Different Factors May Affect Clinical Outcome of Early Laryngeal Cancer

SEHAM E. ABDELKHALEK, M.D.

Abstract

Purpose: To evaluate the effect of patients, tumor and treatment-related variables on survival in patients with T1-T2 N0M0 squamous cell carcinoma of the larynx who treated with radical radiotherapy.

Material and Methods: Eighty-three patients with T1-T2 N0M0 squamous cell carcinoma of the larynx were analysed. Patients were treated with initial opposed lateral fields to treat the primary and draining lymphatic system then these initial fields were reduced for spinal cord shielding. Different dose and fractionations has been used (50Gy/15 fraction, 50Gy/20 fraction, 60Gy/30 fraction and 64Gy/32 fraction, 5 days/week). The following factors were analysed: Age, sex, disease extent, treatment interruption for 1 to 2 days, delay to start radiotherapy, pretreatment Hb level, and dose per fraction.

Results: Mean survival was 8.49 years with STD 5.061. On univariate analysis, there is no significant survival difference regarding to sex, stage, radiotherapy dose received, treatment interruption for 1 to 2 days, as well as the delay to start radiotherapy (mean delay in days 56.84 days). However, there is statistical significant adverse survival outcome with increasing age ($p<0.001$). On the other hand, patients with pretreatment Hb level $>12g/dl$ had significant statistical survival benefit over those $\leq12g/dl$ ($p=0.018$). Multivariate analysis tested different prognostic factors and its impact on overall survival. Ten years increase in age was associated with increase in the hazard ratio by 138% (2.38 times) ($p<0.001$). Also, every one gram increase in pretreatment Hb level reduce mortality risk with hazard ratio 25% ($p=0.031$). However, each month delay to start treatment reduce hazard ratio by 28%.

Conclusion: Pretreatment hemoglobin level and age had a significant effect on survival in patients with early laryngeal carcinoma treated with radical radiotherapy. Sex, disease extent, treatment interruption for 1 to 2 days, time to start radiotherapy, and different dose/fractionations did not affect the overall survival.

Key Words: Laryngeal cancer – Radiotherapy – Haemoglobin – Anaemia – Prognostic factors.

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 of 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, larynx cancer represents one of the only malignancies for which the 5-year survival has not improved during this period [2].

Diagnosis and treatment delays can be broken down in two stages. The first stage, until it reaches specialized care, was influenced both by the patient who denied symptoms as well as delay in primary care. Another stage is diagnosis and treatment themselves. Although the time spent in the first stage is usually longer, being responsible for the advanced stage of the 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].

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

Patients and Methods

This is a retrospective study of 83 patients with T1-T2 N0M0 squamous cell carcinoma of the larynx who has been treated with radical radiotherapy at Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital during the
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period from 1st January 1996 till 31st December 2002. Patients were followed-up for 10 years.

Eligibility criteria:

Eligibility criteria; age > 18 years old, performance status according to Eastern Cooperative Oncology Group (ECOG) ≤2, Staging; T1-T2N0M0, squamous cell carcinoma which confirmed by histopathology examination of tissue obtained at direct laryngoscope and biopsy.

Exclusion criteria:

Metastasis, another pathology, previous malignancy, previous radiotherapy or chemotherapy and serious co-morbidity were excluded from this study.

Pretreatment evaluation:

All patients were 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, CT and/or magnetic resonance (MRI) of head and neck. Dental assessment, nutritional assessment and written informed consent were also done where appropriate.

Radiation therapy:

At this period in our department, we had no CT simulation nor conformal planning system, only conventional simulation and linear accelerator or Cobalt-60 teletherapy device for treatment.

At simulation, the head, neck, and shoulders were immobilized in a hyperextended position using a perforated thermoplastic head mask with the neck supported. A shrinking field technique was used with initial opposed lateral fields to treat the primary and draining lymphatic system then these initial fields were reduced for spinal cord shielding. Different dose and fractionations has been used (50Gy/15 fraction, 50Gy/20 fraction, 60 Gy/30 fraction and 64Gy/32 fraction, 5 days/week). Patients were treated by 6 MV photons of a linear accelerator or Cobalt-60 teletherapy device. Patients were reviewed once a week during treatment.

Follow-up:

Patients were asked to return for follow-up visits 4-6 weeks after the completion of radiation therapy and then every 2 months for the first year, every 4 months for the second year, and then less frequently in subsequent years.

Statistical methods:

The primary end point of this study was the overall survival. Survival was calculated from the date of diagnosis to death or last follow-up evaluation. Survival curves were established with the Kaplan-Meier method and were compared using the Log-rank test and Cox model. Usual statistical tests (χ² test, Fisher’s exact probability test) were used to compare variables in the same treatment group. Differences were considered significant at p<.05. These tests were run on IBM compatible personal computer using the statistical Package for Social sciences (SPSS) for windows 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient’s characteristics:

The patient characteristics are listed in Table (1). Males were approximately 5 times more than the females (83%; 17%). Only 7% were nonsmokers. No treatment interruption in 78%, while 14 patients (17%) experienced 1 day interruption and only 4 patients had 2 days interruption. Patients had pretreatment Hb level more than 12g/dl was 62 (75%). As regard staging, T1N0M0 reported in (55.4%), T2N0M0 (44.6%). Patients received 55Gy/20 fractions was 26 (31%), 50Gy/15 fractions (29%), 60Gy/30 fractions was 18 (21.7%) and only 17 (20.5%) received 64/32 fractions. Mean age was 68 years (STD 10.74), mean survival was 8.49 years (STD 5.061); mean time to start treatment was 56.84 days (STD 24.8583).

