

PATIENT RELATED PROGNOSTIC FACTORS IN HEAD NECK CANCERS: COMORBIDITIES AND AGE - FOCUS ON TUBERCULOSIS AND ON GERIATRIC ONCOLOGY

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PATIENT RELATED PROGNOSTIC FACTORS IN HEAD NECK CANCERS: COMORBIDITIES AND AGE-FOCUS ON TUBERCULOSIS AND ON GERIATRIC ONCOLOGY (Abstract): Head and neck cancers are often diagnosed in the late stages, the evolution being often unfavorable even if the multimodal treatment is administered correctly. In principle, it can be considered that there are three categories of factors involved in prognosis: patient, tumor and treatment related-factors. The **aim** of the study was to highlight the involvement of patient-related factors in the prognosis of locally advanced, recurrent and metastatic head and neck cancers. **Materials and methods:** After the initial selection, including the identification of cases treated in the Oncology Clinic and the Oncology outpatient clinic, the study group included 190 patients. Among them, after applying the general inclusion and exclusion criteria, 149 cases of head and neck cancers were selected. Patients admitted to the oncological record in the period 2002-2021 with all anatomical locations of head and neck cancers, stage III and IV: nasopharynx, oropharynx, larynx, hypopharynx, oral cavity, glands salivation, nasal cavity and paranasal sinuses, cervical lymph node metastases of unspecified starting point - Cancers with Unknown Primary (CUP). **Results:** The presence of comorbidities in the case of patients with head and neck cancer, but especially pulmonary tuberculosis, active, reactivated or sequelae, is associated with an unfavorable prognosis. Studies are needed to analyze in more detail the implication of the association between pulmonary tuberculosis and each subtype of head and neck cancer. **Conclusions:** There is an increased incidence of neurological pathologies, especially stroke compared to the results published in the literature. In our study, age >65 years was not identified as a significant prognostic factor, but a tendency to reduce survival to more than 2 years in the case of geriatric patients should be mentioned. **Keywords:** HEAD AND NECK CANCERS, PROGNOSTIC, OS, COMORBIDITIES, TUBERCULOSIS, GERIATRIC.

INTRODUCTION

Head and neck cancers are often diagnosed in the late stages, the evolution being often unfavorable even if the multimodal

treatment is administered correctly. In principle, it can be considered that there are three categories of factors involved in prognosis: patient, tumor and treatment

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related-factors. If the histological tumor type, TNM staging, the anatomical tumor site, the biological and genetic profile and the type of treatment are factors recognized as being involved in the prognosis, the characteristics of the patient including age, gender, and comorbidities are less evaluated, without a consensus in the reported results. These factors could be directly involved in the prognosis but could also limit the option of oncological active therapies. If the impact of age is currently the subject of studies promoted by the Geriatric Oncology Society (SIOG), there seems to be a mutually reinforcing relationship between tuberculosis and head and neck cancer. Comorbidities are evaluated by doctors within prognostic scores and less individually (1-4).

The aim of the study was to highlight the involvement of patient-related factors in the prognosis of locally advanced, recurrent and metastatic head and neck cancers.

MATERIALS AND METHODS

After the initial selection, including the identification of cases treated in the Oncology Clinic and the Oncology outpatient clinic, the study group included 190 patients. Among them, after applying the general inclusion and exclusion criteria, 149 cases of head and neck cancers were selected.

Inclusion criteria

- Patients admitted to the oncological record in the period 2002-2021 with all anatomical locations of head and neck cancers, stage III and IV according to the International Classification of Diseases (ICD) version 10 of 2019: nasopharynx, oropharynx, larynx, hypopharynx, oral cavity, glands salivation, nasal cavity and paranasal sinuses, cervical lymph node

metastases of unspecified starting point - Cancers with Unknown Primary (CUP);

- Patients for whom there was histopathological confirmation of the disease;
- Patients for whom the date of death is known;
- Patients staged according to AJCC TNM version 6;
- Patients who have undergone at least one type of active oncological treatment for curative or palliative purposes;
- Synchronous and metachronous cancers provided that the first location is in the head and neck area.

