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ORIGINAL ARTICLE

Does treatment interruption and baseline hemoglobin affect overall survival in early laryngeal cancer treated with radical radiotherapy? 10 years follow up

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Summary

Purpose: *In this retrospective study we assessed different factors affecting the outcome of early laryngeal cancer, focusing on the impact of the pretreatment hemoglobin (Hb) level, time interval between diagnosis and start of radiotherapy, as well as treatment interruption during the course of radiotherapy.*

Methods: *We reviewed the hospital records, oncology database and radiotherapy treatment sheets of 88 patients with T1–T3 N0M0 squamous cell carcinoma of the larynx who had been treated with radical radiotherapy at Northamptonshire Centre for Oncology during the period from 1st January 1996 till 31st December 2002 inclusive. Patients were followed up for 10 years.*

Results: *There were no significant overall survival differences with regard to sex , stage, radiotherapy dose received, treatment interruption for 1 to 2 days , as well as the delay to start radiotherapy (mean delay 57 days). However, there was statistically significant adverse overall survival outcome with increasing age ($p<0.001$). On the other hand, patients with pretreatment Hb level >12 g/dl had significant statistical overall survival benefit over those with ≤12 g/dl ($p=0.018$).*

Conclusion: *Pretreatment Hb level had a significant impact on overall survival in patients with early laryngeal carcinoma treated with radical radiotherapy. Time to start radiation treatment, treatment interruption for 1 or 2 days and different dose / fractionations did not affect the overall survival.*

Key words: *hemoglobin level, laryngeal cancer, radiotherapy, treatment interruption*

Introduction

Laryngeal cancer is the most common malignancy of the upper aerodigestive tract; it accounts for nearly 1% of all malignancies and approximately 25% of head and neck tumors. Men are affected 4-5 times more often than women. Laryngeal cancer has a peak incidence at presentation in those aged in their 50s and 60s [1].

While laryngeal cancer is the most curable cancer of the upper aerodigestive tract, the 5-year survival rate of approximately 65% has remained relatively unchanged during the previous three decades. In fact, laryngeal cancer represents one of the malignancies for which the 5-year overall survival has not improved during this period [2].

Diagnosis and treatment delays can be broken down in two stages. The first stage, until the patient reaches specialized care, is influenced both by the patient who denies symptoms, as well as delay in primary care. The second stage is diagnosis and treatment themselves. Although the time spent in the first stage is usually longer, being responsible for the advanced stage of disease, delays in starting treatment may also bring about a worse outcome [3].

Although anemia is a recognized cancer-related disorder, recent studies have focused on its impact rather than its prevalence among patients undergoing radiotherapy [4].

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In this retrospective study we assessed different factors affecting the outcome of laryngeal cancer, focusing on the impact of pretreatment Hb level, time interval between diagnosis and start of radiotherapy, as well as treatment interruption during the course of radiotherapy.

Methods

Eighty-eight patients with T1–T3 N0M0 squamous cell carcinoma of the larynx who had been treated with radical radiotherapy at Northamptonshire Centre for Oncology during the period from 1st January 1996 till 31st December 2002 inclusive were studied. Patients were followed up for 10 years.

Inclusion ctriteria

These included age >18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, stage T1-T3N0M0, and squamous cell carcinoma confirmed by histopathology examination of tissue obtained via direct laryngoscopy and biopsy.

Exclusion criteria

These included metastasis, another pathology, previous malignancy, previous radiotherapy or chemotherapy and serious co-morbidities.

All patients planned for radical radiotherapy were initially seen in a multidisciplinary outpatient clinic. Following this, the pretreatment assessment for radiotherapy planning included an examination under anaesthesia (EUA) and tumor biopsy, and computerized tomography (CT) and /or magnetic resonance imaging (MRI) of the head and neck. Dental assessment, nutritional assessment and written informed consent were also done where appropriate.

In both conventional simulation planning or CT planning we defined the gross target volume (GTV), clinical target volume (CTV), planning target volume (PTV) and organs at risk (OAR). Planning normalized to ICRU reference point (RP) to ensure adequate target coverage , homogeneous dose and doses to OAR were acceptable.

Different doses (Gy) and fractionations were used (50/20, 50/15, 64/32 and 60/30).

Patients were reviewed once a week during treatment.

Follow up included clinical examination and laryngoscopy every 6 months for 2 years; then clinical examination alone annually for 5 years or as needed based on clinical findings.

