

Morphology and morphopathology of hypopharyngo-esophageal cancer

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Abstract

Cervical esophageal cancer and hypopharyngeal cancer represent a major diagnostic issue in early stages, considering the fact that the implication of both cervical esophageal and hypopharyngeal cancers shows a poor prognostic from the very beginning. Positive diagnosis can only be made after histopathological analysis and immunohistochemical analysis in addition. The biptic material is sampled by rigid endoscopy this being the only viable method of assessing data on the tumor prior to the surgery. As much as 95% of tumors located at this site are epidermoid carcinomas with different staging and characteristics, other types of tumors being adenocarcinomas, lymphomas, etc. Several risk factors influence the biology of this site thus inflicting both cellular and molecular modifications that are the origin of cancer development.

Keywords: cancer, cervical esophagus, hypopharynx, carcinoma, risk factors.

Introduction

Modern pathology includes, without making any exception over head and neck organs, cancer in the region of the hypopharynx and cervical esophagus. Because of the implications of the pathology on the neck organs, the functions that are impaired and quality of life of the patient, this pathology is considered to be of outmost importance.

The exposure to different carcinogens for the epithelium of the hypopharynx acts like a trigger for malignant disease. Smoking and alcohol are the most incriminated risk factors for the development of the cervical esophageal cancer and hypopharyngeal cancer. The risk increases by a factor of 5–10 when the two risk factors are combined. This pathology occurs more often in men (70–90%), coming from rural locations (60%). The age category that is most affected by this pathology is 50–70-year-old.

Cervical esophageal cancer and hypopharyngeal cancer represent a major diagnostic issue in early stages considering the fact that the implication of both cervical esophageal and hypopharyngeal cancers show a poor prognostic from the very beginning. 3–10% from the esophageal carcinomas invades the cervical part of the esophagus. The anatomy, treatment and prognosis of the cervical esophagus cancer are intermediary, among the hypopharyngeal and esophageal neoplasms. Hypopharyngeal and cervical esophageal cancer represents, in majority of the cases, an aggressive spinocellular

carcinoma, with a high rate of metastases, growing locally or in a distant focus, being found differentiated forms of carcinoma some 54% being well differentiated infiltrant spinocellular carcinomas, 28% moderate differentiated carcinomas and the rest of 18% being poorly differentiated carcinomas.

The risk factors for the junction neoplasia are the same as in the hypopharyngeal neoplasia: alcohol (80%), tobacco (65%), food habits, Plummer–Vinson syndrome, heredocollateral antecedents. It has been noticed that a low age of apparition of hypopharyngeal and cervical esophagus neoplasia in patients with family history of neoplasia. There is no clear link between lifestyle and hypopharyngeal and cervical esophagus neoplasia. Malignant degeneration is found in pharyngoesophageal diverticulum, corrosive esophagitis, Patterson–Kelly syndrome pathological conditions. The mouth of the esophagus can be invaded by a descendent growing hypopharyngeal cancer (piriform sinus, post-cricoid region, lateral or posterior walls), seldom by local extension (cricoid chondrosarcoma) or by ascending cervical esophagus cancer. Primitive neoplasias that are localized at the pharyngo-esophageal junction are seldom fast diagnosed because the mouth of the esophagus is hard to visualize while attempting indirect laryngoscopy. We have to take into consideration the multiple neoplasia syndrome because the junction neoplasia is frequently associated with other level neoplasia.

☞ Morphopathology of hypopharynx and cervical esophageal cancer

Cervical esophageal cancer and hypopharyngeal cancer is a plurimorph disease in terms of morphopathology with several histological forms [1–3]. There have been a series of classifications that tried to group the modifications involving the hypopharynx and the cervical esophagus. In 2005, at IARC, in Lyon, France, *The World Health Organization* adopted an improved classification on the neoplasia regarding the head and neck region published in the form of the “Blue Book” (Table 1).

