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ORIGINAL ARTICLE

Glottic and supraglottic laryngeal cancer: epidemiology, treatment patterns and survival in 164 patients

I. Petrakos[1], K. Kontzoglou[2], T.P. Nikolopoulos[3], O. Papadopoulos[4], A. Kostakis[2]

[1]Department of Otorhinolaryngology, "Evangelismos" General Hospital, Athens; [2]2nd Propedeutic Department of Surgery, University of Athens, "Laiko" General Hospital, Athens; [3]2nd Department of Otorhinolaryngology, University of Athens, Athens; [4]Department of Plastic and Reconstructive Surgery, University of Athens, "A. Sygros" General Hospital, Athens, Greece

Summary

Purpose: *To evaluate the effectiveness of different therapeutic managements in relation to clinical disease stage, the location of the lesion and to register the rate of disease recurrence of patients with glottic and supraglottic laryngeal cancer, and to also study some specific epidemiologic characteristics.*

Methods: *A series of 164 patients with laryngeal glottic and supraglottic squamous cell cancer (SCC) treated surgically, with radiation therapy (RT), chemotherapy or combination of these was analysed. After treatment, all patients were followed up for an average of 58 months. All data concerning the primary lesion, therapeutic management, recurrence, staging, 5-year overall survival and epidemiological characteristics such as smoking and alcohol abuse were recorded and analysed in combination with the follow up data.*

Results: *The therapeutic approach most commonly used was RT for stage I tumors and surgery for stages II, III and IV. Stage I and II patients treated with RT had high recurrence rate (60%). Patients with recurrence had 45.3% 5-year overall survival rate and average survival time 80 months, whereas patients with no recurrence had 77.4% 5-year overall survival rate and average survival time 173 months (p=0.0001). There was significant difference in survival between stage I and III (p=0.035), stage I and IV (p=0.0038) and stage II and IV (0.0156). The average overall survival time for non smokers was 195 months (median 170), while for smokers it was 99 months (median 100; p=0.0047). The average overall survival time for alcohol abusers was 79 months (median 54), while for those who did not use alcohol it was 153 months (median 150; p=0.016).*

Conclusion: *The 5-year overall survival rate was 61.3%. RT alone in stages I and II proved inferior in decreasing recurrences compared with surgery. Smokers had significantly shorter overall survival.*

Key words: epidemiology, laryngeal cancer, survival, treatment

Introduction

The 5-year overall survival rate for 23 out of 24 cancer types that have been evaluated in the last 25 years (1975-2000) has increased, according to the SEER program, which publishes cancer incidence and survival data from US population. Only laryngeal cancer showed decrease in survival. Five-year overall survival rate decreased from 68.1% (1980-1982) to 64.7% (1992-1999) [1,2].

The analysis of Hoffman et al. [3] who used as databases the SEER program and the National Cancer Data Base and the analysis of Carvalho et al. [4] who used the SEER program, refer that 5-year overall survival rate has decreased in the last decades in laryngeal cancer. Although the exact causative factors for this decrease are not well established, it has been observed that during the same period of time there has been a decrease in surgical treatment and a parallel increase in non surgical treatments, such as RT and chemotherapy.

The purpose of this retrospective study that included patients with glottic and supraglottic SCC was to evaluate the effectiveness of different therapeutic approaches in relation to clinical disease stage, the loca-

Correspondence to: Ioannis Petrakos, MD. Athan. Miaoulis street 44, Piraeus 185 38, Greece. Tel: +30 210 4181666, Fax: +30 210 4180337, E-mail: giannispetrakos@hotmail.com

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tion of the lesion, the rate of disease recurrence and also to study some specific epidemiologic characteristics such as the use of tobacco and alcohol.

Methods

Patients

A series of 164 patients with laryngeal glottic and supraglottic SCC of all clinical stages who were treated with different therapeutic approaches in a Greek tertiary center between October 1972 and July 2005 was analysed. Inclusion criteria were: 1) SCC histopathology; 2) sufficient follow up data; 3) sufficient data for the use of tobacco and alcohol. Exclusion criteria were: 1) previous treatment for laryngeal cancer; 2) systemic disease at the time of diagnosis or other synchronous malignancy; 3) histopathology other than SCC.

The patient staging was based on clinical examination, imaging methods (mainly CT scan) and direct laryngoscopy under general anesthesia. All patients were biopsied for histological disease confirmation.

