CLINICAL, HISTOLOGICAL AND THERAPEUTIC NOVELTIES IN HYPOPHARYNGEAL CANCER

PH.D. THESIS

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1 Part I - Preliminary notions

1.1 Introduction

Malignant tumors of the hypopharynx represent 0.6-1% of total malignant tumors and 7-10% of the malignant tumors of the ENT area. This disease has been in the center of attention for the oncologists, the disease having the tendency of an increasing morbidity. [1, 2]

The main triggering factors of the hypopharyngeal cancer (risk factors) are smoking, alcohol consumption, increasing environmental pollution, long-term untreated pathological processes (chronic pharyngitis, dyskeratosis of the pharynx mucous membrane. [3, 4]

The most important risk factor is smoking. In 98% of cases, patients have been abusive smokers for 15-20 years. As for the gender distribution, even if in the past the incidence of hypopharyngeal cancer was much higher in men, now the ratio decreased to 3/1, in relation to the increasing incidence of smoking in women. This type of cancer in general affects persons of mature age with a maximum frequency in the interval of 40-60 years. In 85-90% of cases, the doctors establish the diagnosis in stages III-IV and only in 10-15% of cases in stages I-II. In 45-60% of cases, the primary lesion is associated with a metastatic satellite adenopathy in the cervical lymph nodes, leading to a difficult and unpleasant treatment and to a poor prognosis. The reader could compare these percentages from the literature with the statistical results obtained by us on the sample of patients that we studied.

Recent findings in molecular medicine have shown that cancer is a genetic disease and that the development of neoplastic cells occurs because of the disorder of proliferation, differentiation and cell apoptosis mechanisms. [5, 6]

1.2 Anatomy of the Hypopharynx

1.2.1 The Configuration of the Hypopharynx

The hypopharynx represents the lowest portion of the pharynx, with the upper limit of the plane corresponding to the hyoid bone and to the upper edge of the epiglottis and with the lower limit of the plane corresponding to the lower edge of the cricoid cartilage. From there the hypopharynx continues with the esophagus, 15 cm from the dental arcade, the entrance of the esophagus being closed at rest by the cricopharyngeus muscle. The hypopharynx is the longest segment of the pharynx, having a cone shape, whose diameter decreases from the top to the bottom. The hypopharynx is linked: anterior to the posterior front laryngeal crown of the larynx, lateral to the common carotid artery, to the internal jugular vein and to the vagus nerve, posterior to the prevertebral fascia and to the bodies of the III-VI cervical vertebrae. Anatomically the hypopharynx is divided in three regions: the pyriform sinus, the retrocricoid area and the posterior wall. [12, 23, 24]

1.2.2 The Structure of the Hypopharynx

From the interior to the exterior, the hypopharynx has four layers: pharyngeal mucosa, pharyngeal aponeurosis, muscular layer (upper constrictive muscle, middle constrictive muscle, lower constrictive muscle, stylopharyngeus muscle, salpingopharyngeus muscle), adventitia. [21, 22, 23, 25]

1.2.3 The Vascularization and Innervation of the Hypopharynx

Arterial Vascularization It is represented by the external carotid artery through its branches (pharyngeal ascending artery, the upper thyroid artery), that forms a rich anastomotic network.
Venous drainage. It forms a submucosal plexus and another one parapharyngeal, both connecting to the internal jugular vein.

Lymphatic system. It forms two networks, one submucosal and one muscular, that drain both into the Gillette retropharyngeal lymph nodes and into the internal jugular lymph nodes. In the pharyngeal submucosa, there is found into the upper side a rich lymphatic network that accompanies the internal branch of the superior laryngeal nerve, the superior laryngeal artery and the superior laryngeal vein, and crossing together the thyrohyoid membrane, then draining into the superior and middle jugular lymph nodes. Into the lower side of the pharyngeal submucosa, the drainage path is represented by the paratracheal lymph nodes, that drain in the lower jugular lymph nodes and in the lower mediastinal lymph nodes.

