

ORIGINAL ARTICLE

Clinical stage of laryngeal carcinoma and lost time at the moment of diagnosis with 15-year-long interval. Are there any changes?

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Summary

Purpose: Despite the fact that laryngeal cancer causes symptoms early, the patients often present with advanced disease.

The aim of this paper was to determine how much time had been lost from the beginning of the symptoms to establishing the diagnosis, and what was the clinical stage of the laryngeal cancer at the time of diagnosis in two examination years (2001 and 2016).

Methods: The research involved 108 patients of both genders, 54 during each examination year, with whom the diagnosis of laryngeal carcinoma was established.

The charts of the patients were reviewed, and the data were analyzed and compared.

Results: The median lost time from the time when the symptoms started to the time of diagnosis was 8.22 months during 2001 versus 8.77 months during 2016, with no statistically

significant difference ($p=0.774$). Early clinical T stage of the disease in 2001 was present in 57.4% of the cases and 70.4% in 2016, with no statistically significant difference ($p=0.161$). Early clinical TNM stage in 2001 was in 48.1%, and 64.8% in 2016, with no statistically significant difference ($p=0.081$). Tracheotomy at the time of establishing the diagnosis was necessary in statistically significantly greater number of patients in 2001 compared to 2016 (59.3% versus 31.5% ; $p=0.004$).

Conclusion: The diagnosis of laryngeal carcinoma is established late, with a long lost time. Favourable is the statistically significant decrease in the number of patients who require tracheotomy at the time of establishing the diagnosis with a 15-year-long interval.

Key words: laryngeal carcinoma, clinical stage, tumor stage, early-stage laryngeal cancer, diagnosis, lost time

Introduction

Head and neck cancers include malignant mucosal and tissues malignant tumours of this region. The majority of them are squamous cell carcinomas, most of which, approximately 60-70%, are found in the oral cavity and larynx [1].

Malignant laryngeal tumours account for 25-30% of all head and neck cancer cases [2]. The incidence among European countries is very variable; the highest rates of laryngeal cancer are observed

in Southern and Eastern Europe [3,4]. Serbia is among the European countries with highest incidence and mortality rates of this carcinoma in men, with high mortality as well. According to data on carcinoma incidence and mortality in 40 European countries in 2012, the highest estimated age-standardized rate of larynx cancer incidence was recorded in Hungary (16.6 in men and 1.9 in women per 100,000), and lowest in Iceland (2.2 in

men and 0.0 in women), while in Serbia it was 14.1 in men and 1.4 in women [4]. According to the same data, the highest estimated age-standardized rate of cancer mortality was recorded in Moldova (10.1 in men and 0.4 in women), the lowest in Iceland (0.0 for both sexes), while in Serbia it was 7.7 in men and 0.7 in women [4]. Laryngeal carcinomas primarily occur in men aged 40 -80 years, with growing incidence in women, but also with increasing tendency of occurrence in younger population. Smoking cigarettes, cigars and pipes, as well as alcohol consumption, are primary etiological factors [5]. If diagnosed early, laryngeal carcinomas are usually curable. However, despite the fact that they cause symptoms early, as well as the fact that the larynx is easily accessible for examination, unfortunately, patients often present with advanced disease.

The purpose of this article was to determine how much time had been lost from the beginning of the symptoms to establishing the diagnosis of laryngeal carcinoma, what was the clinical stage of laryngeal carcinoma at the time of diagnosis, and whether there were changes in these examined parameters in two examination years with 15-year-long interval (2001 and 2016).

Methods

This retrospective study was conducted at the Clinic for Otorhinolaryngology and Head and Neck surgery, at the Clinical Centre of Vojvodina in Novi Sad, Serbia. The study involved patients hospitalized at the Clinic who were diagnosed with squamous cell laryngeal carcinoma

by tumor biopsy specimens taken during direct laryngomicroscopy under general anaesthesia. The study did not include patients with recurrent laryngeal carcinoma, with primary carcinoma of neighbouring anatomic structures which secondarily spread to larynx, nor the patients in whom the cancer was diagnosed in other institutions.

