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SUMMARY OF Ph.D. THESIS

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Motto:

"In all your ways acknowledge Him, and He shall direct your paths."

- Proverbs 3:6

CONTENTS

I. INTRODUCTION

According to the 2009 Explanatory Dictionary of the Romanian Language (DEX 2nd edition, revised and improved), the term ”METASTASIS, *metastases,* defines the occurrence of secondary pathological growth, during a malignant disease, in a body region different from the primary site – from Fr. métastase” [1]; thus, *cutaneous metastases* are characterized by the growth and spread on the epidermis, dermis or hypodermis of malignant cells originating from a distant tumoral site via lymphatic, blood vessel or by direct expansion dissemination [3].

Recognizing cutaneous metastases involves a high degree of suspicion on the part of the clinician, since they are an uncommon occurrence in medical practice [4], having special importance, signaling the advanced stage of the primary malignant neoplasm. Once the origin of the malignant neoplasia is known, local as well as systemic therapy can be initiated and the staging and prognostic factors can be established.

Different studies in the literature [5–7] mention varying percentages of the incidence of cutaneous metastases, between 0.1% and 10%.

Cutaneous metastases can mimic other dermatologic problems (maculae, infiltrated or indurated plaques, nodules with telangiectasias, discoid, papulosquamous, bullous, pigmented tumors [8] etc.), but the most commonly encountered form is the *solitary nodule*, firm, mobile, with rapid growth in size, painless, located on the dermis or the subcutaneous tissue, with the super adjacent cover tissue either intact or eroded [9].

The present thesis consists of a *general part,* comprising the theoretical concepts in the specialist literature on the *anatomy and histology* of the cutaneous tissue (with a detailed presentation of each layer from the epidermis, dermis to hypodermis), general information on the *therapeutic approach* of cutaneous metastases from biopsy to surgical excision and supporting measures such as radiotherapy, chemotherapy, electrochemotherapy, ablation radiofrequency, laser therapy or cryotherapy [10]); *clinical and microscopic aspects* of cutaneous metastases are further detailed through specific studies followed by the *microscopic and immunohistochemical* aspects; the general part ends with data on the

prognosis and management of cutaneous metastases depending on the origin of primary cancer.

The second part of the thesis, the *special part*, presents the working hypothesis and the aims of the research, as well as the materials and methods used, followed by the results found, with the characteristics of the subgroups included and the descriptive statistical and survival analysis of patients with cutaneous metastases of various origin.

The present doctoral study ends with *conclusions and personal contributions*, which concur with a better understanding of the implications that secondary skin problems have in oncologic patients.

Future research will require similar studies, but on larger patient groups, in order to see if the results in the present study correspond to and are valid for the general population.

II. WORKING HYPOTHESIS AND THE GENERAL OBJECTIVE OF THE RESEARCH

The present doctoral study *aims* to analyze in depth the cases of patients with cutaneous metastases, in order to better understand the characteristics of these secondary malignant neoplasms and their prognostic implications.

We performed a retrospective, observational, nonrandomized study, on a group of 126 cases (112 unique patients, some with multiple cutaneous metachronous metastases; no data regarding survival could be obtained for 3 patients, which means that the survival analysis included only 109 patients); the patients were diagnosed with cutaneous metastases in the evolution of malignant neoplasms of different origin.

Data were collected from the medical registers and the documents accompanying the biopsy and surgical resection specimens, as well as from the digital database of the Department of Anatomical Pathology in the *Emergency University Hospital of Bucharest* (*EUHB*) in the period November 2011 – May 2018.

To perform the survival analysis for the patients enrolled in the study it was necessary to obtain information on their status (deceased or alive) and date of death -when applicable; the patients were accounted for on January 8, 2022 (the moment when the statistical analysis was performed).

As far as the *inclusion criteria* were concerned, we included all the cases of metastases on different cutaneous areas (but not mucosae or mucocutaneous areas) originating from carcinomas, adenocarcinomas, melanomas, neuroendocrine tumors and sarcomas; the cases had a histopathologic diagnosis or immunohistochemical confirmation; we excluded the cutaneous manifestations triggered by hematolymphoid neoplasms or the ones that involved only the deep soft tissue; we also excluded the cases for which there were no available histopathological essential data and the cases recorded before November 2011 and the ones after May 2018.

The main objective of the study was to quantify the impact of cutaneous metastases on the evolution of primary malignant neoplasms, impact that was measured with an oncologic criterion – the date of death, analysing the overall survival.

The secondary objectives of the study consisted of: identifying clinical, paraclinical and demographic factors which can influence the evolution of patients with cutaneous metastases and investigating the presence of correlations between different variable included in the study.

The main evaluation criterion of the study was patients' *global survival (GS)*, also called "*overall survival*", *(OS),* which represents the time between when the cutaneous metastases were diagnozed and the patient's death, irrespective of cause; *the secondary criteria* were: the median values of different continuous variables in the study and the absolute and relative frequency of the clinical, paraclinical and demographic variables introduced in the study.

