

Predictors of local failure in early laryngeal cancer*

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The aim of the study was to assess the impact of factors that could predict the probability of local failure in early laryngeal squamous cell carcinoma treated with curative radiotherapy.

Sixty seven patients (12 women and 55 men) with laryngeal cancer stage I (47 patients) and stage II (20 patients) were treated from 1998 to 2003 with curative radiotherapy and retrospectively evaluated.

Median follow-up was 36 months (3–80). Local relapse occurred in 10 patients (15%), regional lymphnodes relapse affected 2 patients. The median time between start of radiotherapy to recurrence was 13 months (3–48). Death due to cancer occurred in 4 patients (2 died from locoregional progression of the recurrence and 2 from distant metastases), whereas 7 patients died from non-cancer related causes. The 2-year overall survival rate was 90% and 5-year OS was 79%. The 2-year local control rate was 82% and 5-year local control was 79%. In the univariate analysis there was a statistically significant decrease in local control influenced by grading ($p < 0.0001$). High risk group of relapse encompassed patients with at least two negative factors: supraglottic tumor, women, radiotherapy prolongation by 3 or more days and high grade tumor and has 3 times worse local control than low risk group ($p = 0.0125$). The highest risk of local recurrence was in the first three years after radiotherapy than later ($p = 0.0057$). On multivariate analysis unfavourable prognostic factors for local control were gender ($p = 0.022$), presence of 2 or more negative risk factors ($p = 0.018$) and lengths of follow up ($p = 0.005$). Radiation dose, stage, age, hemoglobin level and anterior commissure involvement were not significant factors for local control. Overall survival was affected both in the univariate and multivariate analysis by presence of local relapse ($p < 0.005$) and follow up duration ($p < 0.02$). Anemia had borderline significance for overall survival in univariate analysis ($p = 0.064$), but in the multivariate analysis was significant unfavourable factor ($p = 0.008$). Other studied factors (radiation dose, anterior commissure involvement and age) were not reaching level of statistical significant value for overall survival.

Close follow up strategy is recommended for high risk group of patients with two or more risk factors especially in the first three years after radiation therapy.

Key words: early laryngeal carcinoma, radiotherapy, local recurrence, prognostic factors

Larynx carcinoma is a rare type of tumor with a stable incidence of 500 cases per year (around 9 cases/100 000 inhabitants) in Czech Republic, which accounts for 1.5% of all malignancies in men and 0.2% in women. The highest incidence is in the age group of 50–70 years. The stage distribution according to National Cancer Registry data from the year 2000 indicates that majority of cases are in stage I (25%) and stage IV (25%) and less in stage II (16%) and stage III (17% of patients), stage was not assessed in 17% of all cases [9].

Early laryngeal cancer (stage I and II) is highly curable with radical radiotherapy with cure rates 75–95%. Prognosis depends on different prognostic factors such as the tumor site, stage, depth of invasion, age, gender, grade, anterior commissure involvement, performance status and hemoglobin level. Patients treated for laryngeal cancer are at highest risk of recurrence in the first 2–3 years, recurrence after 5 years is rare and usually represents a new primary malignancy [25].

The aim of our study was to assess the impact of different factors that could predict the probability of local failure in early laryngeal squamous cell carcinoma after radical radiotherapy.

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Patients and methods

From January 1998 to December 2003, sixty seven patients with laryngeal cancer stage I (47 patients) and stage II (20 patients) were treated with curative radiotherapy and retrospectively evaluated at the University Hospital Motol, Prague. The median follow-up time was 36 months (range 3–80 months). The median age of patients was 63 years (range 45–84 years). The patients were 12 (18%) females and 55 (82%) males.

Pretreatment evaluation included history and physical examination, baseline hematology and biochemistry, chest X ray, microlaryngoscopy and biopsy was taken under general anesthesia. Primary glottic carcinoma was determined in 62 (93%) and primary supraglottic tumor in 5 (7%) patients. Stage I was found out in 47 (70%) and stage II in 20 (30%) patients (Tab. 1). The biopsy of all patients had proven squamous cell carcinoma. Tumor grading was evaluated in 56 patients and grade 1 was assessed in 37%, grade 2 in 34%, grade 3 in 10% and grade 4 in 1% of patients. In 26 patients with glottic carcinoma (42%) anterior commissure involvement was described.

