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Laryngeal malignancies – epidemiological data and particularities of the cases diagnosed in Western Romania (October 2016–July 2020)

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Abstract

In the last decade, the incidence and mortality associated with laryngeal malignancies has experienced an unfavorable evolution in Romania, in terms of this pathology the country that has become the leader, among the European Union (EU)-27 countries. The aim of the present retrospective study was to analyze the epidemiological data regarding laryngeal cancer and histopathological (HP) particularities in patients diagnosed in Western Romania. Within three years and 10 months (during October 2016–July 2020) in Ear, Nose and Throat (ENT) Clinic of Timișoara Municipal Emergency Clinical Hospital, 194 patients with laryngeal neoplasms (LN) were diagnosed. Most of the patients were male (93.8%), from Timiș County, mainly and the neighboring Counties of Caraș-Severin, Hunedoara, Mehedinți and Arad. Patient's average age (both sexes) was 62.6 years, with a range from 38 to 84 years and the highest percentages in the 60+ age group (48%). Regarding smoker status, the main cause of the development of the LN, 93.9% of patients were active ones. Regarding localization [International Classification of Diseases 11th Revision (ICD-11)], about 69% were malignant neoplasm of glottis (C32.0), followed by supraglottis (C32.1), larynx-unspecified (C32.9), and subglottis (C32.2). From the HP point of view, several types of tumors were identified, most of which were non-keratinized and keratinized squamous cell carcinomas (about 90%). In addition, there were identified types of verrucous carcinoma, acantholytic carcinoma, squamous papilloma, a possible pleomorphic sarcoma, and pyogenic granuloma. The data presented in this study highlight the growing incidence of LN, which mainly affect men, at an increasingly young age. It is imperative to involve specialists from nutrition, general medicine, ENT, dentistry to start awareness programs and to develop prevention protocols.

Keywords: laryngeal cancer, incidence, histopathological aspects, Western Romania.

Introduction

Laryngeal neoplasms (LN) are one of the most common malignancies of the head and neck, in 2020 ranking 20th in terms of the new cases number and 18th in terms of deaths from cancer. Also, LN account for a third of all head and neck cancers (HNC) being a significant source of morbidity and mortality. According to *Global Cancer Observatory* (GLOBOCAN), in 2020, there were 184 615 new cases of laryngeal cancer, determining 99 840 deaths [1]. For the year 2021, in the USA, it was estimated the appearance of 12 620 new cases and 3770 deaths, the 5-year survival rate being 60.7% [2]. In 2020, in Romania, LN determined 1922 new cases, 1108 deaths and a 5-year prevalence (all ages) of 29.68% (per 100 000) [3].

Several risk factors are involved in the malignant pathogenesis of larynx, which are most often diagnosed in patients with a significant history of smoking and may involve larynx different locations [4]. Data have shown a high risk of developing laryngeal cancer in smokers (10–15 times higher compared to non-smokers) and extremely high risk in heavy smokers (30 times higher compared to non-smokers) [5]. At the same time, both the direct proportional relationship between alcohol consumption and laryngeal cancer (quantity-dependent relationship) and between tobacco and alcohol on concomitant use (the synergistic effects) leading to the development of the disease, have been demonstrated [5]. Other factors that contribute to the appearance and development of laryngeal cancer are excess body weight, poor nutrition, genetic syndromes

(e.g., Plummer–Vinson syndrome), workplace exposures [e.g., asbestos, wood dust, paint fumes, polycyclic aromatic hydrocarbons (PAH), nickel, or ionizing radiations, etc.], gender, age, race [6, 7]. More recently, gastroesophageal reflux has been identified as a risk factor for the development of various laryngeal diseases, but despite the large number of studies, a causal relationship with laryngeal cancer has not been fully proven [8–10]. Gastric reflux causes mucosa inflammation (acute/chronic) being a precursor to erroneous cellular replication and malignant processes. Recent studies highlighted the link between laryngeal cancer and esophageal reflux disease, raising the need for prospective studies to clarify the mechanisms involved [11]. Another risk factor worth mentioning, especially in terms of patient survival, is human papillomavirus (HPV) infection. The correlation between HNC and HPV was made more than three decades ago, but despite numerous studies, the role it plays in development, evolution and survival has not been established yet [12, 13]. The main factors in terms of survival are tumor stage and smoker status [12]. LN symptoms are represented by persistent dysphonia, persistent cough, dysphagia, dyspnea, referred otalgia, general signs of asthenia, weight loss, loss of appetite [14, 15]. In addition to severely affecting patient's quality of life (QoL), LN is one of the most common types of malignancy underlying suicide attempts, with an incidence of more than three times higher than the general population [16, 17].

