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Multiple Cancers of the Head and Neck

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ABSTRACT

Multiple head and neck cancers are not rare entities and according to studies in the literature, their incidence is increasing. The emergence of multiple cancers is explained by the phenomenon of "field cancerization". Patients with cancer of the upper digestive and respiratory tract develop most often a second malignancy, usually in the upper aero-digestive tract and among them, those with larynx cancer ranks first among patients with multiple cancers. In the literature and in practice, we met rare combination of multiple cancers, associations that appear to be "random", cannot be explained by any of the hypotheses developed: exposure to carcinogens, genetic susceptibility, and immunodeficiency or cancer treatments after index tumor. Follow-up of patients who have had a head and neck cancer and periodic control are important for early detection of multiple cancers.

Keywords: multiple cancers, field cancerization, head and neck cancers

INTRODUCTION

Cancer or neoplastic disease is a group of diseases whose essential characteristic is uncontrolled and anarchic proliferation of a group of cells.

Neoplastic disease can affect any part of the human body; any organ can develop tumors of different histological types. The head is one of the most complex parts of the human body and therefore must be given the greatest importance of tumors that develop in this region. Head and neck cancer includes mucosal and tissues malignant tumors of this region. Popularly are known as malignant tumors between "dura mater and pleura" (1).

Head and neck tumors grow on mucosa of the aero-digestive tract and are the tumors that occur: oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, and salivary glands, thyroid, parathyroid, bone, soft tissue, neural structures -vascular and skin that part of the human body (2,3).

Head and neck cancer is a deadly disease that has been evidenced since the origin of the

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human race and continues to be a challenge for patients, especially for ENT specialists and oncologists, with major health problems that assume this condition (4,5).

Cancer of the head and neck affects approximately 4% of patients with malignant tumors in the United States. In other countries, the disease is much more common, such as in less developed countries, where cancer occurs at a rate of 35-45% (2,6). The development of cancer is influenced by living conditions so that the disease is twice as common in disadvantaged countries compared with developed countries in economic point of view (7).

The true incidence of multiple cancers is not known, but according to recent studies, it appears to be increasing (8).

Annually are diagnosed about 650,000 new cases of head and neck cancers all over the world, with a ratio of 3:1 between men and women (7). Most are in advanced stages (stage III or IV) (4). The number of deaths from this disease is around 350,000 annually. In men, head and neck cancer is the fourth most common cancer, while in women he is ranked of the ninth (7). Combining both sexes, at global level and in the European Union, squamous cell cancer of the head and neck is ranked sixth in incidence after lung cancer, stomach, breast, colon and cervical and seventh place as mortality in the world (1,9,10).

Over 90% of head and neck cancers are squamous cell tumors, most of which are found in the oral cavity and larynx (approximately 60-70%). Other locations are: nasal cavity, pharynx, middle ear, salivary glands, thyroid gland, less soft tissue, bone and cartilage (1,2,6). The other 10% are adenocarcinomas of salivary origin, melanoma, soft tissue tumors and lymphomas (2,5).

One third of patients with head and neck cancer are present in the early stages of disease (stage I or II) and most of them can be cured by surgery and /or radiotherapy. The rest of them come in advanced stages (stage III, IV) with a severe prognosis. Despite modern treatments and latest medical equipment, the progress regarding survival rate for patients with head and neck cancer had not tremendous growth. This is due, on the one hand, the high risk of recurrence in these patients and on the other hand, frequent metastasis and development of a second primary cancer, especially in the respiratory and upper digestive tract. Molecular genetic analysis can differentiate recurrences from second primary tumors (11).

Multiple cancers of the head and neck

Patients who presented during their life a head and neck cancer and who were treated for it, have a high risk to develop multiple cancers. So, a patient may present during his life, two, tree, four or more cancers, completely separated from each other as histopathological type, place of occurrence, evolution and prognostic. Combinations of two primary cancers occur in 3-5% of patients with history of cancer, associations of three cancers appears in 0.5% of cases and the combinations of four malignant tumors occur in 0.3% of patients (11). Most often, second primary tumors following a head and neck cancer, also develops at this level, due to the persistent carcinogenic influence on the mucosa of upper aero-digestive tract, even after termination of exposure to carcinogens factors, due to a genetic instability, chemotherapy and radiotherapy treatments, genetic susceptibility, immune deficiency and prolonged survival after some primary tumors (4,11-15).

First report of synchronous cancers in the same patient belongs to Billroth in 1889, who reported a case of stomach cancer and the second primary cancer in the external ear. He developed three criteria for the diagnosis of multiple cancers: the two tumors should be different from histological point of view, should grow in different places and the two tumors must produce their own metastasis (16,17).