Innervation of the Hypopharynx. It comes from the pharyngeal plexus, located on the lateral side of the middle pharyngeal constrictive muscle and containing the pharyngeal branches of the glossopharyngeal nerve, of the vagus nerve (internal branch of the superior laryngeal nerve, which has connections to the auricular branch of vagus nerve and to the recurrent laryngeal nerve) and of the cervical ganglia. The pharyngeal plexus generates nerve motor branches for the pharyngeal muscles, sensitive branches for the pharyngeal mucosa and vegetative branches for mucous glands. [21, 22, 23, 25]

1.3 Physiology and Physiopathology of the Hypopharynx

1.3.1 Physiology of the Hypopharynx

The pharynx functions are:

- pharyngeal deglutition
- phonatory function
- sensory function
- it plays a role in the immune system of the body [12, 22, 26, 27]

1.3.2 Syndromes of the Hypopharynx

- pharyngeal dysphagia
- pharyngeal dyspnea
- dysphonia
- sensitive syndrome (odynophagia, hyperesthesia, hypoesthesia, paresthesia)
- dysgeusia[12, 22, 26, 27]

1.4 Hypopharyngeal Cancer Etiopathogenesis

1.4.1 Hypopharyngeal Cancer Etiology

Numerous studies conducted throughout the world have established the influence of the "way of life" in the emergence of cancer. By the "way of life" we understand dietary habits, smoking, alcohol consumption, environmental factors, pollution (physical, chemical or biological), influence
of viruses, genetic predisposition, metabolic and hormonal factors, immune system, psycho-emotional factors. Some harmful food habits - such as: ingestion of concentrated alcohols, associated with the consumption of food with oncogenic potential (prepared in an inappropriate manner), also the cigarette smoke - increase the incidence of hypopharyngeal cancer. [1, 2, 3, 4, 5, 7, 8, 11]

1.4.2 Hypopharyngeal Cancer Pathogeny

The hypopharynx is covered completely by a malpighian epithelium, so that most of the cancers at this level are malpighian differentiated carcinomas. Macroscopically, the hypopharyngeal tumors start with an infiltrative process - **ulcero infiltrative form** - that can ulcerate and that is characterized by an invasion of the mucosa, with a more or less profound destruction of the underlying structures (glands, muscles, membranes, cartilages), or it may occur vegetations - **vegetative form** - this form develops on the surface, without affecting the deep tissue, being a carcinoma isolated on the mucosa, but that propagates at distance, affecting completely or partially the pharyngeal epithelium. There can be met a combination of these processes, the **ulcero-vegetative form**.[12]

The tumor dissemination is realized contiguously, through the lymphatic pathway and less frequently through the hematic path. The growth direction of the hypopharyngeal cancer is determined by the existence of areas of adherence that form obstacles on the way of the tumor growth. The most important path for the tumor dissemination is the lymphatic system. During the invasion of a group of cervical lymph nodes, which makes them clinically identifiable, it is possible that the cancer cells have reached other lymph nodes that are not yet palpable, by contiguity, and not removing them leads to an evolution and to clinical stages with a more reserved prognosis. The distant metastases of the hypopharyngeal cancer can occur in the liver, also in the lungs. Cancer is a genetic disease in which genes involved in cellular functions suffer point mutation, deletion, chromosomal rearrangement that lead to irreversible genetic changes. This genetic alteration comprises the activation of the protooncogenes and the inactivation of the suppressor genes. [9, 10, 13, 14, 15, 16, 17]

1.5 Hypopharyngeal Cancer Diagnosis

The diagnosis of the hypopharyngeal cancer is established through the following steps:

- **Anamnesis** (way of life, in terms of working in harmful conditions, smoking for a long time, alcohol abuse; history of chronic inflammatory processes, treated long time without clinical effect; history of cancer in the ancestry)
- **Symptomatology** (dysphagia, odynophagia, dysphonia, dyspnea, reflex otalgia, weight lose and physical asthenia, cervical adenopathy)
- **Palpation and visual inspection** (it is mandatory for the discovery of the metastatic adenopathies, it investigates the mobility and the state of the laryngeal skeleton)
- **Indirect laryngoscopy**
- **Direct laryngoscopy**
- **Endoscopic examination** (fibrolaryngoscopy)
- **Suspended microlaryngoscopy**
- **Radiologic examination** (without or with contrast agent)
1.6 Hypopharyngeal Cancer Treatment

The treatment of the hypopharyngeal cancer is controversial, due to the discovery of the malady in advanced stages, associated with chronic diseases that increase the risk of the surgical treatment and to the inherent difficulties in conducting appropriate prospective randomized clinical trials. For this reason, associated with the high incidence of early metastases, the survival rate in the hypopharyngeal cancer is the lowest of the head and neck cancer locations. Depending on the tumor stage, the treatment of hypopharyngeal cancer is complex and includes surgery, radiotherapy and chemotherapy.[36, 37]

No single therapeutic method offers a better survival chance. The final therapeutic choice depends on the careful examination of each individual case (paying attention to the tumor stage, physical and emotional condition of the patient, nutritional status and associated diseases), on the medical team experience, on the available treatments related with the extension to the carotid artery, spine, ganglia and distant metastases.

