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PhD THESIS

Synchronous and metachronous malignant tumors – data on epidemiology, diagnostic issues, and treatment

PhD THESIS SUMMARY

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PhD THESIS SUMMARY

Synchronous and metachronous malignant tumors – data on epidemiology, diagnostic issues, and treatment

The doctoral thesis is structured in two parts. The general part consists of eight chapters, presenting the current state of knowledge on the addressed topic through a synthesis of the data from the literature. The part on personal contributions consists of four chapters and includes the results of the three studies carried out during the doctoral research.

GENERAL PART

Chapter 1. Definition

When reporting cases of multiple malignant tumors, the definitions provided by SEER (Surveillance Epidemiology and End Results) or by IACR (International Association of Cancer Registries) are most commonly used. According to the SEER definition, two malignant tumors are considered synchronous if they are diagnosed within a two-month period and are considered metachronous malignant tumors if they are diagnosed more than two months apart. In comparison, according to the IACR definition, two malignant tumors are considered synchronous if they are diagnosed within a six-month period and are considered metachronous malignant tumors if they are diagnosed more than six months apart.

Chapter 2. History

Multiple malignant tumors were first described by Theodor Billroth in 1889. He described a patient with stomach cancer, who was later diagnosed with a malignant tumor of the external ear. [1] Other authors state that Hurt and colleagues first reported multiple primary malignant neoplasms (MPMN) in 1921. [2] Theodor Billroth was the first to establish the criteria for classifying multiple malignant tumors.

Chapter 3. The Prevalence of Multiple Malignant Tumors

According to data obtained by various authors, the prevalence of multiple malignant tumors ranges between 2% and 17%. [3] The variation in the prevalence of multiple malignant tumors may be due to several reasons:

1. Depending on which definition is used to record multiple malignant tumors, the SEER definition or the IACR definition;

2. Depending on the follow-up period of malignant tumor cases; the longer the follow-up period, the more cases of multiple malignant tumors may be documented;

3. Depending on the geographical area;

4. Depending on various environmental factors;

5. Depending on various genetic factors.

Chapter 4. Causes of the increase in the number of multiple malignant tumors

Increasing life expectancy, improving methods for diagnosing and treating malignant tumors, diagnosing and treating a malignant condition at a young age, developing screening methods and increasing adherence to these methods, improving treatments for cardiovascular conditions, prolonged exposure to carcinogenic agents; viral, bacterial, and parasitic infections, lifestyle and occupational factors; other lifestyle-related causes of cancer (obesity, stress), occupation-related cancers, iatrogenic causes due to exposure to various anticancer treatments, genetic defects, immune defects, family history.

Chapter 5. Issues related to diagnosis and treatment

Chapter 6. Paraclinical methods for positive and differential diagnosis in individuals diagnosed with multiple malignant tumors

The paraclinical methods used for positive and differential diagnosis are: pathological anatomy and molecular biology methods, imaging methods.

Chapter 7. Treatment of Multiple Malignant Tumors

Choosing the treatment for multiple malignant tumors can be a challenging task for the clinician.

In the case of synchronous malignant tumors, the therapeutic strategy differs depending on the type and stage of the malignant tumors.

Treatment of metachronous malignant tumors: when the primary malignant tumor is present and active, the therapeutic decision is similar to the situation when synchronous malignant tumors are present. In the case of metachronous malignant tumors, the therapeutic decision is generally simpler compared to the situation when synchronous malignant tumors are present.

Chapter 8. Varia

Individuals who have survived cancer must remain under post-therapy follow-up throughout their lives, regardless of the type of neoplasm with which they were diagnosed. This recommendation is made due to the possible side effects of anticancer treatment, which can occur even several years after the completion of therapy. Additionally, in some cases of cancer, local and/or distant recurrence can appear many years after the initial diagnosis. Another reason for this surveillance recommendation is the possibility of developing multiple malignant tumors due to the long-term persistence of risk factors that led to the appearance of the first malignant tumor.

