

## MINIREVIEW

# DIAGNOSTIC ASPECTS OF THE OESOPHAGEAL CERVICAL CANCER

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### ABSTRACT

Oesophageal cancer is the fourth most frequent cancer of the digestive tube, following gastric, colon and rectal cancer. The oesophageal cervical cancer has a growing incidence, and in 3-5% of cases it is associated with another cancer which is part of Ears-Nose-Throat (ENT) medicine. Generally, oesophageal cancer has a reserved prognosis. The cancer of the superior part of the oesophagus has a bad prognosis due to a late diagnosis. Therefore, an early, correct and complete diagnosis might improve its generally reserved prognosis.

**Key words:** cervical oesophagus, malignant tumors, early diagnosis.

### RÉSUMÉ

Aspects diagnostiques du cancer de l'oesophage cervical

Le cancer de l'oesophage est le 4ème cancer le plus fréquent du tube digestif, après le cancer de l'estomac, du côlon et du rectum. Le cancer de l'oesophage cervical a également une incidence ascendante et dans 3-5% des cas, il existe en association avec un autre cancer dans la sphère ORL. Le pronostic du cancer de l'oesophage est d'habitude réservé, et celui localisé dans l'oesophage supérieur est généralement sombre en raison d'un diagnostic tardif et de quelques possibilités thérapeutiques limitées. Par conséquent, tous les efforts doivent être faits pour un diagnostic précoce, correct et complet afin d'améliorer ces résultats généralement insatisfaisants.

**Mots-clés:** oesophage cervical, tumeurs malignes, diagnostic précoce.

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## INTRODUCTION

The oesophagus is a musculo-membranous duct which connects the hypopharynx to the stomach. With a length varying between 25 to 30 cm, it crosses the cervical region, the posterior mediastinum and the superior abdominal region<sup>1</sup>. The superior limit corresponds to the projection C6-C7 vertebra and the inferior one to the T11 vertebra, behind the chondrocostal articulation<sup>2</sup>. The oesophagus presents 3 physiological strictures: cricoid, aortic bronchus, diaphragmatic. The oesophagus consists of 3 segments: cervical, thoracic and abdominal<sup>3</sup>.

The cervical oesophagus corresponds to the infrahyoid region, situated between the inferior margin of the cricoid cartilage and the horizontal level which crosses the superior margin of the manubrium sterni. With a length of 5-6 cm, it presents a downward path on the median line, easily deviated to the left<sup>1</sup>.

Cervical oesophageal neoplasms represent 10-20% of the total oesophagus cancers<sup>4</sup>. These appear with high frequency in males, aged between 45-70 years old. The chronic inflammation, produced by the gastro-oesophageal reflux, post-caustic ingestion injuries, traumas or high dosed mediastinum radiotherapy, can cause cancer<sup>5</sup>. A series of mutations of the enzymes implicated in alcohol metabolism has been correlated with the appearance of neoplasms of the superior digestive tract<sup>4</sup>. Long time exposure to the polycyclic aromatic hydrocarbons has been associated with a high risk of oesophageal cancer<sup>6</sup>.

From a geographical point of view, most cases are found in Iran, Mongolia, areas within central Asia, North of China, South Africa, where factors such as environment and nutrition seem to have an important role in determining these neoplasms<sup>7</sup>. Numerous studies have proven a series of associations between HPV infection and the cervical oesophagus neoplasm. More than 10% of oesophageal neoplasms have presented HPV-16 and HPV-18 infections<sup>8</sup>.

The most frequent type of neoplasm, commonly located in the cervical part, is represented by the epidermoid carcinoma<sup>9</sup>. Other histological types, with lower frequency, include: adenocarcinomas, lymphomas, leiomyosarcomas, liposarcomas, carcinoids and peripheral neuroectodermal tumors, metastasis. Macroscopically, oesophageal cancer can be infiltrative, vegetative and ulcerated. In general practice they may have a mixed aspect, such as ulcero-vegetative, infiltro-proliferating, etc<sup>2</sup>. Positive diagnosis of cervical oesophageal cancer consists in a detailed history, clinical examination and paraclinical investigations.

Clinical presentation is usually dominated by dysphagia, thoracic pain, sialorrhea, regurgitation and can be associated with halitosis, weight loss,

dysphonia, eructation, hiccups, bleeding, cardiorespiratory disorders, etc<sup>2</sup>. The main symptom is progressive dysphagia, characterized by the difficulty of swallowing, commonly for solids. Its appearance indicates an obstruction of the oesophageal lumen of over 40%<sup>10</sup>. It has an insidious onset and a slow evolution.

