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Review

CLINICAL COURSE OF THE DISEASE AND TREATMENT OUTCOME IN PATIENTS WITH MALIGNANT LARYNGEAL TUMOR: RETROSPECTIVE FIVE-YEAR ANALYSIS

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SUMMARY – The aim was to investigate clinical course of disease in patients with malignant laryngeal tumors with emphasis on various forms of disease recurrence (local recurrence, metastasis to regional lymph nodes, occurrence of second primary tumor). A retrospective research including 78 patients with histopathologically confirmed diagnosis of squamous cell laryngeal carcinoma was conducted. Information on cancer stage, histologic grade, type of treatment and disease recurrence was obtained from medical history. Tissue samples of the patients were submitted to immunohistochemical analysis and assessment of Ki-67 proliferation index expression. The occurrence of second primary tumor was found to be related to the significantly higher Ki-67 proliferation index. The number of patients having not undergone oncologic therapy and remained free from disease recurrence was significantly higher than expected. Treatment outcome depends on patient age, histologic grade, radiotherapy applied, and clinical course of disease. It is necessary to define the predictive factors of various forms of disease recurrence more precisely in order to identify better treatment options for patients with malignant tumors of the larynx.

Key words: *Laryngeal cancer; Treatment outcome; Local recurrence; Second primary tumor*

Introduction

Malignant laryngeal tumors are the second most common tumors of the head and neck[1]. The approach to treating malignant laryngeal tumors can be surgical, oncologic or combined. Despite significant progress in treatment, a significant decrease in the 5-year survival rate has been recorded in the last few decades[2,3]. In the 1975-1977 period, the 5-year survival rate was 66%, whereas in the 2005-2011 period it dropped to 63%[4]. The goal of this study was to present the clinical course of the disease in patients with malignant laryngeal tumors with special reference to different forms of recurrence (local recurrence, metastases to regional lymph nodes or the second primary tumor). Moreover, treatment outcome of our patients will be critically discussed in relation to the treatment methods applied in order to draw conclusions that will enable higher treatment quality for patients with malignant laryngeal tumors.

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Patients and Methods

Patients

We performed a retrospective study on 78 patients suffering from the histopathologically confirmed diagnosis of squamous cell laryngeal carcinoma, who had undergone surgery and postoperative therapy at the Rijeka University Hospital Center Department of Otorhinolaryngology and Head and Neck Surgery and Department of Radiotherapy and Oncology, respectively. Study patients were divided into two groups: one group included 68 (87.2%) patients diagnosed with laryngeal carcinoma and the other group included 10 (12.8%) patients diagnosed with laryngeal carcinoma with metastases to regional lymph nodes. Patient age at the time of diagnosis ranged between 45 and 81, median 60 years. All patients were surgically treated. Partial laryngectomy was performed in 36 patients and total laryngectomy in 42 patients. A total of 55 patients underwent oncologic treatment, adjuvant radiotherapy was administered to 47 patients, and adjuvant chemotherapy/radiotherapy to 8 patients. According to the reference data, tumors were classified as early-stage and late-stage tumors, stage 1 and 2 being classified as early-stage and stage 3 and 4 as late-stage[5]. Thirty-six (46.2%) patients were diagnosed with early-stage disease and 42 (53.8%) patients with late-stage disease. Regarding histologic grade, patients were divided into four groups. The majority of patients belonged to the histologic grade 2 (51.3%), followed by grade 1 (23.1%), grade 3 (14.1%) and finally carcinoma *in situ* (11.5%). The Ki-67 proliferation factor was immunohistochemically determined in preoperative biopsy samples. Data on the clinical course of the disease were obtained from patient medical history, which enabled us to record disease recurrence as local recurrence, metastases to regional lymph nodes and second primary tumor occurrence. Local recurrence was detected in 8 (10.2%), metastases to regional lymph nodes in 9 (11.5%) and second primary tumor in 7 (9.0%) patients. Study patients were observed during a 5-year postoperative period. After 5 years, the total number of survivors was 50 (64.1%).

Methods

Tissue samples of invasive and squamous cell carcinoma *in situ* were immunohistochemically stained. Histopathologic analysis was performed by use of light microscopy. All samples were fixed in 10% buffered formalin (Kemika, Zagreb, Croatia), paraffin embedded and stained with hematoxylin and eosin (HE). The grade of histologic differentiation was determined in samples in accordance with the World Health Organization classification scale.