For the tumors in stages I and II, the treatment is surgical, followed by post surgical radiotherapy. Some of the early stages (T1 and T2), pyriform sinus carcinoma, exolit, with a small volume, were successfully treated only by radiotherapy. [42, 43]

For the tumors in stages III and IV where the resection is possible, the treatment is surgical, post surgical radiotherapy, neoadjuvant chemotherapy. [42, 43]

For the tumors in stage IV where the resection is not possible, the treatment consists in radiotherapy and chemotherapy. [38] The alternative methods that use the neoadjuvant chemotherapy and the radiotherapy may increase the chances of local control in advanced presentations at a level close to that of the resection and of the postoperative radiotherapy. [44, 45]

The neoadjuvant chemotherapy reduces the tumor volume and converts them into operable or radio-treatable tumors. It is used to treat patients who present advanced local lesions to improve the local control and the surviving chance. [41, 42]

An examination of the published clinical results related to the radical radiotherapy for head and neck cancer suggests a significant loss of local control when radiotherapy is administered too long, suggesting that the extension of the standard treatment programs extension over long periods of time should be avoided whenever possible. [46, 47]

Post procedural controls are done monthly in the first year, once every two months in the second year, once every three months in the third year, once every six months in the next years. [39, 40]

2 Part II - Results

2.1 Materials si methods

In this study, we present a sample of 225 patients diagnosed with hypopharyngeal cancer, who had extensions to the surrounding organs and metastatic adenopathy, boarded and treated in the

We used the information from the database of the Emergency Clinical County Hospital of Craiova about the patients diagnosed with hypopharynx cancer that we studied. The Department of Pathological Anatomy archives preserve the tumor tissues taken from the patients. Nevertheless, the clinical observation sheets of patients, registry books and operating protocols, analysis bulletins, imaging examinations of the ENT Clinic (X-rays, CT, MRI, ultrasound images, Endoscopic images), anatomopathological and oncological examinations represented the main source of information for our study.

The method of research that we used was clinical and statistical, retrospective, based on a mixed analytical and descriptive research, represented by a biostatistical and mathematical analysis of the variables in relation with the disease. We developed a working protocol for the sample of patients establishing a database with criteria for inclusion and exclusion.

Inclusion criteria:

- Patients diagnosed with hypopharyngeal cancer, confirmed by histopathological examination;
- Previously untreated patients through chemotherapy, radiotherapy or surgery;
- Patients without major psychiatric disorders;
- There were no conditions related to age, sex, environmental origin;
- Patients informed consent;
- Possibility of periodic follow-up.

Exclusion criteria:

- Patients with associated difficulties and problems that prevented surgical and oncology treatment;
- Patients with local relapses or continued evolution after the primary irradiation.

2.2 Clinical and statistical results

We obtained the following statistical results on a sample of 225 patients with hypopharyngeal cancer, admitted in a five-year period, 2008-2012, in the ENT Clinic of the Clinical Emergency County Hospital of Craiova. In the first part of the study, we make a descriptive statistic of the sample of patients, representing separately the distribution of cases according to various statistics parameters (age, gender, environmental origin, county of origin, occupation, topographical diagnosis, presence or absence of ad-enopathy, anatomopathological diagnosis, stage, and the applied surgical treatment). We realized all the computations, tables and graphs used in the statistical description with Matlab software package. For rigorous definitions of the concepts and the notions of statistics used further, see [18, 19, 20].

We detailed the distribution of cases according to the years included in the study in Table 1 and in Figure 1a.

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>50 (22.22%)</td>
<td>41 (18.22%)</td>
<td>36 (16%)</td>
<td>59 (26.22%)</td>
<td>39 (17.33%)</td>
<td>225</td>
</tr>
</tbody>
</table>

Table 1: Distribution of cases according to the years included in the study
We show the distribution of cases according to the age groups in Table 2 and in Figure 1b.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>30</th>
<th>31 - 40</th>
<th>41 - 50</th>
<th>51 - 60</th>
<th>61 - 70</th>
<th>71 - 80</th>
<th>80</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>1</td>
<td>3</td>
<td>36</td>
<td>102</td>
<td>61</td>
<td>21</td>
<td>1</td>
<td>225</td>
</tr>
</tbody>
</table>

Table 2: Distribution of cases according to the age groups

Figure 1

The patients included in the study sample came from the Oltenia counties (Dolj, Gorj, Olt, Valcea, Mehedinți) and, in 4 isolated cases, from two adjacent counties (Teleorman and Hunedoara). The distribution of cases by counties appears in Table 3 and in Figure 2a.

