ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Head and neck metachronous tumors – clinical, histopathological and immunohistochemical study

ION CRISTIAN MOŢ[1)], MĂRIOARA POENARU[1)], CARMEN AURELIA MOGOANTĂ[2)], ANCA-MARIA ISTRATE-OFIŢERU[3)], IOANA CRISTINA OPRIŞCAN[4)], CRISTIAN ANDREI SARĂU[5)], MARINA DANIELA MĂNESCU[6)], VIORELA ENĂCHESCU[7)], CARMEN ADRIANA DOGARU[7)], CRISTINA POPESCU[8)], RALUCA MORAR[9)], NICOLAE CONSTANTIN BALICA[1)], IOANA DELIA HORHAT[1)]

[1)]*Department of ENT, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*
[2)]*Department of ENT, University of Medicine and Pharmacy of Craiova, Romania*
[3)]*Department of Histology, University of Medicine and Pharmacy of Craiova, Romania*
[4)]*PhD Student, Department of ENT, University of Medicine and Pharmacy of Craiova, Romania*
[5)]*Department of Medical Semiology I, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*
[6)]*Student, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*
[7)]*Department of Family Medicine, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*
[8)]*Department of Anatomy and Embryology, University of Medicine and Pharmacy of Craiova, Romania*
[9)]*PhD Student, Department of ENT, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

Abstract

Multiple primary tumors (MPT) represent an important factor affecting the survival of some patients. They present an incidence of about 0.7–11% of all carcinomas developing in any region of the human body, being either synchronous or metachronous. These tumors raise problems of differential diagnosis, with tumoral relapses and distance metastases; also, they involve problems related to chemotherapy, radiotherapy and surgical treatment. In the present paper, we studied a group of 902 patients diagnosed with head and neck tumors admitted to the Ear, Nose & Throat (ENT) Clinic of the Emergency County Hospital of Timişoara, Romania, and we identified 12 patients with metachronous tumors, representing 1.33% of the hospitalized cases. Of the 12 patients with metachronous tumors, a single case was a woman, the other 11 cases being diagnosed in men. Regarding the age of the patients with metachronous tumors, only a single patient was aged less than 60 years old; most of them (nine patients) were aged between 60 and 69 years old, while two patients were aged over 70 years old. Nine patients were alcohol consumers, while 10 (83.33%) patients were smokers of about 20 cigarettes/day. All the metachronous tumors localized in the head and neck were squamous cell carcinomas. The second primary tumor was identified in the prostate, kidneys, ureter, lungs, salivary gland, thyroid gland, meninges, colon, rectum or skin.

Keywords: metachronous tumors, multiple primary tumors, head and neck cancer, immunohistochemistry.

Introduction

At present, cancer has become a great healthcare problem worldwidely, being the second cause of death after cardiovascular diseases [1]. If in 2008 there were recorded about 8 million deaths all over the world, in 2015 there were recorded about 8.8 million deaths and it is estimated that in 2030 the number of deaths will be of approximately 11 million [2, 3]. As a result of population aging, the number of cancer cases worldwidely increased from 2005 until 2015 by 33%, while the number of deaths increased by 17% [4]. According to some statistical data, in 2015, there were declared about 90.5 million patients with cancer, of which over 69% lived in low and average income countries [5, 6].

Head and neck cancer (HNC), showing cancers localized in the oral cavity, oropharynx and larynx, is the sixth most frequent cancer type all over the world [7, 8]. According to some recent studies, every year approximately 550 000 patients are diagnosed with HNC, with approximately 300 000 deaths [9]. Other studies, more recent, showed that in 2012, worldwidely, HNC had an increasing incidence of 686 000 new cases and 404 000 deaths, every year [10]. Despite highlighting some risk factors and implementation of some measures for fighting these, despite the thorough cellular and molecular biology research and use of modern treatment, the survival rate is quite low in this type of cancer [11].

This relatively low survival rate is explained by the fact that most HNCs are diagnosed in advanced tumoral stages, the tumors presenting a high recurring incidence [12, 13].

Another important factor affecting survival may be the development of various primary tumors in the head and neck, but also in other organs, like synchronous or metachronous tumors.

Multiple primary tumors (MPT) present an incidence of about 0.7–11% of all carcinomas [14, 15]. If the second tumor is diagnosed after more than six months since the first tumor, the latter is called metachronous tumor, and if it is diagnosed earlier than six months since the first diagnosis, it is called synchronous [16, 17]. MPT may develop in any region of the body.

Aim

In this paper, we proposed to study metachronous cancers in a group of patients hospitalized in the Ear, Nose & Throat (ENT) Clinic of Timişoara, Romania, for malignant tumors localized in the head and neck.

Patients, Materials and Methods

The study performed was a retrospective one, investigating patients admitted for various tumors in the head and neck, between 2008–2018, in the ENT Clinic of the Emergency County Hospital of Timişoara, having the purpose of studying metachronous tumors. The study was approved by the Ethics Committee of the Emergency County Hospital of Timişoara.

For the selection of patients with MPT, there were taken into consideration the criteria stated by Warren & Gates, ever since 1932 [18], namely:

- the tumors were confirmed as malignant through histopathological (HP) studies;
- through HP studies there were excluded from the study the patients with metastatic or recurrent tumors, confirmed histopathologically;
- there were excluded the patients with no clear HP confirmation that the second tumor was a metastasis of the first tumor;
- for the tumors occurring in the same organ, they were taken into consideration as metachronous tumors if the HP study highlighted two types of different tumors;
- the tumors were diagnosed clinically and histopathologically after more than six months since the first one, in order to differentiate the multiple synchronous tumors.

The data referring to every patient's age, gender, social environment, clinical and biological aspects, alcohol intake or smoking, the macroscopic aspects of tumors, the development place and the HP diagnosis were taken from the clinical observation sheets and from the HP records.