Immunohistochemical analysis

From the representative laryngeal carcinoma tissue samples a paraffin block was taken and cut into 4-5 μm thick slices. The samples were overnight stored in a thermostat at 37 °C and then deparaffinized through a standard procedure of applying a substitute for xylene (Tissue Clear Sakura; 3x10'), rehydrated in absolute alcohol (2x5'), 96% ethanol (5'), 70% ethanol (5'), and finally rinsed in distilled water. The samples were treated with a visualization system based on the EnVision method. The visualization system (Dako Real EnVision Detection System Peroxidase/DAB+, Rabbit/Mouse K5007, Agilent, Santa Clara, USA) was used in the automatic immunostainer (Dako Autostainer Plus, Agilent, Santa Clara, USA). Diaminobenzidine (DAB) was used as a chromogen. The primary antibody Ki-67 Antigen Clone MIB-1 M7240 (Agilent, Santa Clara, USA) was used. After applying the visualization system, hematoxylin contrasting was applied for 1 minute, followed by rinsing in lukewarm water and dehydration of the cuts in ethanol of different concentration grades (70%, 96% and 100%), after which rinsing in a xylene substitution was performed. Finally, GLC Mounting Medium covering (Agilent, Santa Clara, USA) was done. The Dako Wash Buffer 10x S 3006 (Agilent, Santa Clara, USA) was used for rinsing procedures between stages.

Assessment of Ki-67 proliferation index expression

Assessment of Ki-67 expression on tumor cells was performed in accordance to the current knowledge described in the available references. The expression was assessed by two independent pathologists, N.J. and A.D. The Ki-67 expression was expressed in percentage. Assessment was performed with the following procedure: the structures were quantified with the Alphelys Spot Browser 2 integrated system which consists of the automated microscope (Nikon Eclipse 50i, Nikon, Amstelveen, The Netherlands) with a digital camera (Microvision CFW-1310C, 24 b, resolution of 1360x1024 pixels; Nikon, Amstelveen, The Netherlands) under supervision of the computer program (Alphelys Spot Browser 2.4.4). The system is calibrated in the Nazca program (Microvision Instruments, France) by determining the size of a pixel

for a specific lens (0.3311 μm for 20x lens and 3.320 μm for 2x lens).

After overview, the slide images were taken with 20x enlargement, images which were to be analyzed were taken in specific locations with 200x enlargement and analyzed through the program with constant adjustment of the camera and the microscope. During the analysis of digital images, the structures are detected based on color (wave length, intensity and saturation), grouping and morphological features (size and shape), and are marked with colors which enables control and correction of the detection process. For this purpose, a detection algorithm was created which defined detection conditions for structures of interest for quantification. During the detection process, the program automatically measures the structures detected and calculates set parameters which in this case are the number of positive and negative tumor cell nuclei.

Ethics

Four basic bioethical principles were honored during the research (personal integrity-autonomy, impartiality, beneficence and harmlessness), as well as those derived from them (privacy, trust). The study was conducted in accordance to the Nuremberg Code, the latest review of the Helsinki Declaration and other relevant documents.

Statistical analysis

Statistical processing of collected data was performed with the Statistica® statistical package (version 10.0, StatSoft Inc., Tulsa, OK, USA). The data collected were analyzed with appropriate statistical methods. The level of statistical significance was set at $p<0.05$.

Results

Clinical course of the disease is shown in Table 1. Local recurrence occurred in 8 patients, with a median of 14 months after the operation. Metastases to regional lymph nodes occurred in 9 (11.5%) patients, with a

Table 1. Clinical course of the disease and treatment outcome

	n (%)	Time elapsed from surgery: months, median (q25-q75)
Local recurrence	8 (10.2)	14 (7-16)
Metastases in regional lymph nodes	9 (11.5)	11 (7-15.5)
Second primary tumor	7 (9.0)	13.5 (4-36)
Treatment outcome (survivors)	50 (64.1)	