Early diagnosis plays an important role because it contributes to a high survival rate compared to late diagnosis counterparts [4]. Regarding staging, *in situ* carcinoma is classified stage 0 (the earliest stage) with the best response rates. The other stages are from I to IV, divided into substages, stage IVc being the most advanced with the lowest response rates [18]. In recent years, although a slight decrease in LN incidence has been observed, the mortality rate has increased surprisingly [19]. Until the early 1990s, the standard treatment for LN was total laryngectomy (TL) in combination with radiation therapy (RT) [19]. Early-stage tumors are treated with transoral laser microsurgery (TLM) [19], while in more advanced stages it might be implied partial laryngectomies (endoscopic vs open approach), and combination therapies (surgical, RT and chemotherapy). The treatment protocol for LN stage I and II lacks prospective data as there is no common approach in clinical practice. Consequently, the treatment is somewhat individualized considering tumor specific factors (location, thickness, type, extent, etc.), patient particularities (comorbidities, occupation, swallowing, voice, etc.) and avoiding as much as possible side effects of toxic treatments [19]. Currently, in case of advanced LN, either TL + RT or induction chemotherapy + RT is performed, the latter ensuring organ preservation [20, 21].

Despite various reports currently available, which provide several epidemiological data associated with LN, local epidemiology is precarious, and the global outlook is incomplete. The costs associated with the LN treatment are high and the patient's QoL is extremely affected. Accurate epidemiological information is needed to develop effective strategies for prevention and to contribute to LN early diagnosis.

Aim

The aim of the present study was to analyze the

epidemiological data and histopathological (HP) particularities in patients with LN diagnosed in Western Romania.

Patients, Materials and Methods

Data sources

Data included in this retrospective study were collected from LN patient's medical records (including patients undergoing surgery and RT), between October 2016 and July 2020, admitted in Timișoara Municipal Emergency Clinical Hospital, Romania. Patients diagnosed before October 2016 and received treatment during the study period were not included. There were identified 194 new cases. Data analyzed included gender, age, area, smoking and alcohol consumption status, diagnosis, treatment protocols. Non-smokers were identified as never smoked, smokers were identified as regularly and/or still smokers, heavy smokers were identified as consuming more than 30 cigarettes per day, non-alcoholic patients were referred as never consumed alcohol or used only on very rare occasions, while alcoholics were considered regular basis consumers. Patients with LN were identified according to the International Classification of Diseases 11th Revision (ICD-11), as follows: glottis LN (C32.0), supraglottis LN (C32.1), subglottis LN (C32.2), and unspecified LN (C32.9).

HP evaluations

All the samples harvested were fixed in 10% neutral buffered formalin and included in paraffin, according to the protocol. There were performed 3–4 μ m serial sections stained with Hematoxylin–Eosin (HE).

Ethical considerations and approvals

The current study was evaluated and approved by the Scientific Research Ethics Committee of Victor Babeș University of Medicine and Pharmacy, Timișoara (Approval No. 16/2016). All patients provided written informed consent prior to enrolment in the study.

Statistical analysis

GraphPad Prism 9 and Microsoft Excel 2021 were utilized to separate and evaluate patient information's from datasets. Descriptive analysis was presented for incidence, area, gender, age, smoking and alcohol consumption status, diagnosis, and treatment.

Results

Epidemiological data, special characteristics, and interventions

Between October 2016 and July 2020, a number of 194 patients diagnosed with LN were admitted in Ear, Nose and Throat (ENT) Clinic, Timișoara Municipal Emergency Clinical Hospital. Most of the patients diagnosed were from Timiș County (45%), followed by Caraș-Severin (17.5%), Hunedoara (12%), Mehedinți (9%) and Arad (7%) Counties. About 9.5% of patients were from different Counties (Alba, Bihor, Buzău, Galați, Gorj, Olt, Vâlcea, Vaslui). The repartition according to patient's origin county is shown in Figure 1. The patient's average age was 62.6 years, with a range from 38 to 84 years. The highest percentages were recorded in the age group 60+ (48%) followed by the age

group 50+ (28%), 70+ (16%), 40+ (5%), 80+ (<3%) and 30+ (<1%). Regarding smoking status, 93.9% of patients were active smokers (more than half being heavy smokers), 4.6% were ex-smokers and only 1.5% were non-smokers. Considering daily alcohol consumption (DAC), data revealed that more than 40% of patients were regular alcohol consumers.