For clarifying the HP diagnosis and performing the required immunohistochemical (IHC) studies for a differential diagnosis, in every patient there were analyzed the pieces of surgical resection. For the IHC study, we used the following immunomarkers: Ki67 (monoclonal mouse anti-human Ki67, clone MIB-1, 1/50 dilution, Dako), epithelial membrane antigen (EMA) (monoclonal mouse anti-human EMA, clone E29, 1/50 dilution, Dako), p53 (monoclonal mouse anti-human p53 protein, clone DO-7, 1/100 dilution, Dako), pan-cytokeratin (pan-CK) AE1/AE3 (monoclonal mouse anti-human CK, clone AE1/AE3, 1/100 dilution, Dako), CK7 (monoclonal mouse anti-human CK7, clone OV-TL 12/30, 1/50 dilution, Dako), CK20 (monoclonal mouse anti-human CK20, clone Ks20.8, 1/50 dilution, Dako).

Results

Of the 902 patients diagnosed with head and neck tumors hospitalized within the ENT Clinic of the Emergency County Hospital of Timişoara, between January 1, 2008–December 31, 2018, we identified only 12 patients with metachronous tumors, representing 1.33% of the admitted cases. The number and localization of tumors were quite variable. Thus, nine patients had two tumors, a patient had three tumors, another one four and another five tumors. The localization of multiple metachronous tumors was in various organs: one localization in the oral cavity, pharynx or larynx, and the second localization in the prostate, kidneys, ureter, lungs, salivary glands, thyroid gland, meninges, colon, rectum or skin.

The tumor distribution in the head and neck organs was: a tumor was localized in the right inter-maxillary comissure, a tumor on the maxillary apex, a tumor in the palatine tonsil, five tumors in the pharynx and four in the larynx. A single patient had two metachronous tumors localized in the head and neck: one localized in the right vocal chord and the second in the rhinopharynx.

Another frequent localization of primary metachronous tumors was on the skin. Thus, of the 12 patients with MPT, five (41.66%) had the second tumor localized on the skin.

In our study, primary metachronous tumors mainly occurred in men. Of the 12 patients, a single case (8.33%) was identified in a woman, the rest of 11 (91.67%) cases were diagnosed in men. Regarding the age of patients with metachronous tumors, only one patient was aged less than 60 years old; the majority (nine patients, 75%) were aged between 60 and 69 years old, while two patients were aged over 70 years old. Nine of the patients with primary metachronous tumors came from the rural area, while only three patients came from the urban area. A number of nine (75%) patients were alcohol consumers, while 10 (83.33%) patients were smokers of approximately 20 cigarettes/day.

Regarding the clinical stage of tumor development diagnosed in the ENT Clinic of Timişoara, a single case was diagnosed in the first stage, three cases in the second stage, six cases in the third stage and two cases in the fourth stage.

The HP study showed that all the metachronous tumors localized in the head and neck were keratinized squamous cell carcinomas (SCCs). Of these, a single case was considered as being well-differentiated (G1) (Figure 1), eight cases were moderately differentiated carcinomas (G2) (Figure 2) and three carcinomas were poorly differentiated (G3) (Figure 3). The tumoral stroma had various aspects from a lax type stroma to a desmoid type one, rich in fibroblasts and collagen fibers. The tumoral stroma was the setting for a chronic inflammatory infiltrate, with a heterogeneous arrangement, mainly formed of lymphocytes, plasmocytes, macrophages and rare mastocytes. Here, there were also identified numerous angiogenesis vessels, whose density was correlated with the intensity of the inflammatory infiltrate (Figure 4).

The IHC study showed a relatively high tumor Ki67 proliferation index, especially in poorly or moderately differentiated carcinomas (Figure 5), an intense reaction to anti-p53 antibody (Figure 6) and, also, an intense reaction to anti-EMA antibody (Figure 7). The study of CKs showed that tumoral cells were positive to pan-CK AE1/AE3, still the intensity of the reaction increased from the poorly differentiated forms to the well-differentiated ones (Figure 8). In contrast, CK7 and CK20 were negative to all the SCCs (Figures 9 and 10).

Metachronous tumors located in other organs had HP and IHC aspects different from primary tumors located in the head and neck. Here, we present only one metachronous lung tumor, which on HP and IHC examination proved to be a poorly-differentiated SCC (G3) (Figure 11, A–F).

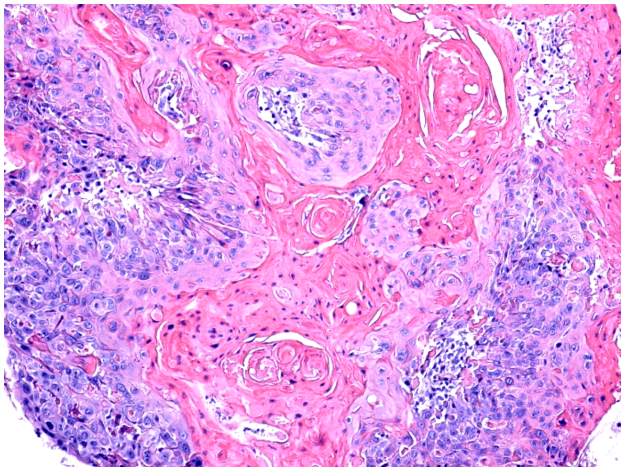

Figure 1 – *Microscopic image of a well-differentiated squamous cell carcinoma with numerous "keratosis pearls" [Hematoxylin–Eosin (HE) staining, ×200].*