Exclusion criteria

- Cases declared oncological for objective reasons without histopathological confirmation;
- Patients alive or lost from evidence at the time of analysis;
- Patients for whom there are no data on the oncological therapies administered or who have only benefited from symptomatic palliative treatment;
- Patients with CUP with metastases in other anatomical regions than the cervical one;
- Patients diagnosed with another malignancy prior to the diagnosis of head and neck cancer;
- Patients with skin carcinomas including malignant melanoma in the head and neck region;
- After applying the general inclusion and exclusion criteria in the study group which included 147 cases, the mean and median age of the patients was 69.1 years, respectively 62 (32-88) years.

RESULTS

Median overall survival (OS) in the study lot was 10 months (1-192) (figs. 1, 2).

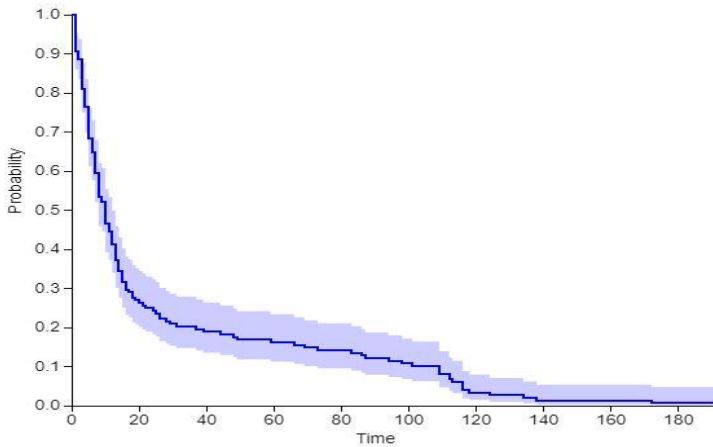


Fig. 1. Kaplan-Meier curves analyzing survival in head and neck cancers

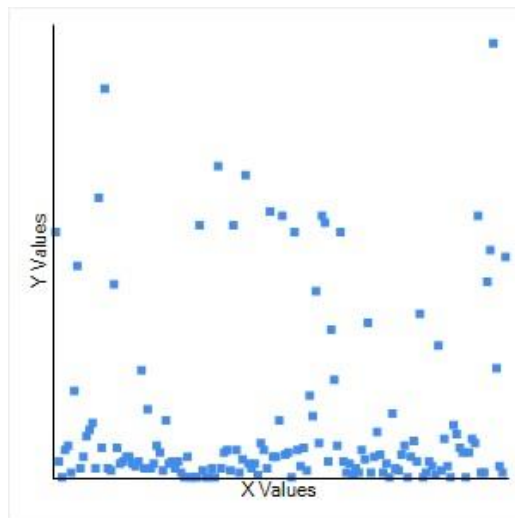


Fig. 2. Relationship of age (horizontal axis) with survival expressed in months (vertical axis)

The male gender was predominant in the study group, 129 cases (86.57%) being men and 19 (12.75%) females. The mean and median age of male patients was 61.4 and 62 (32-81) years, respectively. Median survival for the male patient group was 10 (1-192) months. Mean and median age of female patients was 65.1 and 63,5 (45-88)

years, respectively, and median survival was 5 (1-113) months (fig. 3).

Only one case (0.7%), 66 years old, in the study group was diagnosed and treated for a nasopharyngeal neoplasm, with a median survival of 39 months. The second least common type of head and neck neoplasm was hypo-pharyngeal cancer, diag-

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nosed in 17 cases (11.5%). The mean and median age was 63 and 61.5 (41-82) years, respectively, and the median OS was 5(1-112) months. CUP with cervical metastases were diagnosed in 18 cases (12%). The mean and median age was 63 and 61 (41-82) years, respectively, with a median survival of 6 (1-124) months in this cancer subtype. A number of 43 cases representing 28.9% of the total were located in the oral cavity, the mean and median age being 62.3

and 61 (32-88) years, respectively, and the median survival of 8 months (1-116) months. In the case of oropharyngeal cancers, the median OS of 10 (1-192) months was identified in the group of 25 patients (16.8%) with mean and median age of 60.1 and 60 (44-79) years, respectively. The use of at least one of the treatments with a potential curative purpose (surgery, chemotherapy, radiotherapy) was a mandatory inclusion criterion.