Table 1 – 2005 WHO Classification of the neoplasia in the head and neck region

WHO Classification 2005	Squamous intraepithelial neoplasia (SIN)	Ljubljana Classification Squamous intraepithelial lesions (SIL)
<i>Squamous cell hyperplasia</i>		Squamous cell (simple) hyperplasia
<i>Mild dysplasia</i>	SIN 1	Basal / parabasal cell hyperplasia
<i>Moderate dysplasia</i>	SIN 2	Atypical hyperplasia
<i>Severe dysplasia</i>	SIN 3	Atypical hyperplasia
<i>Carcinoma in situ</i>	SIN 3	Carcinoma <i>in situ</i>

Different forms of carcinomas occur in the cervical esophageal and hypopharyngeal lesions influencing the prognosis, treatment and follow-up.

Squamous cell carcinoma

Squamous cell carcinoma of the upper aerodigestive tract is frequent in men in direct correlation with the consumption of alcohol and tobacco, both men and women [4]. The characteristic squamous differentiation of epidermoid carcinoma is encountered in all the regions of the hypopharynx more frequent in the piriform sinus, posterior hypopharyngeal wall and post-cricoid region. In regards to histopathology, we can observe the squamous differentiation of the hypopharyngo-esophageal epithelium with the impairment of the basal lamina and the underlying structures along with stromal reaction, angiolymphatic and perineural spread (Figure 1).

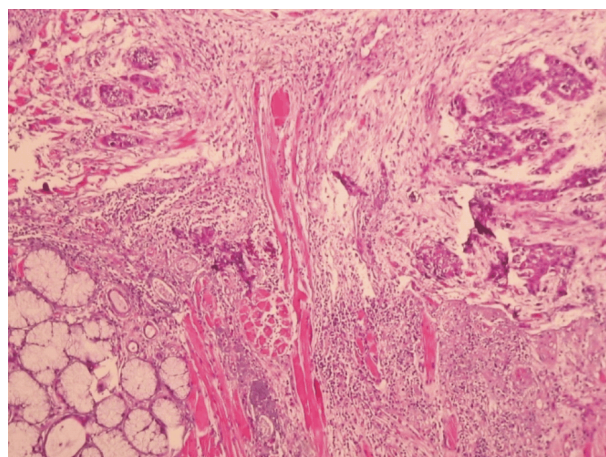


Figure 1 – Well-differentiated spinocellular carcinoma in the piriform sinus (HE stain, ob. 10×).

Wart-like carcinoma

Wart-like carcinoma (Akerman's tumor) is a well-differentiated form of spinocellular carcinoma that can be encountered especially in the mouth or larynx and seldom found in the hypopharynx or cervical esophagus. It has a slow development that implies local infiltration and low risk of metastasis (Figure 2).

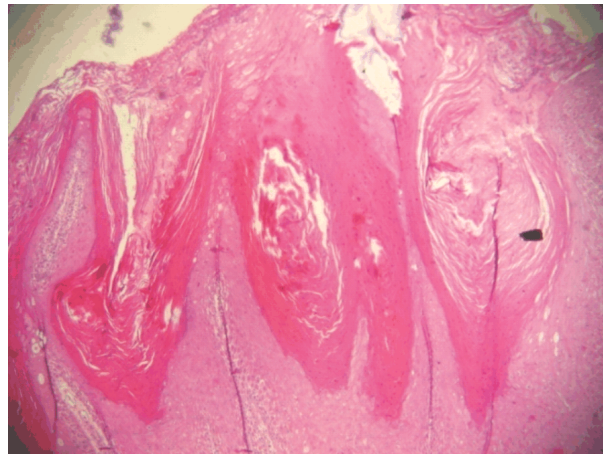


Figure 2 – Wart-like carcinoma. Pharyngo-esophageal junction (HE stain, ob. 4×).

Basal carcinoma

Basal carcinoma (adenoid cyst-like carcinoma) has a predilection for the hypopharynx and the supraglottic part of larynx, but it can be also found in the cervical esophagus. In terms of histopathology there can be observed of cellular aggregation with hyperchromatic nuclei and basophilic cytoplasm separated by gland-like spaces and necrosis areas. This type of carcinoma has an increased rate of apoptosis.

Spindle cell carcinoma

Spindle cell carcinoma is a biphasic tumor consisting in an *in situ* or an invasive squamous cell carcinoma and a malignant component with mesenchymal spindle cells of epithelial origin.