A restriction for patients with a history of cancer in the five years prior to a clinical study is the unconditional exclusion from such studies. [4] Currently, there are diagnostic and treatment guidelines for almost all oncological and hematological malignancies. These diagnostic and treatment guidelines are developed by various international oncology societies, such as ASCO, ESMO, NCCN, or by various national oncology societies. Oncological diagnostic and treatment guidelines promote the newest and best diagnostic and therapeutic options to improve the quality of life and

survival of cancer patients. For individuals with multiple malignant tumors, there are no diagnostic and treatment guidelines. The conduct related to the diagnosis and treatment of patients with multiple malignant tumors must be recommended by a multidisciplinary medical team to achieve the best results.

This multidisciplinary team must be composed of at least: an oncologist, a radiotherapist, a radiologist, a pathologist, a surgeon, and a nuclear medicine physician. Currently, there are diagnostic and treatment guidelines for almost all malignant onco-hematological conditions. These diagnostic and treatment guidelines are developed by various international oncology societies, such as ASCO, ESMO, NCCN, or by different national oncology societies.

PERSONAL CONTRIBUTIONS

Chapter 9. Working Hypothesis and General Objectives

Multiple malignant tumors represent an increasingly common topic in current oncological pathology. Multiple malignant tumors can present diagnostic and treatment difficulties, especially in the case of synchronous malignant tumors. In the case of multiple malignant tumors, there are no established guidelines for diagnosis and treatment; in this situation, the therapeutic approach may be empirical or based on the personal experience of the attending physician. To achieve the best results, cases of multiple malignant tumors should be discussed and treated following the convening of a multidisciplinary committee.

In the special section of the doctoral thesis, studies were conducted aimed at recording and analyzing data on epidemiology, diagnosis, and treatment in patients diagnosed with multiple malignant tumors. To test the proposed objectives, this section of personal contributions was structured into three studies.

The objectives of this doctoral thesis are: 1) to evaluate the epidemiological characteristics of patients with multiple malignant tumors. 2) to highlight and characterize any diagnostic challenges in patients with multiple malignant tumors. 3) to highlight and characterize treatment-related issues in patients with multiple malignant tumors.

The first study recorded data on the epidemiology, diagnosis, and treatment of all patients with multiple malignant tumors included in the analysis. The second study included a group of patients diagnosed with multiple malignant breast tumors and another group of patients diagnosed with a malignant breast tumor associated with another malignant tumor located in any anatomical site other than the breast. In this study, the survival data of the two groups were analyzed.

The third study included a group of patients diagnosed with multiple malignant digestive tumors and another group of patients diagnosed with a malignant digestive tumor associated with another malignant tumor in any anatomical location, except for the digestive tract. In this study, the survival data of the two groups were analyzed.

Chapter 10. Multiple malignant tumors, information on epidemiology, diagnosis, and treatment

This chapter presents the results of the first study, being structured into: introduction, methods, results.

Introduction

According to GLOBOCAN data for the year 2018, 18.1 million new cancer cases (17 million excluding non-melanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding non-melanoma skin cancer) were estimated. [5] With the development of modern diagnostic and treatment procedures, the survival rate of individuals diagnosed with malignant conditions is increasing. This allows more individuals with malignant conditions to survive long enough to develop multiple malignant tumors. [6]

Multiple primary malignant tumors are defined as the presence of more than one synchronous or metachronous malignant tumor in the same individual. [3] The definitions of multiple primary malignant tumors vary from one study to another. [7] Several definitions can be used for multiple malignant diseases. The most commonly used definitions are those given by SEER and IACR. [3]

The first data on multiple primary malignant tumors come from Theodor Billroth. In 1889, he published the case of a patient diagnosed with a squamous cell carcinoma of the right ear and a gastric carcinoma. It was not until 1932 that multiple malignant tumors were classified by Warren and Gates. [8]