Both methods in inferential statistics and descriptive statistics were used. The α significance level in the study was 0.05, so *p values* under 0.05 were considered statistically significant.

III. THE GENERAL RESEARCH METHODOLOGY

The biopsy and surgical excision specimens harvested and analysed in the Department of Anatomical Pathology in *EUHB* were processed with special methods for *histopathological and immunohistochemical examination*.

The *optical microscopy* examination required prior preparation of the resection samples; after harvesting, they were transported in a liquid medium (formaldehyde 10%), then appropriately oriented and processed to be fixated in paraffin. The steps to examination were: fixation, dehydration, clearing, embedding, sectioning, deparaffinization and staining. Dehydration and clearing were performed after the histopathological cups were statined and the specimen was dried, embedded and labelled.

Certain specimens required an *immunohistochemical examination (IHC),* a complex diagnostic method that involves the histopathological preparation of the harvested material, followed by the biochemical and immunological special antigen-antibody reactions, in order to identify as accurately as possible the cell components and tissues.

This method (IHC) was used especially to diagnose poorly differentiated cancers and the rare tumors. IHC allows both the phenotypic analysis and the identification of histogenesis and neoplastic proliferation. IHC complements the histopathological diagnosis when regular staining does not supply information on the origin of the secondary cancer and has an important predictive role in some cases.

The biopsy and resection specimens analyzed in the Department of Anatomical Pathology in *EUHB* were evaluated, and the data were recorded in the documents accompanying the harvested specimens, later in registers and in the hospital's digital system. Accessing these sources, we have drawn up a database comprising the patients with cutaneous metastases of different origins, recorded from November 2011 until May 2018. The data were statistically analyzed in January 2022.

The following variables were introduced in the database for the *statistical analysis:*

- The date when the cutaneous metastasis was diagnosed, the date of patients'death, sex, age, the origin of the primary tumor, the location of the cutaneous metastasis – on body regions (head, neck, axilla, thorax, abdomen, umbilicus, limbs); the largest size of the cutaneous metastasis (or the sum of sizes in case of multiple lesions);

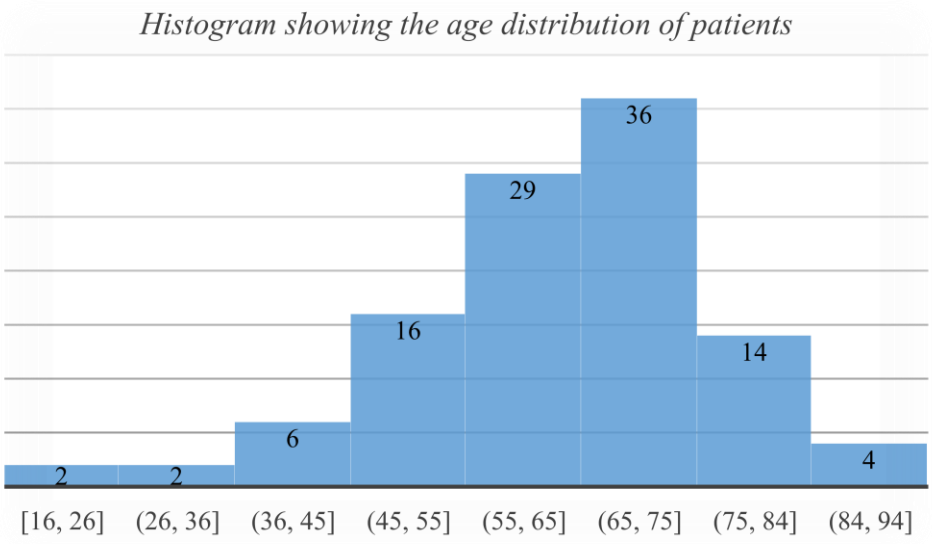
- The presence or absence of: another simultaneous cancer; other comorbidities (such as anemia, type 2 diabetes, hypertension, dyslipidemia, ischemic coronary disease); multiple metastases (except for cutaneous types); complications such as: necrosis, ulceration, erosion, etc.;

- Laboratory findings: fibrinogen, LDH, INR, the erythrocyte sedimentation rate (ESR), total cholesterol, triglycerides, total proteins (TP), albumin, uric acid, from the hemogram: number of erythrocytes, hemoglobin (HGB), hematocrit and erythrocyte indices, number of leukocytes, leukocyte formula, platelet count.

