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Review Article

Epidemiological factors in patients with larynx cancer treated by surgery, radiotherapy or therapeutic associations

Abstract

The aim of this research was to analyze the influence of epidemiological factors in patients with laryngeal carcinoma treated by surgery, radiotherapy or therapeutic associations. A quantitative retrospective analysis was performed, based on a master's thesis, of 34 individuals with this pathology, taking into consideration: gender, age, life habits and type of treatment. These factors were associated with the projections of the number of new cases, starting in 2018, according to INCA and IARC data. Due to lifestyle, men are more likely to get laryngeal cancer, and the association of alcohol and tobacco increases the chance and degree of manifestation of this carcinoma. In relation to age, the age group between 55 and 69 years is the most affected. The most indicated treatment is radiotherapy due to the low rate of serious complications, with minimal effect on the patient's life, which does not need hospitalization; besides being a non-invasive, extremely precise technique used in tumors that need a great accuracy, which allows the elimination of the tumor, preserving the structure and functionality of the larynx.

Introduction

The larynx is an organ that makes up the upper airways and communicates the laryngopharynx to the trachea. Palpable anterior is considered an important reference in surface anatomy [1]. Its cavity is divided into three portions: supraglotte, glottis and infraglottis. Being a vocal organ, it is essential in the formation of sounds and voice production. However, its anatomical proximity to structures of the masticatory apparatus and digestive system, causes serious pathological disorders, such as laryngeal cancer, to affect not only the larynx, but also structures close to it, generating significant functional damage, social and psychological in the patient, certainly changing their quality of life [2].

The laryngeal tumor is one of the neoplasms that most affect the quality of life of the patient, with predominance in the male gender and considered one of the most common tumors in the head and neck region. Because they correspond to about 25% of the malignant tumors that affect this area and 2% of all malignancies, they deserve special attention. The disease can develop in one of the three portions in which the organ is divided, with approximately 2/3 appearing in the vocal fold, located in the glottis, and 1/3 affecting the supraglottis. The most prevalent histological type in more than 90% of the patients is epidermoid carcinoma, a malignant tumor originating from the epithelial cells present in the squamous layer of the larynx mucosa [3]. The symptomatology is wide, and several signs and symptoms such as odynophagia, hoarseness and aphonia can be noticed.

Cancer is the second leading cause of death worldwide and will account for about 9.6 million deaths in 2018, according to data from the International Agency for Research on Cancer (IARC) [4]. Overall, about 1 in 6 deaths is due to cancer. For the year 2018, the National Cancer Institute (INCA)[5] estimates, for Brazil, 7670 new cases of laryngeal cancer, 6390 cases for males and 1280 for females.

For the year 2018, in Brazil, there are estimated 7670 new cases of laryngeal cancer. The estimate is 6.17 cases/100.000 men and 1.2 cases/100.000 women, being considered the eighth type of malignancy that affects the male gender and the sixteenth most frequent in the female [5]. Men over the age of 40 are more affected by the disease due to the combination of risk factors that favor their development, with alcohol and tobacco being the most harmful agents. Smokers are 10 times more likely to develop laryngeal cancer, and people who associate smoking with alcoholic beverages, the incidence rises to 43 times. In order to choose a more adequate and

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effective treatment, there is a need to understand the evolution of laryngeal carcinoma, to classify the staging and the best therapeutic approach [6].

The understanding of the dissemination of laryngeal carcinoma is important for tumor staging purposes and for a better definition of the therapeutic approach, which considers factors such as: age, gender, size, extension, patient health status, team experience and availability of services. Treatment includes the following therapies: surgery, radiation therapy, chemotherapy and immunotherapy. These can be used alone or in combination, aiming at regional control and patient survival, with the preservation of the surrounding regions [7,8].