Table 1. Stage and tumor location distribution in early laryngeal cancer

Tumor location and stage	Number of pts	%
Glottic carcinoma	62	93%
stage Ia	37	55%
stage Ib	9	14%
stage II	16	24%
Supraglottic carcinoma	5	7%
stage I	1	1%
stage II	4	6%
Subglottic carcinoma	0	0%
Total	67	100%

Radiotherapy prolongation is associated with decreased local control and in our series the median prolongation was 4 days (range 0–19), which was caused by public holidays, linear accelerator breaks and patients comorbidity. Only 17 patients (27%) finished radiotherapy with maximum 2 day prolongation (Fig. 1).

Patients were irradiated using linear accelerator and CT localisation of target volume was used. In all patients radiotherapy was prescribed according to ICRU guidelines in 2 Gy daily fractions, 5 days per week and 3D treatment planning was employed. The treatment volume included the primary tumor site in stage I glottic cancer. Additional volume electively encompassed high risk lymphnodes in levels II and III bilaterally in stage II glottic carcinoma with supraglottic extension or primary supraglottic tumors stage I or II. In case of subglottic extension of primary glottic cancer lymphnodes level IV were electively irradiated. The dose to the primary site was 66 Gy in stage Ia disease glottic carcinoma and

70 Gy in stage Ib and II glottic carcinoma and stage I and II supraglottic cancer. The dose to electively irradiated lymphnodes was 50 Gy. Isocentric technique of 2 anterior oblique fields was used for primary tumor. For irradiation of clinically negative neck were used two opposing lateral fields with shielding of the spinal cord at 40 Gy and posterior lymphnodes were treated with lateral appositional electron beams to 50 Gy. High energy photon beams 4 MV or 6 MV were used. All patients completed treatment.

Statistical analysis. The data were analyzed with statistical software SPSS version 10.0, p-values of less than 0.05 were considered to indicate statistical significance. Univariate analyses of survival were carried out by the Kaplan-Meier method and the evaluation of differences between the groups was performed with the log-rank test. A multivariate analyses of survival according to risk factors was performed with the use of the Cox proportional-hazards regression model using forward stepwise method.

Relapse free survival (RFS) was defined as the time between start of radiotherapy and the first relapse. Overall survival (OS) was defined as the time between start of radiotherapy and death due to any cause or last follow up examination.

Results

At the time of reporting 2005, 56 patients were alive with a median follow up 41 months (range 10–80 months), 11 patients died. Death due to cancer occurred in 4 patients (2 from locoregional progression of the recurrence and 2 from distant metastases), whereas 7 patients died from non-cancer related causes. The 5-year overall survival rate was 90% and 5-year disease free survival rate was 79%. The median OS and DFS was not reached (Fig. 2)

Local relapse occurred in 10 patients (15%), 6 recurrences were salvaged with laser chordectomy, 2 with partial laryngectomy, 1 with total laryngectomy and 1 patients refused any further treatment. Regional lymphnodes relapse occurred in 2 patients. The median time to recurrence was 13 months (3–48). Voice preservation was achieved in 98% of all patients.

Prognostic factors influencing recurrence such as stage, gender, tumor grading, radiotherapy prolongation by 3 or more days, age, tumor location, radiation dose, anterior commissure involvement, hemoglobin level and follow up duration were studied.

On univariate analysis unfavorable prognostic factors for local control were grading ($p < 0.0001$), (Fig. 3) and length of follow up less than 36 months ($p = 0.0057$), (Fig. 6 and Fig. 7).

Higher rates of local relapse were reported in supraglottic vs glottic tumors (60% vs 84%), women vs men (67% vs 85%) and radiotherapy prolongation by 3 or more days (80% vs 88%), but results did not reach level of statistical significance. Two risk groups were obtained combining these risk factors. High risk group contains patients with presence of 2 or more negative prognostic factors (supraglottic tumor,

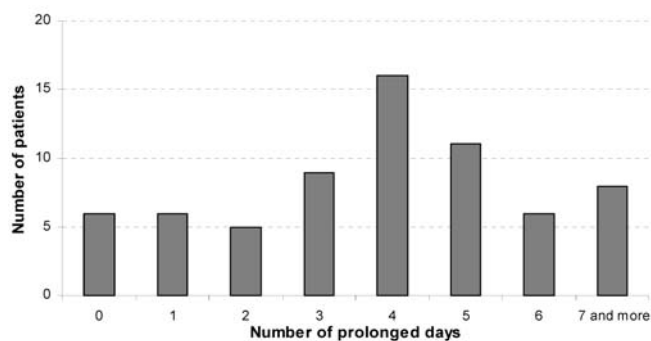


Figure 1. Radiotherapy prolongation by days.