These two authors established three key criteria for classifying malignant tumors as multiple primary malignant tumors; these criteria are: (1) each of the malignant tumors must show a clear picture of malignancy; (2) each malignant tumor must be distinct; (3) The possibility that a malignant tumor represents a metastasis of another malignant tumor must be excluded. [9] According to Moertel and colleagues, when it is found that a patient has multiple primary cancers of different tissues or origins, he or she is an individual "predisposed to cancer." [9] There is a higher risk for the occurrence of multiple primary malignant tumors in certain categories of individuals, and it is necessary to monitor these individuals more closely. The categories with a higher risk of developing multiple malignant tumors are as follows: • those with a history of smoking and alcoholism; • those with a family history of cancer; • those with a first cancer diagnosis at a young age; • those with genetic syndromes that predispose them to the development of malignant tumors.

Method

The study conducted is a retrospective observational cohort study and included a total of 118 adult patients with multiple malignant tumors who presented to the oncology and radiotherapy departments of the "Sf. Nicolae" Hospital in Pitești. Patient inclusion took place between January 2020 and June 2023. The follow-up of patients included in the study continued until October 1, 2024. Patient data related to staging, treatment, and survival were updated every three months when changes occurred.

In this study, to classify multiple malignant tumors as synchronous or metachronous, SEER rules were used, which consider that the time interval between

the diagnosis of the first and the second malignant tumor must be a maximum of two months for the tumors to be considered synchronous or more than two months for the tumors to be considered metachronous.

Results

The percentage of individuals diagnosed with multiple synchronous and metachronous malignant tumors is 6.145%.

The incidence data obtained in this study are similar to those reported by other authors. In the specialized literature, of all individuals diagnosed with malignant tumors, the percentage diagnosed with multiple malignant tumors ranges between 2% and 17%.

It is noted that the case series identified, collected, and published as part of the doctoral thesis is the second largest in Romania.

Among the 118 individuals with multiple synchronous and metachronous malignant tumors, 57 are female patients and 61 are male patients. In the group of 118 individuals with multiple malignant tumors, most individuals had two malignant tumors (109 individuals), a minority had three malignant tumors (8 individuals), and a single individual was diagnosed with four malignant tumors.

The average follow-up period for patients from the diagnosis of the second malignant tumor was 17.43 months; the shortest follow-up period for a patient is 2 months, and the longest follow-up period for a patient is 58 months.

The percentage of women diagnosed with synchronous and metachronous malignant tumors is 6.148%.

The percentage of men diagnosed with synchronous and metachronous malignant tumors is 6.143%.

The most common type of cancer found in women in the studied group was breast cancer; it was present in 36 of the women in the study.

The most common type of cancer found in men in the studied group was prostate cancer; it was present in 20 of the men in the study.

There is a higher incidence of multiple malignant digestive tract tumors in men (29 cases) compared to the incidence found in women in the studied group (20 cases). A higher incidence of multiple cancers secondary to smoking (lung cancer, ENT cancer, bladder cancer) is observed in men – 33 cases, compared to 9 cases in women. Most likely, this association is due to the higher number of smokers among men compared to women in the studied group. Of the 118 patients in the study, 58 have no relatives with malignant diseases, while 60 patients have first, second, and third-degree relatives with various malignant diseases. The percentage of those with hereditary-collateral history of malignant tumors is similar between the two groups, with synchronous and metachronous malignant tumors.

In 38 patients from the studied group, highly suggestive exogenous risk factors for the development of malignant diseases were identified. The identified risk factors

are: smoking, alcohol consumption, various medical treatments, and work in a toxic environment.

Out of the 118 patients in the group, 5 patients had diagnostic problems; of these, 2 cases had synchronous malignant tumors, and 3 cases had metachronous malignant tumors.

Out of the 118 patients in the group, 25 patients were found to have treatment-related problems; among these patients, 9 had multiple synchronous malignant tumors, and 16 had metachronous malignant tumors.