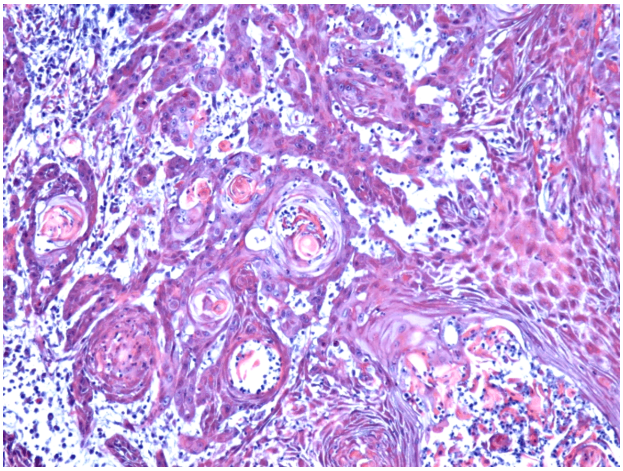

Figure 2 – *Moderately differentiated carcinoma with the tendency of forming "keratosis pearls" (HE staining, ×200).*

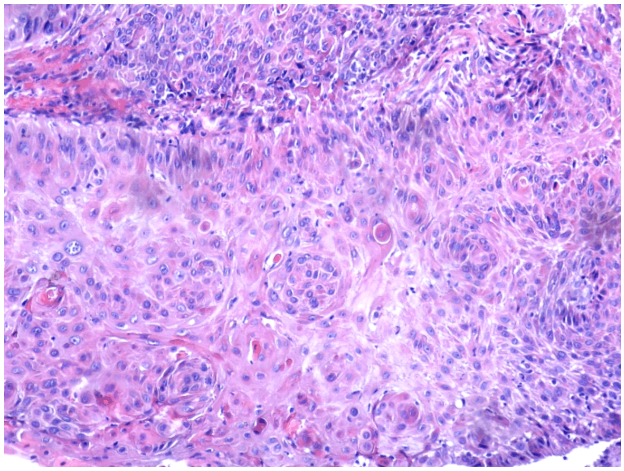

Figure 3 – *Poorly differentiated squamous cell carcinoma made of medium and large size, arranged in islands, nests and rows, with a reduced cytoplasm, with large, hypochromic and pleomorphic nuclei (HE staining, ×200).*

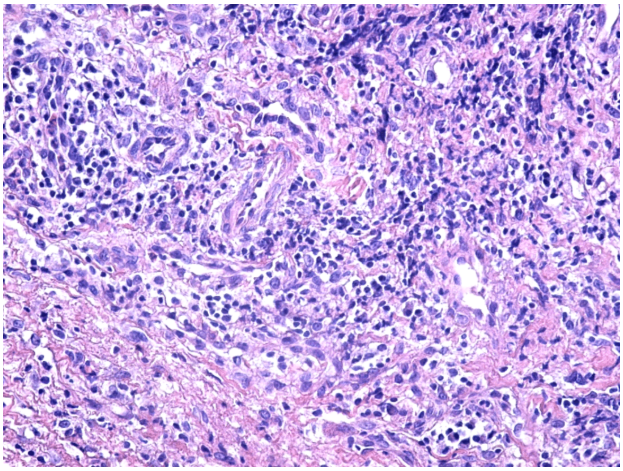

Figure 4 – *Tumoral stroma infiltrated with lymphocyte inflammatory cells heterogeneously disseminated and with numerous angiogenesis vessels (HE staining, ×200).*

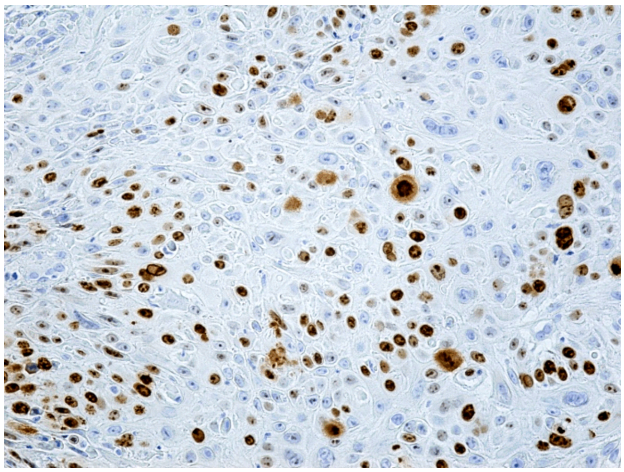

Figure 5 – *Poorly differentiated carcinoma with a Ki67 proliferation index higher than 30% (Anti-Ki67 antibody immunostaining, ×200).*

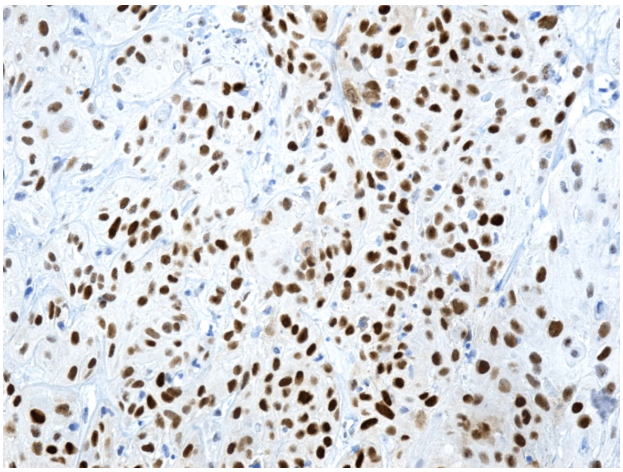

Figure 6 – *Image of poorly differentiated carcinoma with an intense reaction to p53 (Anti-p53 antibody immunostaining, ×200).*

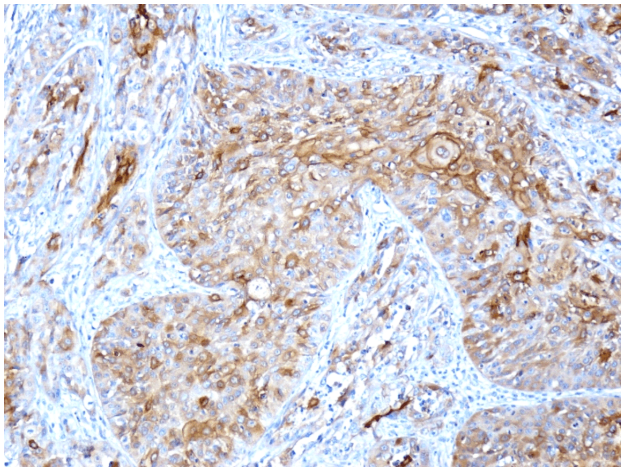

Figure 7 – ***Poorly differentiated squamous cell carcinoma with an intensely positive reaction to EMA (Anti-EMA antibody immunostaining, ×200). EMA: Epithelial membrane antigen.***