The patients were split into two groups. The first group was made of patients in whom the laryngeal carcinoma was diagnosed during 2001, and the second group of those in whom the diagnosis was established after 15 years, in 2016. Both groups consisted of 54 patients. Data from the patients' records for both examined years were analyzed (anamnesic data, clinical otorhinolaryngology status, intraoperative findings, need to perform tracheostomy at the same time when the diagnosis of the tumour was established). Classification of the clinical stage of carcinoma was done according to the current TNM classification [6] on the basis of the clinical examination, with no additional radiologic diagnostics.

The study was carried out according to the principles of the Helsinki declaration and was approved by the local ethical committee (protocol number 00-15/1112).

Statistics

For statistical processing of the obtained data, SPSS 21 software package was used. Numeric features were presented via median values (arithmetic mean) and measures of variability (value range, standard deviation) and the attributive features by using frequencies and percentages. The comparison of numeric feature values of the two groups was performed by applying the Student's t-test. Testing the difference in attributive feature frequencies was done by applying the chi square test (χ^2). $p < 0.05$ was considered statistically significant.

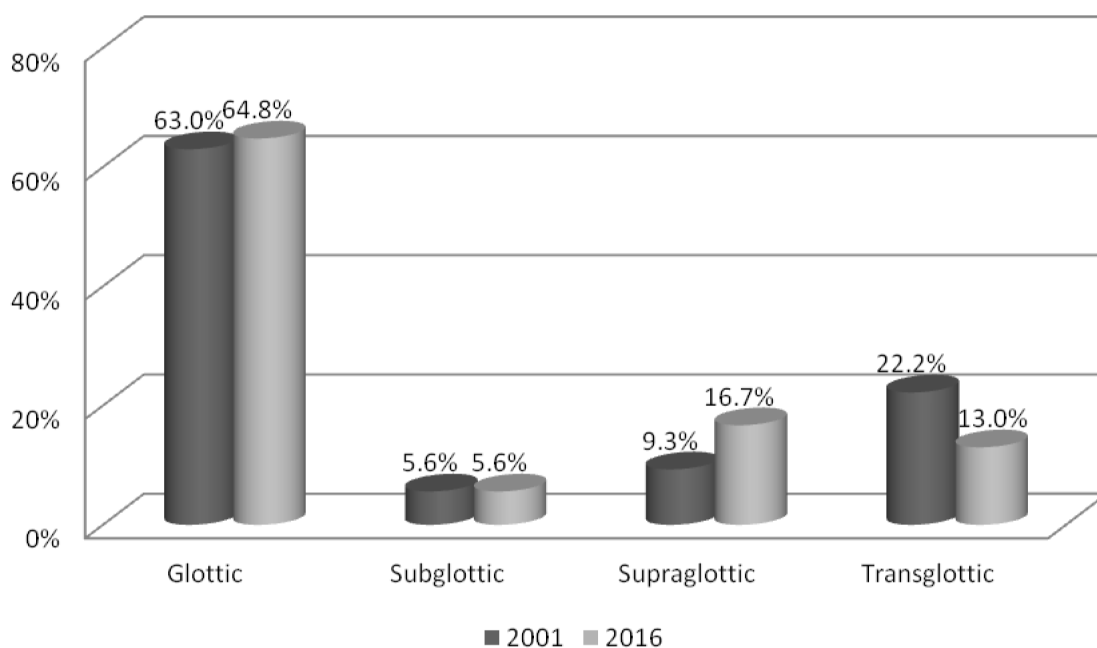


Figure 1. Location of laryngeal cancer. No statistically significant difference in the distribution of patients according to laryngeal carcinoma location in the two examined years was recorded ($\chi^2=2.473$; $p=0.480$).

Results

The research involved 108 patients, 54 in each examined year; 98 (90.7%) were men and 10 (9.3%) women. In 2001 there were 53 (98.1%) men and 1 (1.9%) woman, and in 2016, 45 (83.3%) men and 9 (16.7%) women. Because there was only one female patient in 2001, it was not possible to statistically process the gender distribution between two groups in two examined years.

In 2001, the age of the patients ranged between 42 and 79 (mean 60), and in 2016 from 37 to 83 (mean 63.4), with no statistically significant difference in age distribution ($t\text{-test}=1.817$; $p=0.072$).