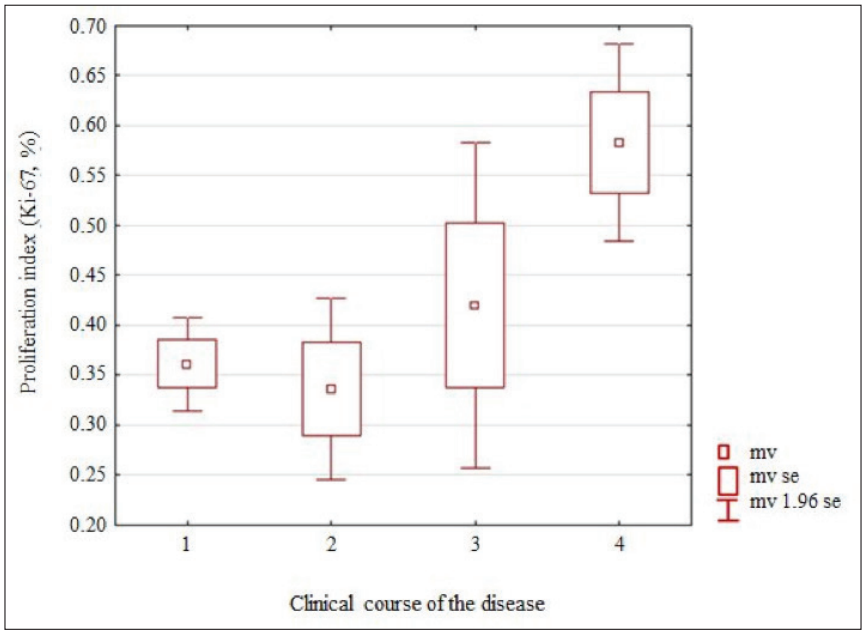

Fig. 1. Clinical course of the disease according to Ki-67 proliferation index.

Clinical course of the disease: 1 – no recurrence; 2 – local recurrence; 3 – metastases to regional lymph nodes; 4 – second primary tumor

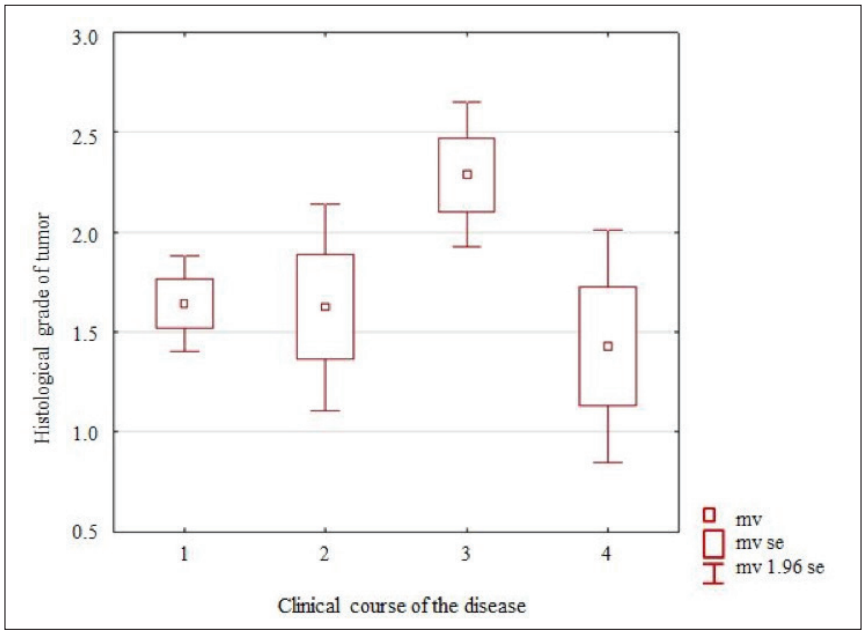

Fig. 2. Clinical course of the disease according to histologic grade of tumor.

Clinical course of the disease: 1 – no recurrence; 2 – local recurrence; 3 – metastases to regional lymph nodes; 4 – second primary tumor

