90	0.002	93	0.02
Tumour Stage					
T_1	79	87		98	
T_2	38	71	0.01	81	$<10^{-4}$
Differentiation					
Well	39	100		100	
Moderately	49	77	0.002	92	0.01
Poorly	29	68		82	
Localization					
Glottic	94	88		97	
Supraglottic	23	61	0.001	72	$<10^{-4}$
Alcohol					
>21/14 units	31	84		100	
<21/14 units	86	82	0.8	89	0.2
Smoking					
Yes	99	83		92	
No	18	77	0.2	88	0.5
Sex					
Male	99	86		94	
Female	18	58	0.02	76	0.07

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TABLE II
COX REGRESSION ANALYSIS

Model Variable	Coefficient (β)	*p* value	Exp (β)	95% CI for Exp (β)
Tumour recurrence				
Haemoglobin	0.9265	0.0094	2.52	1.15–5.50
Differentiation	–0.7111	0.0086	0.49	0.28–0.83
Corrected survival				
Differentiation	–0.8403	0.0116	0.43	0.22–0.82
T Stage	1.9230	0.0003	6.80	2.42–19.2
Crude survival				
Differentiation	–0.7069	0.0019	0.49	0.31–0.77
Location	–1.6457	0.0001	0.19	0.08–0.43
Alcohol	–2.2601	0.0005	0.10	0.02–0.37

et al., 1993; Sakata *et al.*, 1994; Barton *et al.*, 1997). The two-year local control rate for our T_2 patients (71 per cent) is consistent with those found at other centres in Scotland (Scottish Oncology and Radiology Group, 1997) but compares less favourably with rates of 72–85 per cent reported in the studies described above. We found that pre-treatment haemoglobin levels below 13 g/dl in males and 11.5 g/dl in females was a significant prognostic indicator in patients treated with primary radiotherapy for T_1 and T_2 squamous cell carcinoma of the larynx. Our results demonstrate two-year locoregional control estimates of 90 per cent for non-anaemic patients and 58 per cent for anaemic patients ($p = 0.002$). This represents a true advantage for patients with normal haemoglobin levels undergoing radiotherapy for laryngeal carcinoma. This advantage did not translate as comprehensively to the two-year adjusted survival estimates with rates of 93 per cent for non-anaemic patients and 88 per cent for anaemic patients being only marginally significant ($p = 0.02$). In the multivariate analysis the influence of haemoglobin on tumour recurrence and survival was repeated. Recurrence-free survival was significantly influenced by haemoglobin levels in the Cox models but this influence diminished with adjusted survival ($p = 0.06$). The amount of published literature documenting the effect of pre-treatment haemoglobin on local-regional control and survival in early laryngeal cancer is limited. Some studies have shown links between anaemia and outcomes in either glottic or supraglottic series. (Blitzer *et al.*, 1984; Fein *et al.*, 1995) while others have reported significant influences in post-treatment haemoglobin levels only (van Acht *et al.*, 1992). This report clearly shows the influence of pre-treatment haemoglobin on tumour recurrence following primary radiotherapy for T_{1-2} carcinoma of the larynx but fails to demonstrate a significant link between haemoglobin levels and survival.

The biological link between anaemia, malignant tumours and their reduced responsiveness to radiotherapy remains unclear. Hypoxia may play an important role in determining the resistance of tumour cells to radiation (McCormack and Smith, 1990). The partial pressure of oxygen measured in the metastatic lymph nodes of head and neck cancer patients has been shown to be lower in tumour cells than in normal tissue (Lartigau *et al.*, 1993). Studies have also shown the prognostic benefit of a high pO_2 in tumour cells by demonstrating decreased responsiveness to irradiation by hypoxic tumours (Gatenby *et al.*, 1988). Research is now needed to determine if oxygen delivery to tumours is reduced as a result of low haemoglobin levels or if local tumour factors themselves alter the blood supply to malignant cells.

The correction of anaemia with blood transfusions is rapid but is not risk free (Cumming *et al.*, 1989) and some consider the use of transfusions to be detrimental to outcomes in patients with cancer (Blumberg *et al.*, 1986). The anaemia of malignancy may result from a number of causes (Spivak, 1994) but common to many is the failure to produce or utilize erythropoietin. The availability of recombinant human erythropoietin (r-HuEPO) has led to new therapeutic options in the treatment of anaemia in malignancy (Sweeney *et al.*, 1998). Studies have shown that r-HuEPO is efficacious and safe (Lavey and Dempsey, 1993; Dusenberry *et al.*, 1994) but does take time to become effective (Dusenberry *et al.*, 1994). The question of whether improvement in haemoglobin levels with r-HuEPO therapy can improve outcomes in squamous cell carcinoma of the head and neck still remains to be answered. In demonstrating the influence of pre-treatment haemoglobin on malignant tumour recurrence we hope to stimulate examination of a role for r-HuEPO in the correction of anaemia before primary radiotherapy of squamous carcinoma of the larynx.

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