Among bad habits, cigarette smoking predominated compared with non-smoking in both years; in 2001 there were 46 (85.2%), and 41 in 2016 (75.9%), with no statistically significant difference in two examined years ($\chi^2=1.478$; $p=0.224$). The ratio of alcohol consumers to alcohol non-consumers was

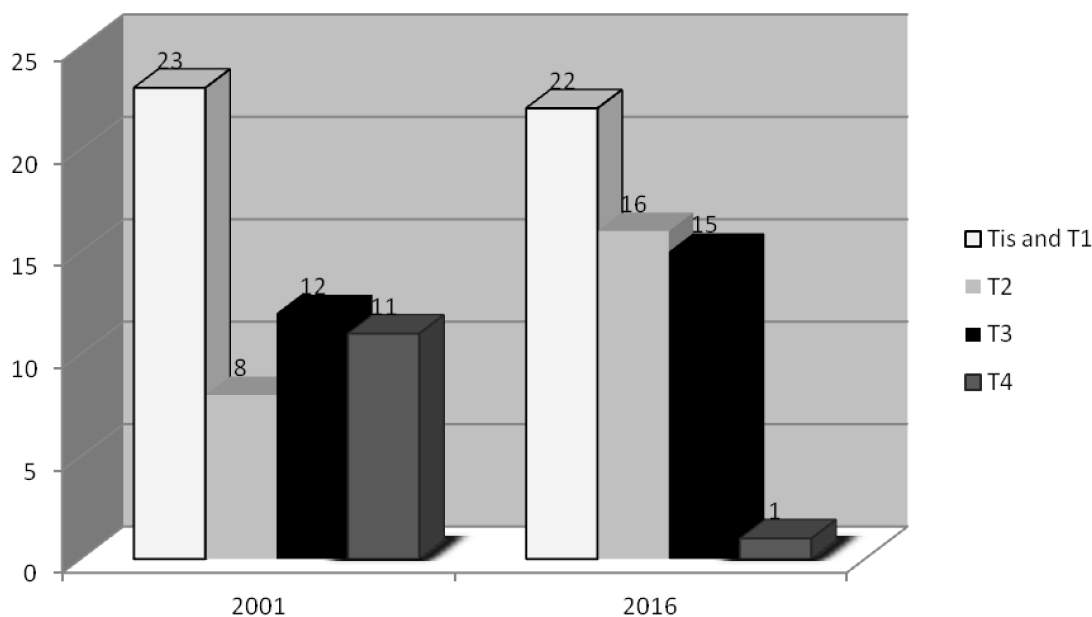


Figure 2. T stage of laryngeal cancer. T: primary tumour, Tis: *in situ* tumour.