Treatment

Patients were treated surgically, with RT using linear accelerator or cobalt unit, chemotherapy or combination of these. The choice of therapeutic management depended on the stage of disease, the location of the lesion and the general condition of the patient, which in some cases modified the treatment decision.

Statistical analysis

All data concerning the primary lesion, including anatomical site, therapeutic management, recurrence, staging and epidemiological characteristics such as smoking and alcohol abuse, were recorded and analysed in combination with the follow up data with the application of chi-square test. Survival analysis was realized using the Kaplan-Meier method and log-rank test with 95% confidence intervals (95% CI). SPSS statistical software (SPSS Inc, Chicago, Illinois) was used for statistical analysis. A p-value of <0.05 was considered significant.

Results

Of 164 patients, 154 (93.9%) were male and 10 (6.1%) female. The mean patient age was 61 years (range 31-86); it was 61.5 years for males and 57.1 for females. Forty-nine (29.8%) patients had stage I, 58 (35.3%) stage II, 50 (30.4%) stage III and 7 (4.5%) stage IV according to TNM classification. Of the patient cohort 84.1% were smokers and 44.5% alcohol abusers. The average follow up, after the treatment was 58 months (range 1-312) (Figure 1).

The anatomical location of the lesions is shown in Figure 2. From 164 patients 91 (59.14%) had glottic and 73 (40.86) supraglottic SCC. Among TNM stages, stage II prevailed (35.4%; Figure 3).

Out of 49 patients with stage I, 36 had glottic and 13 supraglottic SCC, while of 58 stage II patients, 32 had glottic and 26 supraglottic disease. From the cohort of 50 stage III and 7 stage IV patients, glottic and supraglottic SCC was diagnosed in 26 and 24 patients, respectively, for stage III, and in 3 and 4 patients for stage IV.

Of all patients 30.7% had surgical treatment alone and 35.6% RT alone as initial management, while the

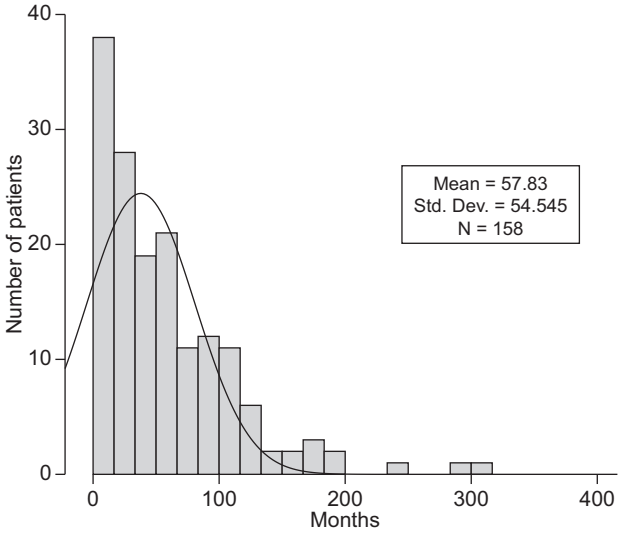

Figure 1. Distribution of patient follow up.

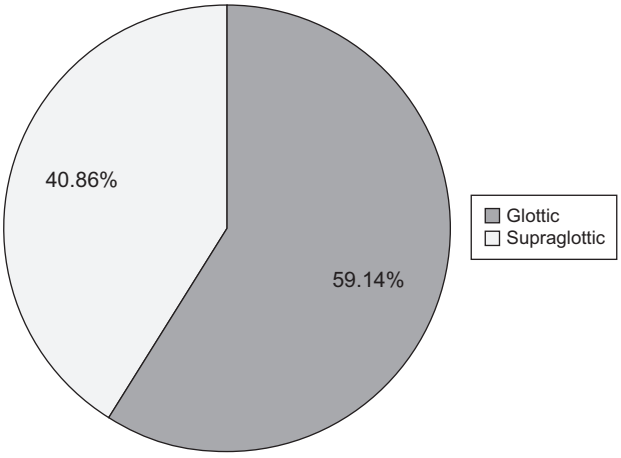

Figure 2. Anatomical tumor location.