Nonspecific symptomatology requires a rigorous differential diagnosis with catarrhal oesophagitis, stenosis of various aetiologies, varicose oesophages, oesophagus paralysis, fibro stenosis, pseudo tumors tuberculosis, benign tumours<sup>1</sup>.

Paraclinical protocol for cervical oesophagus tumors includes a simple radiography or an esophagoscopy with barium meal, which can indicate the location of the tumor, extensions, macroscopic type, etc. The tumor may present as an irregular, incomplete image, with circumscribed atony and the absence of peristalsis. As the tumor mass progresses, the image becomes more conclusive, with the possibility of a more accurate localization and macroscopic characteristics.

CT scan is a more precise method of diagnosis, which offers detailed information regarding tumor extension, while magnetic resonance imaging (MRI) provides detailed data, including tumor invasion to adjacent structures and cervical lymphatic nodes implication.

Flexible or rigid, esophagoscopy shows direct image of the tumor, macroscopic form, and offers the possibility of collecting bioptic fragments. The histopathological exam represents the investigation of choice for diagnosis of certainty, necessary for neoplasm staging. An additional method of examination is immunohistochemistry examination, that can present a series of intrinsic characteristics of the tumor (the presence of the receptors of the specific cellular anomaly), used for specific oncological treatments. The molecular markers, found in the cervical oesophagus cancer, are represented by EGFR and HER2 (oncogene) and p53 and APC (suppressor tumor genes).

The endoscopic ultrasound is an investigation which combines endoscopy with ultrasound, allowing the visualization of the digestive walls and surrounding structures. It is considered the best technique for the evaluation of depth infiltration of the tumor and degree of local extension. If needed, it can be used associated with Doppler ultrasound, for the study of the blood flow and also for tissue sampling.

The narrow band imaging (NBI) represents a modern method of examination which improves diagnostic accuracy by using some filters for the wave length corresponding to the colors blue, green and red<sup>11</sup>.

Chromatography is an adjuvant method of the endoscopy, which offers a better image of the mucus lesions (margins, area and color). These are based on the principle of some morpho-functional changes due to the absorption of different dyes. In order to illustrate the multiple localizations or mucosa metastasis, a blue staining of toluidine is used<sup>12</sup>.

PET-CT combines two types of scanning, that shows the results in one image which contains detailed information regarding the tumor invasion in the surrounding structures, in the lymphatic nodes or identifies the metastases<sup>13</sup>. A disadvantage of this investigation is the difficulty of differentiation between the neoplastic lesion and the inflammatory one. Approximately 50% of oesophageal cancers present signs of invasion of the tracheobronchial tract. Bronchoscopy is made for the identification of possible pulmonary metastasis or tracheal extensions<sup>14</sup>.

The stage on the moment of diagnosis allows the elaboration of a personalized treatment plan for each patient. Staging systems have evolved throughout the years and have perfected constantly the diagnosis. The most frequently used system of staging is the TNM, which uses 3 criteria to describe the stage of the illness: presence of the primary tumor, metastatic invasion of regional lymph nodes and presence or absence of remote metastasis.

Oesophageal cancer represents a neoplasia with a sombre prognosis. The average survival rate does not surpass 12 months, and less than 10% of the patients are still alive after 5 years. Most of the cervical oesophageal neoplasms are found in advanced stages at the time of the diagnosis. Over 55% of them are diagnosed in stage III or IV TNM<sup>11</sup>.

## **DISCUSSION**

Oesophageal neoplasms represent a high percent of all oesophageal tumors, determining over 40% of dysphagia<sup>4</sup>. The probability of appearance of cancer at the level of cervical oesophagus is based on most studies, between 10-20% of the total oesophageal malignancies, with predilection for the male gender<sup>4</sup>. Numerous risk factors have been identified, involved in the appearance of oesophageal neoplasms. The contributing factors are represented by malignant heredity, chronic oesophageal inflammation, cigarette smoke, hot drinks and alcohol, old post-traumatic scars, tuberculosis, syphilis, etc.

Most frequently, cervical oesophageal neoplasm remains asymptomatic until the appearance of the dysphagia, when over 50% of the oesophageal lumen is compromised<sup>2</sup>. The nonspecific symptoms at onset determine difficulties of diagnosis and treatment. Clinical onset is represented by intermittent

dysphagia, which progressively evolves, associated with thoracic or retrosternal pain, eructation and rapid weight loss. The more precocious postprandial regurgitations are, the tumor has a higher localization. Due to nonspecific and unpredictable symptoms, intense monitoring of the patients with known disorders like Barret oesophagus, post-caustic stenosis and Plummer-Vinson syndrome is required.