As of October 1, 2024, of the 118 patients with synchronous and metachronous malignant tumors, 71 patients are alive, and 47 have died. Of the 61 men included in the study, 27 (44.26%) had died by October 1, 2024; among the men who died in this group, 12 (44.44%) had multiple synchronous malignant tumors, and 15 (55.55%) had multiple metachronous malignant tumors.

Of the 57 women included in the study, 21 (36.84%) had died by October 1, 2024; among the women who died in this group, 5 (23.8%) had multiple synchronous malignant tumors, and 15 (71.42%) had multiple metachronous malignant tumors.

The percentage of deceased men is higher than the percentage of deceased women in the studied cohort.

In the studied cohort, there are four cases of malignant conditions suspected to be secondary to previous anticancer treatment. The incidence of those presenting secondary cancers following the treatment of another cancer is 3.38% of the patient cohort included in the study.

In 38 individuals from the studied cohort of 118 patients, a second malignant disease was discovered during post-therapeutic follow-up after the first malignant disease. The percentage of individuals in this group is 32.2%.

Considering this high percentage of patients diagnosed during this follow-up period, and the fact that the follow-up period is only 4 years and 9 months in this study, it is deemed mandatory to adhere to the post-therapeutic follow-up schedule after the treatment of a malignant disease.

Chapter 11. Examining the prognostic value of a synchronous cancer diagnosis following an initial breast cancer diagnosis

This chapter presents the results of the second study, structured into: objective, methods, results, conclusion. Objective: This study aims to examine the prognostic value of a synchronous cancer diagnosis following an initial breast cancer diagnosis, focusing on survival rates specific to different cancers and the correlation between primary breast cancer and secondary cancers.

Methods: We conducted a retrospective analysis of patients treated at Saint Nicholas Hospital in Pitești, Romania, from January 2016 to January 2024. Inclusion criteria were: a confirmed diagnosis of primary breast cancer and a synchronous secondary cancer diagnosed within two months. Data collection included demographic, clinical, and pathological characteristics, as well as treatment details and follow-up outcomes.

Statistical analyses were performed using SPSS software version 26.0, utilizing Kaplan–Meier survival curves, Cox regression models, and other relevant statistical tests.

Results: Out of 73 initially identified patients, 49 met the inclusion criteria. The mean age was 59.6 years, with most patients being postmenopausal. Synchronous cancers were primarily contralateral breast cancer (44.9%) and genital organ cancer (12.24%). Patients with synchronous bilateral breast cancer had significantly better overall survival (33 months) compared to those with other types of synchronous cancer (23.5 months). Multivariate analysis indicated a higher risk of death when breast cancer is associated with another type of synchronous cancer (HR = 1.6, 95% CI 1.22–2.10, p = 0.003).

Conclusion: The diagnosis of synchronous cancer following an initial diagnosis of breast cancer has a significant impact on prognosis, with synchronous bilateral breast cancer being associated with better survival outcomes compared to other types of synchronous cancers. These findings highlight the importance of vigilant screening and personalized treatment strategies for patients with synchronous malignancies.

Discussion

Examining the prognostic value of the diagnosis of synchronous cancer following an initial diagnosis of breast cancer has significant clinical implications. The occurrence of multiple primary malignancies in a single patient, especially when one of the cancers is breast cancer, can complicate treatment decisions and affect overall survival outcomes. Previous studies have indicated that, when synchronous cancers occur, although relatively rare, these present distinct challenges and require nuanced treatment strategies compared to cases with a single primary malignant tumor. [10, 11] In our study, the focus was on investigating survival rates and clinical outcomes of patients diagnosed with both primary breast cancer and synchronous secondary cancer. The classification of synchronous cancers, defined as those occurring within two months of each other, follows SEER criteria. This strict timeline ensures that these cancers are indeed synchronous, rather than metachronous, which usually appear after a longer interval from the initial cancer diagnosis.