In 1932, Warren and Gates have proposed some criteria for the definition of the second primary cancer: tumors have to be malignant and this have to be histologically confirmed, tumors must be separated from normal tissue, non-neoplastic and it must be eliminated the possibility that the second primary tumor to be the metastasis of the index tumor (17-19).

Hong and colleagues in 1990, based on criteria described by Warren and Gates added other data for defining multiple tumors: the tumors have to be histologically certified as malignant; if they are identical as histological type, it must be an interval of at least three years between the two malignancies and/or be a distance of at least 2 cm of mucosa unchanged between the index tumor and second primary tumor; it has to exclude the possibility that the second tumor to be a metastasis of the index

tumor. Hong and colleagues were concerned in especially with the multiple tumors arising in the lung, they stated that any primary tumor that occurs in the lung presenting as a solitary nodule within three years from the original tumor is considered a second cancer until proven otherwise (16,19,20).

Development of multiple malignant lesions can be explained by the so-called "field cancerization", phenomenon that occurs during aero-digestive tract when mucosa at this level is exposed to the same types of carcinogens, if they act consistently and for a long time (8,21, 22). The term "field cancerization" was first used by Slaughter and Southwick, in early 1953, when they studied cancers of the oral cavity. The authors have not developed a definition, but suggested several criteria to describe the term field cancerization:

(a) Oral cancer develops in multiple areas of precancerous changes.
(b) The tumor is surrounded by abnormal tissue.
(c) Oral cancer is composed of several independent lesions that sometimes join together.
(d) The persistence of abnormal tissue after surgery may explain the occurrence of relapses and multiple cancers.

Organs in which the phenomenon of field cancerization are: squamous cell cancer of the oral cavity, oropharynx and larynx, lung, esophagus, vulva, cervix, colon, breast, bladder and skin (23).

With the discovery of molecular genetic studies, there were two hypotheses to explain these findings: abnormal areas represent independent clones with a unique pattern of genetic damage (tumors are unrelated genetically speaking) and these areas of abnormality are genetically linked and come from a common cell clone (cell transformation followed by daughter cell migration and tumor genetic connection) (24,25). Thus appears the theory of the monoclonal origin beside polyclonal theory. In the monoclonal theory, malignant tumor cells migrate from the primary carcinoma and form foci development potential of secondary carcinoma. Polyclonal theory assumes that secondary independent foci are formed in the mucosa where "field cancerization" is the most severe (25).

It is important to differentiate between recurrence and second primary cancer. Risk of relapse in the first three years after treatment of squamous cell cancer of the upper digestive and respiratory tracts is much greater than the risk of second cancers. After the third year, second primary tumor development is a major cause of morbidity and mortality (26).

Multiple cancers are divided into three types, depending when they appear at patients. Notions of synchronous cancers and metachronous were first introduced by Warren and Gates, in 1932, the concept of simultaneously cancers being more recently (27). So, the tumors can be: simultaneous tumor that develops in parallel with the initial tumor; synchronous tumors, which develop within six months of initial cancer diagnosis and metachronous tumors that occur at least six months initial primary tumor development (13,28).

A second primary tumor can occur at any time of life of patients, with an incidence of 15% for synchronous cancers and about 4% of the metachronous (24).

Routine screening is very important in detecting multiple tumors, which can reveal synchronous tumors in about 9-14% of patients, of which 42-70% are in the head and neck, 5-26% in the lung and 15-43% in the esophagus. Metachronous cancers are found in approximately 10-20% of patients with ENT cancers at a median time of 31-43 months of initial primary tumor detection (29).

The incidence of multiple tumors increases in time, approximately 11-19% of patients developing multiple cancers at 5 years after treatment of the first tumor, the incidence increased to 30% of patients at 10 years after the original tumor (30,31).

The risk of second cancer occurs mainly in patients with early stages of initial tumor due to higher survival rate compared with patients in advanced stages. Also, the risk of second cancer is higher in people younger than 60 years, for the same reasons (32).

The risk of death from second primary cancer in patients with early stage head and neck cancer is greater than the risk of death from the original tumor. The risk of developing second primary cancer increases by 3% per year in patients who have survived a head and neck cancer (1,9,10).

The prognosis of patients with multiple cancers is dark, those with synchronous tumors with a worse prognosis than patients who develop metachronous tumors (28).

Combinations of multiple cancers in ENT area

From the above described, there is a fairly high incidence of multiple cancers in patients with head and neck cancer. These patients may have two or more malignancies, usually all in ENT area.

There were no clear reasons to explain the appearance of multiple cancers in one person. Several hypotheses have been developed: the phenomenon may be due to exposure to the same carcinogens (most commonly accepted hypothesis), may be due to genetic susceptibility or to an immune compromised, may be due to initial treatment performed to treat the index tumor or be a random appearance (33).