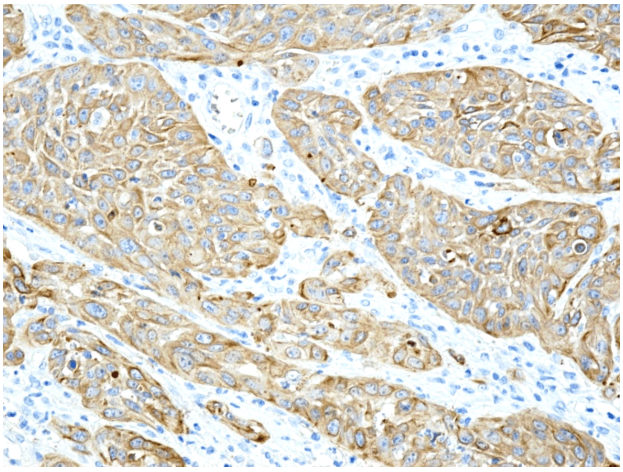

Figure 8 – ***Poorly differentiated carcinoma with a moderate positive reaction in the tumoral cells to pan-CK AE1/AE3 (Anti-pan-CK AE1/AE3 antibody immunostaining, ×200). Pan-CK AE1/AE3: Pan-cytokeratin AE1/AE3.***

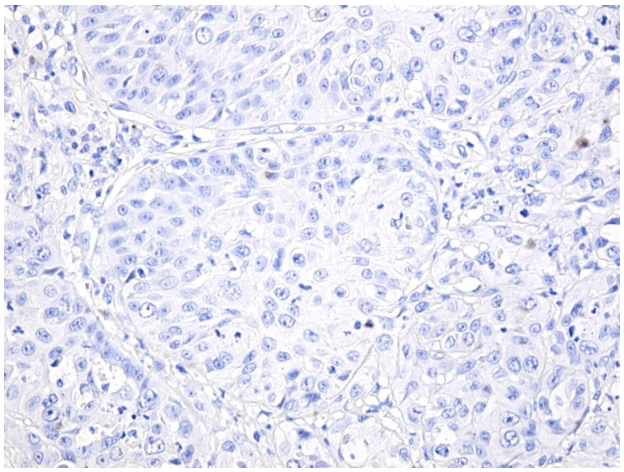

Figure 9 – ***Poorly differentiated squamous cell carcinoma with a negative reaction to CK7 (Anti-CK7 antibody immunostaining, ×200). CK7: Cytokeratin 7.***

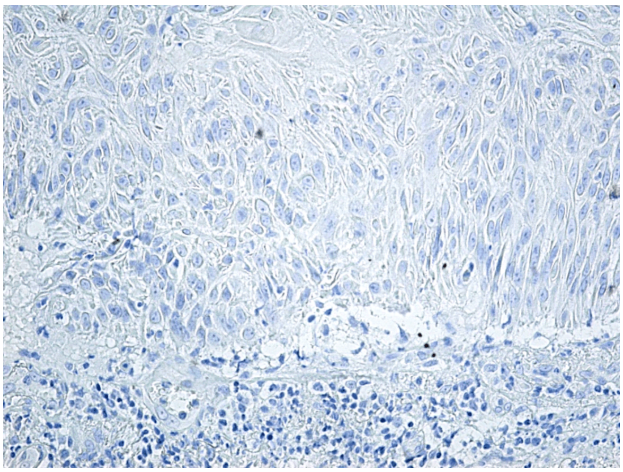

Figure 10 – ***Poorly differentiated squamous cell carcinoma with a negative reaction to CK20 (Anti-CK20 antibody immunostaining, ×200). CK20: Cytokeratin 20.***

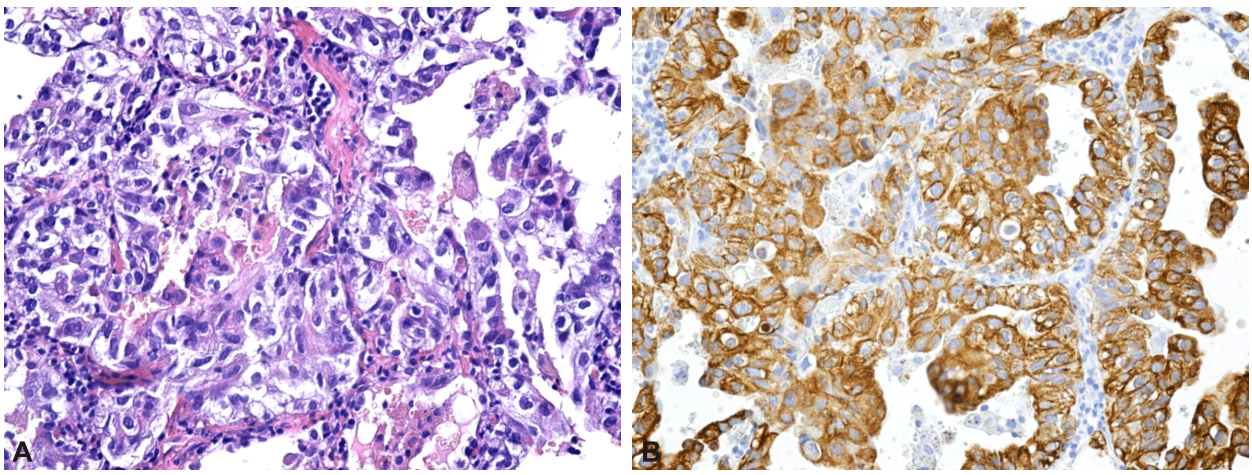

Figure 11 – ***Histopathological and immunohistochemical (IHC) aspects of a metachronous lung tumor: (A) Weakly differentiated squamous cell lung carcinoma (G3), consisting of large, varied, predominantly polyhedral cells, with acidophilic inhomogeneous cytoplasm and large, hypochromic and nucleolated nuclei (HE staining, ×200); (B) Intense reaction of tumor cells to pan-CK AE1/AE3 (Anti-pan-CK AE1/AE3 antibody immunostaining, ×200).***