It is known that patients with BRCA mutations have an increased risk of developing multiple primary malignant tumors. [12] Additionally, the presence of

synchronous cancers in organs such as the gastrointestinal tract, urinary system, and thyroid has been documented, highlighting the need for comprehensive screening and monitoring in patients diagnosed with primary breast cancer. [13] Despite these data, our study did not find significant differences between BRCA 1/2 status in patients with synchronous breast cancer and those with other types of synchronous cancer. Integrating genetic profiling and biomarkers, such as BRCA status and hormone receptor status, is essential for individualizing therapeutic strategies in patients with synchronous cancer. Studies have shown that the genomic landscape of breast cancer can influence the development and progression of secondary cancers, affecting prognosis and therapeutic outcomes. [14]

Our observation showed that the most frequent synchronous neoplasms were contralateral breast cancer (44.9%) and cancers of the genital organs (12.24%). According to literature data, a lobular component of breast carcinoma nearly doubles the risk of developing contralateral breast cancer, especially synchronous bilateral breast cancer. [15, 16] In our study, 27% of patients with synchronous bilateral breast cancer presented with lobular histology. Published data indicate that age and menopausal status at the time of breast cancer diagnosis are risk factors for developing a second cancer. [15, 17] Lv et al. reported that 84.6% of patients with synchronous malignancies were over 50 years old. [18] In our cohort, the average age at diagnosis was 59.6 years, with most patients being postmenopausal. The occurrence of a second primary tumor is associated with a significantly increased risk of death and reduced overall survival. [13]

The results published by Carmichael et al. showed significantly worse overall survival among patients with synchronous contralateral breast cancer compared to those with metachronous or unilateral breast cancer. [18] A retrospective study [19] that analyzed the impact of synchronous breast cancer on survival, compared to other types of synchronous cancer, reported that the breast–breast association was correlated with better survival compared to breast–non-breast associations. Similar results were observed in our study, with a significant survival advantage among patients with synchronous bilateral breast cancer compared to other cancer associations.

The retrospective design of the study may introduce selection bias and limits the ability to establish causal relationships between the diagnosis of synchronous cancer and breast cancer prognosis. In addition, the relatively small sample size limits the generalization of the results to larger populations. Multicenter studies with larger cohorts are needed to validate these observations.

Relying on medical records and, sometimes, on patient self-reports for data collection may lead to inaccuracies or missing information, influencing the results. The variable duration of follow-up may lead to underestimation or overestimation of the true prognostic value of the diagnosis of synchronous cancer. There may also be unmeasured confounding factors—such as genetic predispositions or environmental factors—that can influence the prognosis of patients with synchronous cancers.

Differences in treatment protocols, both for breast cancer and for synchronous cancers, between centers or over time, can affect outcomes and may limit the study's ability to standardize conclusions. The heterogeneous nature of synchronous cancers

(different types and stages) further complicates the analysis and interpretation of their prognostic value in relation to breast cancer. The absence of a well-matched control group, consisting of patients with breast cancer without synchronous cancers, limits the ability to isolate the specific impact of synchronous cancer on prognosis.

Patients who survive long enough to develop a second cancer may inherently have different characteristics compared to those who do not develop one, which introduces a survival bias. Ultimately, the study does not fully account for the influence of socio-economic and demographic factors on outcomes, factors that may represent additional confounding variables.

Chapter 12. Study III – Multiple synchronous versus metachronous malignant tumors involving the digestive tract: predictors of survival in a single-center retrospective study

This chapter presents the results of the second study, structured as follows: objective, methods, results, conclusion. Objective: Multiple primary malignant tumors (MPMT) involving the digestive tract pose diagnostic and therapeutic challenges, and the differences in survival between synchronous and metachronous forms are not yet well defined. This study assessed predictors of overall survival (OS) in patients with at least one tumor located in the digestive tract or its accessory organs.