Gender repartition was found to be significantly higher in males. 93.8% of males were diagnosed with various types of laryngeal, or pharyngo-laryngeal malignancies. The distribution of general characteristics in terms of gender, age and disease stage were as follows: (i) gender (male) – 100% (2016), 90% (2017), 94% (2018), 90% (2019), and 95% (2020); (ii) age (both sexes) – 60 (2016), 63.7 (2017), 61.5 (2018), 62.1 (2019), and 65.6 (2020). Of the total cases, *in situ* carcinoma accounted for 2.6%. Carcinomas identified in early stages (stages I and II) accounted for 26.3% (2016 – 33.33%, 2017 – 26.7%, 2018 – 22.58%, 2019 – 22.21%, and 2020 – 26.67%) and those identified in advanced stages (stages III and IV) represented 73.7%

(2016 – 66.67%, 2017 – 73.3%, 2018 – 77.42%, 2019 – 77.79%, and 2020 – 73.7%). The details related to staging and treatment are presented in Table 1, while data related to studied year gender repartition is shown in Figure 2.

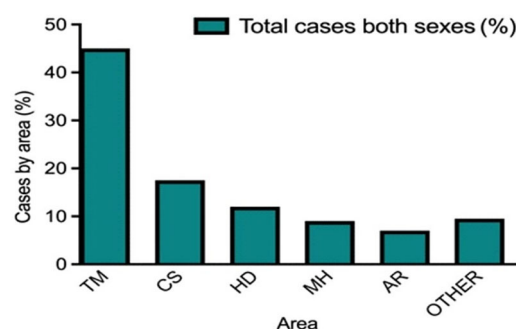


Figure 1 – Repartition according to patient's origin county. TM: Timiș County; CS: Caraș-Severin County; HD: Hunedoara County; MH: Mehedinți County; AR: Arad County; Other: Various counties of Romania.

Table 1 – TNM stage and specific characteristics and treatment

2017						
Stage	Cases (%)	Age (mean) [years]	Diagnostic	Surgical treatment	Observation	
T1N0M0 stage I	10	58.7	LN	Suspension microlaryngoscopy with CO ₂ laser lesion ablation	–	
T2N0M0 stage II	16.7	63.6	LN	Frontolateral partial laryngectomy with tracheostomy. Type IV CO ₂ laser cordectomy	Radiotherapy	
T3N0M0 stage III	36.7	63.2	9 – LN 2 – PLN	TL with selective neck dissection levels II–IV and tracheostomy	Radiochemotherapy	
T3N0M0 stage III	3.3	71	LN	TL with bilateral cervical lymphadenectomy	–	
T3N1M0 stage III	10	54.2	LN	TL with bilateral cervical lymphadenectomy levels II, III and Va	Radiochemotherapy	
T4AN0M0 stage IVA	13.3	66.5	PLN	Tracheostomy	Radiochemotherapy	
T4AN0M0 stage IVA	3.3	71	LN	TL with cervical lymphadenectomy levels II–IV	Radiochemotherapy	
T4AN1M0 stage IVA	6.7	65	LN	Suspension microlaryngoscopy with biopsy	Radiochemotherapy	
2018						
Stage	Cases (%)	Age (mean) [years]	Diagnostic	Surgical treatment	Observation	
T1N0M0 stage I	9.68	66.2	LN	Frontolateral partial laryngectomy with tracheostomy. Type IV and V cordectomy	–	
T2N0M0 stage II	12.9	49.75	3 – LN 1 – PLN	Vertical partial laryngectomy	Radiochemotherapy	
T3N0M0 stage III	58.06	55.8	LN	TL with cervical lymphadenectomy levels II–IV	Radiochemotherapy	
T4AN0M0 stage IVA	16.13	68.8	LN	TL with ipsilateral hemithyroidectomy and cervical lymphadenectomy level II–V. TL with partial pharyngectomy	Radiochemotherapy	
T4AN1M0 stage IVA	3.23	61	PLN	TL with partial pharyngectomy and bilateral cervical lymphadenectomy	–	
2019						
Stage	Cases (%)	Age (mean) [years]	Diagnostic	Surgical treatment	Observation	
T1N0M0 stage I	11.11	64	LN	Type IV cordectomy and frontolateral partial laryngectomy with tracheostomy was performed	–	
T2N0M0 stage II	11.1	65	LN	Suspension microlaryngoscopy with type IV cordectomy. Laryngofissure cordectomy	–	
T3N0M0 stage III	44.46	61.9	6 – LN 3 – PLN	TL with bilateral cervical lymphadenectomy was performed in LN. TL with ipsilateral hemithyroidectomy and cervical lymphadenectomy. Tracheostomy was performed in PLN	Radiochemotherapy	
T3N1M0 stage III	13.88	66	LN	TL with partial pharyngectomy and bilateral cervical lymphadenectomy. TL with selective cervical lymphadenectomy	Radiochemotherapy	
T3N1M1 stage IVC	2.78	66	LN	–	Radiochemotherapy	
T3N2M0 stage IVA	2.78	62	LN	TL with bilateral functional cervical lymphadenectomy	–	
T4AN0M0 stage IVA	11.11	63.3	PLN LN	TL with right tongue base tumor excision and bilateral selective cervical lymphadenectomy. TL with bilateral cervical lymphadenectomy	Radiochemotherapy	
T4AN2M0 stage IVA	2.78	46	PLN	–	Radiochemotherapy	