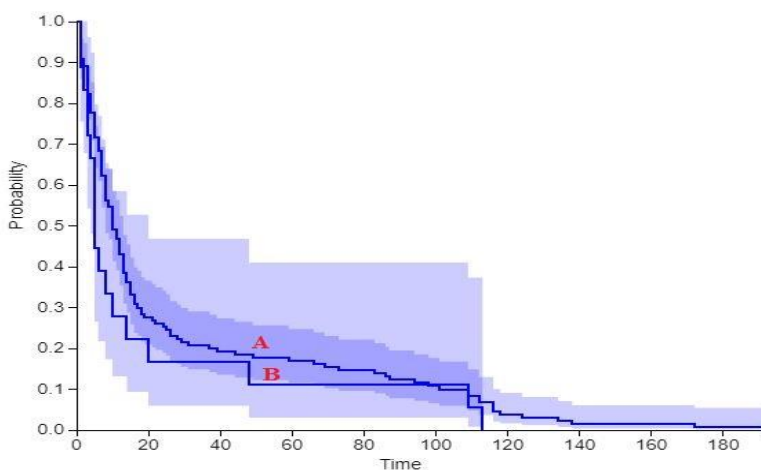


Fig. 3. Kaplan-Meier curves comparing survival in head and neck cancers by gender: A - men, B - female

The comorbidities reported (declaratively or based on the records of the medical documents presented by the patient) were identified in 62 cases (41.6%), 87 of the patients (53.38%) not declaring the presence of known pathologies. With a $P=0.427$ value, the association of comorbidities with median survival does not show statistical significance. In the group of patients without comorbidities, the median survival was 10 (1-138) months, and in the group of patients with comorbidities median OS was 11 (1-192) months. Hypertension, ischemic heart disease, type II diabetes mellitus

(DM), and history of stroke were the most frequently reported associated diseases (figs. 4, 5). The presence of pulmonary tuberculosis either in medical history, as a disease reactivated during multimodal treatment, or identified as imaging sequela has been evaluated as a predictor of survival in head and neck cancers. Even though a negative correlation of pulmonary tuberculosis with prognosis was identified, it was not considered statistically significant ($P=0.55$). Active pulmonary tuberculosis or sequela of tuberculosis were identified in 13 cases (8.72%), the remaining 136

(91,27%) being cases without other comorbidities other than tuberculosis. The mean and median age of patients diagnosed with tuberculosis was 55,8 and 55 (32-71) years,

respectively, and that of patients without a history of tuberculosis or active disease of 62,4 and 62 (41-88) years, respectively (figs. 6, 7).

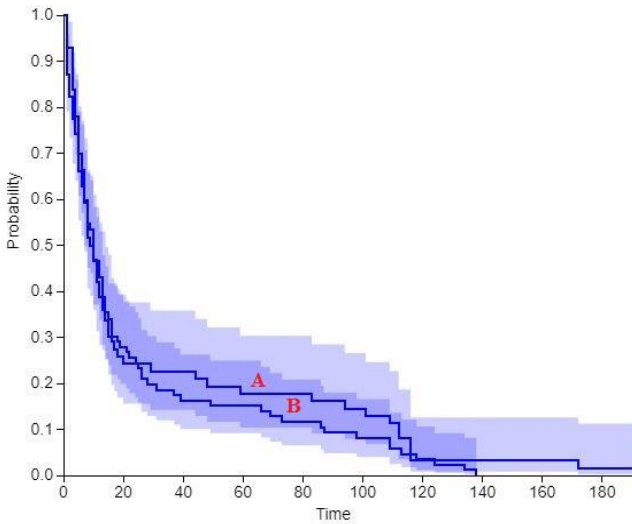


Fig. 4. Kaplan-Meier curves comparing survival in head and neck cancers according to the absence (A) or presence (B) of comorbidities