Statistics

The primary end point of this study was overall survival. Survival was calculated from the date of diagnosis to death or last follow up evaluation.

Table 1. Patient and tumor characteristics

Characteristics	*N*	*%*
Sex		
Female	14	16.9
Male	69	83.1
Smoking		
Current	36	43.4
Unknown	22	26.5
Ex smoker	19	22.9
Non smoker	6	7.2
Stage		
T1N0M0	46	55.4
T2N0M0	24	28.9
T3N0M0	13	15.7
RT Dose (Gy) and fractionation		
55/20	26	31.3
50/15	22	26.5
60/30	18	21.7
64/32	17	20.5
Treatment interruption (days)		
0	65	78.3
1	14	16.9
2	4	4.8
Death		
No	48	57.8
Yes	35	42.2
Anemia (g/dl)		
>12	62	74.7
≥12	21	25.3

Survival curves were established with the Kaplan-Meier method and were compared using the log-rank test and Cox model. Usual statistical tests (x^2 test, Fisher's probability test) were used to compare variables in the same treatment group . Differences were considered significant at p<0 .05. These tests were run on a IBM compatible personal computer using the Statistical Package for Social Sciences (SPSS) for Windows 10.0 (SPSS Inc., Chicago, IL,USA).

Results

Patient characteristics

Table 1 shows patient and tumor characteristics.

Males were approximately 5 times more than females (83% : 17%). Only 7% were nonsmokers. Seventy-eight percent of the patients had no treatment interruption, while 14 patients (17%) had 1-day interruption and only 4 patients had 2-day interruption. Sixty-two (75%) patients had pretreatment Hb level >12 g/dl. Stage T1N0M0 had 55% of the patients, T2N0M0 29% and T3N0M0 16%. Twenty-six patients (31%) received 55Gy/20 fractions: 29% 50Gy/15 fractions, 18 (21.7%) 60Gy/30 fractions and only 17 (20.5%) received 64Gy/32 fractions . Mean age was 68±10.74 years, mean survival was 8.49±5.061 years, and mean

Table 2. Results of univariate Cox regression analysis of survival in relation to different risk factors

Model	*Variable*	*R*	*Standard error of R*	*Wald* x^2	*P*	*Hazard ratio*	*95.0% CI for hazard ratio*	
							Lower	*Upper*
1	Sex (male)	0.013	0.449	0.001	0.977	1.013	0.420	2.442
2	Age (decades)	0.825	0.188	19.196	< 0.001	2.282	1.578	3.301
3	Smoking			2.559	0.465			
	(Current)	-0.031	0.760	0.002	0.967	0.969	0.219	4.298
	(Unknown)	0.174	0.782	0.049	0.824	1.190	0.257	5.508
	(Ex smoker)	0.605	0.769	0.618	0.432	1.831	0.405	8.271
4	TTT Inter (0)			0.565	0.754			
	TTT Inter (1)	-0.256	0.484	0.280	0.597	0.774	0.300	2.000
	TTT Inter (2)	-0.580	1.017	0.325	0.568	0.560	0.076	4.111
5	Hb (g)	-0.306	0.130	5.554	0.018	0.736	0.571	0.950
6	RT Dose (Gy)			4.725	0.317			
	55/20	-0.382	0.586	0.427	0.514	0.682	0.216	2.150
	50/15	0.252	0.540	0.218	0.640	1.287	0.447	3.706
	60/30	0.322	0.571	0.317	0.573	1.379	0.451	4.223
	64/32	0.915	0.673	1.851	0.174	2.498	0.668	9.338
7	TNM (stage)	0.181	0.217	0.693	0.405	1.198	0.783	1.835
8	Delay To Start (month)	-0.159	0.231	0.477	0.490	0.853	0.543	1.340

R: Regression coefficient, TTT: time to treat. Hazard ratio was calculated for values included in parentheses

time to start treatment was 56.84±24.8583 days.

Survival

As seen in Table 2, there was no significant survival differences with regard to sex , stage, radiotherapy dose received , treatment interruption for 1 to 2 days , as well as delay to start radiotherapy (mean delay 56.84 days, range 22-115). However, there was statistically significant adverse overall survival outcome with increasing age (p<0.001). On the other hand, patients with pretreatment Hb level >12 g/dl had statistically significant survival benefit over those with ≤ 12 g/dl (p=0.018; Figure 1).