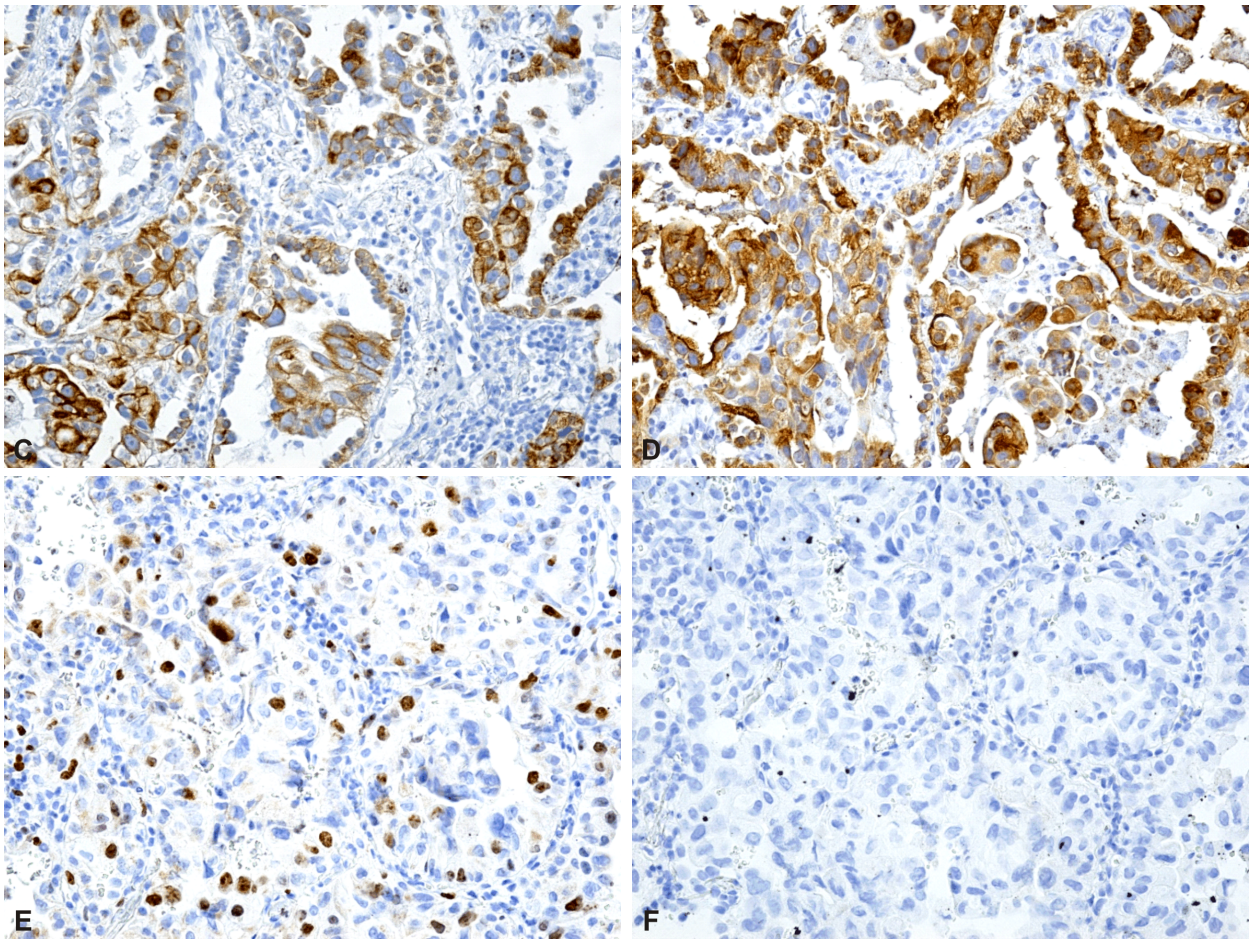

Figure 11 (continued) – ***Histopathological and immunohistochemical (IHC) aspects of a metachronous lung tumor: (C) Moderate IHC reaction of tumor cells at CK7 (Anti-CK7 antibody immunostaining, ×200); (D) Intense IHC reaction of tumor cells to EMA (Anti-EMA antibody immunostaining, ×200); (E) Tumor cells with a low Ki67 proliferation index (Anti-Ki67 antibody immunostaining, ×200); (F) Negative IHC reaction of tumor cells to p53 (Anti-p53 antibody immunostaining, ×200).***

Discussions

In the last years, MPT present a special interest, due to the increase of the number of patients diagnosed with such tumors. This increase of MPT may be attributed to the increasing incidence of malignant tumors, to the increase of life duration and survival rate of patients with cancer, to the improvement and diversity of para-clinical diagnosis techniques, to the intensity of screening activities of people with a high risk for developing neoplasias and to a careful monitorization of patients with neoplasms by the healthcare services [19].

Various studies showed that the patients with neoplasms localized in the head and neck present a higher risk for developing a second primary cancer, in comparison to the rest of the population of the same age [20, 21]. For the HNCs, the incidence of a second primary cancer, worldwidely, was estimated at about 3.4% every year [22–24]. The most frequent localizations of MPT in the patients with head and neck neoplasms are represented by the digestive tract (especially in the esophagus and stomach), by the tracheobronchial tree and the urinary bladder [25–27].