2020					
Stage	Cases (%)	Age (mean) [years]	Diagnostic	Surgical treatment	Observation
T1N0M0 stage I	6.67	62	LN	Suspension microlaryngoscopy with CO ₂ laser lesion ablation	–
T1N1M0 stage III	6.67	61	PLN	Tracheostomy	Radiochemotherapy
T2N0M0 stage II	13.33	66	LN	Urgent tracheostomy	Radiochemotherapy
T3N0M0 stage III	46.66	64.2	LN	TL with bilateral cervical lymphadenectomy and tracheostomy	–
T3N1M0 stage IV	13.33	64.5	LN	TL with ipsilateral hemithyroidectomy and cervical lymphadenectomy	–
T3N3M0 stage IVB	6.67	68	PLN	TL with selective cervical lymphadenectomy level II–V and right radical neck dissection	Radiochemotherapy
T4AN0M0 stage IVA	6.67	72	PLN	Tracheostomy	Radiochemotherapy

LN: Laryngeal neoplasm; PLN: Pharyngo-laryngeal neoplasm; TL: Total laryngectomy; TNM: Tumor, node, and metastasis.

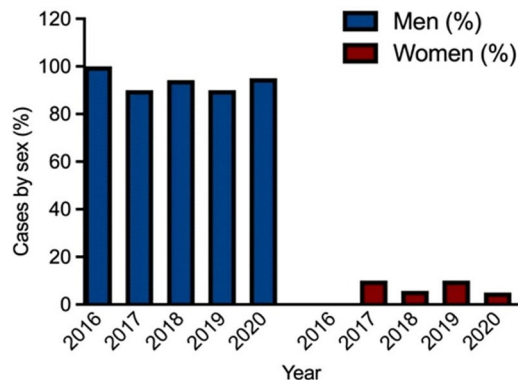


Figure 2 – Studied year gender repartition.

In incipient carcinomas of the glottic larynx (T1–T2N0M0) suitable for an approach to organ preservation, the main indication is RT or surgery (endoscopic resection or partial laryngectomy +/- laterocervical lymphadenectomy) followed by adjuvant RT (if present, such as positive margins, lymph node metastases, angiolymphatic invasion). In incipient cases in which the definitive RT is chosen, the use of three-dimensional conformal RT (3D-CRT) or intensity modulated RT/volumetric modulated arc therapy (IMRT/VMAT) techniques is recommended. For T1N0M0, the recommended dose is 63 Gy administered in doses/fractions of 2.25 Gy or 50 Gy with 3.12 Gy/fraction, administered at the level of the larynx. For T2N0M0, the recommended dose is slightly higher than 65.25 Gy administered in fractions of 2.25 Gy at the level of the larynx.