Quality of life assessment is of paramount importance in the treatment of patients with head and neck cancer, as these usually cause significant aesthetic and functional impairment. The identification and description of disease effects and treatment in individuals' lives may result in changes in the therapeutic and rehabilitation procedures and, consequently, assist the physician and the patient in deciding on the best therapy to be used. Therefore, the objective of this study was to analyze the epidemiological factors that influence the development of laryngeal carcinoma, considering the risk factors and the types of treatment performed by the patients.

Methodology

A quantitative and retrospective study, using epidemiological data from a master's study, performed with patients treated for laryngeal carcinoma at Hospital Felício Rocho, Belo Horizonte, Minas Gerais, Brazil, between 1989 and 2002. It was not necessary to submit this work to the Ethics Committee because it is a study without the identification and contact with the patients, nor the application of a questionnaire or the performance of invasive procedures. The study also consisted of bibliographic research using scientific articles from databases such as PubMed, Google Academic and Scielo. The inclusion criteria used were: articles from the year 2006, whose selected descriptors were laryngeal carcinomas, treatments, age, gender and life habits; in english and portuguese. Exclusion criteria were studies published before 2006, with data not related to the survey of epidemiological factors in laryngeal malignancies, texts found in unreliable databases, other types of cancer and in another language.

Theoretical reference

Larynx: The larynx is a complex musculocartilaginous organ located in the infra-hyoid region and capable of performing several important functions, the main one being linked to the protection of the lower airways, followed by respiratory and phonatory functions. The larynx allows air to enter the lungs, preventing the inhalation of substances passing through the common regions of the respiratory and digestive tract. In certain groups of animals acts producing the emission of sounds, such as the modulation of the human voice, which leads to the transmission of signals that determine behaviors. In order to perform these functions, the linear mucosal tube that composes the larynx is capable of altering its conformation through a complex interaction between cartilages, ligaments and muscles [9].

Larynx cancer: According to INCA [10], (2018), cancer is the name given to a set of more than 100 diseases that have in common the disordered growth of cells that invade other tissues and organs and can spread to various regions of the body.

Carcinoma is the type of cancer that arises when the cell of any epithelial tissue undergoes a malignant alteration.[11] In the case of carcinoma of the larynx, there is a change in the mucosa of the organ, causing a disordered cellular growth. According to studies by INCA[5] (2018), tumors that affect the head and neck region, laryngeal cancer is the most frequent and represents the second most common type of respiratory cancer in the world, with about 25% of malignant neoplastic tumors and 2% of all malignancies.

Epidemiology

Data from INCA [10], (2018) show that 80 to 90% of all cancers are associated with environmental factors, and the development of malignant neoplasia is directly related to the time and intensity at which cells are exposed to sources that lead to of the disease.

The highest frequency of laryngeal carcinoma incidence is related to males and over 40 years of age. This is due to lifestyle, especially with regard to smoking and alcoholism. In addition to acting alone, the association of alcohol and tobacco is also an important risk factor for the development of malignant tumors, with continuous cigarette use and alcohol consumption acting synergistically, making this combination the most imminent carcinogenic fator [12]. Patients with laryngeal cancer who maintains smoking and/or drinking have a reduced probability of cure and an increased risk of developing a secondary tumor in the head and neck [6].

Another factor that contributes to the development of cancer is age. Data from the Brazilian Institute of Geography and Statistics (IBGE) [13], show that, by 2060, a quarter of the Brazilian population should be over 65 years of age. Aging results in cellular changes, increasing the chances of occurrence of malignant changes. The fact that the body is constantly and permanently dividing its own cells is a risk factor for the elderly. This is because, during the process of mitosis, it is common to see changes in cellular genetic material that, under normal conditions, are corrected and eliminated by the immune system. However, in elderly people, this may not occur correctly, contributing to the appearance of defective cells and, consequently, to their excessive and disorderly growth, leading to the onset of câncer [14]. In addition, it should be considered that elderly people are exposed, throughout life, to several risk factors that cause cancer, leading to modifications in the structure of cellular DNA [6].