In our study, the incidence of metachronous tumors was 1.33%, but some studies showed that MPT may have a much higher incidence, from 2% to 17% [28–30]. Also, similarly to other studies [31], we observed that head and neck metachronous tumors occurred in a great percentage (91.67%) in men. We consider that the high incidence of metachronous head and neck tumors in men may be due to smoking and alcohol intake, risk factors that men are more exposed than women. In our study, 75% of the patients were alcohol consumers, while 83.333% were tobacco smokers. Multiple epidemiological studies showed that smoking and alcohol intake are major risk factors for head and neck tumors, respiratory tract tumors, digestive tumors or urinary bladder tumors [32–36]. Based on these studies, for more than 10 years, the *World Health Organization* (WHO) established alcohol intake and smoking as type I carcinogenic factors for the oral cavity, pharynx, larynx and esophagus. Other factors involved in the onset of MPT are environmental factors, genetic mutations, performing treatments for neoplasms (chemotherapy, radiotherapy), malnutrition, immunological deficiencies, human papillomavirus (HPV) infection, etc. [16, 19].

Regarding the age of the patients with metachronous tumors, in our study 75% of patients were aged between 60 and 69 years old. Most studies showed that MPT mainly

developed in the elderly [21, 37], but in some countries, due to the increase of alcohol intake and smoking in the youth, head and neck metachronous tumors started to be diagnosed also in individuals under the age of 55 years old [31, 38].

Like other researchers [39, 40], we also consider that the main risk factor for oropharyngeal cancers is smoking, as tobacco contains about 50 types of carcinogenic substances capable of producing deoxyribonucleic acid (DNA) changes, being in direct contact with the oral cavity mucosa during smoking [41–43]. Numerous studies showed that approximately 75% of HNCs are caused by smoking and alcohol intake [44]. Other studies showed that the risk for oral cancer decreases by approximately 35%, 1–4 years after quitting smoking, and by approximately 80%, 20 years after quitting. Even after the diagnosis of oral cancer, quitting smoking is important in order to improve the survival rate; the patients that continue to smoke present a higher risk for cancer recurrence and present a weaker response to treatment than those who quit smoking [45, 46].

Regarding the localization of multiple tumors, in our study, the second most affected organ was the skin. Thus, of the 12 patients with HNCs, five (41.66%) cases presented skin tumors, especially basocellular and spinocellular carcinomas on the face. Most studies showed that the most affected areas of the second primary neoplasm were the lungs and the esophagus [13, 47, 48]. The main reasons for which there appear MPT in the head and neck, respiratory tract and digestive tract, are represented by alcohol intake and smoking. Therefore, some studies showed that some head and neck neoplasms should be monitored by screening the respiratory and digestive tracts, especially in men, in order to obtain an early diagnosing of new MPT, either synchronous or metachronous ones [31].

It is obvious that the prognosis of patients with MTP and the survival rate are more reduced in comparison to the patients without MTP, especially in the patients where the second localization of primary tumors is the esophagus or the respiratory tract [24, 27]. Although some studies consider that the patients with a second primary malignity may have a more favorable prognosis than those with recurrences of the primary tumor localized in the head and neck [49], there are studies that show a second primary malignity represents the main cause of death on a long term [50].

Conclusions

Metachronous MPT represented only 1.33% of the head and neck tumors admitted to the ENT Clinic of the Emergency County Hospital of Timişoara, between 2008–2018. Of the 12 patients with metachronous tumors, nine patients had two primary tumors, a patient had three tumors, one four tumors and one five tumors. The second most frequent localization of primary tumors was the skin. In our study, metachronous primary tumors occurred mainly in men aged over 60 years old. The main risk factors in the onset of metachronous neoplasias were smoking and alcohol intake.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Ion Cristian Moț and Ioana Delia Horhat equally contributed to the manuscript.

References

[1] Toporcov TN, Wünsch Filho V. Epidemiological science and cancer control. Clinics (Sao Paulo), 2018, 73(Suppl 1): e627s.

[2] Benson JR, Jatoi I. The global breast cancer burden. Future Oncol, 2012, 8(6):697–702.

[3] Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. Breast Cancer (Dove Med Press), 2019, 11:151–164.

[4] Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, Dicker DJ, Chimed-Orchir O, Dandona R, Dandona L, Fleming T, Forouzanfar MH, Hancock J, Hay RJ, Hunter-Merrill R, Huynh C, Hosgood HD, Johnson CO, Jonas JB, Khubchandani J, Kumar GA, Kutz M, Lan Q, Larson HJ, Liang X, Lim SS, Lopez AD, MacIntyre MF, Marczak L, Marquez N, Mokdad AH, Pinho C, Pourmalek F, Salomon JA, Sanabria JR, Sandar L, Sartorius B, Schwartz SM, Shackelford KA, Shibuya K, Stanaway J, Steiner C, Sun J, Takahashi K, Vollset SE, Vos T, Wagner JA, Wang H, Westerman R, Zeeb H, Zoeckler L, Abd-Allah F, Ahmed MB, Alabed S, Alam NK, Aldhahri SF, Alem G, Alemayohu MA, Ali R, Al-Raddadi R, Amare A, Amoako Y, Artaman A, Asayesh H, Atnafu N, Awasthi A, Saleem HB, Barac A, Bedi N, Bensenor I, Berhane A, Bernabé E, Betsu B, Binagwaho A, Boneya D, Campos-Nonato I, Castañeda-Orjuela C, Catalá-López F, Chiang P, Chibueze C, Chitheer A, Choi JY, Cowie B, Damtew S, das Neves J, Dey S, Dharmaratne S, Dhillon P, Ding E, Driscoll T, Ekwueme D, Endries AY, Farvid M, Farzadfar F, Fernandes J, Fischer F, G/hiwot TT, Gebru A, Gopalani S, Hailu A, Horino M, Horita N, Husseini A, Huybrechts I, Inoue M, Islami F, Jakovljevic M, James S, Javanbakht M, Jee SH, Kasaeian A, Kedir MS, Khader YS, Khang YH, Kim D, Leigh J, Linn S, Lunevicius R, El Razek HMA, Malekzadeh R, Malta DC, Marcenes W, Markos D, Melaku YA, Meles KG, Mendoza W, Mengiste DT, Meretoja TJ, Miller TR, Mohammad KA, Mohammadi A, Mohammed S, Moradi-Lakeh M, Nagel G, Nand D, Le Nguyen Q, Nolte S, Ogbo FA, Oladimeji KE, Oren E, Pa M, Park EK, Pereira DM, Plass D, Qorbani M, Radfar A, Rafay A, Rahman M, Rana SM, Søreide K, Satpathy M, Sawhney M, Sepanlou SG, Shaikh MA, She J, Shiue I, Shore HR, Shrime MG, So S, Soneji S, Stathopoulou V, Stroumpoulis K, Sufiyan MB, Sykes BL, Tabarés-Seisdedos R, Tadese F, Tedla BA, Tessema GA, Thakur JS, Tran BX, Ukwaja KN, Uzochukwu BSC, Vlassov VV, Weiderpass E, Wubshet Terefe M, Yebyo HG, Yimam HH, Yonemoto N, Younis MZ, Yu C, Zaidi Z, Zaki MES, Zenebe ZM, Murray CJL, Naghavi M. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol, 2017, 3(4):524–548.