In advanced cases of T3N0–3M0 glottal cancer that may be suitable for surgery, several approaches are valid: early surgery with laterocervical lymphadenectomy, neoadjuvant radiochemotherapy, or neoadjuvant induction chemotherapy with evaluation for the next therapeutic step. If neoadjuvant radiochemotherapy will be given, the recommended concomitant chemotherapy is with Cisplatin 100 mg/m² every three weeks or Carboplatin + 5-Fluorouracil (5FU); the alternative would be Cisplatin 40 mg/m² per week (most often used in Romania). RT will be administered in different doses on different volumes, depending on the risk of invasion of the anatomical area of interest, such as: 70 Gy in 2 Gy fractions administered in high-risk areas (primary tumor/larynx and macroscopic nodes with malignancies, including areas with a high risk of microscopic invasion), 59–63 Gy in fractions of 1.8–2 Gy in the intermediate risk area (regions in the tumor neighborhood) and 46–54 Gy in fractions of 1.6–2 Gy in the low risk area (where the probability of tumor presence is low – usually for prophylactic purposes). In the case of induction chemotherapy, the recommended regimens are TPF (Docetaxel, Cisplatin, and 5FU) administered at

three weeks, and after three cycles is re-evaluated imagistically and depending on the tumor response can be supplemented with RT (if complete or partial response) or surgery (if there is no response, or tumor progression). Adjuvant RT/radiochemotherapy is recommended depending on the risk factors, such as: positive or close resection margins, T4N2–3, angiolymphatic or perineural invasion. In this case, the radiation doses administered are in the range of 60–66 Gy, with 2 Gy/fraction at the high-risk level (laryngeal lodge, tracheostoma, positive edge), 59–63 Gy in fractions of 1.8–2 Gy at the level of the intermediate risk area (the neighboring regions tumor), and 46–54 Gy in fractions of 1.6–2 Gy in the low-risk area. The recommended concomitant chemotherapy is with Cisplatin 100 mg/m² every three weeks or Cisplatin 40 mg/m²/week. In T4AN0–3M0 stages of glottic cancer, the standard indication is surgery first followed by RT/adjuvant radiochemotherapy under the same conditions as in T3 cases (depending on risk factors). If the patient refuses laryngectomy or is inoperable, neoadjuvant radiochemotherapy or induction chemotherapy can be used. In supraglottic cancers, the therapeutic approach is similar. The difference is that in adjuvant RT is also indicated in case of N1 or T3. RT in supraglottic cancers is administered in doses as in glottic cancers.

Regarding tumor location, laryngeal involvement was registered in 78.35% of patients, followed pharyngo-laryngeal tumors (21.65%). Considering ICD-11 codes there were noted 194 patients. Patient's distribution by year ranged from 71 to 50 without any particular trend. The highest numbers of admissions were recorded for glottis (C32.0, ~69%), followed by supraglottis (C32.1, ~16%), unspecified larynx (C32.9, ~13%), and subglottis LN (C32.2, ~2%).

HP evaluations

Following HP analysis, several types of tumors were identified, most of which were non-keratinized (49.53%) and keratinized (40.95%) squamous cell carcinomas (SCC). In addition, there were types of verrucous carcinoma (2.86%), acantholytic carcinoma (2.86%), squamous papilloma (1.9%), a possible pleomorphic sarcoma (0.95%) and pyogenic granuloma (0.95%). The analysis regarding tumor differentiation revealed the following observations: ~51% of samples were G1 stage (well differentiation), ~38% of samples were G2 stage (moderate differentiation), while ~9% were G3 stage (poor differentiation). The remaining 2% were patients with atypic carcinoma (*in situ*, acantholytic, verrucous, etc.). Regarding the T stages for G1: 31.4% were in T1 stage, 12.9% in T2 stage, 37.8% in T3 stage, while 17.9% were in T4 stage. Lymph node metastases were identified in samples with G1 in a percentage of 2.8%, G2 in a percentage of 24.6% and in G3 in the percentage

of 36.4%. Only 3.6% of patients were diagnosed with distant metastasis.

In Figure 3A, we identified moderately differentiated non-keratinizing SCC showing nests and cords of markedly atypical cells infiltrating the *lamina propria*, while in Figure 3B is presented SCC infiltrating the hyaline cartilage as large nests of tumor cells. Keratinizing SCC infiltrating as solid nests and cords of markedly atypical cells separated by a desmoplastic stroma with abundant inflammatory lymphocytic infiltrate (Figure 3C) and SCC infiltrating the fat as large nests with central areas of keratinization (Figure 3D) were often identified.

In very few cases, verrucous laryngeal carcinoma (VLC) has been identified. VLC showed typical bases of proliferation that are large and bulbous and invade *lamina propria* in a pushing manner (Figure 4A) and

surface papillae, hyperkeratosis, orderly maturation, and low-grade nuclei (Figure 4B).

Another type of LN rarely identified in the studied cases was acantholytic SCC (ASCC). ASCC shows the loss of cell-to-cell connections between keratinocytes, resulting in pseudoglandular spaces (Figure 4C). SCC with acantholysis is a high-risk HP variant (Figure 4D).