Adenoid carcinoma with squamous cells

Adenoid carcinoma with squamous cells is a histological variant of the epidermoid carcinoma characterized by tumoral cell acanthosis with the formation of pseudolumens thus having a false aspect of glandular differentiation.

Lymphoepithelial carcinoma

Lymphoepithelial carcinoma counts for as much as 0.5% of malignant tumors in the hypopharynx and trachea [5].

Adenosquamous carcinoma

Adenosquamous carcinoma, with an epithelial origin, is much more aggressive than the epidermoid carcinoma having a rate of more than 75% regional lymph node spread and 25% distant site metastasis, with a 5-year survival rate of 15 to 25% [1].

Adenocarcinoma

Adenocarcinoma is an epithelial malignant tumor with glandular differentiation that is usually located in the lower third of the esophagus. In terms of histological aspect, adenocarcinoma is a form derived from Barrett esophagus and the epithelium can be both papillary and tubular. Its differentiation can lead to the formation of endocrine cells, Paneth cells, mucous cells and squamous epithelium (Figure 3) [6–8].

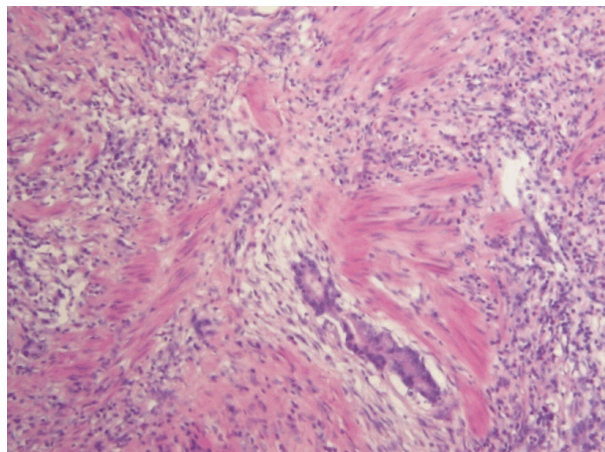


Figure 3 – Adenocarcinoma with muscle layer infiltration. Lateral pharynx wall (HE stain, ob. 10×).

Our research on a group of 47 patients showed the predominance of the spinocellular carcinoma in the cervical esophageal cancer and hypopharyngeal cancer (Table 2).

Table 2 – Histological findings in personal research study group

Histological type	Total (47 patients)	
	No. of cases	%
Spinocellular carcinoma	44	94
Wart-like carcinoma	1	2
Rhabdomyosarcoma	1	2
Adenocarcinoma	1	2

⚡ Morphopathogenesis

Tumoral growth, after carcinogenic exposure, produces molecular alterations that affect cellular functions and favors tumoral cell development. The first to occur is the increase of cellular proliferation. Weinberg demonstrated that this process occurs by the activation of Ras-kinase by mutation or the activation of growth factors receptors. To this process adds the increase of cellular proliferation, increase in the lifespan of the cell and the decrease of the apoptosis.

Viral oncogenes are responsible for the inhibition of the mechanisms involved in the apoptosis process. Suppressor genes, such as the p53 gene, have an important role in the apoptosis and the uncontrollable growth processes [9, 10].

The development of the spinocellular neoplasia in the hypopharynx consists in prior cellular modifications due to repeated injuries. The result is the hyperplasia. Irreversible genetic mutations lead to the appearance of dysplasia or *in situ* carcinoma (ISC), premalignant lesions. The appearance of keratosis is clinically called

leukoplasmia. The inflammation process that is present in premalignant lesions is responsible for the decrease of local blood flow and the proliferation of fibrous stroma, thus resulting in erythroplasia [11, 12].

Histological alterations are always associated with molecular modifications. According to Rubin Grandis *J et al.*, the early phenomena in as much as 90% of the cases of carcinogenesis is the over expression EGFR and TGF α receptors. Patients with high levels of these factors have a decrease in survival rates [13, 14].