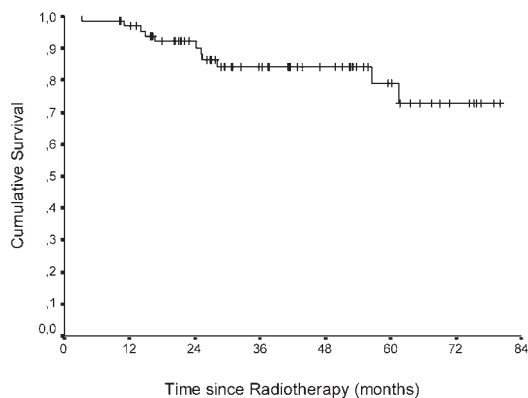


Figure 2. Kaplan Meier overall survival curve for early laryngeal cancer treated with curative radiotherapy.

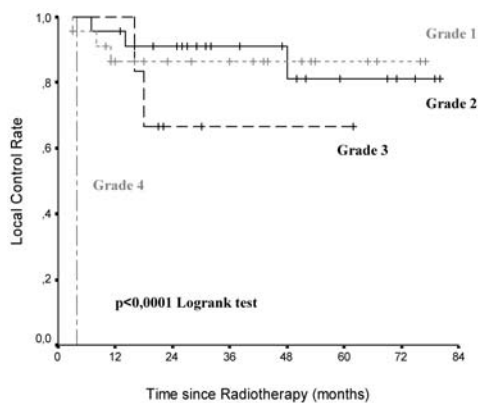


Figure 3. Local control associated with tumor grading.

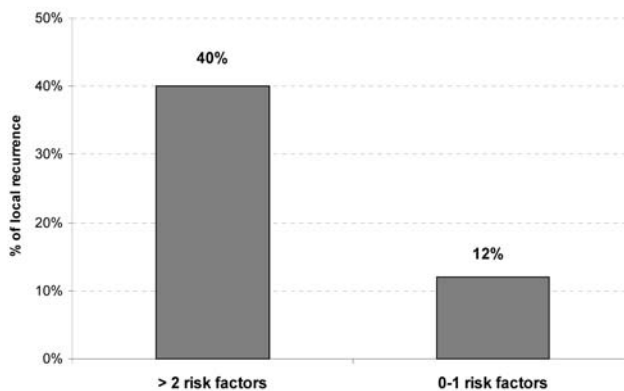


Figure 4. Impact of presence of risk factors at local recurrence incidence.

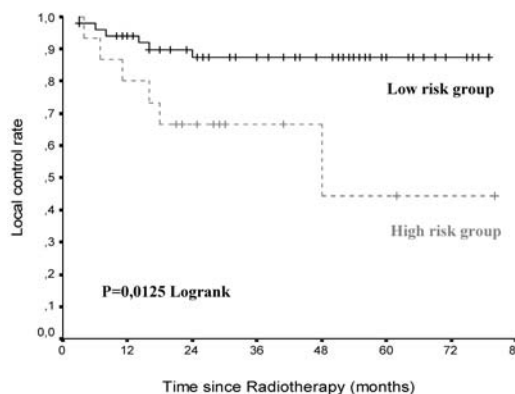


Figure 5. Kaplan-Meier relapse free survival according to risk groups.

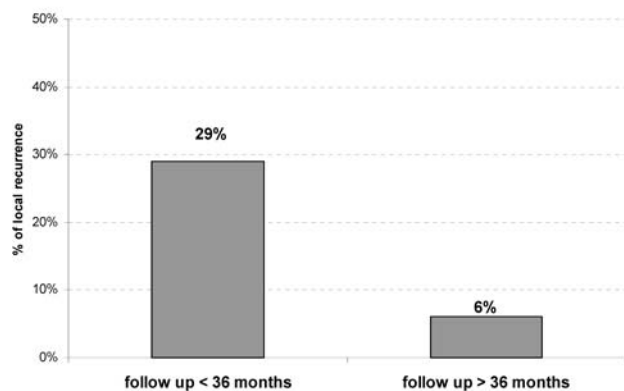


Figure 6. Relationship of follow up duration and risk of local relapse.