Squamous cell papilloma is characterized by a papillary proliferation of stratified squamous epithelium with variable hyperkeratosis or parakeratosis, mitotic activity restricted to basal/parabasal layers and retention of cellular polarity and normal maturation in suprabasal layers as can be observed in Figure 4E. The squamous papilloma has a broad base that doesn't infiltrate the underlying *lamina propria* and is accompanied by an inflammatory lymphocytic infiltrate (Figure 4F).

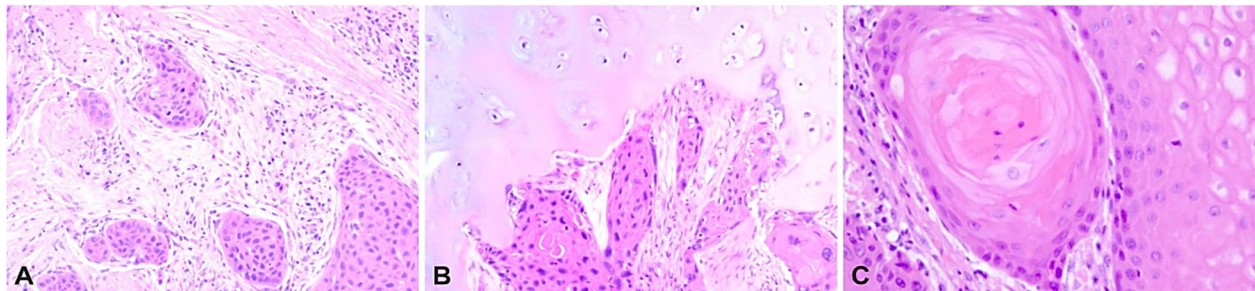


Figure 3 – (A) Moderately differentiated non-keratinizing SCC; (B) SCC: large nests of tumor cells infiltrating the hyaline cartilage; (C) SCC: keratinizing type; (D) SCC: large nests of tumor cells with central areas of keratinization infiltrating the adipose tissue. HE staining: (A, B and D) $\times 100$; (C) $\times 200$. HE: Hematoxylin–Eosin; SCC: Squamous cell carcinoma.