Early activation of the telomerase with an increase of its activity is common for the morphopathogenesis of the squamous cell carcinoma of head and neck. Normal appearing mucosa lacks telomerase [15, 16].

Telomerase activity has been correlated with lymphatic spread in patients with esophageal cancer [17, 18]. Inhibiting the activity of the telomerase can increase the chemosensitivity of the tumors and in patients with esophageal cancer, it can be used as an indicator for chemotherapeutic response [19, 20]. There are evidence that in patients with squamous cell carcinoma of the hypopharynx and cervical esophagus occur the inhibition of the suppressor genes and the activation of oncogenes. P16 protein that is coded by 9p21 chromosome is seldom deactivated thus appearing cellular proliferation. An increase in the activity of the p53 gene, coded by 17p13 chromosome has the result of decreased apoptosis and cellular repair [21].

Tumoral growth is associated with the dissolution of the basal membrane and the extracellular matrix, detaching and migration of cells in the submucosal layer. Tumoral growth to a volume that would affect the surrounding tissue requires an increase in the oxygen and nutrient intake, with the formation of new blood vessels [22].

Neoangiogenesis is associated with an increase in inflammatory cells and rapid tumoral growth, metastasis and thus a poor prognosis. The invasion of the lymph and blood vessels followed by tumoral cell migration are necessary for tumoral spread.

The proliferation of fibrous stroma is concurrent with the angiogenesis and peritumoral inflammation. Squamous cell carcinoma leads to the proliferation of the fibroblasts, which in exchange produce factors and substances that stimulate tumoral growth.

Recent studies show the role of the hepatocyte growth factor HGF in the progression of the hypopharynx growth. HGF is involved in both physiological and pathological processes such as embryogenesis, organ regeneration, inflammation and tumoral invasion. Kim CH *et al.* realized several immunohistochemical studies on 40 samples of normal and tumoral infiltrated mucosa using HGF and c-Met antibodies and they have demonstrated the implication of the HGF and c-Met in lymphatic spread. E-cadherin plays an important role in intercellular adhesion and according to Kim CH *et al.* HGF can modulate E-cadherin expression and intracellular location in hypopharynx cancer patients. These modifications can influence overall prognosis of hypopharynx cancer [23, 24].

The identification of growth factors, cytokines and other molecules that contribute to the pathogenesis of squamous cell carcinoma in the head and neck area has

simplified the description of the activation mechanisms and possible backdoors for molecular therapies. COX-2 is known to be an important factor in the genesis of tumors that inhibits apoptosis, increase in angiogenesis and invasivity, modulating inflammation and immunosuppression and the conversion of pro-carcinogens into carcinogens.

According to Okawa T *et al.* (2005), the heparinase is involved in tumoral angiogenesis mediated by COX-2 in case of esophageal cancer [25]. Spinocellular carcinoma cells of the hypopharynx to which NF-kB and STAT3 have been blocked using genetic methods have an increased degree of cellular death and tumoral inhibition. Molecular inhibitors for trigger signal that activate NF-kB, AP1 and STAT3 are developed as potential therapeutic agents in the hypopharynx and cervical esophageal cancers.

Mutant p53 genes detection in the surgical safety margins of resection has been considered a prediction factor for infiltrated margins and future recurrence sites. Over expression of the telomerase and mutant p53 detected in tissue biopsies as well as those from saliva, show the possibility for screening in head and neck neoplasia [26, 27]. The identification of the over-expression of proteins, such as cytokines and angiogenesis factors, in blood samples can be used as a prediction factor for recurrence development [28–30].

☞ Tumoral grading

Tumoral grading in the epidermoid cancer of the hypopharynx and esophagus is in direct correlation to the mitotic activity, nucleus alterations and differentiation status. Well-differentiated tumors have a similar cytological and histological aspect as normal esophageal epithelium that means an important percentage of squamo-keratinised large cells and few basal-like little cells located at the periphery of the tumor.