<table>
<thead>
<tr>
<th>County</th>
<th>Dolj</th>
<th>Valcea</th>
<th>Olt</th>
<th>Mehedinți</th>
<th>Gorj</th>
<th>Teleorman</th>
<th>Hunedoara</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>124</td>
<td>34</td>
<td>29</td>
<td>19</td>
<td>15</td>
<td>3</td>
<td>1</td>
<td>225</td>
</tr>
</tbody>
</table>

Table 3: Distribution of cases by county

Considering the risk factors, it is interesting to study the distribution of patients related to the environmental origin, i.e. urban or rural environment. We detailed this in Table 4 and in Figure 2b.

<table>
<thead>
<tr>
<th>Origin</th>
<th>Urban</th>
<th>Rural</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>95</td>
<td>130</td>
<td>225</td>
</tr>
</tbody>
</table>

Table 4: Distribution of cases by environmental origin (urban or rural)
The presence of women in the studied sample was extremely low, in a proportion of only 4% of cases. We presented the distribution of patients by sex in Table 5 and in Figure 3a.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>216 (96%)</td>
<td>9 (4%)</td>
<td>225</td>
</tr>
</tbody>
</table>

Table 5: Distribution of cases by sex

Regarding the occupation of patients, we were interested in our study only if the patients were employed, retired, unemployed, or without occupation (social cases). These categories reflect the patients’ lifestyle correlated with risk factors. We detailed the distribution of cases by the patients’ occupation in Table 6 and in Figure 3b.

<table>
<thead>
<tr>
<th>Occupation</th>
<th>retired</th>
<th>social cases</th>
<th>employed</th>
<th>unemployed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>131 (58%)</td>
<td>74 (33%)</td>
<td>46 (7%)</td>
<td>4 (2%)</td>
<td>225</td>
</tr>
</tbody>
</table>

Table 6: Distribution of cases by patients’ occupation
Considering the topographical situation of the hypopharynx, in the immediate vicinity of the larynx, analyzing the statistics over the five years, we found that the hypopharyngeal tumor evolved concomitantly with the laryngeal localization. We show in Table 7 and in Figure 4a the distribution of cases according to the localization of the neoplastic tumor. The pharyngolaryngeal localization prevailed, in 82% of cases.

<table>
<thead>
<tr>
<th>Localization</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>pharyngolaryngeal</td>
<td>185</td>
<td>82.22%</td>
</tr>
<tr>
<td>pyriform sinus</td>
<td>33</td>
<td>14.67%</td>
</tr>
<tr>
<td>oropharynx</td>
<td>6</td>
<td>2.67%</td>
</tr>
<tr>
<td>retrocricoid</td>
<td>1</td>
<td>0.44%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>225</strong></td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Distribution of cases according to the localization of the neoplastic tumor

In the great invasion, hypopharyngeal cancer causes adenopathy with an aggressive evolution, with ganglia immobility. We show the distribution of cases by adenopathy in Table 8 and in Figure 4b.

<table>
<thead>
<tr>
<th>Adenopathy</th>
<th>with</th>
<th>without</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>146</td>
<td>79</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 8: Distribution of cases by adenopathy
At the hypopharynx level, from the histological point of view, cancers are in the form of epidermoid carcinomas with different forms of differentiation. The undifferentiated epidermoid carcinoma was the most common in the patients sample that we studied. We detailed the distribution of cases by the anatomopathological diagnosis in Table 9 and in Figure 5a.

<table>
<thead>
<tr>
<th>Carcinoma type</th>
<th>poorly differentiated squamous</th>
<th>moderately differentiated squamous</th>
<th>well-differentiated squamous</th>
<th>non-keratinized squamous</th>
<th>leiomyosarcoma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>184 (81.78%)</td>
<td>30 (13.33%)</td>
<td>7 (3.11%)</td>
<td>3 (1.33%)</td>
<td>1 (0.44%)</td>
<td>225</td>
</tr>
</tbody>
</table>

Table 9: Distribution of cases by the anatomopathological diagnosis

Few symptoms and the presence of only the cervical adenopathy makes the patients to ask for medical help often only in the advanced stages of the disease. Due to this fact, the staging was advanced, most of the cases being in stages III and IV. In Table 10 and in Figure 5b we detailed the distribution of cases by the staging diagnosis. The percentages are similar to those found in the specialty literature.