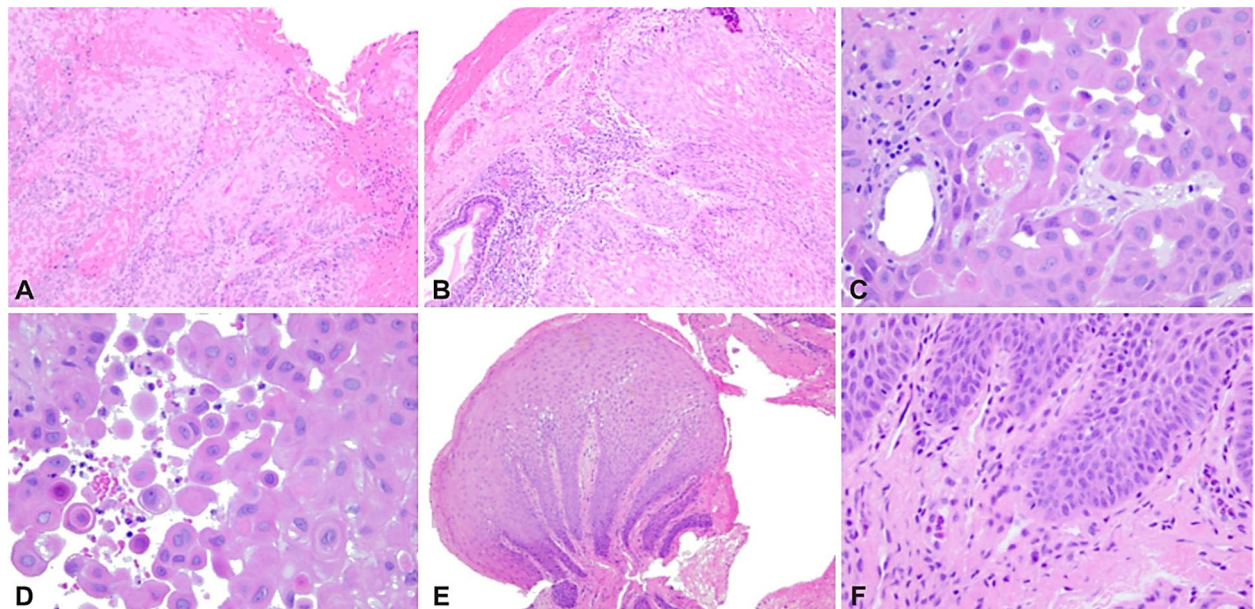


Figure 4 – (A) SCC, verrucous type: tumor cells infiltrating the lamina propria in a pushing manner; (B) SCC, verrucous type: papillary-type surface with hyperkeratosis, orderly maturation, and low-grade nuclei; (C) SCC, acantholytic type: loss of cell-to-cell connections between keratinocytes, resulting in pseudoglandular spaces; (D) SCC, acantholytic type: a high-risk histopathological variant of SCC; (E) Squamous cell papilloma: a papillary benign proliferation of stratified squamous epithelium with variable hyperkeratosis or parakeratosis, mitotic activity restricted to basal/parabasal layers and retention of cellular polarity and normal maturation in suprabasal layers; (F) Squamous cell papilloma: the broad base of the lesion that doesn't infiltrate the underlying lamina propria, accompanied by an inflammatory lymphocytic infiltrate. HE staining: (A, B and E) $\times 100$; (C, D and F) $\times 200$. HE: Hematoxylin–Eosin; SCC: Squamous cell carcinoma.

Discussions

Head and neck SCC originate from epithelial cells in the mucosa of the oral cavity, larynx, pharynx, and nasal sinuses. There are four stages of the HP evolution: (i) epithelial cell hyperplasia, (ii) mild, moderate, and severe dysplasia, (iii) *in situ* carcinoma and, (iv) invasive carcinoma [22]. Currently, according to *European Cancer Information System* (ECIS), the estimated incidence by country compared to European Union (EU)-27 and expressed as relative change of age-standardized rate (ASR) reveals the highest value in Romania (86.5%), followed by Poland (59.6%), Hungary (55.8%), Slovakia (44.2%) and Bulgaria (34.6%) [23]. Regarding patients' mortality (aged 0–84 years), more than four decades ago, the ASR identified different values from today values. Thus, in 1980, in males, France (11.1%) was the country with the highest values recorded, followed by Spain (7.5%), Italy (6.4%), Poland (5.9%), Romania (5.2%) and Germany (2.2%), while regarding females, the countries with the highest values were Romania (0.63%), followed by Poland (0.45%), France (0.36%), Italy (0.28%), Spain (0.24%) and Germany (0.15%) [24]. More recently, in 2017, the highest values recorded for males were registered in Romania (5.9%), followed by Poland (4.1%), Spain (2.5%), Italy (1.7%) and Germany (1.2%), and in females the first place was occupied by Poland (0.46%), followed by Romania (0.28%), Germany (0.18%), Italy (0.18%) and Spain (0.15%) [24].

The latest reports place Romania in first place among the EU-27 countries in terms of LN mortality, with a 133.3% relative change rate of ASR. In these statistics, Romania was followed by Poland (104.2%), Bulgaria (95.8%), Lithuania (79.2%) and Hungary (75%) [23]. According to the same report, countries that in the past had an increased incidence of mortality, now presented a significantly reduced values: France 37.5% (relative change of ASR), Spain 8.3% and Italy 16.7% [23].

LN main risk factor is tobacco use, associated with over 90% of LN, especially the glottic area [7]. More than 70 carcinogenic compounds, directly related to the development of HNC, have been identified: 19 PAH, eight nitrosamines (NA), 13 aromatic amines (AA), two aldehydes (ALD), six various hydrocarbons (HC), 15 other organic compounds (OC), nine inorganic compounds (IC) [25]. Regarding LN, a direct link has been shown for orally PAH intake [25]. In the present study, 94% patients were active smokers.

From HP point of view, the following variants were highlighted: (i) papillary SCC, (ii) verrucous carcinoma, (iii) SCC with spindle cells and (iv) basal SCC [26]. Surface squamous epithelial changes (which include reactive hyperplasia and intraepithelial dysplasia) are the most common types of lesions among HNC [26]. The HP classification is without consensus among specialists, affecting the therapeutic protocol [26]. However, there is a clear consensus on low- and high-grade dysplasia. The type of keratinization is useful for: (i) highlighting the intermediate filaments of abundant cytoplasmic keratin and/or the extracellular keratin material that LN express, and (ii) distinguishing it from other HP types of SCC [27]. In the present study, over 90% of samples were classified as SCC (keratinizing and non-keratinizing).