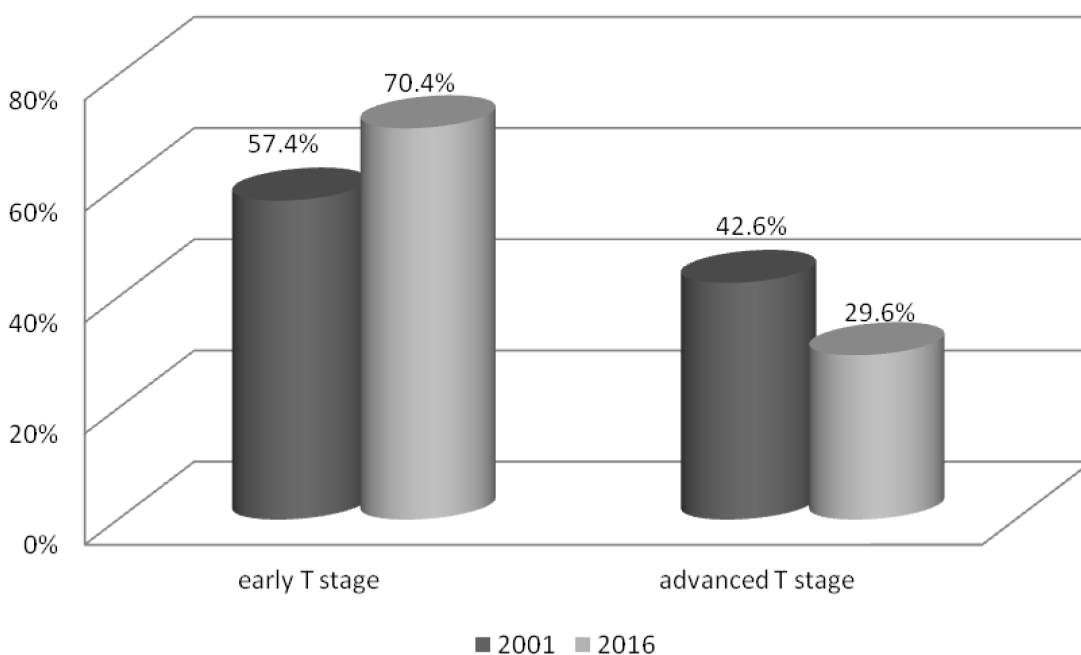


Figure 3. Distribution of early (Tis, T1 and T2) and advanced (T3 and T4) laryngeal cancer. No statistically significant difference in the distribution of patients with early and late stages in the two examined years was found ($\chi^2=1.967$; $p=0.161$). T: primary tumour, Tis: *in situ* tumour.

50:50 in 2001, while in 2016 it was 53.7:46.3 in favour of the alcohol consumers, again with no statistically significant difference ($\chi^2=0.148$; $p=0.700$). Combination of bad habits (cigarette smoking and alcohol consumption) was present in 44% of participants in 2001, and in 46.3% in 2016, with no statistically significant difference ($\chi^2=0.037$; $p=0.847$).

Duration of the symptoms of disease before establishing diagnosis (lost time) was 8.22 months on average in 2001 (range from 1 to 72 months). In 2016 the duration of the symptoms of disease ranged from 0.75 to 36 months (8.77 months on average), with no statistically significant difference between two groups ($t=0.288$; $p=0.774$). The main individual symptom of the disease was hoarseness in 31(57.4%) and 41(75.9%) cases in 2001 and in 2016 respectively, while hoarseness combined with other symptoms (otalgia, headache, painful and difficult swallowing, foreign body sensation in the throat, dyspnoea) was present in 37% of patients in 2001 and 14.9% in 2016. Regarding other symptoms in 2001, two patients felt pain when swallowing, and one patient felt dyspnoea and dysphagia; in 2016, two patients had dyspnoea, and one complained about either dysphagia or dyspnoea. The data regarding symptoms of the disease were too scattered for valid statistical analysis and comparison.

In both groups, the tumour was most often with glottic localization (in 62.9% in 2001 and 64.8% in 2016). Distribution of patients according to laryngeal carcinoma location is given in Figure 1. No statistically significant difference was found in

the distribution of the patients according to laryngeal carcinoma location in the two examined years ($\chi^2=2.473$; $p=0.480$).

The T stage of disease in both groups was most often T1 (T1,T1a and T1b), as shown in Figure 2. By grouping patients into early T stages (Tis- *in situ*, T1 and T2) and late T stages of carcinoma (T3 and T4), we found early carcinoma in 2001 in 31 (57.4%) patients and 38 (70.4%) in 2016, as shown on Figure 3. No statistically significant difference existed in the distribution of patients with early and late stages in the two examined years ($\chi^2=1.967$; $p=0.161$). The N stage was most often N0 in both groups (Figure 4). Since M was M0 in all patients on the basis of the clinical findings and lung radiography within the preoperative prepara-

Table 1. TNM clinical stage of laryngeal cancer

Stage	Year		
	2001 n (%)	2016 n (%)	Overall n (%)
0	1 (1,85)	0 (0,00)	1 (0,93)
I	19 (35,19)	22 (40,74)	41 (37,96)
II	6 (11,11)	13 (24,07)	19 (17,59)
III	16 (29,63)	16 (29,63)	32 (29,63)
IVA	11 (20,37)	3 (5,56)	14 (12,96)
IVB	1 (1,85)	0 (0,00)	1 (0,93)
IVC	0 (0,00)	0 (0,00)	0 (0,00)
Overall	54 (100,0)	54 (100,0)	108 (100,0)

T: primary tumour, N: regional lymph node, M: distant metastasis, n: number of patients