<table>
<thead>
<tr>
<th>Staging</th>
<th>IV</th>
<th>III</th>
<th>II</th>
<th>I</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>192 (85.33%)</td>
<td>26 (11.56%)</td>
<td>6 (2.67%)</td>
<td>1 (0.44%)</td>
<td>225</td>
</tr>
</tbody>
</table>

Table 10: Distribution of cases by the staging diagnosis
For the statistical description of the surgical treatments applied on the patients from our sample, we delimited and decided to represent three categories: patients who had no surgical intervention, patients with acute respiratory failure on which were performed only tracheotomies of necessity and the patients who received radical surgical treatment. We show the distribution of these categories in Table 11 and in Figure 6. The radical surgical treatment consisted in total laryngectomy with partial pharyngectomy.

<table>
<thead>
<tr>
<th>Surgical treatment</th>
<th>no operation</th>
<th>laryngectomy totala cu hipofaringectomie partiala</th>
<th>tracheotomie de necesitate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>154 (68.44%)</td>
<td>36 (16%)</td>
<td>35 (15.56%)</td>
<td>225</td>
</tr>
</tbody>
</table>

Table 11: Distribution of cases by the applied surgical treatment

2.3 Statistical correlations

In the second part of the study, we analyze the existence of correlations between the statistical variables presented separately in the first part. We distinguish between two types of variables:
numerical ones, as is the age (in fact the only statistical numerical variable in the study) and the
categorical ones (gender, occupation, environmental origin, topographical diagnosis, etc.). In the
case of age, we analyze the distribution correlated with a categorical variable (e.g. distribution of
age by counties) and calculate the average, the median, the quartiles Q1 and Q3 and the standard
deviation (see [20] for the definitions of these concepts). In addition to calculating these values,
we represent the distributions of age according to other parameters by boxplot graphs (see [18]).
In this situation, the age coupled with a definite variable, we use the Student test (see [18, 20])
for the analysis of the statistical independence between the two variables. In the case of age
distribution over the years included in the study (Table 12 and Figure 7a) and in the case of age
distribution according to the patients’ sex (Table 13 and Figure 7b) the Student test reveals no
correlation age – years or age – sex.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Average</th>
<th>Median (Q2)</th>
<th>Q1</th>
<th>Q3</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - 2008</td>
<td>50</td>
<td>58.82</td>
<td>58</td>
<td>54</td>
<td>65</td>
<td>9.11</td>
</tr>
<tr>
<td>Age - 2009</td>
<td>41</td>
<td>60.24</td>
<td>58</td>
<td>53.75</td>
<td>68.5</td>
<td>8.91</td>
</tr>
<tr>
<td>Age - 2010</td>
<td>36</td>
<td>55.47</td>
<td>55</td>
<td>52</td>
<td>60.5</td>
<td>6.29</td>
</tr>
<tr>
<td>Age - 2011</td>
<td>59</td>
<td>58.27</td>
<td>57</td>
<td>52</td>
<td>63</td>
<td>8.56</td>
</tr>
<tr>
<td>Age - 2012</td>
<td>39</td>
<td>57.56</td>
<td>57</td>
<td>50.25</td>
<td>64</td>
<td>9.14</td>
</tr>
</tbody>
</table>

Table 12: Distribution of cases by age groups and by year

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Average</th>
<th>Median (Q2)</th>
<th>Q1</th>
<th>Q3</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - Women</td>
<td>9</td>
<td>52.11</td>
<td>57</td>
<td>37.25</td>
<td>65.25</td>
<td>14.85</td>
</tr>
<tr>
<td>Age - Men</td>
<td>216</td>
<td>58.43</td>
<td>57.5</td>
<td>53</td>
<td>64</td>
<td>8.19</td>
</tr>
</tbody>
</table>

Table 13: Distribution of cases by age groups and by sex

![Figure 7](image)