Factors associated with adverse outcome

Ten-year increase in age was associated with 2.38-fold increase (138%) in the hazard ratio (p<0.001). Also, for every one gram increase in the pretreatment Hb level the mortality risk decreased by 25% (p=0.031; Table 3).

Discussion

Our analysis demonstrated that for every one gram increase in the pretreatment Hb levels the mortality risk decreased by 25% (p=0.031). One of the first studies to illustrate the impact of anemia on locoregional tumor control in head and neck cancer patients came from the Danish Head and Neck Cancer II Study (DAHANCA II) [5]. A strong correlation between the pretreatment Hb levels and local control was noted in male patients with pharyngeal tumors. Male patients with pharyngeal cancer who were treated with misonidazole and had pretreatment Hb levels of ≥14.5 g/dl had 5-year local tumor control rate of 61% as compared with only 14% in the placebo-treated patients with pretreatment hemoglobin values <14.5 g/dl [5]. Also, Fein et al. reported a strong correlation between Hb levels and local control

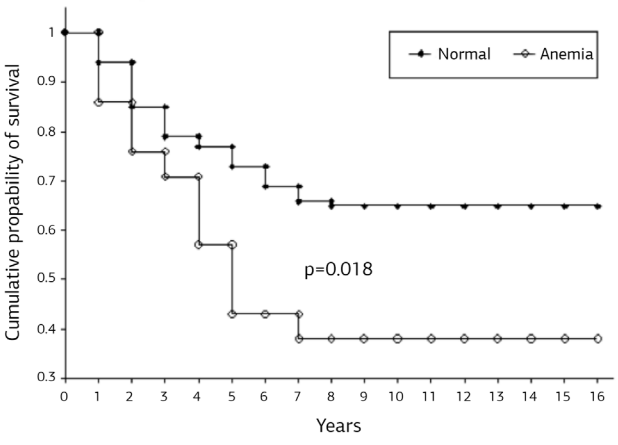

Figure 1. Overall survival in relation to Hb level.

Table 3. Results of univariate Cox regression analysis of survival in relation to different risk factors

Variable	*Partial R*	*Standard error of partial R*	*Wald x^2*	*P*	*Hazard ratio*	*95.0% CI for hazard ratio*	
						Lower	*Upper*
Age (decades)	0.867	0.195	19.793	< 0.001	2.380	1.625	3.488
Hb (g)	-0.286	0.133	4.647	0.031	0.751	0.580	0.974
Delay to start (month)	-0.325	0.216	2.276	0.131	0.722	0.473	1.102

R: Regression coefficient. Hazard ratio was calculated for values included in parentheses

and survival in a study with 109 patients with T1-T2 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy [6]. Patients who presented with Hb values >13.0 g/dl had significantly higher 2-year rates of locoregional tumor control (95 vs 66%, p=0.0018) and survival (88 vs 46%, p < 0.001) as compared with patients with Hb values <13.0 g/dl [6].

Kumar and colleagues assessed the impact of radiation-related factors on complete response rates at the primary tumor and lymph node sites, local control, and overall survival. The factors analysed were total radiation dose to the primary site, total posterior neck dose to lymph nodes, dose/fractionation to the primary site, radiation-related treatment interruptions, and pre-therapy Hb levels. The primary site response rate was affected by treatment interruptions (p=0.04) and pre-therapy Hb levels (p=0.004). The lymph node response rate was only affected by pretreatment Hb levels (p=0.001). Locoregional failure-free survival (p=0.0005) and overall survival (p=0.002) were only affected by pretreatment Hb level [7].

Also, Cho et al. studied the pretreatment Hb levels in relation to local control in patients with T1-T2N0 larynx cancer treated with radiotherapy. They found that pretreatment hemoglobin levels <10 g/dl predicted local failure and poorer overall survival. The relative risk for 5-year local relapse by Hb quartile was 2.70, 2.33, 1.91 and 1.00 (p = 0.034) [8].

Large retrospective analyses have demonstrated the dramatic adverse impact of anemia on locoregional tumor control and survival. A study has revealed Hb levels as a powerful prognostic factor, provide compelling evidence for the value of reversing anemia and hence tumor hypoxia in head and neck cancer patients [9].