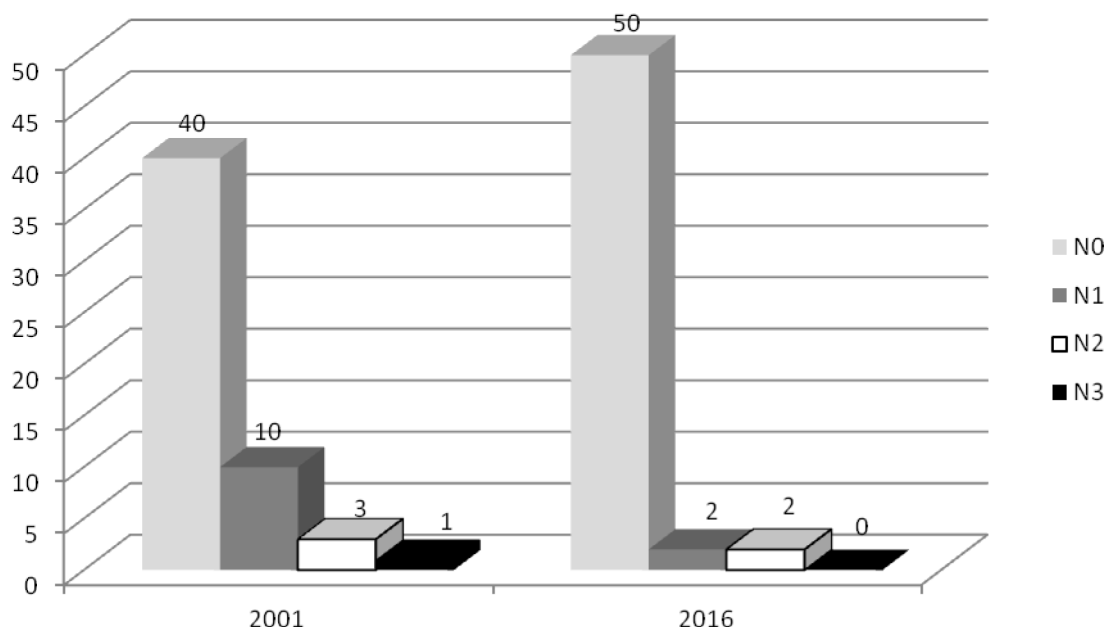


Figure 4. N stage of laryngeal cancer. N: regional lymph node.

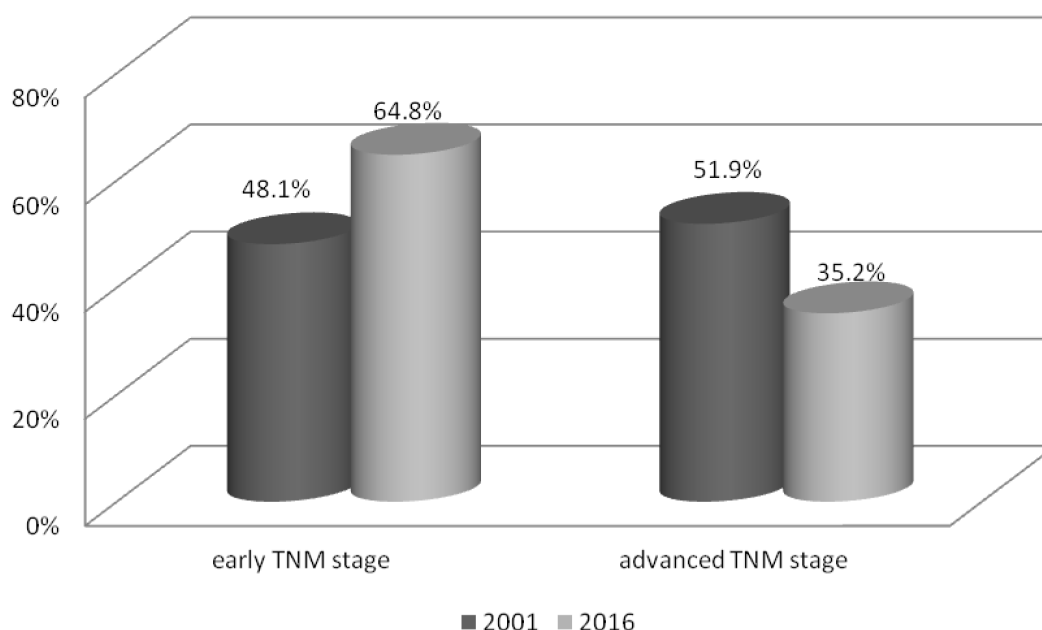


Figure 5. Distribution of early (stage 0, I and II) and advanced (stage III and IV) clinical TNM stages of laryngeal cancer. No statistically significant difference was recorded in the distribution of early and advanced clinical TNM stages between the two examined years ($\chi^2=3.051$; $p=0.081$). T: primary tumour, N: regional lymph node, M: distant metastasis.