Etiologic factors associated with the development of laryngeal carcinoma are linked to a poor diet of nutrients, to very temperate or greasy foods, to very hot or very cold

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fluids, gastroesophageal reflux, human papillomavirus (HPV) infections and genetic syndromes; as well as occupational exposure to certain elements such as: wood dust, chemicals used in metallurgy, petroleum, plastics, textile industries and asbestos, which contribute to an increased risk of occurrence. Stress and misuse of voice are also damaging factors to the larynx. Speaking very loudly and without pauses provoke vocal calluses [15].

Regardless of the stage at which a tumor is detected there is a need to classify each case according to its extent. The method used for tumor classification is called staging, which records the evolution of the disease and whether it is restricted to the organ of origin or extends to other organs and tissues. The need to classify cancers is based on the fact that survival rates are different when the disease is restricted to the organ of origin and when it is spread to other organs. Staging a malignant tumor means evaluating its degree of spreading. To this end, there are internationally established rules, which are constantly improving [16].

Staging of a tumor considers not only the growth rate and extent of the disease, but also the type of tumor and its binding to the host. The classification of malignant neoplasms into groups obeys to some factors, such as tumor location, size or volume, direct and lymphatic invasion, distant metastasis, histopathological diagnosis, systemic manifestations, duration of signs and symptoms, gender, age of the patient, among others. The most commonly used classification system is that proposed by the International Union Against Cancer (UICC) and is called the TNM Malignant Tumor Classification System. This system is based on the anatomical extension of the disease, taking into account the characteristics of the primary tumor (T), lymph node characteristics of the organ in which the tumor is located (N), and the presence or absence of distant metastases (M). These parameters receive graduations, generally from T0 to T4, from N0 to N3 and from M0 to M1, respectively. The treatment of cancer will depend on the staging of the disease. A well-conducted staging will lead to properly applied therapeutic conducts [16].

Treatments

The choice of the best treatment for laryngeal cancer will depend on several factors, such as: age, gender, size and extent of tumor volume and patient health status, taking into account the team's experience and the availability of services in the region of housing. The treatment indicated may be: surgery, radiotherapy, chemotherapy and immunotherapy, and can be used alone or in combination with other therapies, using two or more forms of treatment in the same tumor.[8]

Surgery

Surgery is commonly used in the removal of laryngeal carcinoma, but for this technique to be indicated, one must take into account the stage of the cancer, type, location and involvement of surrounding tissues [17].

For each region of the affected larynx and tumor stage, there is a type of surgery indicated, such as: endoscopic surgery, where the endoscope passes through the patient's oropharynx to where the tumor is located, and is applied to biopsy or treat tumors of the larynx at an early stage ; cordectomy, used to treat superficial and very small glottic cancers where all or part of the vocal folds are removed; partial laryngectomy, which removes part of the larynx, removing all cancerous tissue and preserving the organ as much as possible; and total laryngectomy, which removes the entire larynx, causing the patient to lose speech but maintains the swallowing system intact [17].

Radiotherapy

This treatment modality consists in the use of ionizing radiation in the treatment of benign and malignant tumors. Within radiotherapy there are two modalities that stand out: teletherapy and brachytherapy, both used in the treatment of laryngeal cancer.

The teletherapy or external radiotherapy consists of the use of radiation from an external source that ensures distances of approximately 50 cm to 1 m from the source to the patient. Within it there are modalities that will be indicated for each stage of laryngeal cancer, such as: 3D conformational radiotherapy, which is strongly used in the treatment of early stage cancer and consists of imaging tests such as magnetic resonance and computed tomography accurately map the location of the tumor, thus performing the radiotherapy planning. The other modality is intensity-modulated radiotherapy, which is indicated for advanced tumors, and uses non-uniform planar fluence bundles, being specific for each patient, in order to guarantee the distribution of the desired dose [8,18].

Brachytherapy is a form of radiotherapy that uses sources of ionizing radiation in direct contact with the tissue to be irradiated. It can be used alone or in association with external radiotherapy and is rarely used to treat laryngeal câncer [18].