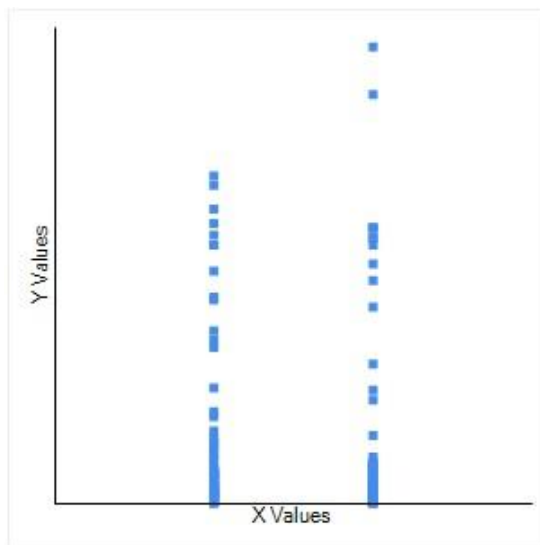


Fig. 5. Correlation of the presence of comorbidities (horizontal axis: left – no declared comorbidities, right – one or more comorbidities present) with survival expressed in months (vertical axis)

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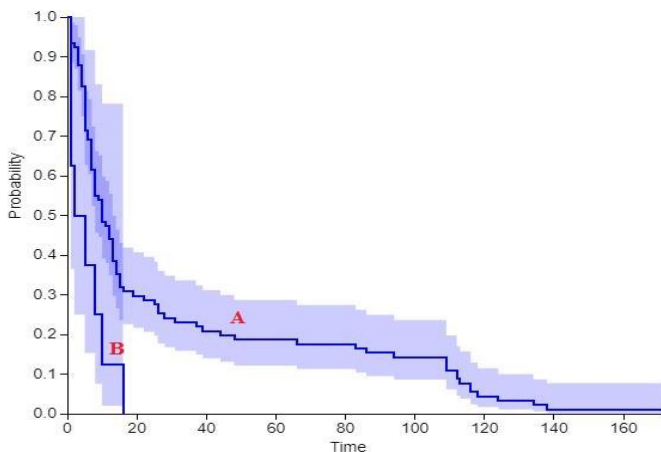


Fig. 6. Kaplan-Meier curves comparing survival in head and neck cancers according to the absence (A) or presence (B) of tuberculosis (active disease, reactivated or sequelae) after oncological diagnosis

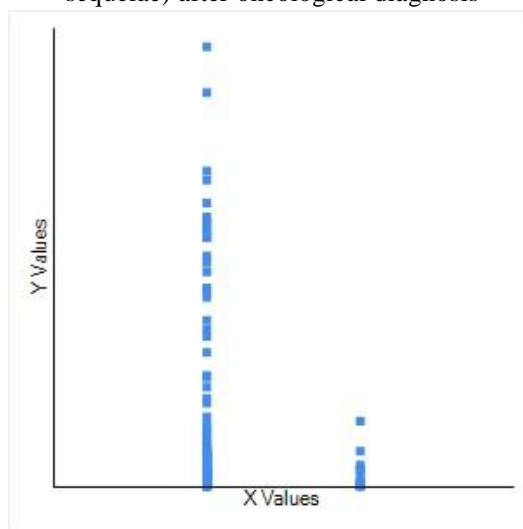


Fig. 7. Correlation of active disease, reactivated or sequelae of pulmonary tuberculosis (horizontal axis: left – no tuberculosis, right – tuberculosis) with OS in months (vertical axis)

For the correlation of age at diagnosis with the prognosis, the median OS was comparatively analyzed in the group of patients aged ≤ 65 years and >65 years. Even though a negative correlation was identified between advanced age and median survival,

a $p=0.4$ value did not reveal a conclusive statistical significance. A number of 96 (64.4%) patients included in the study were aged ≤ 65 years, the mean and median age in this group being 56,4 and 57 (32-65) years, respectively. Median survival for patient

≤65 years was 9 (1-192) months. A number of 53 (35.6%) cases were diagnosed at ages >65 years. In this group, the mean and me-

dian age was 72.1 and 71 (66-88) years, respectively, and the median survival was 11 (1-134) months (figs. 8, 9).