Methods: We retrospectively reviewed 1,920 oncology cases (January 2020–June 2023) from Saint Nicholas Hospital, Romania. Of the 118 patients with MPMT, 45 had ≥ 1 tumor of the digestive tract. These were classified as patients with synchronous (< 2 months) or metachronous (> 2 months) cancers according to SEER rules. Clinical, pathological, treatment, and follow-up data were analyzed; overall survival was assessed using Kaplan–Meier methods and Cox regression.

Results: Fifteen patients (33%) had synchronous tumors, and 30 (67%) had metachronous tumors. Overall, 17 out of 45 patients (37.8%) had died by the last follow-up. The restricted mean survival time (RMST) was 31.3 months for those with synchronous tumors compared to 68.3 months for those with metachronous tumors (HR = 2.49, 95% CI 0.95–6.50, p = 0.062; log-rank p = 0.053). Curative-intent treatment of the first tumor was associated with significantly improved survival (RMST 58.2 vs. 29.4 months; HR = 20.5, 95% CI 3.68–114, p < 0.001). In multivariate Cox regression analysis, advanced nodal stage (N2–N3) remained independently associated with reduced survival (adjusted HR 3.86, 95% CI 1.04–14.3, p = 0.044). The adjusted effect of synchronous versus metachronous classification was attenuated (adjusted HR 2.22, 95% CI 0.84–5.86, p = 0.10).

14.9 Conclusions

In this single-center series, synchronous multiple primary malignant tumors of the digestive tract showed a tendency toward shorter survival compared to metachronous forms; however, the difference did not reach statistical significance after adjustment. Advanced lymph node stage (N2–N3) and palliative treatment intent were the main independent factors associated with poor prognosis.

These data support the need for rigorous and prolonged surveillance after treatment of digestive tract cancers, as well as an individualized and multidisciplinary approach when multiple primary tumors are identified.

Given the small sample size and the retrospective design, the results should be considered preliminary and hypothesis-generating. Their validation in larger, multicenter cohorts, with the integration of molecular data, is essential before making firm clinical recommendations regarding risk stratification and the adaptation of surveillance protocols for patients at risk of multiple primary malignant tumors.

Final conclusions

The presence of multiple malignant tumors can still be diagnostically and therapeutically challenging, despite major advances in medicine regarding diagnostic and therapeutic possibilities.

In the 21st century, cancer has become a major health problem. According to Globocan data from 2022, the global incidence of cancer was 19,976,499 cases; in the same year, 9,743,832 deaths due to cancer were recorded. The same statistical data source, Globocan, estimates that by 2045 cancer incidence will reach 32,600,000 cases, with 16,900,000 deaths. With the increase in the incidence of malignant tumors, there may be a rise in the number of cases of synchronous and metachronous malignant tumors. With the help of improved cancer screening methods and increased adherence to these early diagnostic methods, the number of newly diagnosed cancer cases will rise. Additionally, due to improvements in diagnostic and treatment methods, the number of cancer survivors will increase, and thus there is a possibility that the number of patients diagnosed with multiple malignant tumors may also grow.

Multiple metachronous and/or synchronous malignant tumors represent a situation that is incompletely understood in terms of cause, diagnosis, and treatment. The situation in which a patient is diagnosed with multiple synchronous and/or metachronous malignant tumors can present difficulties in diagnosis and treatment, and this situation can be more challenging in the case of synchronous malignant tumors.

The studies conducted for this doctoral thesis are retrospective in nature, and the aim was to identify various epidemiological characteristics and potential diagnostic and treatment issues encountered in the studied cohort. The limitations of the research for the doctoral thesis were due to the small patient cohort, consisting of only 118 patients, and the short follow-up period of the patient cohort, which was only 4 years. Another limitation of the study for the doctoral thesis is the lack of funding, which prevented the performance of various paraclinical tests needed to characterize the multiple malignant tumors found in the studied cohort.

To date, multiple case reports of multiple malignant tumors have been presented in Romania, but few authors have reported case series with more than 100 patients.