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Univariate analysis:

As seen in Table (2), there is no significant survival difference regarding to sex, stage, radiotherapy dose received, treatment interruption for 1 to 2 days, as well as the delay to start radiotherapy (mean delay in days 56.84 days). However, there is statistical significant adverse survival outcome with increasing age ($p<0.001$). On the other hand, patients with pretreatment Hb level $>12$g/dl had significant statistical survival benefit over those $\leq12$g/dl ($p=0.018$) Fig. (1).

Factors associated with adverse outcome:

Table (3) shows multivariate of different prognostic factors and its impact on overall survival. Ten years increase in age was associated with increase in the hazard ratio by 138% (2.38 times) ($p<0.001$). Also, every one gram increase in pretreatment Hb level reduce mortality risk with hazard ratio 25% ($p=0.031$). However, each month delay to start treatment reduce hazard ratio by 28%.

![Figure 1: Survival in relation to Hb level.](image)

Discussion

Our analysis demonstrates that, every one gram increase in pretreatment Hb level reduce mortality risk with hazard ratio 25% ($p=0.031$). One of the first studies to illustrate the impact of anemia on loco-regional tumor control in head and neck cancer patients came was Danish Head and Neck Cancer II Study (DAHANCA II) [5] which reported a strong correlation between the pretreatment hemoglobin 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 hemoglobin levels of >14.5g/dl had five-year local tumor control rate of 61% as compared with only 14% in the placebo-treated patients with pretreatment hemoglobin values <14.5g/dl [8]. Also, Fein, et al., reported a strong correlation between hemoglobin levels, local control, and survival in a study of 109 patients with T1-T2 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy [6]. Patients who presented with hemoglobin values >13.0g/dl had significantly higher two-year rates of loco-regional tumor control (95% versus 66%, \( p=0.0018 \)) and survival (88% versus 46%, \( p<0.001 \)) as compared with patients with hemoglobin values <13.0g/dl [6].

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

Also, Cho, et al., studied pretreatment hemoglobin and local control in patients with T1-T2N0M0 larynx cancer treated with radiotherapy. They found pretreatment hemoglobin level predicted for local failure and poorer overall survival. The relative risk for 5-year local relapse by hemoglobin 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 upon loco-regional tumor control and survival. These studies, which have revealed hemoglobin 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 hemoglobin concentration after radiotherapy is an important prognostic factor. There was a very strong correlation between hemoglobin concentration and tumor local control probability. Hemoglobin concentration at the beginning of radiotherapy does not correlate with treatment outcome, but any decrease of hemoglobin during therapy is a strong prognostic factor for treatment failure [10]. The same conclusion was reached by Warde, et al., 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 the pretreatment Hb was not a prognostic factor for DSS, nor were any other analyzed factors. Pretreatment Hb is not a significant prognostic factor for LC in patients with T1 squamous cell carcinoma of the glottic larynx, but it does predict for a poorer OS without affecting DSS. This suggests 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 treatment was 56.84 days (STD 24.8583); this delay was not found to be associated with a significant survival difference. This considered average time to start but prolonged delay will affect survival, as each month delay to start treatment reduce hazard ratio by 28%.

According to Primdahl et al., currently more image 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 upon treatment onset, which in Denmark increased from 50 to 70 days between 1992 and 2002 [8]. The authors estimated that the increase of 20 days could reduce control rates in 10% [3]. Jimmy J. and his 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 loco-regionally advanced head and neck cancer (LAHNC), the median diagnosis to treatment interval (DTI) was 34 days (range, 7-441 days). A longer duration was not significantly associated with loco-regional control (\( p=11 \)), distant metastases-free survival (\( p=32 \)), or overall survival (\( p=0.07 \)) [13]. Jensen et al., reported a median increase of 46% in tumor volume in 62% of the patients awaiting treatment onset after the 28 day median [14].

Same findings by Rudoltz and his colleagues reported in their study; elapsed days was found to be the most prognostic significant factor for local control (\( p=0.0001 \)) and survival in patients treated with radiotherapy for T1 squamous cell carcinoma.
of the glottis. On 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) [18].

Although, no clinical evidence for a detrimental effect of waiting time on treatment outcome was found 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 case, 90% of waiting times were <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 times on treatment outcome; waiting times of 40 days were significantly associated with increased risk of local failure compared with delays of 30 days or 31-40 day [18].

In our study, there was no impact of radiotherapy 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]. Nishimura et al., found that only a 1-week interruption of RT, 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 his 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 one hundred and nine patients. They concluded that extending the overall treatment time was found to adversely influence local control [21].

Different dose/fractionations in used in our study did not also affect the overall survival. Local control probabilities of T1, 2 glottic laryngeal cancers were evaluated in relation to dose and fractionation of radiation therapy (RT). Multivariate analyses demonstrated that only overall treatment time (OTT) was a significant variable for local control. Total RT 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].

Conclusions:

Pretreatment hemoglobin level and age had a significant survival effect in patients with early laryngeal carcinoma treated with radical radiotherapy, we recommend pretreatment Hb level and anaemia work up with its correction which may be helpful. Sex, disease extent, treatment interruption for 1 to 2 days, time to start radiotherapy, and different dose/fractionations did not affect the overall survival.

References