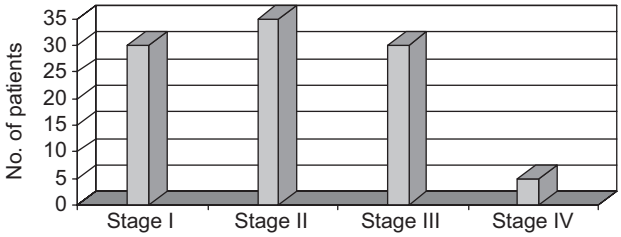

Figure 3. Distribution of patients according to stage.

rest of the patients were subjected either to pre- or post-operative RT and surgery or chemoradiation alone or combined with surgery (Figure 4). Thirty-three stage I patients with glottic SCC were treated with RT, with surgery 3 and with combined surgery and RT 1. In those with supraglottic SCC 5 had RT, 3 surgical treatment and 3 were treated with chemoradiation.

Stage II patients with glottic SCC were treated with surgery (n=10), with RT (n=9), with surgery and RT (n=9), with chemoradiation (n=2) and with chemoradiation following surgical treatment due to residual disease (n=2). Of those with supraglottic SCC 6 had surgical treatment, 6 RT, 6 surgery and RT, 3 chemoradiation and 5 chemoradiation following surgery because of limited response to initial therapy.

Fifteen stage III patients with glottic cancer were subjected to surgery, 6 to RT, 3 to surgery and RT, and 2 to surgery and chemoradiation. Of those with supraglottic SCC 11 had surgery, 1 RT, 6 surgery and RT, 2 chemoradiation, 2 surgery and chemoradiation and 2 had chemoradiation following surgery because of limited response to initial therapy.

Stage IV patients with glottic SCC were treated with surgery (n=1) and with surgery and RT (n=2). Of those with supraglottic cancer, 2 had surgery and 2 surgery and chemoradiation.

The distribution of staging and treatment modalities according to stage are presented in Table 1. Stage I patients had mostly non surgical management (81.6%)

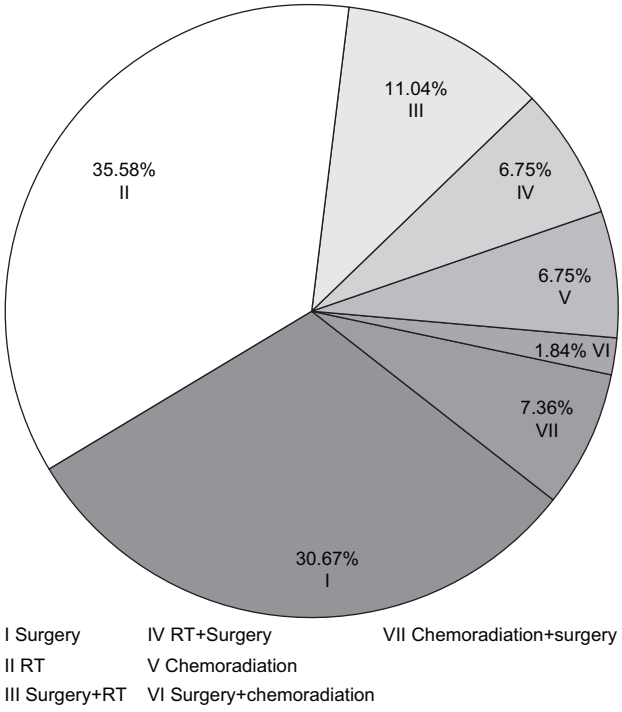

Figure 4. Distribution of patients according to treatment.

Table 1. Distribution of treatment modalities in relation to disease stages

Treatment	*Disease stages*			
	I (%)	*II (%)*	*III (%)*	*IV (%)*
Surgical	18.4	65.5	81.6	100
Non surgical	81.6	34.5	18.4	0.0

and specifically RT, whereas patients of the remaining stages were treated predominantly by surgery.

During follow up after initial treatment (range 2-75 months, median 12), 64 patients (39%) developed local recurrence. Of the recurrences 54.7% occurred in the first year, 20.3% in the second year and 9.4% during the third year. Thirty-one patients (18.9%) developed distant metastases and second primary lesions.

Recurrences were associated with treatment modality (surgical / non surgical; p=0.001) (Table 2). Recurrences occurred mostly in non-surgically treated patients (chemoradiation) and were not related either to alcohol abuse (p=0.21) or to tobacco use (p=0.20).

The distribution of patients according to disease outcome is depicted in Table 3. Disease-related death rate was 15.8%, and 62.8% of the patients were alive without recurrence.

The mean survival time of stage I patients was 137 months (median 148, range 88-288). Stage II patients had mean survival time 149 months (median 128, range 111-187). The mean survival time of stage III patients was 111 months (median 82, range 74-147), while that of stage IV patients was 22 months (median 23, range 16-28).