Verrucous laryngeal SCC (VLSCC) is a malignant

tumor, quite rare among LN, accounting in 1–4% of cases [28, 29]. This type of tumor, highly differentiated variant of SCC, is most common in glottis and is characterized by slow growth and a low rate of metastases, having a favorable prognosis with early detection and appropriate treatment [26, 28, 29]. Cases of VLSCC have been identified in males aged 51 and 63 years, respectively. In the first case, the patient diagnosed with stage III LN, smoker, was diagnosed with chronic respiratory failure, sinus tachycardia, being tracheostomized. Laryngeal endoscopy revealed a vegetative, glottic LN that occupies the entire glottic floor (VLSCC affecting the bilateral glottic and subglottic level with paraglottic space invasion). TL with lymph node dissection was performed. In the second case, the patient diagnosed with stage IV LN, smoker, was also suffering from hypertension and type 2 diabetes. Following the examination, infiltro-vegetative tumor was observed, which involved the right hemilarynx (immobile hemilarynx) and right piriform sinus with a diminished glottic space. The patient refused treatment and was discharged on request. Regarding the diagnosis of VLSCC, it is performed on biopsy, single or multiple [28]. VLSCC showed bases of proliferation that were large and bulbous and invades their own lamina in a pushing manner, these characteristics being associated with a better therapeutic result. ENT exam revealed: (i) vegetative tumor that occupies the entire glottic level, (ii) vegetative tumor located on the left hemilarynx extended in supraglottic and subglottic level, (iii) infiltro-vegetative tumor located in the right hemilarynx (immobile hemilarynx), extending to the anterior commissure and the contralateral vocal cord, as well as the laryngeal face of the epiglottis with an efficient glottic space. The mean age of patients diagnosed with squamous papilloma was 60.5 years.

One of the unusual variants of SCC is acantholytic carcinoma (also known as adenoid carcinoma and previously known as cylindromas), which usually develops in the sun-exposed areas of the skin and lips and is extremely rare in other areas, such as the respiratory tract or digestive tract [30, 31]. In HNC, this type of neoplasm can be aggressive, with a low rate of distant metastases, the lungs being the most common places for distant metastases [32]. Acantholytic laryngeal SCC (ALSCC) represents only about 0.2–1% of all HNSCC cases [33]. In our study, 2.86% of patients were ALSCC, males, with a mean age of 53.3 years. ENT exam revealed: (i) vegetative tumor comprising the entire right vocal cord, without extension at the level of the anterior vocal commissure or left vocal cord, with efficient glottic space, (ii) giant supraglottic tumor, with the impossibility of visualizing the vocal cords (the piriform sinuses being free of tumor), (iii) infiltro-vegetative tumor of the left hemilarynx extended contralaterally and to the subglottic space. Depending on each case, it was performed either a right open cordectomy; a TL with bilateral lymph node dissection (level III on the right, and level II–III on the left); a TL extended to the first two tracheal rings with total left thyroid lobectomy and level II–V cervical lymph node dissection.

Squamous papilloma is another rare subtype of HNC, with predominant laryngeal involvement, especially supraglottis. The patients mean age diagnosed with squamous papilloma was 49.5 years. It occurs either *de novo* or in

association with precursor papillomas, usually the keratinizing type (with intraepithelial cells characterized by maturation with parakeratin) [26]. In the present study, at laryngeal endoscopy, ENT exam revealed a supraglottic, exophytic, clearly contoured and delimited LN, involving the laryngeal face of the epiglottis (petiole), right ventricular band with clinically cervical N0. The mean age of patients diagnosed with squamous papilloma was 59 years.

Another rare type of HNC is sarcoma. Sarcomas are complex soft tissue tumors of mesenchymal origin and undifferentiated pleomorphic sarcoma (malignant fibrous histiocytoma) being the most common identified among adults [34]. Pleomorphic laryngeal sarcoma (PLS) is very rare, being registered a lack of data in the literature. We identified a 68-year-old male case of PLS (0.95%).

Conclusions

The data presented in this study highlight the increased incidence of LN, which mainly affect men, at an increasingly young age. An overwhelmingly high percentage of patients are smokers and without a clear prevention and early treatment policies, Romania will continue to occupy the first place among EU-27 states. It is imperative to work together with nutritionists, general practitioners, ENT specialists, dentists to start awareness programs and develop prevention protocols.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Adrian Mihail Sitaru and Daniela Flondor equally contributed to the manuscript.

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