Progression of illness determines the installment of a progressive oesophageal syndrome, with the sensation of foreign body in the throat, with alteration of general state. Without correct treatment, the evolution of cervical oesophagus cancer is unfavorable, characterized by cachexia and dehydration due to lack of appropriate nutrients, invasions and fistulas in the surrounding organs. It is required to take into consideration that some complications may appear through the extension to the trachea or by compressing the recurring nerves. The supraclavicular and the jugular carotid lymphatic nodes need to be carefully observed, because the precocious metastasis. Appearance of pain indicates the presence of some complications through the extension of the tumor outside the oesophagus.

Differential diagnosis includes multiple oesophageal afflictions, the intrinsic dysphagia (oesophageal) from the extrinsic (through compression). The dysphagia appears through compression given by the thyroid tumours, which invades the oesophagus, vertebral osteophytes, tracheal lesions, etc. Intrinsic stenosis could be caused by a number of oesophageal inflammatory mechanisms nonspecific and specific (tuberculosis, syphilis, mycosis and oesophageal diverticulitis), benign oesophageal tumours (leiomyoma, fibroid, papilloma and cyst), foreign oesophageal antigens, scleroderma, Plummer-Vinson syndrome, myasthenia gravis, etc.

The imaging methods offer information with regards to the location of the tumor, the profound invasion and infiltration, as well as dissemination. Ultrasound examination, with or without contrast substance, could be misleading during the onset period. The imaging aspect depends on the anatomic pathology of the tumor. It can highlight filling defects, gaps in vegetative forms and the niche in ulcerated forms. The infiltrating stenosis forms determines the image of the shrinking of the oesophageal lumen, with the appearance of variant forms of the radiological aspect such as „rat's tail“ and „funnel“. Ultrasound allows evaluation of the walls rigidity at the tumors level, the changes of peristalsis and the oesophageal dilation. The evaluation of the oesophageal motility can be achieved through the video fluoroscopy. For the evaluation of the inferior limits of the tumors, the examination is conducted in

Trendelenburg position, which allows the barium reflex to the tumor.

Esophagoscopy is an elective investigation for a more precise diagnosis. This can be achieved with a rigid tube by the ENT doctor or with a flexible tube by the gastroenterology doctor. After this investigation, the injuries are directly appreciated, along with the state of the oesophageal lumen and its walls (immobile, rigid or without normal movements), allowing the bioptic sampling to achieve the histopathological exam and eventually, the immunohistochemistry tests. It also allows process the washing, exfoliating brushing, lavage, with the achievement of the cytological examination, which could show malignant cells in a proportion of almost 90%<sup>1</sup>. The immunohistochemistry analysis of the oesophageal tumor tissue shows an overexpression of oncogene HER2 in 7.7% of cases and of p53 of over 50%<sup>15</sup>.

The overexpression of p53, detected in the analyzed cases through the immunofluorescence, is correlated with the prognosis of the degree of differentiation and the degree of proliferation.

In the situation in which the oesophageal tumor presents extension to the cervical lymphatic nodes, a CT/MRI is required, in order to establish an appropriate therapeutic response.

Over the past years, there has been developed a series of imaging techniques, which uses the properties of the interaction between the light and tissues, in order to increase accuracy of the early neoplasm diagnosis. One of them is represented by the narrow band imaging, which allows the visualization of the oesophageal mucus and that of the microvascular network, extremely useful for the evaluation of the process of neovascularization at a local level. The performance of this investigation could be significantly improved when it is combined with the magnification examination<sup>16</sup>.

The oesophageal cancer's prognosis is generally sombre if it isn't diagnosed precociously. Therefore, the oesophageal echoendoscopy is very important, together with flow cytometry, as it measures modification of the cell's DNA, as well as chromatography and blue staining of toluidine, which detects dysplastic modifications and indicates the location where the biopsy can be performed.

## CONCLUSION

Cervical oesophagus cancer represents a neoplasm with an increasing incidence, which is associated many times with another form of cancer in ENT. In most of the cases, the diagnosis is established in an

advanced stage, sometimes with loco-regional extension or with metastasis.

In order to improve survival rates and prognosis, special attention needs to be given to clinical and paraclinical investigations, which will allow to initiate an early treatment.

## Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article“

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law.“

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