Radiotherapy generates adverse effects, ranging from mild to severe, such as: painful wounds in the oral cavity and oropharynx, making swallowing difficult; xerostomia due to partial or total loss of salivation; flushing and blistering of the skin in the irradiated region; loss of taste; hearing problems; respiratory problems due to edema, and dental caries. Persons treated with radiation in the neck and oropharynx should be aware of their oral health [18].

Chemotherapy

Chemotherapy, other than surgery and radiotherapy, is a form of systemic treatment, that is, it acts throughout the body. Some tumor cells can detach from the primary tumor and migrate to other organs and tissues. Many times chemotherapy becomes the best form of treatment. Several factors, such as total tumor volume, cellular kinetics and intrinsic sensitivity, influence the anti-neoplastic agent response. These drugs used to treat cancer affect both normal and neoplastic cells [19,20].

Alternatives for the use of chemotherapy are: (I) induction or neoadjuvant, which is used before radiotherapy or surgery, to decrease tumor volume size, facilitating further

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treatment or alleviating problems caused by that tumor; (II) to simultaneous, which is applied together with radiotherapy, to treat laryngeal cancer in advanced stages; (III) the sandwich or adjuvant, which will apply, after surgery, chemotherapy and radiotherapy with the aim of eliminating the remaining cells; (IV) the maintenance or palliative, which will apply the chemotherapy to reduce the symptoms of cancer, post-metastasis [21].

The side effects will depend on the chemotherapy used, dosage and duration of treatment, being common: mucositis, infection, dehydration, weight loss, nausea, vomiting, diarrhea, electrolyte imbalance and hair loss [21].

Immunotherapy

Immunotherapy promotes the stimulation of the immune system, using modifying substances. It is composed of different drugs, which are applied intravenously or subcutaneously to the patient. It generally causes fewer side effects than chemotherapy and radiotherapy, and immunological reactions may result from the interaction of the antigen-antibody or the mechanisms involved in cellular immunity [22,23].

This therapy provides tools for the immune system to identify and combat tumor cells, and may act in two ways, according to the substances used and the mechanisms of action: active, when stimulating and restorative substances of immune function and tumor cell vaccines or specific immunotherapy are administered for the purpose of enhancing resistance to tumor growth; and passive or adoptive, when the antitumor antibodies or exogenous mononuclear cells are administered, aiming to provide the immunological capacity to combat the disease [22,23].

Immunotherapy is still a modality in development, and it is necessary to wait for more conclusive results on its efficacy and clinical applicability in the different types of tumors. Its improvement and the creation of new therapeutic interventions, with even more efficient responses and minimal or no toxicity, depend on the persistent continuity of research for treatment [24].

The development and optimization of immunotherapy provide this modality a great notoriety, making it one of the pillars in the fight against cancer, by having a more specific action, reducing the aggressiveness to healthy cells [24].

Results and Discussions

Epidemiological data of the sample

The master's thesis [25], allowed us to obtain epidemiological data on 34 patients with laryngeal cancer treated at Hospital Felício Rocho in Belo Horizonte - Minas Gerais, in the period 1989 and 2002 (Table 1). From these data the following information was extracted: age, gender, tumor grade, life habits and treatment.

Gender

Data from the International Agency for Research on Cancer (IARC) [26], show that by the year 2018 there would be 18.078.957 cancer cases worldwide. Of this total, 177.422 cases are related to laryngeal cancer. According to the INCA[5] estimate, for the year 2018, 7670 new cases of laryngeal carcinoma would be registered in Brazil, 6390 in men and 1280 in women (data not shown).

Data from IARC[27] are similar to those provided by INCA[5] when citing that, for 2018, in Brazil alone, there would be 7947 cases, 6534 for males and 1413 for females. Therefore, there is no significant difference between the estimated data of new cases of laryngeal cancer in Brazil for the year 2018, according to the INCA and IARC, showing that the percentage of cases evaluated by the two institutions is proportional, for both genders (data not shown).