median of 11 months after the operation. In 7 (9%) patients, the second primary tumor occurred at completely different locations, i.e., esophagus in 2 cases, and base of the tongue, lungs, rectum, bladder and colon in one case each, with a median of 13.5 months after the operation. Fifty (64.1%) patients survived the analyzed period. Local recurrence and metastases to regional lymph nodes occurred in only 2 (2.5%) cases and second primary tumor only in patients without local recurrence or metastases to regional lymph nodes. There was no difference in the incidence of different manifestations of disease recurrence according to gender (Pearson χ^2 test, χ^2=1.31, p=0.726) or age (Man Whitney U test, Z=0.255, p=0.798). Some manifestations of disease recurrence during the clinical course of the disease had statistically significantly different Ki-67 proliferation index values (ANOVA, F=3.59, p=0.017). The occurrence of second primary tumor was associated with a significantly higher Ki-67 proliferation index compared to patients who had no disease recurrence and patients with local recurrence or local metastases (Fig. 1). Histologic findings of tumor grade showed no statistically significant differences in the clinical course of the disease (Kruskal-Wallis ANOVAFF: H=4.66, p=0.199), although it should be noted that the highest tumor grade was recorded in the group with local metastases (Fig. 2). Concerning clinical course of the disease in relation to the stage of carcinoma, there were no statistically significant differences in the incidence of particular types of disease recurrence (Pearson χ^2 test, χ^2=4.13, p=0.247) (Table 2). Clinical course of the disease showed significant differences according to the oncologic therapy administered (Table 3). The number of patients who had not received any form of oncologic therapy and later had no local recurrence, metastases to regional lymph nodes or second primary tumor was statistically significant (Pearson χ^2 test, χ^2=13.35, p=0.038). The reason for this was the fact that according to the guidelines applied, our patients with early-stage carcinoma did not receive radiotherapy or radiochemotherapy.

Table 2. Clinical course of the disease according to stage of carcinoma

	Stage of carcinoma		Total
Clinical course	Early	Late	
Local recurrence	6	2	8
Metastases in regional lymph nodes	2	5	7
The second primary tumor	4	3	7
No recurrence	24	32	56
Total	36	42	78

Table 3. Incidence of certain types of disease recurrence according to type of oncologic treatment

	Clinical course of the disease				
Therapy	No recurrence	Local recurrence	Metastases to regional lymph nodes	Second primary tumor	p
Radiotherapy	34	5	3	5	0.038
Radiotherapy/ chemotherapy	3	3	2	0	
No therapy	19	0	2	2	

Table 4. Treatment outcome according to patient and disease characteristics

	Outcome		
Characteristic	Survivors	Deceased	p
Gender, male/female	43/7	25/3	0.485
Age, median (q25-q75)	57 (54-66)	70 (58-74)	<0.001
Stage of carcinoma (early/late)	27/9	23/19	0.052
Histologic grade of tumor	1.5 (1-2)	2(2-2)	0.010
Ki-67 proliferation index	37.7%±18.0%	39%±19.5%	0.656

The relations of treatment outcomes (survivors/deceased during the study period) with other patient and disease characteristics was researched (Table 4). Treatment outcome (survivors/deceased during the study period) showed no statistically significant gender difference (Fisher exact test, p=0.485). Patient age was significantly related to treatment outcome, i.e., survivors were significantly younger (Mann Whitney U test, Z=3.51, p<0.001). The result is shown in Figure 3. Treatment outcome in relation to patient age

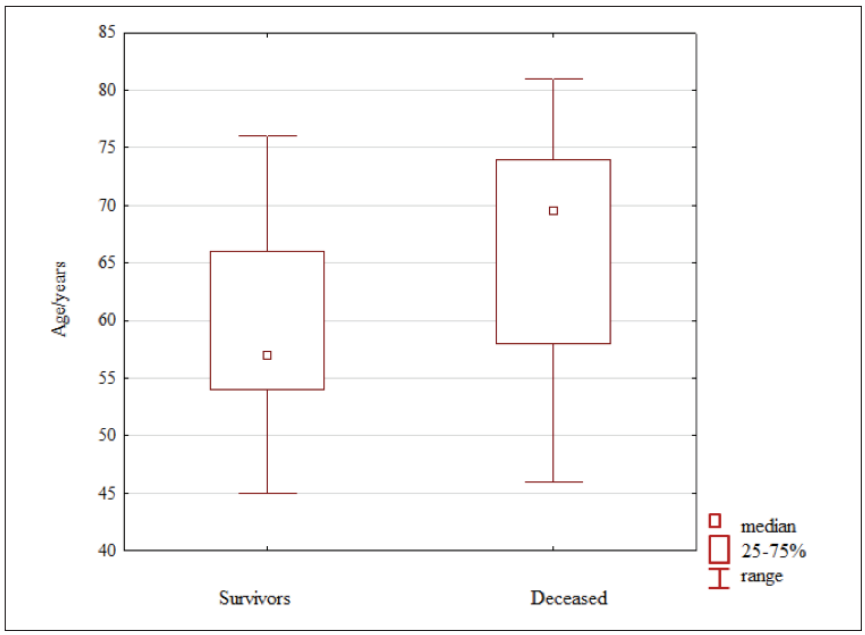

Fig. 3. Treatment outcome according to patient age.

