UNIVERSITY OF MEDICINE AND PHARMACY
CRAIOVA
PhD STUDIES

THESYS
CURRENT DIAGNOSTIC AND THERAPEUTIC PRINCIPLES IN THE TREATMENT OF MALIGNANT LARYNGEAL TUMORS

ABSTRACT

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INTRODUCTION

The present thesys is a clinical, histopathological, immunochemical and statistical study, carried out in the ENT Department of the County Clinical Hospital of Craiova. The study was carried out with the help of the Pathology Laboratory of the same hospital. The study was carried out between 2009 and 2013. In the present study a total number of 382 patients with malignant laryngeal tumors were included.

STATE OF KNOWLEDGE

The current state of knowledge is structured in 4 separate chapters: the anatomy of the larynx, the physiology and physiopathology of the larynx, the positive diagnosis of laryngeal malignant tumors and the surgical means of treatment.

Chapter I details the anatomy of the larynx, the cartilages that make up its structure, the intrinsic and extrinsic muscles, the laryngeal ligaments as well as the vascular and nervous supply of the larynx. Special attention is paid to the vocal cord anatomy and to the natural laryngeal barriers against local spreading of the cancerous cells.

Chapter II talks about phonation and laryngeal physiology. We pay special attention to the site occupied by the larynx at the crossroads of the digestive and the respiratory tract.

In Chapter III the complete diagnosis of the malignant laryngeal tumors is presented, starting from patient history, ENT clinical exam, endoscopic means of evaluating the larynx and paraclinical and imaging findings. We take a look at the decisive role of tumoral biopsy and modern approaches to the matter.

Chapter IV looks at the treatment of laryngeal cancer. We discuss different ways of approaching a laryngeal tumor based on its primary situs within the larynx. Endoscopic and classical surgical techniques are presented. We take a look at conservative surgery versus radical surgery. The primary determining factor of what type of surgical approach to choose is
the TNM staging, which is also presented in this chapter. We further look at combined therapeutic measures and salvation surgery.

**PERSONAL CONTRIBUTION**

Chapter V is dedicated to personal study and it presents the clinicostatistical study carried out between 2009 and 2013 in the ENT Department of the Clinical County Hospital of Craiova.

The study of laryngeal cancerous tumors began by selecting the 382 cases of laryngeal cancer out of the total 11250 patients admitted between the years 2009 and 2013. The patients were fully examined and complete history was taken. A full ENT exam (completed with endoscopic examination) was performed on each patient. Clinical correlations between the primary tumor site and symptoms were performed.

The patients underwent paraclinical and imaging tests. CT scans, IRM scans, cervical ultrasound, direct laringoscopy and microlaringoscopy were key tests for assessing tumor spread. The tumoral biopsy was a key point in directing further treatment.

Comorbidities were taken into discussion; tumoral growth and symptoms evaluation and correlation were carried out systematically.

Depending on the response to therapy, quantified by statistical qualitative, quantitative and descriptive methods, we could correlate the clinical stages of the disease with the CT or IRM imagery and opt for the best means of treatment.

The objectives of the clinical study were multiple:

- To study the aetiology and the frequency of laryngeal neoplasia,
- To refresh the anatomical keypoint features and establish new keypoints for laryngeal fibroscopy,
- Correlations between imaging exams and follow-up to the therapeutic response,
- The study of the primary tumoral situs, the applied treatment and the surgical procedures that were used,
- Establishing key points for each surgical procedure, (either classical or endoscopic), with the strict awareness of the limitations of each technique,
- Reporting our results to the findings in literature and the possible opening of new lines of research,
- The creation of a guideline for the diagnosis and treatment of patients with malignant laryngeal neoplasia.
The working method used was that of the retrospective clinical and statistical study, based on an analytical and descriptive research. This was represented by a biostatistical and mathematical exam of the variables present in patients with the current disease.

The examination of patients was standardized by protocol, thus enabling a proper diagnosis as correctly as possible and the best means of treatment.

The key points in the files of patients included in the study were patient history, the clinical ENT exam, flexible laryngoscopy, rigid laryngoscopy, suspended laryngoscopy and the tumoral biopsy.