[5] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet, 2016, 388(10053): 1545–1602.

[6] GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet, 2016, 388(10053):1459–1544.

[7] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018, 68(6):394–424.

[8] Reid K, Soundy A. A qualitative study examining the illness narrative master plots of people with head and neck cancer. Behav Sci (Basel), 2019, 9(10):110.
[9] Rogers SN, Semple C, Babb M, Humphris G. Quality of life consideration in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol, 2016, 130(Suppl S2):S49–S52.
[10] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015, 136(5): E359–E386.
[11] Mascitti M, Rubini C, De Michele F, Balercia P, Girotto R, Troiano G, Lo Muzio L, Santarelli A. American Joint Committee on Cancer staging system 7th edition *versus* 8th edition: any improvement for patients with squamous cell carcinoma of the tongue? Oral Surg Oral Med Oral Pathol Oral Radiol, 2018, 126(5):415–423.
[12] McGurk M, Chan C, Jones J, O'Regan E, Sherriff M. Delay in diagnosis and its effect on outcome in head and neck cancer. Br J Oral Maxillofac Surg, 2005, 43(4):281–284.
[13] Priante AV, Castilho EC, Kowalski LP. Second primary tumors in patients with head and neck cancer. Curr Oncol Rep, 2011, 13(2):132–137.
[14] Demandante CG, Troyer DA, Miles TP. Multiple primary malignant neoplasms: case report and a comprehensive review of the literature. Am J Clin Oncol, 2003, 26(1):79–83.
[15] Jiao F, Yao LJ, Zhou J, Hu H, Wang LW. Clinical features of multiple primary malignancies: a retrospective analysis of 72 Chinese patients. Asian Pac J Cancer Prev, 2014, 15(1): 331–334.
[16] Gokyer A, Kostek O, Hacioglu MB, Erdogan B, Kodaz H, Turkmen E, Hacibekiroglu I, Uzunoglu S, Cicin I. Clinical features of the patient with multiple primary tumors: single center experience. North Clin Istanb, 2017, 4(1):43–51.
[17] Suzuki T, Takahashi H, Yao K, Inagi K, Nakayama M, Makoshi T, Nagai H, Okamoto M. Multiple primary malignancies in the head and neck: a clinical review of 121 patients. Acta Otolaryngol Suppl, 2002, (547):88–92.
[18] Warren S, Gates O. Multiple primary malignant tumors. A survey of the literature and a statistical study. Am J Cancer, 1932, 16:1358–1414.
[19] Jena A, Patnayak R, Lakshmi AY, Manilal B, Reddy MK. Multiple primary cancers: an enigma. South Asian J Cancer, 2016, 5(1):29–32.
[20] Morris LGT, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol, 2011, 29(6):739–746.
[21] Tabuchi T, Ito Y, Ioka A, Miyashiro I, Tsukuma H. Incidence of metachronous second primary cancers in Osaka, Japan: update of analyses using population-based cancer registry data. Cancer Sci, 2012, 103(6):1111–1120.
[22] Yamamoto E, Shibuya H, Yoshimura R, Miura M. Site specific dependency of second primary cancer in early stage head and neck squamous cell carcinoma. Cancer, 2002, 94(7):2007–2014.
[23] Rennemo E, Zätterström U, Boysen M. Impact of second primary tumors on survival in head and neck cancer: an analysis of 2,063 cases. Laryngoscope, 2008, 118(8):1350–1356.
[24] Iwatsubo T, Ishihara R, Morishima T, Maekawa A, Nakagawa K, Arao M, Ohmori M, Iwagami H, Matsuno K, Inoue S, Nakahira H, Matsuura N, Shichijo S, Kanesaka T, Yamamoto S, Takeuchi Y, Higashino K, Uedo N, Miyashiro I, Higuchi K, Fujii T. Impact of age at diagnosis of head and neck cancer on incidence of metachronous cancer. BMC Cancer, 2019, 19(1):3.
[25] León X, Del Prado Venegas M, Orús C, Kolañczak K, García J, Quer M. Metachronous second primary tumours in the aero-digestive tract in patients with early stage head and neck squamous cell carcinomas. Eur Arch Otorhinolaryngol, 2005, 262(11):905–909.
[26] López Mollá C, Estellés Ferriol E, Carrasco Llatas M, Seijas Rosales T, Morales Suárez-Varela M, Dalmau Galofre J. [Malignant multiple neoplasms in head and neck squamous cell carcinoma]. Acta Otorrinolaringol Esp, 2008, 59(9):427–432.
[27] Chen MC, Huang WC, Chan CH, Chen PT, Lee KD. Impact of second primary esophageal or lung cancer on survival of patients with head and neck cancer. Oral Oncol, 2010, 46(4):249–254.
[28] Weir HK, Johnson CJ, Thompson TD. The effect of multiple primary rules on population-based cancer survival. Cancer Causes Control, 2013, 24(6):1231–1242.
[29] Coyte A, Morrison DS, McLoone P. Second primary cancer risk – the impact of applying different definitions of multiple primaries: results from a retrospective population-based cancer registry study. BMC Cancer, 2014, 14:272.
[30] Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T, Omlin A. Multiple primary tumours: challenges and approaches, a review. ESMO Open, 2017, 2(2):e000172.
[31] Lv M, Zhang X, Shen Y, Wang F, Yang J, Wang B, Chen Z, Li P, Zhang X, Li S, Yang J. Clinical analysis and prognosis of synchronous and metachronous multiple primary malignant tumors. Medicine (Baltimore), 2017, 96(17):e6799.
[32] Gallus S, Altieri A, Bosetti C, Franceschi S, Levi F, Negri E, Dal Maso L, Conti E, Zambon P, La Vecchia C. Cigarette tar yield and risk of upper digestive tract cancers: case-control studies from Italy and Switzerland. Ann Oncol, 2003, 14(2): 209–213.
[33] Ishiguro S, Sasazuki S, Inoue M, Kurahashi N, Iwasaki M, Tsugane S; JPHC Study Group. Effect of alcohol consumption, cigarette smoking and flushing response on esophageal cancer risk: a population-based cohort study (JPHC study). Cancer Lett, 2009, 275(2):240–246.
[34] Moy KA, Fan Y, Wang R, Gao YT, Yu MC, Yuan JM. Alcohol and tobacco use in relation to gastric cancer: a prospective study of men in Shanghai, China. Cancer Epidemiol Biomarkers Prev, 2010, 19(9):2287–2297.
[35] Leon ME, Peruga A, McNeill A, Kralikova E, Guha N, Minozzi S, Espina C, Schüz J. European Code against Cancer, 4th edition: Tobacco and cancer. Cancer Epidemiol, 2015, 39(Suppl 1): S20–S33.
[36] Jiang H, Livingston M, Room R, Gan Y, English D, Chenhall R. Can public health policies on alcohol and tobacco reduce a cancer epidemic? Australia's experience. BMC Med, 2019, 17(1):213.
[37] Hori M, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H; Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2009: a study of 32-population based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol, 2015, 45(9):884–891.
[38] Zhai C, Cai Y, Lou F, Liu Z, Xie J, Zhou X, Wang Z, Fang Y, Pan H, Han W. Multiple primary malignant tumors – a clinical analysis of 15,321 patients with malignancies at a single center in China. J Cancer, 2018, 9(16):2795–2801.
[39] Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, Boyle P. Tobacco smoking and cancer: a meta-analysis. Int J Cancer, 2008, 122(1):155–164.
[40] Ciolofan S, Ioniţă E, Mogoantă CA, Popescu FC, Anghelina F, Chiuţu L, Stanciu G. Malignant melanoma of nasal cavity. Rom J Morphol Embryol, 2011, 52(2):679–684.
[41] Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M; Comparative Risk Assessment Collaborating Group (Cancers). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet, 2005, 366(9499):1784–1793.
[42] Gillison ML. Current topics in the epidemiology of oral cavity and oropharyngeal cancers. Head Neck, 2007, 29(8):779–792.
[43] Ram H, Sarkar J, Kumar H, Konwar R, Bhatt ML, Mohammad S. Oral cancer: risk factors and molecular pathogenesis. J Maxillofac Oral Surg, 2011, 10(2):132–137.
[44] Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F, Soerjomataram I. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. CA Cancer J Clin, 2017, 67(1):51–64.
[45] Warnakulasuriya S. Living with oral cancer: epidemiology with particular reference to prevalence and life-style changes that influence survival. Oral Oncol, 2010, 46(6):407–410.
[46] Gray JL, Maghlouth AA, Hussain HA, Sheef MA. Impact of oral and oropharyngeal cancer diagnosis on smoking cessation patients and cohabiting smokers. Tob Induc Dis, 2019, 17:75.