Significant survival differences were registered between stage I and III (p=0.035), stage I and IV (p= 0.0038) and stage II and IV (p=0.0156). The overall survival rate was 62.8% (Figure 5).

Table 2. Distribution of treatment modalities in relation to recurrence

Recurrence	*Treatment*		*p-value*
	Surgical (%)	*Non surgical (%)*	
Patients with recurrence	22.0	67.2	0.001
Patients without recurrence	78.0	32.8	

Table 3. Patient distribution according to outcome

Survival	*Number of patients*	*%*
Disease-related death	26	15.8
Other causes of death	29	17.7
Survival without recurrence	103	62.8
Lost to follow up	6	3.7

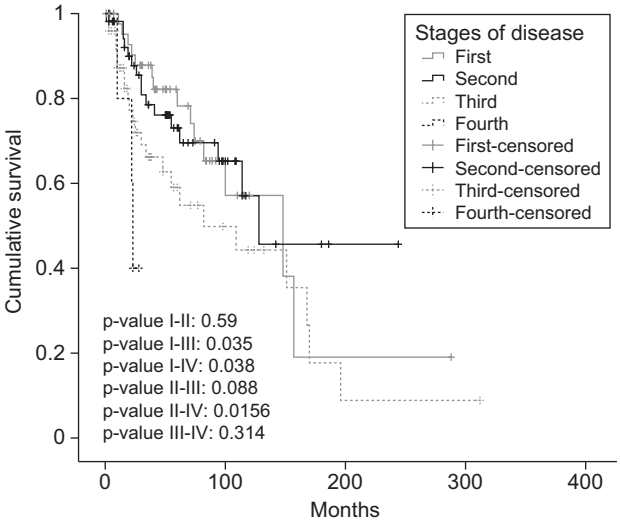

Figure 5. Overall survival according to disease stages.

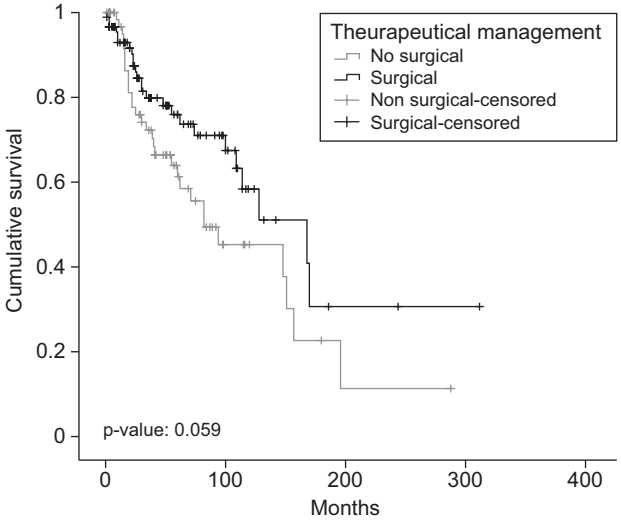

Figure 7. Overall survival according to therapeutic modality.

No statistically significant difference was recorded in survival in relation to anatomical site (glottic vs. supraglottic; p=0.50; Figure 6). The mean survival time in patients with glottic SCC was 127 months (median 148, range 97-156). For supraglottic SCC the mean survival time was 151 months (median 109, range 106-197).

Survival according to therapeutic modalities (surgical vs. non surgical treatment) differed marginally (p=0.059; Figure 7) with median time for non surgical treatment 82 months (mean 112) and for surgical management 168 months (mean 162).

Recurring patients had significantly shorter survival than patients without recurrence (p=0.0001; Figure 8). In particular, median survival time was 80 and 173 months in recurrent vs. non recurrent patients.

The median survival time of smokers vs. non smokers was 100 and 170 months respectively (mean 91 and 195 respectively; p=0.0047; Figure 9). The mean survival time for alcohol abusers was 79 months while it was 153 months for those who did not consume alcohol (median 94 and 151 months, respectively; p=0.016; Figure 10).

Discussion

The overall 5-year survival rate of laryngeal SCC in our study was 61.3%. Hoffman et al. [3], as well as other authors [5-7], have reported similar results (overall 5-year survival rate: 62-66%).