(a) Distribution of cases by age groups and by year

(b) Distribution of cases by age groups and by sex

Figure 7

In the case of age distribution depending on the county of origin (Table 14 and Figure 8a),
we discovered an interesting correlation. The Student test rejects the HO statistics hypothesis
that the counties Dolj and Mehedinți have the same average of the age distribution, with p-
value = 0.0494. Within the same Student test limits, the other counties (Valcea, Olt, Gorj)
have statistically the same average of the age distribution as Dolj county. With three cases, respectively one case, the Teleorman and Hunedoara counties are statistically irrelevant.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Average</th>
<th>Median (Q2)</th>
<th>Q1</th>
<th>Q3</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - DJ</td>
<td>124</td>
<td>57.45</td>
<td>57</td>
<td>52</td>
<td>63.5</td>
<td>9.07</td>
</tr>
<tr>
<td>Age - VL</td>
<td>34</td>
<td>68.52</td>
<td>57</td>
<td>55</td>
<td>65</td>
<td>7.66</td>
</tr>
<tr>
<td>Age - OT</td>
<td>29</td>
<td>57.96</td>
<td>58</td>
<td>51.75</td>
<td>65</td>
<td>7.71</td>
</tr>
<tr>
<td>Age - MH</td>
<td>19</td>
<td>61.47</td>
<td>61</td>
<td>56</td>
<td>67.75</td>
<td>8.32</td>
</tr>
<tr>
<td>Age - GJ</td>
<td>15</td>
<td>58.13</td>
<td>60</td>
<td>53.5</td>
<td>62</td>
<td>8.61</td>
</tr>
<tr>
<td>Age - TR</td>
<td>3</td>
<td>66.7</td>
<td>69</td>
<td>63.75</td>
<td>69</td>
<td>4.04</td>
</tr>
<tr>
<td>Age - HD</td>
<td>1</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 14: Age distribution depending on the county of origin

Another correlation that we discovered is age – occupation (Table 15 and Figure 8b). This dependence of the average age on the patient occupation was expected a priori, knowing that the retired persons have a certain age threshold, and it was useful for checking the methods and software used for statistical calculations. In this situation, the Student test rejects the H0 hypothesis that the re-tired and the social cases have the same average of the age distribution, with p-value = $6.8 \cdot 10^{-20}$. The same Student test accepts the H0 hypothesis that the employees and the social cases have the same average of the age distribution. With four cases, the unemployed category is statistically irrelevant.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Average</th>
<th>Median (Q2)</th>
<th>Q1</th>
<th>Q3</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - retired</td>
<td>131</td>
<td>62.42</td>
<td>62</td>
<td>56.25</td>
<td>69</td>
<td>7.31</td>
</tr>
<tr>
<td>Age - social cases</td>
<td>74</td>
<td>52.51</td>
<td>53</td>
<td>49</td>
<td>57</td>
<td>6.79</td>
</tr>
<tr>
<td>Age - employed</td>
<td>16</td>
<td>51.37</td>
<td>51.5</td>
<td>46.5</td>
<td>55.5</td>
<td>5.13</td>
</tr>
<tr>
<td>Age - unemployed</td>
<td>4</td>
<td>51.25</td>
<td>52</td>
<td>45</td>
<td>57.5</td>
<td>7.41</td>
</tr>
</tbody>
</table>

Table 15: Age and occupation distribution

Also for the age distribution related to the staging diagnosis (Table 16 and Figure 9), the Student reveals a statistical correlation. The H0 hypothesis that the age distributions for stage
IV and stage III have the same average is rejected, with p-value = 0.0262.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Average</th>
<th>Median (Q2)</th>
<th>Q1</th>
<th>Q3</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - Stage IV</td>
<td>192</td>
<td>58.38</td>
<td>58</td>
<td>53</td>
<td>65</td>
<td>8.76</td>
</tr>
<tr>
<td>Age - Stage III</td>
<td>26</td>
<td>55.38</td>
<td>55.5</td>
<td>52</td>
<td>60</td>
<td>6.46</td>
</tr>
<tr>
<td>Age - Stage II</td>
<td>6</td>
<td>63.5</td>
<td>63</td>
<td>55</td>
<td>70</td>
<td>9.31</td>
</tr>
<tr>
<td>Age - Stage I</td>
<td>1</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 16: Age distribution related to the staging diagnosis

In investigating the correlations between the categorical variables the main statistical instrument is the cross table, and the statistical test that decides whether two variables are independent or not is Pearson $\chi^2$ test (or chi2), see [18, 20]. Further, we present pairs of categorical variables for which the Pearson test rejects the H0 statistical hypothesis that the variables are independent.