tion for general anaesthesia, a division was made to TNM stages of the disease presented in Table 1. By distributing the patients to early (stages 0, I and II) and late TNM stages (stages III and IV), it was found that 26 (48.1%) patients in 2001 and 35 (64.8%) in 2016 were in an early stage with no statistically significant difference ($\chi^2=3.051$; $p=0.081$; Figure 5).

Tracheotomy concurrent with the established laryngeal carcinoma diagnosis, was necessary in 32 (59.3%) patients in 2001, and in 17 (31.5%) patients during 2016 ($\chi^2=8.405$; $p=0.004$).

Discussion

Highest rates of laryngeal cancer in men are observed in the countries of Southern and Eastern Europe [3,4] including Serbia. High disease incidence should be sought in the presence of bad habits, primarily cigarette smoking, but also alcohol consumption. The results of this study confirm the high rate of smokers (85.2%; 75.9%) and alcohol consumers (50% and 53.7%) in 2001 and 2016 respectively, while the combination of smoking cigarettes and consumption of alcohol is high as well. The results of the study published by Zuo et al. [7] demonstrated strong correlation referring to dose-response and time-response between cigarette smoking and risk of laryngeal cancer for both men and women. The disease occurred in only 1% of non-smokers, and was related to other risk factors among which the particularly

significant human papillomavirus - HPV infection [8].

Although tobacco use is one of the most preventable risk factors, the reasons for such high presence of smoking should be sought in the delays in the implementation of tobacco preventive measures [9]. In the examined environment of Serbia particularly significant was also the consumption of hard drinks and fruit-derived spirits, typical also for Hungary and Russia [10].

Laryngeal carcinoma is a disease with the highest male to female ratio [11]. Because of only one female in 2001 it was not possible to make a more valid statistical analysis, however noticeable is the increase in the number of affected females as reported also in other studies [12], primarily due to adopting bad habits as well as increasing exposure of women to carcinogens in working environment.

The findings from this study can be compared to the results of most studies specifying that laryngeal carcinoma occurs from fourth to seventh decade, with most cases in the sixth decade [12], although a trend from the lower limit to the occurrence towards younger population is noticeable. It is interesting that the number of newly diagnosed patients was the same in both years.

The most common location of laryngeal carcinoma was in glottis in both years (62.9% and 64.8%), just as other authors stated [12], and therefore the most common symptom is hoarseness, alone or combined with other symptoms. Brand-

storp-Boesen et al. [12] more often found carcinoma with supraglottic localization in women. Transglottic localization, which ranks second in incidence in all patients in the study, and is confirmed as an adverse prognostic factor by Vlachtsis et al. [13].

Since the hoarseness, as the most common symptom of glottic carcinoma, is easily noticeable, the long lost time prior to establishing the diagnosis is unjustified. One can notice that even after visiting a general practitioner, a number of patients with hoarseness are not further referred to a specialist examination, although there is a rule where any person with hoarseness persisting for three weeks or more should be assessed urgently by the otorhinolaryngologist [14]. The lost time in a patient with carcinoma could be divided into three main intervals. The first one is patient's delay interval from the moment when the symptom began till the visit to the general practitioner. The second one is the diagnostics interval, the period from the visit to the general practitioner to the referral to an otorhinolaryngologist, reception in a competent hospital, biopsy and pathologic confirmation of the carcinoma. The third lost time interval is the treatment planning interval, starting with the establishing the pathologic diagnosis till the beginning of treatment [15]. In this research, the first two out of all described delay intervals were measured (patient's delay and diagnostics interval), because it is very difficult to separate them in a retrospective analysis. The lost time was on average 8.22 and 8.77 months in the two examined years respectively, with no statistically significant difference; the shortest was three weeks, but the longest even up to 6 years, which is an unjustifiable and disturbing long period. By comparing pretreatment delay in 1992 and 2002 in Denmark, Primdahl et al. [15] reported a significantly shorter lost time which was analyzed in this study as well (patient's delay and diagnostics) and which was 82 days (2.9 months) in 1992 and 93 days (3.3 months) in 2002.