The key points in patient history were:
1. General data of the patient – name, surname, sex, age, residence, workplace, past workplaces,
2. The reasons of admission: dysphonia, aphonía, dyspneea, dysphagia, cervical mass, hemoptysis, weakness, weight loss, local pain, otalgia, halytosis,
3. History of the illness (symptoms’ debut, evolution, further treatments and their results, paraclinical tests, reoccurrence of the disease and complications),
4. Personal records (surgical procedures, tuberculosis, lues, diabetus melitus),
5. Family data (familial neoplasia, tuberculosis, HBP, genetical anomalies),
6. Further personal and work-related data (hobbies, smoking, alcohol and/or drug consumption, workplace pollution, residencial area pollution, spreading viral diseases around the patient’s residence).

The clinical ENT exam was focused on:
1. The head and neck inspection, where we looked for suspect cervical mass, skin discoloration or hyperpigmentation, perioral cyanosis, cutaneous lesions, postoperative scar tissue, laryngeal movement during breathing and swallowing,
2. The palpatory inspection of the laryngeal and anterior cervical regions further completed the mobility exam of the larynx and increased detection and description of cervical tumoral mass.
3. Indirect laryngoscopy is a quick and easy method to asses the endolaryngeal aspect in any patients and was extremely helpful, allowing us to quickly inspect the hypopharynx, the larynx, and the mobility of the vocal cords,
4. The flexible laryngoscopy furthered the anterior exam by properly assesing the endolaryngeal spread of tumors, the invasion of neighbouring zones (piriform fossae), and by properly identifying the primary site of the lesion,
5. Rigid laringoscopy was most important in patients with particularities of the head and neck region where the previous exams were unable to determine the primary tumor and its primary site. The image provided is of top quality since no processing is involved,

6. Laryngeal videostroboscopy implies viewing the larynx and its movement in stroboscopic light, allowing us to discern the vibration patterns of the vocal cords. This means of exploring the larynx was extremely useful in diagnosing small lesions in incipient stages or in the follow-up of vocal cordectomies.

7. Suspended laryngoscopy was the key investigation as it allowed the most correct and detailed examination of the larynx, as it was performed under general anesthesia. Furthermore this allows contact endoscopy to be performed and also therapeutic and diagnostic procedures – excisions, biopsies and partial vocal cordectomies. Hopkins tubes of 0, 30 and 70 degrees were used for a better identification of the primary site of the lesion, and for assessing its extension.

In Chapter VI we reevaluated the cases diagnosed in the ENT Department of the Clinical County Hospital in Craiova, between the years 2009 and 2013. Out of the total number of admissions in this period (11250) we selected 382 patients (3.4%). These patients were diagnosed with laryngeal malignancies in different stages of evolution and were relevant for our study. In this chapter the results of the clinical, hystopathological and immunochemical studies are included.

Laryngeal cancer was most frequent in the following age groups: 51 to 60 years old with 40% of the patients, closely followed by the 61 to 70 years old age group, with a percentage of 31.5% of the total patients. The lowest incidences were identified in the 31 to 40 years old age group with a percentage of 0.5% and in the 81 to 90 years old group with a similar percentage.

During this period out of the total number of patients included in the study, 7 patients (1.8%) were diagnosed during stage I of the disease, 19 (5%) patients were diagnosed in stage II of the disease, 92 (24%) patients were diagnosed in stage III and the bulk of patients, 262 (69.2%), were diagnosed in the final fourth stage of the disease.
We also note that in 236 patients the primary site of the tumor was the glottis (61.78% of the total number of patients in the study), in 101 patients the tumor originated in the supraglottic region (26.43%) and only in 45 patients the origin of the tumor was infraglottic (11.78%).
From the bulk of 382 patients in our study, 168 patients representing 43.75% underwent total or partial laryngectomies. The rest of the patients, namely 56.25% of them, underwent an emergency tracheostomy and later on a tumoral biopsy, the current tumoral state at the time of diagnosis disabling them from undergoing further surgical treatment. All patients underwent a TNM staging of the disease.