Table 1: Data referring to patients with laryngeal carcinoma. Data from patients of the Hospital Felício Rocho, from 1989 to 2002, analyzed in a master's thesis.

Patient	Age	Gender	Grade	Alcoholist	Smoker	Treatment
1	62 years	F	I	no	yes	radiotherapy
2	59 years	M	I	no	yes	radiotherapy
3	49 years	M	I	no	yes	radiotherapy
4	71 years	F	I	no	yes	radiotherapy
5	55 years	F	II	yes	yes	radiotherapy
6	55 years	M	II	no	yes	radiotherapy
7	54 years	M	II	yes	yes	radiotherapy
8	66 years	M	II	no	no	radiotherapy
9	68 years	M	II	no	yes	radiotherapy
10	46 years	M	II	yes	yes	radiotherapy
11	67 years	M	II	no	yes	radiotherapy
12	51 years	M	II	yes	yes	radio and chemo
13	65 years	M	II	yes	yes	radiotherapy
14	56 years	M	II	yes	yes	radio and chemo
15	71 years	M	II	yes	yes	radiotherapy
16	47 years	M	II	yes	yes	radio and chemo
17	53 years	F	II	no	yes	radiotherapy
18	55 years	F	II	no	yes	radiotherapy
19	46 years	M	II	no	yes	radiotherapy
20	69 years	M	II	no	yes	radiotherapy
21	59 years	M	III	yes	yes	chemotherapy
22	51 years	M	III	yes	yes	chemotherapy
23	59 years	M	III	yes	yes	radiotherapy
24	65 years	F	III	yes	yes	radiotherapy
25	58 years	M	III	yes	yes	radiotherapy
26	61 years	M	III	yes	yes	radiotherapy
27	66 years	M	III	yes	yes	radiotherapy
28	57 years	M	III	yes	yes	radiotherapy
29	55 years	M	III	yes	yes	chemotherapy
30	70 years	M	III	yes	yes	radiotherapy
31	74 years	M	III	yes	yes	radiotherapy
32	62 years	M	III	yes	yes	radiotherapy
33	57 years	M	III	yes	yes	radiotherapy
34	64 years	M	III	yes	yes	radiotherapy

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The proportionality of cases of laryngeal carcinoma in Brazil is confirmed when comparing the sample of 34 patients of the Hospital Felício Rocho, used in the preparation of the master's thesis, 25 with data from INCA [5] and IARC [26]. The data used in the dissertation were analyzed between 2002 and 2004, and are dated from 1989 to 2002 and, even after a period of time corresponding to 16 years, it is noticed that, even with a smaller sample, when compared to the number analyzed by the others the male and female rates of laryngeal carcinoma remained constant, with a prevalence in the male population (Chart 1).

Data from the IARC still prove that the number of people who will develop this disease in Brazil will have a considerable increase over the years. This high index can be explained, in part, by the fact that the population is aging, which contributes directly to the development of the disease. Another hypothesis for this increase in the rate of occurrence of laryngeal carcinoma is related to the increasing consumption of alcohol and tobacco. In addition, there are large numbers of young people who consume these products, increasing the risk and the chances of developing this disease earlier.

Relationship between staging versus lifestyle

Analyzing the tumor stage of the sample of 34 patients, 4 (12%) people presented grade I; 16 (47%), grade II and 14 (41%), grade III (Chart 2).

Of the 4 grade I patients, 100% were only smokers (Chart 3A). Of the 16 grade II patients, only 1 (6%) did not use alcohol or tobacco, 7 (44%) used only tobacco and 8 (50%) used alcohol and tobacco. The remaining 14 patients belong to grade III, and 100% of them used alcohol and tobacco in an associated way (Chart 3C).