Also, similar results [8,9] are described for 5-year

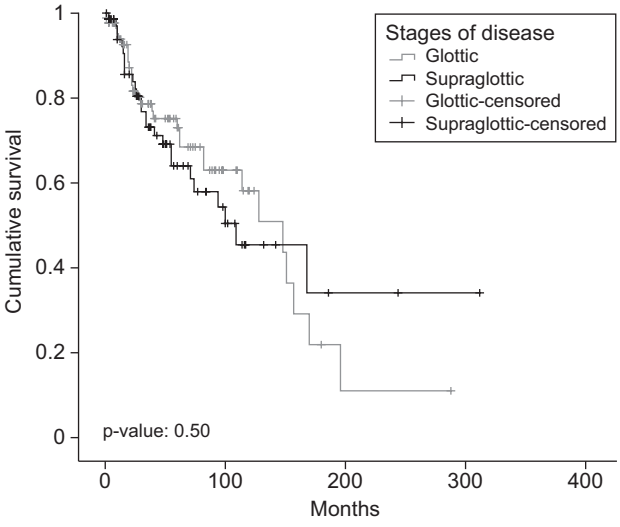

Figure 6. Overall survival according to disease localization.

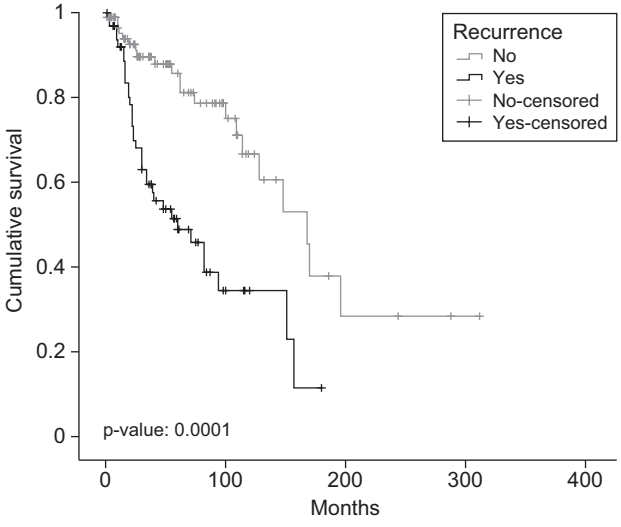

Figure 8. Overall survival according to recurrence.

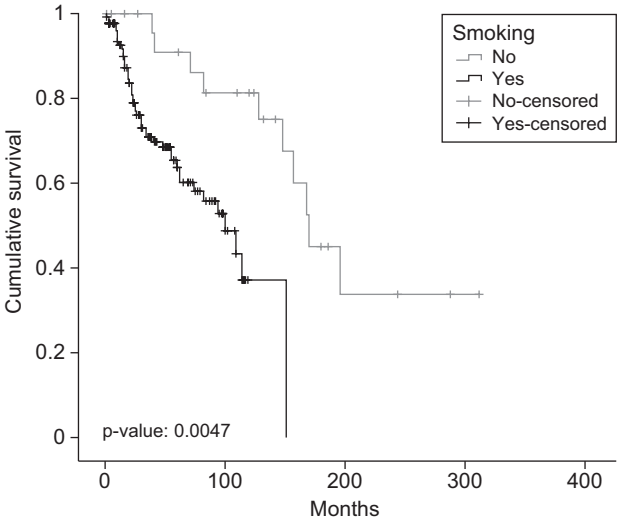

Figure 9. Overall survival according to smoking.

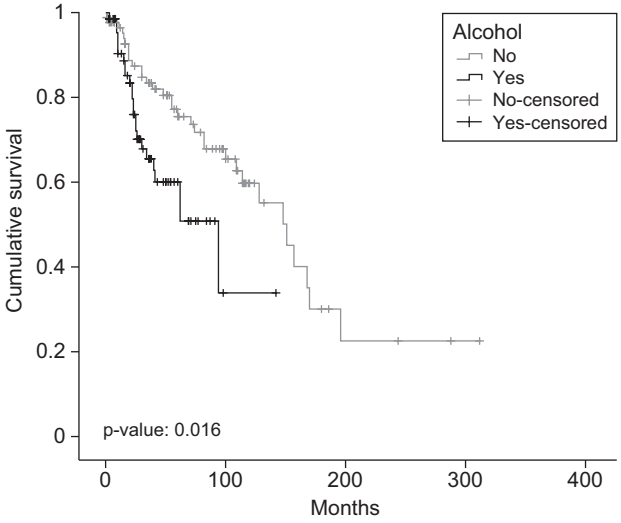

Figure 10. Overall survival according to alcohol abuse.

overall survival rate related to the stage of disease. Specifically, in our analysis 5-year overall survival rate for stage I was 78.2%, for stage II 71% and for stage III 55%.