A retrospective analysis of 847 cases of laryngeal supraglottic squamous cell carcinoma treated with radiation alone showed that the Hb concentration after radiotherapy is an important prognostic factor. There was a very strong correlation between Hb concentration and tumor local control probability. Hb concentration at the beginning of radiotherapy did not correlate with treatment outcome, but any decrease of Hb during therapy was a strong prognostic factor for treatment failure [10]. The same conclusion was reached by Warde et al. [11], who reported that pretreatment Hb is an independent prognostic factor for local control in patients with T1/T2 carcinoma of the glottis treated with RT [11]. Canaday et al. in their study concluded that the pretreatment Hb level was not a prognostic factor for disease specific survival (DSS), nor were any other analyzed factors. Pretreatment Hb was not a significant prognostic factor for local control in patients with T1 squamous cell carcinoma of the glottic larynx, but it did predict for a poorer overall survival without affecting DSS. The authors concluded that patients with lower pretreatment Hb may have confounding medical problems that detract from their overall survival [12].

In this study we assessed the mean delay to start radiotherapy was 56.84±24.8583 days; this delay was not found to be associated with a significant survival difference .

According to Primdahl et al., currently more imaging studies are ordered and radiotherapy has a more complex planning, however they mention equipment availability (linear accelerator) as a preponderant factor in the greater delay seen on treatment onset, which in Denmark increased from 50 to 70 days between 1992 and 2002. The authors esti¬mated that the increase of 20 days could reduce control rates by 10% [3]. Caudell and colleagues assessed the impact of prolonged diagnosis-to- treatment interval (DTI) that falls in the time frame associated with the increasing complexity of planning treatment for patients with locoregionally advanced head and neck cancer (LAHNC). The median DTI was 34 days (range 7-441). A longer DTI was not significantly associated with locoregional control (p=0.11), distant metastases-free survival (p=0.32), or overall survival (p=0.07) [13]. Jensen et al. reported a median increase of 46% in tumor volume in 62% of the patients waiting for treatment onset after a median of 28 days [14].

Rudoltz and his colleagues reported same findings in their study [15]; elapsed days were found to be the most significant prognostic factor for local control (p=0.0001) and survival in patients treated with radiotherapy for T1 squamous cell carcinoma of the glottis. In univariate analysis, only elapsed treatment days and dose per fraction were significant factors for local control. Local control was 100% if treatment was completed within 42 days, 91% for 43-46 days, 74% for 47-50 days, 65% for 51-54 days, and 50% for 55-66 days (p=0.0001) [15].

There was no clinical evidence for a detrimental effect of the waiting time on treatment outcome in two retrospective studies of head and neck cancers treated with radiotherapy alone. Brouha et al. [16] studied the outcome of 362 patients with early-stage laryngeal cancer with a median waiting time of 43 days and found no significant correlation between outcome and waiting time. Barton et al. [17] also found no significant effect of waiting time. In this study, 90% of the waiting time was <31 days. Another retrospective study of outcome data for 623 patients with early-stage head and neck cancers did find a deleterious effect of treatment waiting time on treatment outcome; waiting time of ≤40 days was significantly associated with increased risk of local failure compared with delays of 30 days or 31–40 days [18].

In our study there was no impact of treatment interruption for 1-2 days on overall survival. Barton et al. in their study found that each day of treatment interruption resulted in an increase in the hazard of local relapse by 4.8% (p=0.006), which would result in a decrease in local control of 1.4% for each day of uncompensated treatment interruption [19].

This was not the case in the Nishimura et al. study who found that only a 1-week interruption of radiotherapy, due to holidays, significantly reduced the 5-year local control probability of T1 glottic tumors from 89 to 74% (p<0.05) [20].

In another study by Fein and colleagues, evaluating the treatment- and patient-related prognostic factors that may influence local control in the treatment of T1-T2 squamous cell carcinoma of the glottic larynx in 109 patients, they concluded that extending the overall treatment time adversely influenced local control [21].

Nishimura et al. [20] using different dose/fractionations compared with our study did not also find any adverse effect on overall survival. Local control probabilities of T1,2 glottic laryngeal cancer were evaluated in relation to the dose and fractionation of radiation therapy. Multivariate analyses demonstrated that only overall treatment time (OTT) was a significant variable for local control. Total radiotherapy dose, normalized total doses at a fraction size of 2 Gy, and fraction size were not significant. Local control probability of T1 tumors with an OTT of 42-49 days was significantly higher than that of tumors with an OTT of > 49 days (p<0.02) [20].

Conclusion

Pretreatment Hb level had a significant effect on survival in patients with early-stage laryngeal carcinoma treated with radical radiotherapy. Time to start radiation treatment, treatment interruption for one or two days and different dose / fractionations did not affect the overall survival.

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