As we can see from the percentages, most patients were diagnosed within late stages of the disease which makes us question the addressability towards ENT consultations. Most patients were diagnosed during the IVth stage of the disease – 69.2%. The most frequent type of surgery performed was the total laryngectomy with radical modified neck dissection.

CHAPTER VII. The hystology and immunochemistry study represents a conduit of treatments and also its follow-up. After obtaining the hystopathology result from the tumoral biopsy we could deliberate and choose a means of treatment for our patients – surgical or oncological. The immunochemistry findings were extremely helpful in difficult differential diagnostics and in the long-term progress of the disease, proving to be a good prognosis factor.

Hystological analysis of the tumoral fragments identified the main microscopic parameters of the tumors such as type, grading, the depth of tumoral invasion in healthy tissues, perivascular and perineural invasion and prognostic scores regarding the T and N staging of the TNM.

Of all tumors analysed we uncovered 22 in situ carcinomas (5.65%), 16 microinvasive carcinomas (4%), 162 poorly differentiated carcinomas (42.5%), 124 moderately differentiated carcinomas (32.5%), 42 well-differentiated carcinomas (11%), 8 papillary carcinomas (2%), 1 leiomiiosarcoma (0.25%), 1 condrosarcoma (0.25%), 6 basaloïd carcinomas (1.45%), 1 verucous carcinoma (0.25%), 1 malign melanoma (0.25%) and one spindle-cell carcinoma (0.25%).

The immunochemistry findings traced the expression of the following antigens: EGFR, VEGF, the p53 oncoprotein and the Ki-67 protein. These antigens were only determined in select complex tumoral cases. Numbers from these findings were correlated with further therapeutic conduit, prognosis and follow-up.

Special attention was given to the expression of the EGFR antigen which constitutes a biomarker for identifying patients that may benefit from accelerated carbogen (98% O₂; 2% CO₂) radiotherapy and nicotinamide (ARCON). This type of approach is aimed as regional
CONCLUSIONS

1. The present paper is an ENT retrospective clinical, statistical, histological and immunochemical study carried out during a 5 year period (01.01.2009-31.12.2013) in our Department. It stages the investigation of laryngeal tumors and aims to create a protocol for investigating and treating this pathology.

2. Of all the admitted patients in our Department for the given period, 3.4% of them were diagnosed with malignant laryngeal tumors. This represents a total of 382 patients. The percentage we uncovered is comparable to those presented in literature.

3. The age group with the highest incidence was 51 to 60 years of age with 152 diagnosed patients, respectively 40% of the total patients. The age groups with the lowest incidence, 0.5%, were the ones ranging from 31 to 40 and 81 to 90 years of age. The most targeted of sexes were the males, accounting for 97% of the total patients.

4. Symptoms displayed by the patients are closely linked to the primary site of the tumor within the endolarynx. The most common site for primary tumors was the glottis with 61.78% of all cases, namely 236 patients.

5. Of all the histological types of tumors we came across, the most frequent one was the squamous cell carcinoma which accounted for 379 cases, thus representing an overwhelming 99% of the total patients. We wish to point out that current international studies determine an occurrence rate of 95% for the same type of lesion.

6. Most of our patients were diagnosed in the IVth stage, 69.2% of the total patients were diagnosed and admitted in this stage of the disease, namely 262 individuals.

7. Of the total number of patients only 168 underwent curative surgery (43.75%), the rest were out of surgical reserve.

8. Both functional endoscopic and radical surgical techniques were used, but the most common one was the total radical laryngectomy with bilateral radical modified neck dissection.

9. There was a total number of 134 total laryngectomies accounting for 35% of all the patients admitted in this study. We explain this unusually high number in close respect
with the late diagnosis of the laryngeal tumors (most patients diagnosed were already in the IVth stage of the disease).

10. Taking into account the growing incidence of laryngeal neoplasia, the long admission periods for this type of disease, the extensive surgical interventions performed and the postoperative functional loses, we strongly advise towards initiating a diagnostic and a screening guide to help lessen the high numbers of patients diagnosed within late stages of the disease and thus shift the balance to our advantage as therapists and also to the patients’ advantage.
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