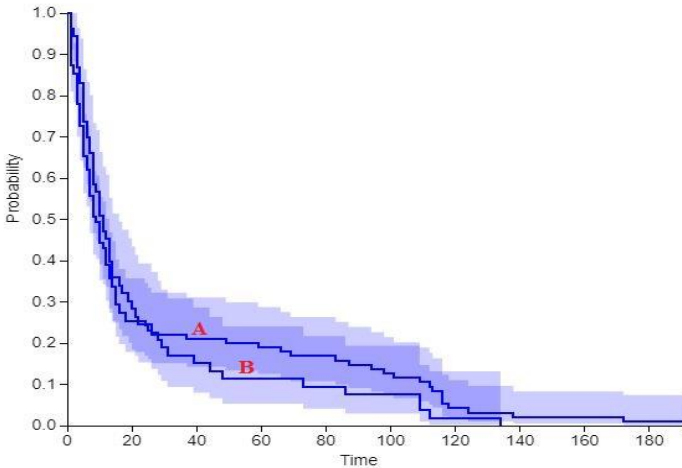


Fig. 8. Kaplan-Meier curves comparing survival in head and neck cancers by age: A ≤65 years, B >65 years

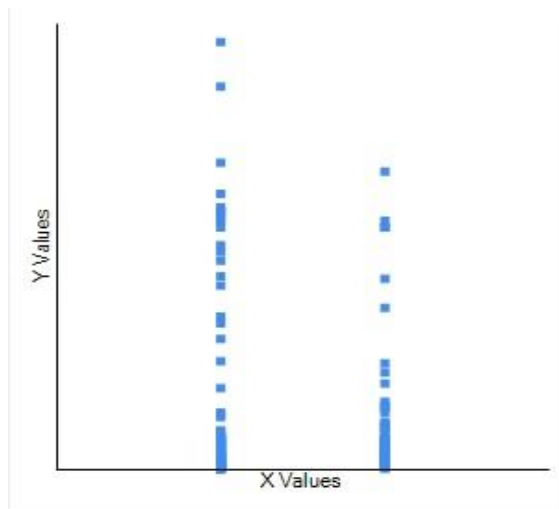


Fig. 9. Correlation of age (horizontal axis: left - age: ≤65 years, right - age >65 years with survival expressed in months (vertical axis)

The co-occurrence of comorbidities is identified as an unfavorable prognostic factor both in our study and in the litera-

ture. In the proposed study, hypertension and cardiovascular diseases, diabetes and neurological diseases are the most fre-

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quently reported comorbidities in association with head and neck cancers. The advantage in terms of median OS in the group of patients without reported comorbidities is one month. Chronic obstructive pulmonary disease and dyslipidemia are reported in the literature as being among the most common pathologies associated with head and neck cancers, but are not found in the proposed analysis. It is possible that these diseases are underdiagnosed, and the identification of comorbidities based on medical records and patient statements is another possible source of error. It should be noted the high rate of chronic neurological pathologies associated with head and neck cancers, especially the sequelae of stroke, as possible consequences of the therapeutic neglect of hypertension and diabetes. The presence of comorbidities is associated with an increased risk of mortality 30 days after completion of treatment, and the possibility of survival at 1 year in the case of patients with severe comorbidities is considered below 50%. Active pulmonary tuberculosis, sequelae of tuberculosis or disease reactivation during oncological treatment is identified in 8.72% of head and neck cancers. Even if the negative correlation of the association of the two diseases with the prognosis was not statistically significant, lower survivals are noted in the group of patients who associate tuberculosis and head and neck cancer. The relationship between the two diseases is considered bidirectional, the presence of the disease in the antecedents favoring carcinogenesis. A cancer diagnosis can increase the risk of pulmonary tuberculosis by 2.9 times compared to the general population. The risk of tuberculosis in the case of patients with head and neck cancer is

considered to be higher in the first 6 months after treatment, but remains high afterwards. The mechanism of this association is not elucidated, but it is assumed that nutritional status and immunosuppression associated with oncological therapies increase this risk. Referring to subjects without any cancer, the adjusted hazard ratio (HR) for pulmonary tuberculosis for patients with head and neck cancer not receiving chemotherapy and radiotherapy is 1,26, but it is 3,74 for patients with head and neck cancer receiving chemotherapy or radiotherapy. However, there are no consistent data to analyze each anatomical location of head and neck cancers (5-11).

Cases of multiple myeloma, leukemia, esophageal cancer, lung cancer, pancreatic cancer are also associated with an increased risk of developing primary or reactivated tuberculosis. In an endemic area of Korea, a 10-time higher incidence of tuberculosis is reported in patients diagnosed with cancer than in the general population. According to Preda *et al.* carcinogenesis induced by M. tuberculosis infection could be associated with some factors including immunosuppression, pro-inflammatory cytokines related to infection, and DNA damage (12, 13).