[47] Rusthoven K, Chen C, Raben D, Kavanagh B. Use of external beam radiotherapy is associated with reduced incidence of second primary head and neck cancer: a SEER database analysis. Int J Radiat Oncol Biol Phys, 2008, 71(1):192–198.
[48] Bugter O, van Iwaarden DLP, Dronkers EAC, de Herdt MJ, Wieringa MH, Verduijn GM, Mureau MAM, Ten Hove I, van Meerten E, Hardillo JA, Baatenburg de Jong RJ. Survival of patients with head and neck cancer with metachronous multiple primary tumors is surprisingly favorable. Head Neck, 2019, 41(6):1648–1655.
[49] Spencer SA, Harris J, Wheeler RH, Machtay M, Schultz C, Spanos W, Rotman M, Meredith R, Ang KK. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. Head Neck, 2008, 30(3): 281–288.
[50] Jung YS, Lim J, Jung KW, Ryu J, Won YJ. Metachronous second primary malignancies after head and neck cancer in a Korean cohort (1993–2010). PLoS One, 2015, 10(7): e0134160.

Corresponding authors
Carmen Aurelia Mogoantă, Lecturer, MD, PhD, Department of ENT, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40728–020 623, e-mail: carmen_mogoanta@yahoo.com

Cristian Andrei Sarău, Lecturer, MD, PhD, Department of Medical Semiology I, "Victor Babeş" University of Medicine and Pharmacy, 6 Revoluţiei Avenue, 300054 Timişoara, Timiş County, Romania; Phone +40741–128 900, e-mail: csarau@gmail.com

Received: September 22, 2019

Accepted: March 18, 2020