high grade, women a radiotherapy prolongation) and was associated with statistically significant higher relapse rate (which occurred in 40%), on the contrary patients in low risk group with 0–1 factor had local relapse in 12% ($p=0.0125$), (Fig. 4 and Fig. 5). Anterior commissure involvement, stage, radiation dose, age and hemoglobin level during radiother-

apy seems not to have any prognostic impact for local relapse. On multivariate analysis unfavorable prognostic factors for local control were lengths of follow up ($p=0.005$), presence of 2 or more negative risk factors ($p=0.018$) and gender ($p=0.022$). The explanation for statistical significance of gender in multivariate analysis, which was not reached in

univariate analysis could be grading stratification (all women had good differentiated tumors, despite the fact that they had higher rates of local relapse independent of other risk factors).

Overall survival was in the univariate analysis affected by the presence of local relapse ($p < 0.0001$), (Fig. 8), tumor location ($p = 0.0018$), stage of the disease ($p = 0.0169$) and follow up duration ($p = 0.0002$). In the multivariate analysis were as important factors influencing overall survival found presence of local relapse ($p = 0.007$) and follow up duration ($p = 0.012$). Decreased hemoglobin level (less than 120 g/l) seems to have some prognostic influence which is on the border of statistical significance in univariate analysis ($p = 0.064$) for overall survival, but in multivariate analysis was significant ($p = 0.008$) (Fig. 9). Other factors (anterior commissure involvement, age, radiation dose and gender) affecting survival were not reaching level of statistical significance.

Late effects were evaluated according to RTOG/EORTC late reactions scale in 39 patients (57%) and only one case of hoarseness grade 3 was detected, other late toxicity was neglectable.

Discussion

Different prognostic factors affecting local control in early laryngeal cancer were published. T stage [3, 14, 19, 22, 23] and tumor size was evaluated as important prognostic factor for local recurrence [7], but in other studies were not significantly associated with prognosis [1, 16, 27]. Worsened prognosis is connected with arytenoid involvement [16]. Most authors revealed that anterior commissure extension has poor outcome [3, 10, 13, 15, 17, 19, 28] and some of the authors recommend surgery treatment instead of radiotherapy in these cases [28]. On the other hand there are some studies which found no prognostic impact of anterior commissure involvement [1, 16, 27]. Poor prognosis is associated especially when anterior commissure and bilateral vocal cord involvement is present [18]. Another studies revealed that involvement of posterior of third vocal cord has worse prognosis [22]. Extension to one third or more of the vocal cord has impact on lower local control [19, 22]. Subglottic extension seems to be predictor of poor outcome of radiotherapy alone in T2 glottic lesions [10, 15, 17, 18]. Glottic tumors behave prognostically better than supraglottic cancer [23]. Macroscopically visible tumors [6, 7] and bulky glottic tumors [13] are unfavorable prognostic factor for local relapse. This suggests that a classification based on the actual size of the tumor could be a better predictor of outcome than the conventional T-staging. Some authors recommend classify T1 glottic tumors as small or bulky, which better corresponds to local relapse rates [20].

Factors related to patients revealed that unfavorable prognosis for OS have patients older than 65 years and those who suffered from second malignancy [13]. Gender and age seems not to be important for local recurrence in other studies

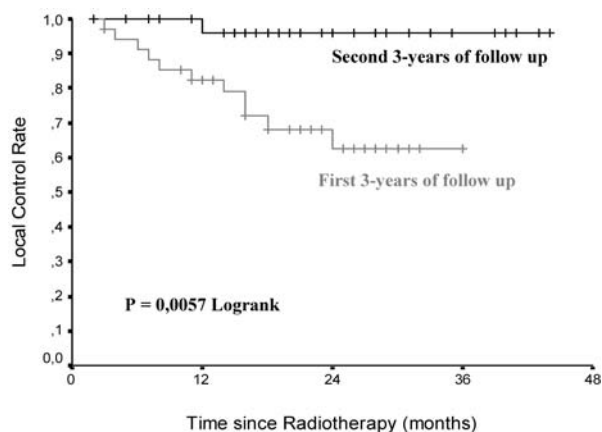


Figure 7. Kaplan-Meier relapse free survival in the first 3-years and second three years of follow up.