The study by Matsuo *et al.* mentions higher values of the risk of associating tuberculosis in patients with head and neck cancers, the authors considering that the risk being as much as 16 times higher than in the general population. In this context, the authors consider prophylactic therapy appropriate, especially for patients who require long-term treatment under continuous hospitalization, the risk being both for patients and for the community. Wang and colleagues consider the relationship be-

tween tuberculosis and cancer to be symbiotic, with both diseases having similarities in their effect on the immune system and pathogenesis (14-16).

In our study, using the threshold of 65 years to define geriatric patients, 35.6% of cases fell into this category. Median survival is superior (11 months) both for patients older than 65 years, as well as for those aged up to 65 years, in relation to the values obtained for the general group. Even though approximately 30% of head and neck cancers are elderly (>70 years), this subcategory of geriatric patients is under-represented in clinical trials. However, there is a tendency to reduce survival rates after the first 2 years of follow-up. According to the MARCH-NC meta-analysis, only 5% of elderly patients are included in the database. Mere assessment of eligibility for maximal multimodality treatment based on age or Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance indices cannot identify those patients for whom standard treatment may be detrimental. The use of scales and instruments that evaluate comorbidities, social, nutritional status and poly-medication confirms that applying the principles of geriatric oncology could limit acute and late adverse effects by identifying cases that require de-escalation of treatment. Thus Zhou *et al.* proposed a nomogram with prognostic purpose for elderly patients with cancers of the oral cavity. Hemoglobin level, neutrophil-to-lymphocyte ratio (NLR), body mass index (BMI) and nodal tumor invasion status are included in this nomogram. The Geriatric Oncology Society (SIOG) proposes, along with the G8 geriatric scale, the comprehensive geriatric assessment (CGA) for the pre-therapeutic identification of

fragile patients. A G8 score ≤ 14 can be considered suggestive both for the prognosis and for the radiotherapy discontinuation rate and for a prolonged postoperative recovery. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) can be used to predict the adverse effects of chemotherapy. Evaluation using the G8 questionnaire includes 8 items (diet, weight loss, mobility, neuropsychiatric impairment, polymedication, age and self-reported health status) and is easier than CGA, De-escalation of radiotherapy treatment including both dose reduction total, the dose per fraction and the number of fractions, but also the reduction of target volumes are concepts addressed in geriatric oncology of head and neck cancers. At least 4 scales Charlson Comorbidity Index (CCI), Osaka head and neck comorbidity index (OHNCI), the Adult Comorbidity Evaluation-27 (ACE-27) Kaplan Feinstein Comorbidity Index (KFI) are currently used to evaluate comorbidities and their involvement in prognosis. However, as demonstrated by Kallogjeri *et al.* the use of scales such as ACE-27 is easy, but useful in predicting the impact of comorbidities on survival, especially in the case of more lethal cancers such as breast cancer and prostate cancer. Geriatric Depression Scale (GDS), Cumulative Illness Rating Scale-Geriatric, Mini-Nutritional Assessment, Functional Assessment of Cancer Therapy-General (FACT-G) are evaluation scales used to quantify some characteristics of geriatric patients, being useful in defining the administration criteria of active oncological therapy and especially tolerance to chemotherapy. The geriatric frailty present more intensely in the case of these patients can be explained by

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the history of smoking and alcohol consumption, but also of cardiovascular and metabolic comorbidities. Being less represented in clinical trials, elderly patients with head and neck cancers must be included in trials to accurately identify prognostic factors and optimal therapeutic management (17-23).

CONCLUSIONS

The presence of comorbidities in the case of patients with head and neck cancer, but especially pulmonary tuberculosis, active, reactivated or sequelae, is associated with an unfavorable prognosis. Studies are needed to analyze in more detail the implication of the association between pulmonary tuberculosis and each subtype of head and neck cancer. There is an in-

creased incidence of neurological pathologies, especially stroke compared to the results published in the literature. In our study, age >65 years was not identified as a significant prognostic factor, but a tendency to reduce survival to more than 2 years in the case of geriatric patients should be mentioned.

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All the authors contributed equally to this study.

CONFLICT OF INTEREST AND FUNDING

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