was additionally analyzed through logistic regression, which showed that the model was statistically highly important, and that patient age was a significant predictor of treatment outcome (model assessment χ^2=14.05, p<0.001). The result of logistic regression is shown in Figure 4. Depending on the stage of carcinoma, marginally, there were significantly more deceased in the group of patients suffering from late-stage carcinoma (Fisher exact test, p=0.052). Treatment outcome also showed a significant difference according to tumor histologic grade (Man Whitney U test, Z=2.57, p=0.010) (Fig. 5). Treatment outcome

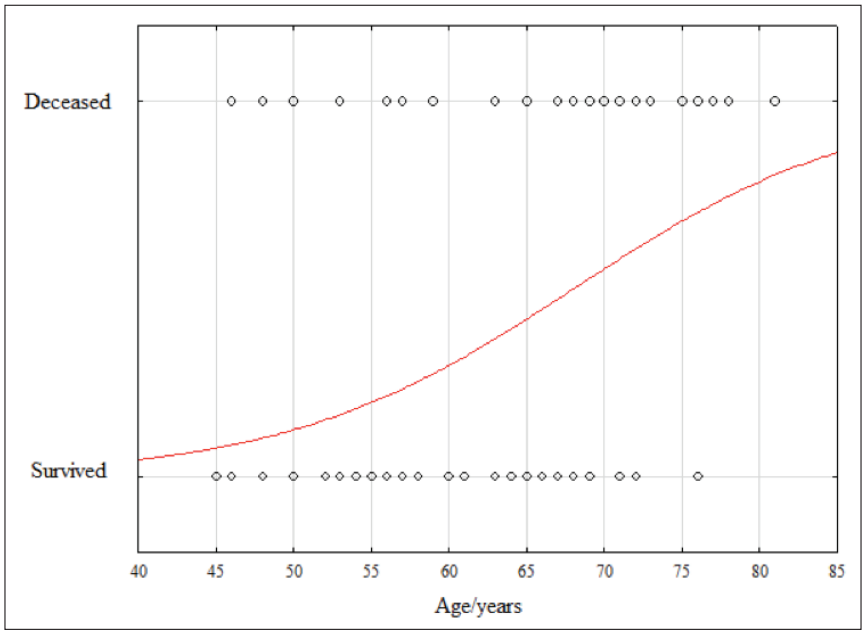

Fig. 4. Logistic regression curve for predicting treatment outcome according to patient age.

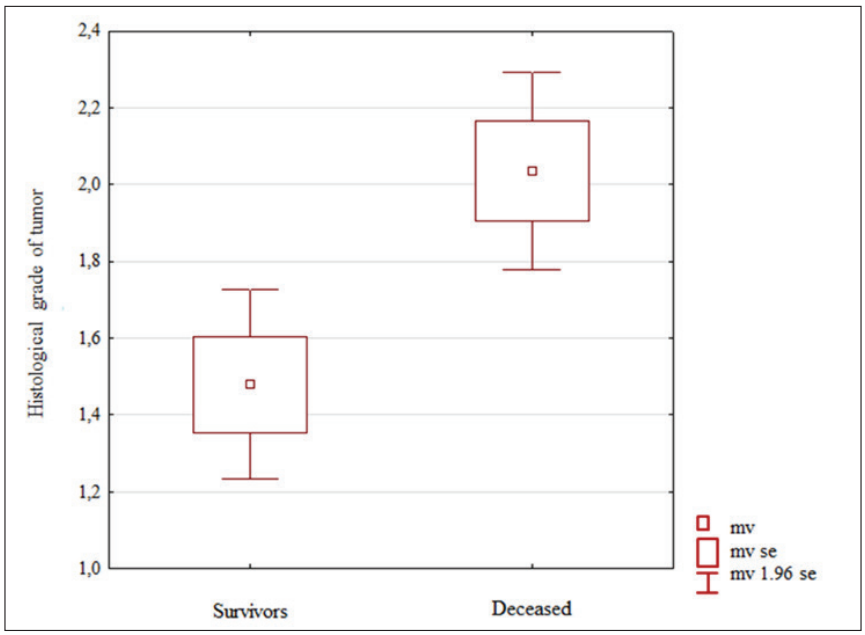

Fig. 5. Treatment outcome according to tumor histologic grade.

was not related to the Ki-67 proliferation index value (t-test, t=0.44, p=0.656).