Poor differentiated tumors have a high level of basal-like cells with lots of mitosis. Moderate differentiated tumors have an intermediate structure between poor and well differentiate carcinoma. Undifferentiated tumors have increased number of mitosis and necrosis with a delayed inflammatory response. Most adenocarcinomas from Barrett mucosa are well and moderate differentiated tumors. Most undifferentiated carcinomas operated on in our clinic have been undifferentiated ones. By using two study groups in our research, we revealed the predominance of the well-differentiated spinocellular carcinoma in the esophageal and hypopharynx lesions (Table 3).

Table 3 – Spinocellular carcinoma grading. Personal research data

Spinocellular carcinoma grading	Total		Study Group I		Study Group II	
	No.	%	No.	%	No.	%
Well differentiated (G1)	24	54	15	60	9	48
Moderate differentiated (G2)	13	28	6	24	7	36
Poor differentiated (G3)	7	18	4	16	3	16
Total	44	100	25	100	19	100

☞ Tumoral spread

Hypopharyngeal and cervical cancer cancers tend to spread by local extension in the primer site, lymphatic system and blood stream. Considering late diagnosis up to 30% of cancers have distant site metastasis. Detecting the site of origin and the way of spreading is essential for the management of this type of tumors.

Local extension

Local extension to the hypopharynx and the cervical esophagus is produced by the initial tumor, which, in most cases, is located in the piriform sinus (86% according to Kirchner JA, 1975). Posterior hypopharyngeal wall and the post-cricoid region come second and third (10%, respectively 5% according to Kirchner JA, 1975, and Carpenter RJ 3rd *et al.*, 1976). Exception to this order is represented by the northern countries where post-cricoid tumors are the most prevalent as pointed out by a study performed by Saleh EM *et al.* in Egypt [4, 26, 27].

Usually, hypopharyngeal tumors invade the upper esophageal gorge and the cervical esophagus by direct extension. The pharyngo-esophageal junction can also be invaded by an upgoing tumor parted from the cervical esophagus. Submucosal spread is frequent thus, although resection margins appear clean, usually tumoral invaded [31, 32].

Ho CM *et al.* described three classes of submucosal spread:

- Type I: macroscopically visible submucosal spread with mucosal lifting;
- Type II: submucosal spread only visible as histological finding;
- Type III: skip lesions at distant tumoral site [11].

“Satellite” tumors appear at distant sites from the original tumor because of tumoral microembols via lymph vessels located in the submucosal layer. According to Wei WI *et al.*, resection margins for the hypo-pharyngeal cancer are 3 cm inferiorly, 2 cm sideways, 1.5 cm superiorly with an increase of 1 cm in irradiated patients [12, 33, 34].

The hypopharynx and the cervical esophagus can present multiple synchronous or metachronous tumors. Synchronous tumors, away located, are diagnosed in the same time as the original tumor or as far as six months. If this time gap is prolonged to more than six months, they are called metachronous tumors. Multiple tumors of the aero-digestive tract have an incidence of as much as 9%.

Direct spread

The muscular layer of the hypopharynx has minimal resistance to the neoplastic invasion, thus being impossible to appreciate clinically. In correlation to the origin, the direct spread has different patterns.

In one study conducted by Oscar Lambert Center on 652 patients with hypopharyngeal cancer it has been found that the cervical esophagus is invaded by post-cricoid tumors (52%), posterior wall of the hypopharynx (36%) and piriform sinus (20%) [33–35].

The cervical esophageal tumors invade nearby

structures after having over-fulfilled the tunica adventitia: trachea, great cervical vessels, thyroid gland, recurrent nerves, mediastinal tissue, prevertebral longitudinal ligament, thoracic duct and lung tissue.

Lymphatic spread

Lymphatic ganglia spread occurs in more than 75% of hypopharyngo-esophageal cancer patients at the moment of clinical diagnostic or imagistic analysis. As much as 10% of patients have bilateral ganglia growth. There are six different sites of lymphatic ganglia in the cervical region:

- Level I: submental (IA), submandibular (IB) lymph nodes;
- Level II: upper jugular lymph nodes;
- Level III: middle jugular lymph nodes;
- Level IV: lower jugular lymph nodes;
- Level V: spinal lymph nodes (VA), transverse cervical and supraclavicular lymph nodes (VB);
- Level VI: median region lymph nodes.