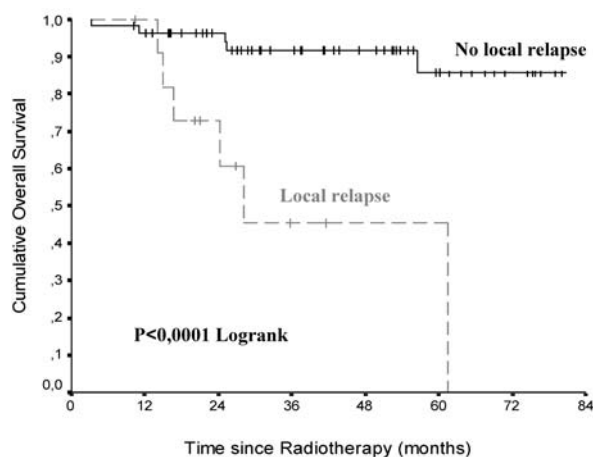


Figure 8. Kaplan-Meier overall survival curve – statistically significant influence of local relapse occurrence.

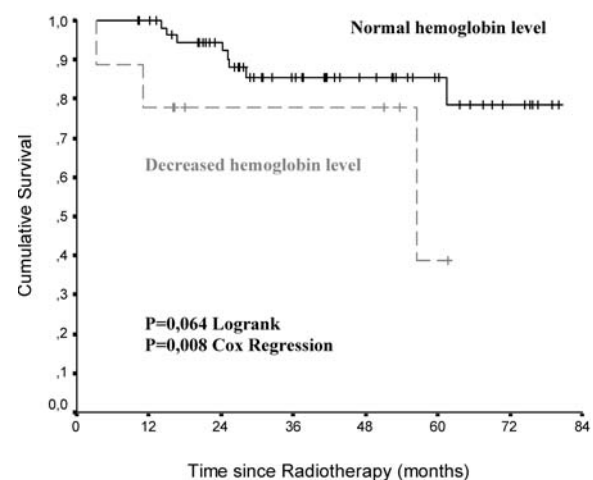


Figure 9. Kaplan-Meier overall survival curve – influence of hemoglobin level ≤ 120 g/l during radiotherapy.

[3, 4, 24, 27]. Decreased local control and overall survival is associated with low pretreatment hemoglobin [5, 8, 11] and also with hemoglobin levels during treatment [13]. Other factors influencing local relapse are smoking [2, 7] and diabetes mellitus [19]. Other authors have not revealed prognostic importance of smoking habits [4]. Karnofsky performance status less than 80 is significant factor of worsened survival [6]. Persistent dysphonia after radiotherapy is significantly associated with lower local control [1, 6, 7, 15, 19].

Among prognostic factors related to radiotherapy are total dose and fraction size of radiotherapy. Total dose less than 65 Gy correlates with poorer outcome [17, 24]. Daily dose lower than 2 Gy (5 fractions per week) has negative impact on local control [3, 10, 27]. Longer treatment duration indicates worsened locoregional control especially when split course radiotherapy is performed [22]. Overall time [3] of radiotherapy ≤ 43 days has better locoregional outcome (but authors have used larger daily fractions 2.25 Gy) [17]. Other authors find out, that there is no significant difference in local control between overall radiotherapy time 40–42 days or 43–46 days [12]. In other studies is a visible trend to statistical significant worsened local control with overall treatment time longer than 50 days [4]. The treatment year of radiotherapy correlate with decreased local control [17]. Treatment energy and treatment technique seems not to be important, when ICRU recommendations are maintained [4, 24].

Histopathological predictors of outcome such as grading [23, 26] influences local recurrence. On the other hand molecular markers as overexpression of p53 has not sure prognostic impact, some studies showed no predictive impact on locoregional control or survival in early glottic cancer treated with radiotherapy [21], but other study proved that p53 overexpression was associated with bulky tumor and poor local control in T1 glottic cancer [20].

Conclusion

We identified high risk group of patients treated with curative radiotherapy for early laryngeal cancer, where relapse rate according to presented prognostic factors was more than three times higher. Presence of two or more followed factors was associated with statistically significant worsened locoregional control 71% vs 94% local control if at least one negative prognostic factor was present ($p=0.0125$).

Close follow up strategy is recommended for this high risk group of patients with two or more risk factors (woman, primary supraglottic tumor, grade 3 or 4, radiotherapy prolongation by 3 or more days) especially in first three years after radiation therapy. Careful clinical examination and repetition of any abnormal imaging staging methods are included in follow up, with attention to radiotherapy late effects evaluation.

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