For tumors of the upper aero-digestive tract, the most common site of development of the second primary tumor is also the aero-digestive tract.

Patients who develop second primary cancer (the second most common cancer is lung cancer) have a survival rate of 32% at 10 years compared with 77% survival rate that sufferers have one neoplasia (24).

Patients with aggressive cancers, such as lung cancer have a lower survival rate and therefore rarely develop multiple cancers because the patient does not live enough. In addition, other cancers, such as Hodgkin's disease and testicular cancer are associated with a high rate of occurrence of multiple cancers due to higher cure and that patients with these cancers are young (34).

Patients suffering from cancer of the larynx, squamous cell variant are most likely to develop multiple cancers. At these, more than 60% of the second primary tumors develop in aero-digestive tract, usually in the head and neck or lung, less in the esophagus (29,35).

The risk of second cancer in a patient with cancer of the larynx is estimated at 10-24% of cases (29). The incidence of second primary tumors increases linearly in time: 11 to 19% of patients develop second primary tumor within 5 years after treatment, the incidence increased to 30% at 10 years (6).

In about 1% of laryngeal cancers appear synchronous cancers and in 5-10% of cases can be found metachronous. A second primary tumor following a cancer of the larynx develops most frequently in the lungs and of these 10% are synchronous, 30% occur in the first year after initial tumor, 30% in the first 5 years and rest during the first 20 years (36). Most of the times, the second primary cancer follows a supraglottic cancer, more rarely after a cancer of the glottic (three times more frequently in supraglottic cancer than in glottic cancer) (30,31, 36). Patients with supraglottic laryngeal tumors have 14 times greater risk of developing lung cancer than the normal population and three times greater risk of developing a second primary tumor in lung those with glottic cancer (37). Therefore, a patient with laryngeal cancer who presents an isolated pulmonary nodule is considered that this is a second primary cancer and not a metastasis, until certainty histopathological diagnosis (24).

Patients with cancer of the oral cavity have risk of developing second primary cancer aero-digestive tract of 10-35%. So, patients with cancer of the floor of mouth and tongue cancer frequently develop second primary cancer (21). Tonsillar cancer patients also have an increased risk of developing multiple cancers, the risk ranges from 18.6 to 35%. The risk of developing second primary cancer in patients with oropharyngeal cancer ranges from 17-57% (37).

Posterior wall of the pharynx tumors have a high rate of developing multiple tumors. In patients with cancers of the oral cavity and oropharynx, the second most common cancer occurs in the esophagus (24).

The risk of developing a second cancer in patients who have suffered from nasopharyngeal cancer is relatively small (29).

Regarding the risk of developing a second malignancy in patients who have had a cancer of the nasal cavity, it is 15%, of which 40% developed in the head and neck and of these, two thirds of the larynx and pyriform sinus (38).

There have been described cases where the second primary tumor is a tumor of the thyroid gland (35). Papillary thyroid cancer metastasized to lymph nodes is the most common malignancy found incidentally in a patient with head and neck cancer. Regional lymph nodes or radical surgery performed during surgery for head and neck cancers is very important to detect such metastases of thyroid cancer. 0.7% of patients with squamous of carcinoma cell carcinoma of the head and neck have lymphatic metastasis of papillary thyroid carcinoma, even if it is hidden (38).

The second most common malignancies found incidentally is chronic lymphocytic leu-

kemia and nonHodgkin lymphoma (about 0.4% of lymph node removal) (38). The relative risk of developing a second cancer after treatment of nonHodgkin malignant lymphoma is about 10% in the lung, 38% in salivary glands and 10% in the thyroid (39).

In practice, we meet quite frequent cases of association between cancers of the upper digestive and respiratory tracts with skin cancer, mostly basal cell carcinoma, which although is not an aggressive cancer is also a malignant tumor. ❑

CONCLUSIONS

Multiple cancers of the head and neck are not rare entities. In recent years, due to increased life expectancy and high population survival, there is an increase in the number of patients who develop multiple cancers. So it is very important that a patient who has survived to a cancer of the upper digestive and respiratory tracts to be monitored and investigated regularly for early detection of second primary cancers. In patients who have had cancer of the larynx, panendoscopy is very important and mandatory.

Lifestyles, genetic susceptibility, immune deficiencies, cancer treatments for tumor index are several factors incriminated in the occurrence of multiple cancers. Some we can influence, such as smoking and alcohol consumption, others we cannot. So, the whole population has to adopt a life without tobacco and alcohol, not only those who have had cancer.

A patient who suffered a head and neck cancer is exposed to a lifetime risk of developing a second malignancy. ❑

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