Considering the etiology of laryngeal tumors and the magnitude of the risk due to the interaction between the consumption of alcoholic beverage and the cigarette, whose adverse effects are not simply additives, but multiplicative. Individuals who consume excessively and simultaneously alcohol and tobacco, attain high risks of developing this pathology [28].

Thus, life habits have a direct influence on the development of laryngeal cancer, where people who associate alcohol and tobacco have a higher level of tumor staging among 34 patients.

Influence of age on tumor development

The age group of the 34 patients was analyzed, being 8 with age between 40 and 54 years, 22 between 55 and 69 years and 4 between 70 and 84 years, representing a proportion of 23, 65 and 12%, respectively (Chart 4A).

In the same period in which patients from the Hospital Felício Rocho were treated, from 1989 to 2002, all the cases recorded by the INCA [29], of incidences of laryngeal carcinoma were analyzed (Chart 4B). The age group of 40 to 54 years represented 27% of the cases, patients with age between 55 and 69 years were 49% of the sample and people with age between 70 and 84 years represented 24% of this total. For the year 2018, the IARC [30], estimated, for Brazil, 19% of patients affected in the age group between 40 and 54 years, 52% for 55 to 69 years, and 29% for 70 to 84 years (Chart 4C).

When comparing the graph of the Hospital Felício Rocho with that of the INCA, it can be observed that, between the years of 1989 and 2002, the most affected age group was 55 to 69 years and, comparing the IARC projection for 2018, the same age group.

Analyzing the ages of patients with laryngeal carcinoma involved in other studies, several articles were found which, according to the authors, had a mean age of 60 years [31-33]. These data corroborate the predisposition found in the analysis of this work.

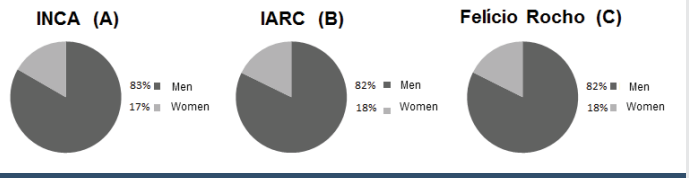

Figure 1: Carcinoma of the larynx with respect to gender. (A) Estimation of laryngeal cancer for the year 2018 of INCA. (B) Estimation of laryngeal cancer for the year 2018 of IARC. (C) Patients of the Felício Rocho Hospital treated between the years 1989 to 2002.

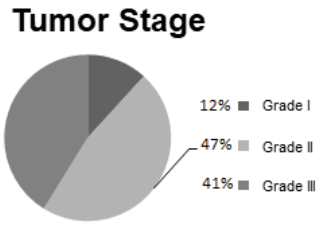

Figure 2: Tumoral Staging. Degree of tumor staging of the patients of Hospital Felício Rocho between the years of 1989 and 2002.

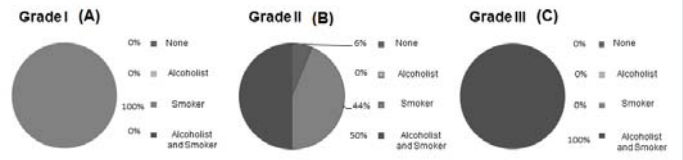

Figure 3: Relation between tumor staging and life habits. (A) Statistical relationship versus life habits of grade I patients. (B) Statistical relationship versus lifestyle habits of grade II patients. (C) Statistical relationship versus life habits of patients with grade III.

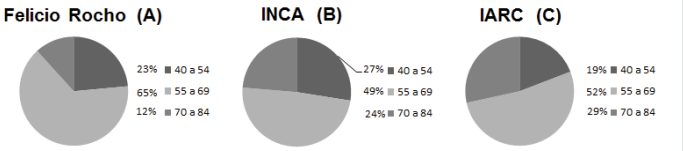

Figure 4: Comparison of the age range of patients with laryngeal cancer in different institutions. (A) Age group of patients suffering from laryngeal cancer at Hospital Felício Rocho in the years 1989 to 2002. (B) Age range of laryngeal cancer cases, according to INCA, from 1989 to 2002. (C) Age range of patients according to IARC estimate for the year 2018.