Discussion

In this research, the clinical course of the disease was followed through local recurrence, metastases to regional lymph nodes and occurrence of the second primary tumor. Local recurrence occurs in the larynx itself if primary therapy included partial laryngectomy, or in the peristomal area if primary therapy included complete laryngectomy. Treating the recurrence is a great challenge. A surgery in the previously operated or irradiated area is technically more demanding than in patients who were not previously subjected to such procedures. Planning of radiation therapy is also more demanding because previous treatment has disturbed normal anatomic relationships. The incidence of local recurrence in our patients was 10.2%. There are no literature data that would exclusively deal with local recurrence of laryngeal tumors, but it is stated that local recurrence of tumor of the head and neck occurs in 10% to 50% of patients depending on tumor localization. Therefore, it can be concluded that the incidence of recurrence in our group of patients was as expected[6]. After having completed surgical treatment, the median of recurrence incidence in our patients was consistent with literature data reporting that recurrence is most common in the first three years after treatment has been completed[7].

The incidence of metastases to regional lymph nodes depends on the localization of laryngeal carcinoma[8]. In supraglottic carcinoma, metastases appear in 25%-50%, in carcinoma of the glottis in 10%, and in carcinoma of the subglottis in 30% of cases. The majority of our patients were diagnosed with carcinoma of the glottis. Regarding this fact, the incidence of metastases to regional lymph nodes in our patients was expected and consistent with literature data[9].

In our study, the occurrence of second primary tumor was recorded in 9% of patients. Our results are similar to those reported by Spector *et al.*, who found the incidence of second primary tumor to be 8.9%[9]. The majority of our patients had second primary tumor in the esophagus, while other patients had tumors in the base of the tongue, lungs, rectum and bladder. Hsu *et al.* conducted a research on the incidence of second primary tumor in patients suffering from laryngeal cancer and observed the highest incidence in the head and neck region, esophagus and lungs[10]. A few years later, similar data were confirmed by Morris *et al.*, who examined the incidence of second primary tumor localization in head and neck carcinoma[11].

The five-year survival rate of our patients was 64.1%, which coincides with literature data[12].

Studies focus on examining the oncogenes and proliferation markers which could be taken as predictors of second primary tumor. In our research, patients who developed second primary tumor had statistically significantly increased Ki-67 proliferation index values as compared with patients who had no recurrence and those who developed local recurrence or metastases to regional lymph nodes. Enhanced expression of the Ki-67 proliferation index can be used as an indicator of wider workup when making the initial diagnosis, but also during follow-up examinations, especially in the first 14 months because the incidence of second primary tumor was observed within 13.5 months after the primary tumor diagnosis was made.

Moreover, it is well known that second primary tumor can be the main cause of death, which justifies the need for additional examinations in patients with enhanced expression of Ki-67 proliferation factor. Sassi *et al.* conducted a research which confirmed the significant impact of second primary tumor on survival and pointed to the fact that such second primary tumor could shorten the survival period by up to 20%[13].

To our knowledge, there are no studies relating the expression of Ki-67 proliferation factor and the occurrence of second primary tumor. Therefore, this is a new insight into the behavior of the head and neck cancer, which requires additional research that could confirm our results.

One of the challenges faced by otolaryngologists is treatment of clinically negative regional lymph nodes of the neck (so-called 'N0 neck'). In such patients, there is always a question of the presence of occult metastases at the time of diagnosis, which would become clinically significant in a certain period. If the likelihood of the presence of metastases is higher than 20%, neck dissection is required. In such patients, histopathologic grade could be one of the significant factors when making the treatment plan. Our research demonstrated that patients who developed metastases to regional lymph nodes had the highest histologic grade. Therefore, it can be concluded that a more aggressive approach to treatment (elective neck dissection, chemotherapy) should be considered when treating patients with N0 of the neck and higher histologic

grade in order to prevent development of metastases to regional lymph nodes.