We didn't find statistically significant difference between stages I and II. This could be attributed to:

a) The large variance of survival time from few months until more than 20 years, especially in first two stages, as depicted in Figure 1.

b) In stage I, 75% of the patients were treated with RT and 60% of those recurred, whereas in stage II the preferred treatment modality was surgery (65.5%). Only 15% of stage II patients underwent RT, but again the recurrence rate was also high (60%). Different therapeutic approaches among stages, as well as the large number of recurrences, which appeared in stage I patients treated with RT, could affect statistical significance.

As mentioned above, a great number of patients (60%) in stage I and II who underwent RT developed recurrence. Nevertheless, many authors report that RT, especially in stage I, has comparable survival rate with surgery [10-14]. However, RT performed in our radiotherapy center did not have the desired results. There is also a recent meta-analysis [15] of 131,694 laryngeal cancer patients by Chen and colleagues and the American Cancer Society, which showed an increase in the proportion of patients undergoing primary surgery for early-stage cancer from 20% in 1985 to 33% in 2007, whereas the use of RT decreased from 64 to 52%. In the same analysis, the 4-year survival rate for those treated with surgery was 79% while for those treated with RT it was 71%.

We also observed that there was not statistically significant difference between survival and anatomical disease site (p=0.50). The therapeutic management of stage I and II may play a role. The majority of patients with stage I glottic SCC and a significant number of stage II patients were treated non surgically, leading to large recurrence rate and therefore to a lower survival rate. Having in mind that two thirds of the patients have stage I and II disease, it becomes obvious how this could affect statistical analysis and therefore the weakness of finding statistically significant difference between survival and anatomical site.

The treatment modalities used depended on the anatomical site, disease stage and the presence of metastasis on initial assessment. There was a marginally significant difference between survival and therapeutic management (p=0.059). In the analysis of Chen and colleagues [15] there was an increase (38%) in the use of chemoradiation in advanced-stage patients, whereas total laryngectomies were decreased to 10%. The 4-year survival rate of those treated with chemoradiation vs. total laryngectomy was 48 and 51%, respectively. The increase in the use of chemoradiation started the same period (1991), when the Department of Veterans Affairs [VA] Laryngeal Cancer Study Group published a randomized trial with 332 patients, which showed that induction chemotherapy followed by RT in a subset of patients with advanced-stage cancer permitted successful treatment without diminishing the chance for cure [16].

RT is a reliable alternative to surgery for T1 tumors of glottic and supraglottic SCC. Its main advantage is the preservation of voice and speech. However, some authors [17] reported that the final percentage of total laryngectomies performed in patients initially treated with RT was significantly higher compared to the percentage of patients initially treated with surgery [18]. In addition, even if "close fields" of RT are used for laryngeal carcinoma in order to limit patient's exposure

to radiation, RT cannot be reused in the same anatomical area, if that was necessary after relapse, due to limited resistance of normal tissues to ionizing radiation.

Approximately 10% of stage I glottic cancer patients will develop a second primary tumor in the upper aerodigestive tract, more aggressive and more advanced [19]. This seems to be the result of "field cancerization", a term that expresses the exposure of aerodigestive epithelium to chronic carcinogenic insults. As a result there is a predisposition of developing premalignant and malignant lesions. The majority of second primary tumors involves lung, esophagus and head and neck area [20].

Conclusions

The therapeutic approach most commonly used for stage I tumors was RT, while for other stages it was surgery. Recurrences were increased in stage I and II patients treated with RT, compared with those of the same stages and treated with surgery.

The overall 5-year survival rate (61.3%) of our study is in accordance with reports of other authors. We found a significant difference between smokers and non smokers (p=0.0047) and between alcohol abusers and non alcohol abusers (p=0.016). Significant differences in survival between stage I and III (p=0.035), stage I and IV (p=0.0038) and stage II and IV (p=0.0156) were observed. No significant difference (p=0.5) in survival between glottic and supraglottic SCC was noted. Recurring patients (n=64; 39%) had significantly shorter survival (p=0.0001). It is worth mentioning that significantly higher recurrence rates were observed in stage I where the therapeutic modality most used was RT (75%). Comparison of the therapeutic modalities (surgical vs. non surgical management) showed a difference close to statistical significance (p=0.059).

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