We show the correlation between the topographical diagnosis and the staging diagnosis in the cross Table 17. The H0 hypothesis (the statistical independence of the two variables) is rejected with p-value = 1.548 · 10^{-9}. Figure 10 shows the histogram of the cases distribution by the topographical diagnosis and by the staging diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>Stage</th>
<th>IV</th>
<th>III</th>
<th>II</th>
<th>I</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>pharyngolaryngeal</td>
<td></td>
<td>166</td>
<td>16</td>
<td>3</td>
<td>0</td>
<td>185</td>
</tr>
<tr>
<td>oropharynx</td>
<td></td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>retrocricoid</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>pyriform sinus</td>
<td></td>
<td>20</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>192</td>
<td>26</td>
<td>6</td>
<td>1</td>
<td>225</td>
</tr>
</tbody>
</table>

$\chi^2 = 59.6749$, p-value = 1.548 · 10^{-9}

Table 17: Distribution by the topographical diagnosis and by the staging diagnosis
Figure 10: Distribution by the topographical diagnosis and by the staging diagnosis

We show in the cross Table 18 and in Figure 11a the cases distribution by the topographical diagnosis and by the surgical treatment. The H0 hypothesis related to the statistical independence is rejected by the Pearson test (chi2) with p-value = 0.0147.

<table>
<thead>
<tr>
<th>Topographical diagnosis</th>
<th>Surgical treatment</th>
<th>no surgical intervention</th>
<th>radical surgery</th>
<th>tracheotomies of necessity</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>pharyngolaryngeal</td>
<td>122 (79%)</td>
<td>35 (100%)</td>
<td>28 (78%)</td>
<td></td>
<td>185</td>
</tr>
<tr>
<td>pyriform sinus</td>
<td>26 (17%)</td>
<td>7 (21%)</td>
<td>0</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>oropharynx</td>
<td>6 (4%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>retro larynx</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>36</td>
<td>35</td>
<td></td>
<td>225</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 15.8263, \text{ p-value} = 0.0147 \]

Table 18: Cases distribution by the topographical diagnosis and by the applied surgical treatment

In the cross Table 19 we show the distribution by the anatomopathological diagnosis and by the surgical treatment. The H0 hypothesis about statistical independence of the variables is rejected by the Pearson chi2 test with p-value = 0.0185.

<table>
<thead>
<tr>
<th>Anatomopathological diagnosis</th>
<th>Surgical treatment</th>
<th>no surgical intervention</th>
<th>radical surgery</th>
<th>tracheotomies of necessity</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>poorly differentiated squamous</td>
<td>127 (82.4%)</td>
<td>31 (88.57%)</td>
<td>26 (72.22%)</td>
<td></td>
<td>184</td>
</tr>
<tr>
<td>moderately differentiated squamous</td>
<td>22 (14.28%)</td>
<td>6 (16.67%)</td>
<td>7 (19%)</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>well differentiated squamous</td>
<td>2 (1.30%)</td>
<td>4 (11.71%)</td>
<td>0</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>non keratinized squamous</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>leiomyosarcoma</td>
<td>0</td>
<td>0</td>
<td>1 (2.86%)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>36</td>
<td>35</td>
<td></td>
<td>225</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 18.3877, \text{ p-value} = 0.0185 \]

Table 19: Cases distribution by the anatomopathological diagnosis and by the applied surgical treatment
2.4 Clinical cases study

2.4.1 Clinical case I

The patient is a 48 years old male, from urban area, employed, has a medical history of pulmonary tuberculosis, he is smoker and alcohol consumer. The symptoms he presented in the ENT service were dysphagia with odynophagia predominantly on the left side, moderate dyspnoea, dysphonia, irritative cough. The patient was clinically examined from an ENT point of view through the inspection and palpation of the neck, by indirect laryngoscopy, by direct laryngoscopy and by computed tomography.

Figure 12: 3D reconstruction of the cervical region (based on computed tomography).
The CT imaging showed the localization of the tumor in the left pyriform sinus, with extension to the cervical esophagus, with the invasion of the thyroid cartilage and mass effect on the left hemilarynx, with its immobilization (see the CT axial slices in 13).

Figure 13: Axial slices in the CT showing the localization and the extension of the tumor.