Our research did not prove interdependence of cancer stage (early or late) and clinical course of the disease in terms of local recurrence, metastases to regional lymph nodes or occurrence of second primary tumor. This is consistent with the data reported by Shah *et al*., who believe that regional metastases are the main cause of unsuccessful treatment and death in patients with squamous cell carcinoma of the larynx[14]. Our results do not coincide with the present conclusions, which can be explained by the fact that our patients mostly suffered from carcinoma of the glottis, and it is well-known that lymphatic drainage of the glottis region is poorly developed and therefore the incidence of metastases is low. Our results showed a high incidence of local recurrence in early-stage carcinoma, which could be explained by the fact that those patients had a high histologic grade, thus proving the need to incorporate other parameters besides TNM staging in therapeutic guidelines.

We also analyzed the interrelation of clinical course of the disease and oncologic treatment. In our study, the share of patients who were not subjected to oncologic treatment and did not later develop local recurrence or metastases to regional lymph nodes was expected. The results could be explained by the fact that, according to the guidelines, patients in the early-stage of the disease mostly were not treated with oncologic therapy. Since their disease was in its early stage, the probability of recurrence in the form of local recurrence, metastases to regional lymph nodes or occurrence of second primary tumor was significantly lower. The exception for applying oncologic therapy despite early-stage carcinoma was the presence of risk factors such as positive margins, extracapsular spread to lymph nodes, multiple positive lymph nodes, or perineural, lymphatic or vascular invasion in tumor tissue samples.

Conclusion

Medical progress has resulted in more accurate diagnostic procedures and more sophisticated surgical procedures. The survival of oncologic patients has been improved, thus enabling malignant diseases to be considered chronic illnesses today and not illnesses that would inevitably lead to death in a short period of time. The stated changes are also reflected in treatment of patients. Emphasis is on timely diagnosis of the disease but also on regular follow-ups after the initial treatment has been completed in order to detect a probable recurrence. Our study has offered data on the clinical course of the disease in patients suffering from laryngeal cancer in relation to the incidence of recurrence in the form of local recurrence, metastases to regional lymph nodes and occurrence of second primary tumor. Treatment of recurrence is extremely demanding and additional tools should be used when selecting therapy in order to lower the number of recurrences. It is our opinion that further research should be aimed at defining tumor markers which could offer information on the incidence of recurrence. This would then justify administration of a more aggressive therapy in patients with a higher recurrence incidence. At the same time, emphasis should be put on timely diagnosis of the second primary tumor, so that its treatment could start as early as possible and be more successful. We believe that this could be achieved by modeling the existing guidelines related to check-ups.

It can be concluded that malignant laryngeal tumors, clinical course of the disease and its recurrence in such patients have not been sufficiently researched. We therefore advocate further research to define the predictive factors for each of the described recurrence forms more precisely, so that patients suffering from malignant laryngeal tumors could receive better treatment.

Acknowledgment

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Sažetak

KLINIČKI TIJEK BOLESTI I ISHOD LIJEČENJA KOD BOLESNIKA S MALIGNIM TUMORIMA GRKLJANA: RETROSPEKTIVNA PETOGODIŠNJA ANALIZA

J. Vukelić, R. Dobrila-Dintinjana, B. Marijić, D. Maržić i *T. Braut*

Cilj je bio istražiti klinički tijek bolesti kod bolesnika sa zloćudnim tumorima grkljana s osvrtom na razne oblike povrata bolesti (lokalni recidiv, metastaze u regionalne limfne čvorove, pojavnost drugog primarnog tumora). Proveli smo retrospektivno istraživanje na 78 bolesnika s patohistološki potvrđenom dijagnozom planocelularnog karcinoma grkljana. Iz povijesti bolesti dobili smo podatke o stadiju karcinoma, histološkom gradusu, vrsti provedenog liječenja te o povratu bolesti. Na patohistološkim uzorcima tkiva tih bolesnika učinili smo imunohistokemijsku analizu i procjenu ekspresije proliferacijskog čimbenika Ki-67. Pojava drugog primarnog tumora vezana je uz značajno veći proliferacijski indeks Ki-67. Značajno veći je bio udio bolesnika kod kojih nije provedena onkološka terapija, a koji naknadno nisu razvili neki od oblika povrata bolesti. Ishod liječenja ovisi o dobi bolesnika, histološkom gradusu, primijenjenoj radioterapiji i kliničkom tijeku bolesti. Potrebno je preciznije definirati prediktivne čimbenike rizika za razne oblike povrata bolesti kako bismo bolje i kvalitetnije liječili bolesnike s malignim tumorima grkljana.

Ključne riječi: *Karcinom grkljana; Ishod liječenja; Lokalni recidiv; Regionalni recidiv; Sekundarni primarni tumor*