Latero-cervical lymph nodes are relatively easy to detect by palpation but postpharyngeal, paratracheal and upper mediastinal lymph nodes require CT scan or MRI analysis [36, 37]. Contralateral lymph node invasion is as high as 30%. In one study performed by Buckley JG *et al.* (2000) on 100 patients with N0 hypopharynx cancer it was shown that ipsilateral lymph node invasion is 36% and contralateral lymph node invasion is 27% [38].

Lymph node spread was investigated in Oscar Lambert Center and revealed a high frequency of lymph node spreading in the ipsilateral II and III levels and contralateral II level (Table 4).

Table 4 – Lymph node site invasion

Lymph node	Level					
	I	II	III	IV	V	VI
<i>Ipsilateral</i>	3%	49%	38%	14%	4%	–
<i>Contralateral</i>	–	6%	3%	3%	1%	–

“Skip metastasis” is considered to appear when level IV lymph nodes are invaded yet level II and III lymph nodes are still clear. Contralateral metastasis appear late in 9% of the cases of ipsilateral neck dissection.

Lymphatic drainage for the cervical esophagus is done both upwards in the cervical lymph nodes and downwards in the upper mediastinal lymph nodes (Tanabe G *et al.*, 1986) or lymph nodes around the stomach (Akiyama H *et al.*, 1981) [36, 38, 39].

Distant site lymphatic spread

Distant site lymphatic metastasis is frequently encountered in the evolution of the hypopharynx cancer detected after autopsy in as much as 50% of the cases. Distant sites of metastasis are lung, liver, bones and brain. In regards to late diagnosis of cervical esophageal cancer, visceral metastasis occurs in 25–30% of all cases. Metastasis is influenced by the grade of differentiation of the carcinoma, undifferentiated ones having a double risk rate than well-differentiated ones. The esophageal cancer can also have metastasis in ovaries, kidneys and suprarenal glands (Figure 4).

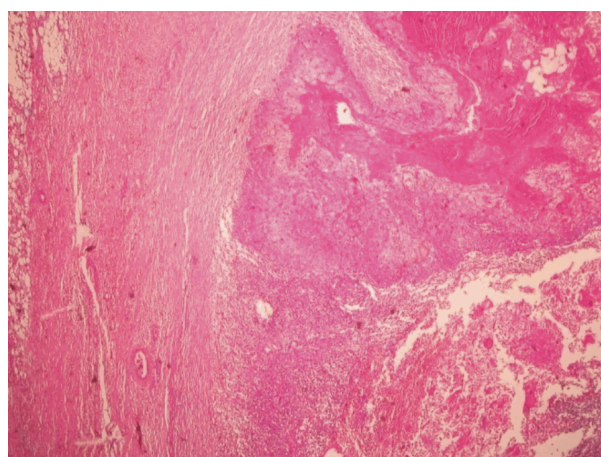


Figure 4 – Lymph node metastasis from moderate differentiated carcinoma. Upper jugular lymph node (HE stain, ob. 10×).

Conclusions and Future Perspectives

Despite modern methods and techniques of diagnose and staging, different types of surgical excision and reconstructive techniques, development in the radiotherapy and chemotherapy protocols there is still a poor prognostic for hypopharyngeal and cervical esophagus cancer. Surgical efforts can be considered to be palliative from the very beginning considering survival rates at three and five years; therefore, our main goal is to improve the quality of life for these oncological patients. The best medical approach is dictated by different sets of factors that include general status of the patient, local and systemic implications, type of neoplasia, tumor grading, histological findings, medical resources and last but not least the acceptance of illness by the patient and his approval for medical attention.

After further analysis of the 47 patients, it shows that 89% of the patients of the first study group and all the patients of study Group II (100%) have a histological pattern of spinocellular carcinoma. Study Group I revealed the existence of three special cases of patients that required further immunohistochemical analysis after which rare tumors have been discovered at the pharyngo-esophageal junction: wart-like carcinoma (Akerman's tumor), rhabdomyosarcoma, adenocarcinoma [40, 41].

Acknowledgments

This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/89/1.5/S/64109.

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Received: July 27th, 2011

Accepted: May 30th, 2012