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Relationship between staging and treatment performed

The 34 patients analyzed [24] were classified according to the type of therapy used. These values were entered into a chart for analysis. Of those, 28 (82%) were treated only with radiotherapy, 3 (9%) only used chemotherapy and the remaining 3 (9%) used the association of chemotherapy with radiotherapy (Chart 5).

A predominance of radiotherapy was observed as a form of treatment, relative to the other types of therapies. Thus, the indicated treatment was related to the tumor grade, obtaining the following results: of the 4 grade I patients, 100% were treated with radiotherapy alone (Chart 6A); of the 16 grade II, 3 (19%) were treated with radiotherapy associated with chemotherapy and 13 (81%) only with radiotherapy (Chart 6B); of the 14 grade III patients, 3 (21%) were treated with chemotherapy alone and 11 (79%) with radiotherapy alone (Chart 6C).

It is observed that there is no indication pattern of treatment in relation to tumor staging, but the fact remains that for both stages, radiotherapy treatment was predominant. Among the treatments indicated for the 34 patients the surgery was not indicated.

According to Salvajoli et.al (2013) [8], for grades I and II, the patient should be treated with intent to preserve the larynx, voice and ability to swallow. Radiotherapy is the most appropriate modality for this treatment because it is a noninvasive technique and does not demonstrate the morbidity presented by laryngeal cancer surgery.

A study by Chera et al., [34], aimed to evaluate the results of radiotherapy in patients with squamous cell carcinoma at an early stage in the glottic region. We analyzed the medical records of 585 patients with T1N0 and T2N0 of the larynx between the years of 1964 and 2006 treated with radiotherapy, arriving at the conclusion that radiotherapy has the capacity to cure a high proportion of patients, with a low rate of serious complications.

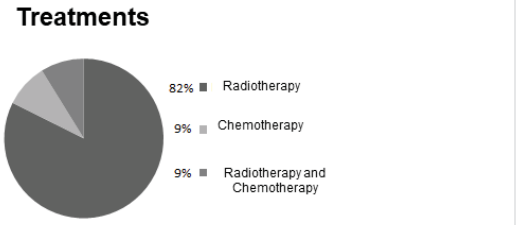

Figure 5: Types of treatments for laryngeal cancer. Therapies used in the treatment of patients at Hospital Felício Rocho.

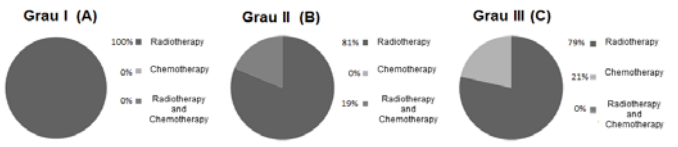

Figure 6: Relation of tumor grade with the indicated treatment. (A) Grade I, indicated therapy: radiotherapy. (B) Grade II, indicated therapy: radiotherapy and radiotherapy associated with chemotherapy. (C) Grade III, indicated therapy: radiotherapy and chemotherapy.

Conclusion

Male individuals are more likely to develop laryngeal carcinoma due to individuals' lifestyles, such as continued cigarette use and excessive alcohol consumption, which directly influence the increase in the risk factor for the development of the disease. The association of these factors, besides contributing directly to the development of the tumor, increases the degree of manifestation of the disease. In addition, people aged 55 to 69 years are among the most affected group of people. It was also observed, according to INCA and IARC estimates, that the number of people affected by laryngeal carcinoma will increase significantly over the years, always maintaining the same proportion for people of the masculine and feminine genres. As a form of treatment, radiotherapy was the most used technique because it is not invasive, presents a low rate of severe complications and does not have the morbidity presented by the surgery, that is, it eliminates the tumor and maintains the functionality of the larynx.

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