The lost time is extremely significant because it leads to further growth of a tumour and reduces the possibility to properly treat it. It was shown that in glottic larynx cancer, one month delay led to a 4% decrease in survival [16]. Teppo et al. in 2003 [17] and 2008 [18] showed that longer diagnostic delays worsened survival in laryngeal cancer patients. Cut off points at which the delays showed significant adverse impact in prognosis of laryngeal cancer were ≥ 3 months in patient's delay and ≥ 6 months in professional delay, which is also applicable in patients in this study. The same authors emphasize that a patient should always be examined properly at the initial time in order to shorten the professional delay in laryngeal cancer diagno-

sis because even in the examined environment a number of patients is being unjustifiably kept by an otorhinolaryngologist and is not referred to further diagnostics to a designated higher institution [17,18].

Clinical stage at the time of diagnosis is the most important determinant of prognosis in head and neck cancer [19]. The most common T-tumour stage in the total sample was T1 stage with 40%. In the second place was T3 with 25%, while the third most common tumor stage was T2 with 22.2%. It is interesting that in 2001, the advanced T4a stage was present in even 11 (20.4%) patients, while this stage was diagnosed in 2016 in only 1 (1.9%) patient, which is definitely a favourable trend together with the increase in the number of patients in T2 stage. Early T stage (Tis, T1 and T2) in 2001 was present in 31 (57.4%), and in 2016 in 38 (70.4%) patients. Although without a proven statistical significance, apparent is the increase in the number of patients with early stage of carcinoma as a favourable trend, since, regardless of the treatment modality, early T laryngeal carcinomas have an 80-90% probability of cure, whereas for more advanced tumours this is approximately 60% [20].

Regarding the N stage in the total sample, the regional neck lymph nodes were not clinically palpable (N0) in 83.3% of the cases. During 2001, the percentage of N0 was 74.1% while in 2016 it increased to 92.6%. Taken as a whole, in 2016 the results were much more favourable than in 2001, although with no statistically significant difference. When observing the TNM clinical stage, the greatest number of patients were in stage I, then III and II. Early TNM stage of disease (stages 0, I and II) was present in 61 (56.5%) patients (26/48.1% in 2001 and 35/64.8% in 2016). Although with no statistically significant difference, noticeable is the decrease in the percentage of patients diagnosed in advanced stage between the two examined years. The stage of disease is in direct proportion with the survival rate. Although we analyzed the clinical and not postoperative, real stage of disease, it can also be considered as an indicator of the disease prognosis. In their paper on clinical and molecular prognostic factors in operable laryngeal carcinoma, by using univariate analysis, Vlachtsis et al [13] found statistically significant effect of the T stage, TNM stage and tumor localization on overall survival. By using univariate analysis, Yu et al [21] showed that the localization of a tumour, its pathologic grade, T stage, N stage and clinical stage of disease represented prognostic factors for patient's survival.

Although widely accepted, TNM classification has numerous deficiencies [22]. This is particularly

significant in the clinical stage assessment, because its determination is susceptible to a subjective assessment of an otorhinolaryngologist. Thereby, wrong assessment is more common with advanced laryngeal carcinomas since the early invasion of the cartilage cannot be clinically assessed with certainty, and the problem of subjectivity is also present in determining the signs of hemilaryngeal fixation and the assessment of the nodal status of the neck via palpation.

The proof of the favourable trend in patients' diagnostics in the early stage of disease is the decrease in the number of tracheotomies at the same time when the carcinoma diagnosis was established. This is the only parameter with statistically significant difference in two examined years.

The presented results showed that laryngeal carcinoma diagnosis is established unjustifiably late with a long lost time, with no shortening tendency in two examined periods.

Although there is an obvious increase in the number of patients diagnosed in early, compared to those diagnosed in advanced clinical stage of disease in the examined interval, this is not accompanied with statistical significance.

The presented results impose the need to work harder regarding measures for primary and secondary prevention of this significant oncologic problem.

Conflict of interests

The authors declare no conflict of interests.

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