The software tools for imaging analysis and 3D reconstruction helped to a good localization the tumor and appreciation of tumor extension. Thus, in the Figure 14, in the two-dimensional slices the tumor position is indicated by a 2D cursor, and in the 3D reconstruction a schematic instrument shows the area of the larynx compressed by the tumor.
The software package used for imaging analysis removed the skin tissue and indicates even more visible through a schematic instrument the area where the tumor compresses the larynx (see Figure 15).
2.4.2 Clinical case II

The patient is a 70 years old male, from rural area, retired, has a medical history of pulmonary tuberculosis, he is smoker and alcohol consumer. The symptoms he presented in the ENT service were dysphagia with odynophagia predominantly on the right side, irritative cough. The patient was clinically examined from an ENT point of view through the inspection and palpation of the neck, by indirect laryngoscopy, by direct laryngoscopy and by computed tomography.
Figure 16: 3D reconstruction of the cervical region (based on computed tomography).

The CT imaging shown the localization of the tumor in the right pyriform sinus and epiglottis (see the CT axial slices in 17).
Figure 17: Axial slices in the CT showing the localization and the extension of the tumor.

With the help of the software tools for imaging analysis and 3D reconstruction we obtained the Figure 18, where in the two-dimensional slices the tumor position is indicated by a 2D cursor, and in the 3D reconstruction a schematic instrument shows the area of the larynx compressed by the tumor.
The software package used for imaging analysis removed the skin tissue and indicates even more visible through a schematic instrument the area where the tumor compresses the larynx (see Figure 19).
3 Conclusions

3.1 General conclusions

Together with laryngeal cancer, hypopharyngeal cancer represents one of the most common neoplastic pathologies in the ENT sphere.

In this thesis, we performed a clinical and statistical study of the hypopharyngeal cancer, on a sample of 225 patients admitted to the ENT clinic of the Clinical Emergency County Hospital of Craiova in a five-year period, 2008-2012. In the first part of the work, we synthesized notions of anatomy, physiology and pathophysiology of the hypopharynx and we have brought into question the etiopathogenic factors of the hypopharyngeal cancer, clinical and imaging methods used for diagnosis. The types of treatment (surgical and oncology) were also briefly presented in that part.

In the second part, we analyzed statistically the sample of patients, depending on the various parameters, and we correlated the statistical results with clinical aspects. At the beginning of this part, we briefly defined the statistical terms and mathematical instruments of the statistical analysis that we used in the text. In the end of the work, we presented two clinical cases studies, in which an important role had modern software tools for imaging analysis and 3D reconstruction based on computed tomography.

The following general conclusions are drawn:

- As in the medical literature, we noted the predominance of the male sex cases in the hypopharyngeal cancer (96%);
- In the case of the studied sample, the average age was in the range of 55-60 years, even if the medical literature indicates an average over 60 years. As a peculiarity of the study...
of various statistical correlations, we discovered in Mehedinți County an average age, 61 years, higher than in the other counties;

- The predominant localization of the tumor was the pharyngolaryngeal one (82%);
- The predominant stage of the tumor was IV (85%).
- The adenopathy was present in 65% of the cases.
- The predominant anatomopathological diagnosis was the poorly differentiated squamous carcinoma (82%).
- The advanced tumor staging of the majority of the patients lead to a small percentage of radical surgical treatment, only 16% of cases. The radical surgical treatment consisted in total laryngectomy with partial pharyngectomy;
- As in the medical literature, the main etiological factors involved in triggering the hypopharyngeal cancer were represented by tobacco and alcohol consumption.

3.2 Original contributions

The main contributions added by this thesis are:

- The update of the information from medical literature on diagnosis and therapeutical methods in hypopharyngeal carcinoma;
- Clinical and statistical aspects relevant to this type of oncology pathology in Oltenia area;
- The therapeutical conduct applied in the ENT Clinic from Craiova presented in a retrospective, descriptive, analytical study in the period 2008-2012 on a selected sample of 225 patients;

In addition to the clinical and statistical study, an original and specific part of the thesis is formed by an imaging study on the usefulness and value of the software 3D imaging reconstruction techniques based on the computed tomography in the indication of the type of the surgical and resection intervention with cancer safety margins and ganglion evidation. For an extension of the thesis and for future research subjects, we could approach the association of CT 3D imaging reconstruction with MRI, PET-CT sources (an area known as image fusion in medical software application), with the biopsy examination + IHC, with the global volumetric evaluation of the tumor and cervical and mediastinal ganglions.
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