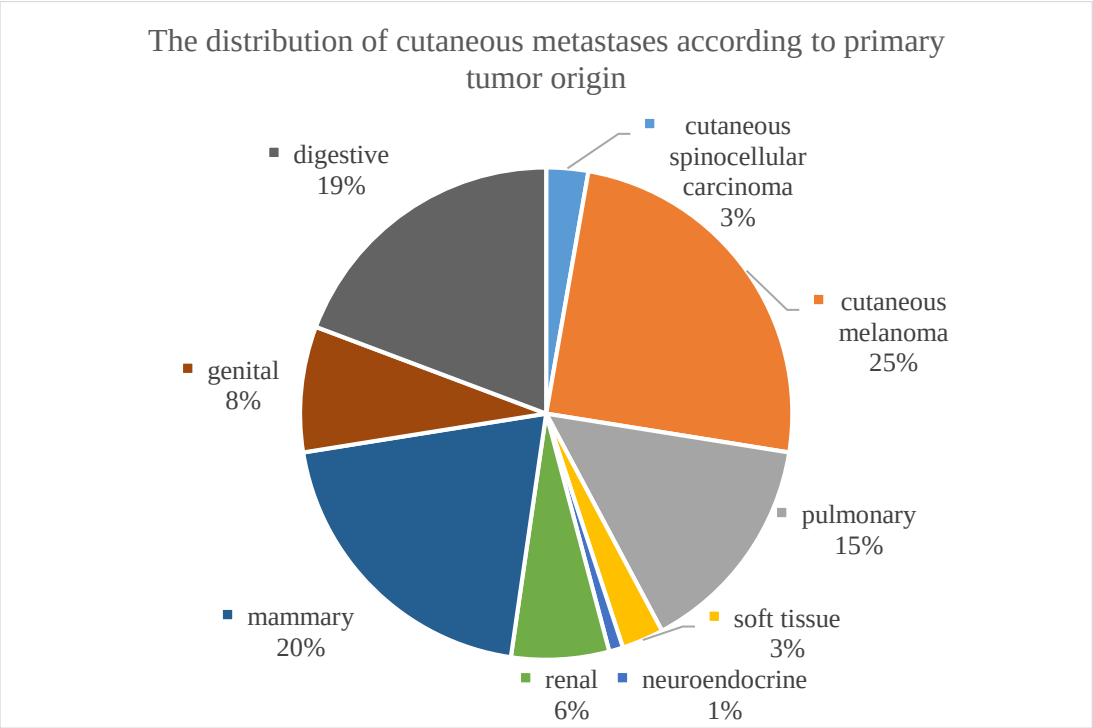
IV. THE SPECIAL PART – CHAPTER SYNOPSIS

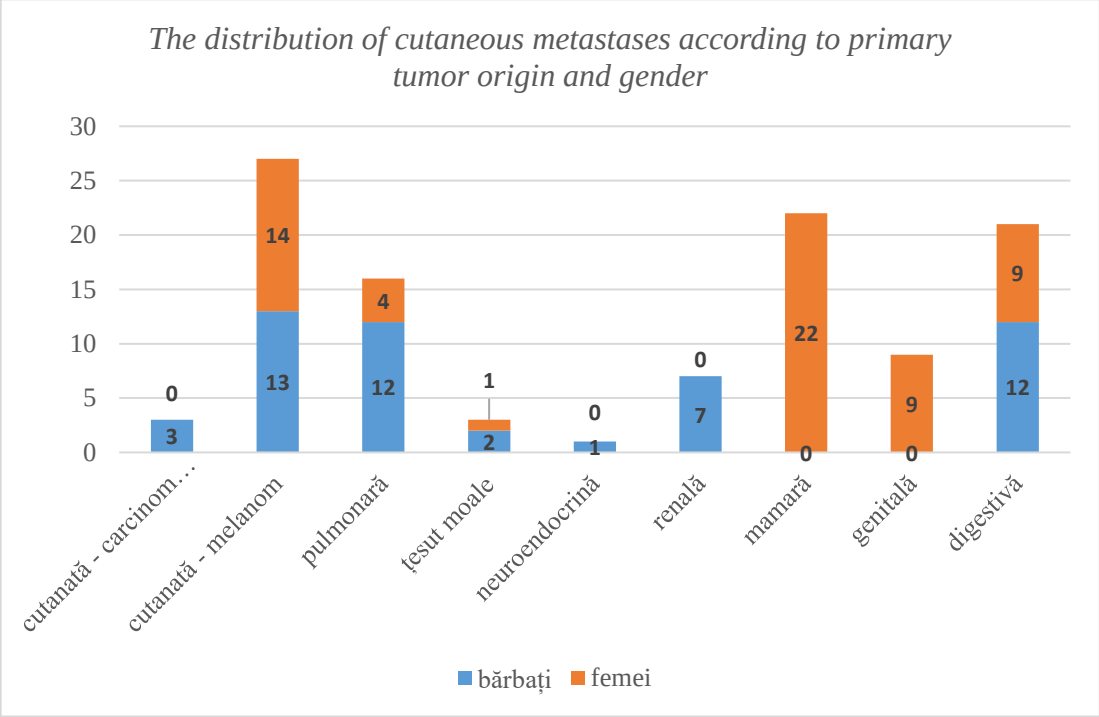
Chapter 7.1 of the doctoral thesis presents *data on the general group of patients* with cutaneous metastases**,** 109 unique patients (some with multiple secondary malignant neoplasms); the information concerns their age, distribution of metastases and the presence of complications.

59 of the patients were women and 50 were men, aged between 16 and 94 years of age – and their distribution is presented in the following histogram:



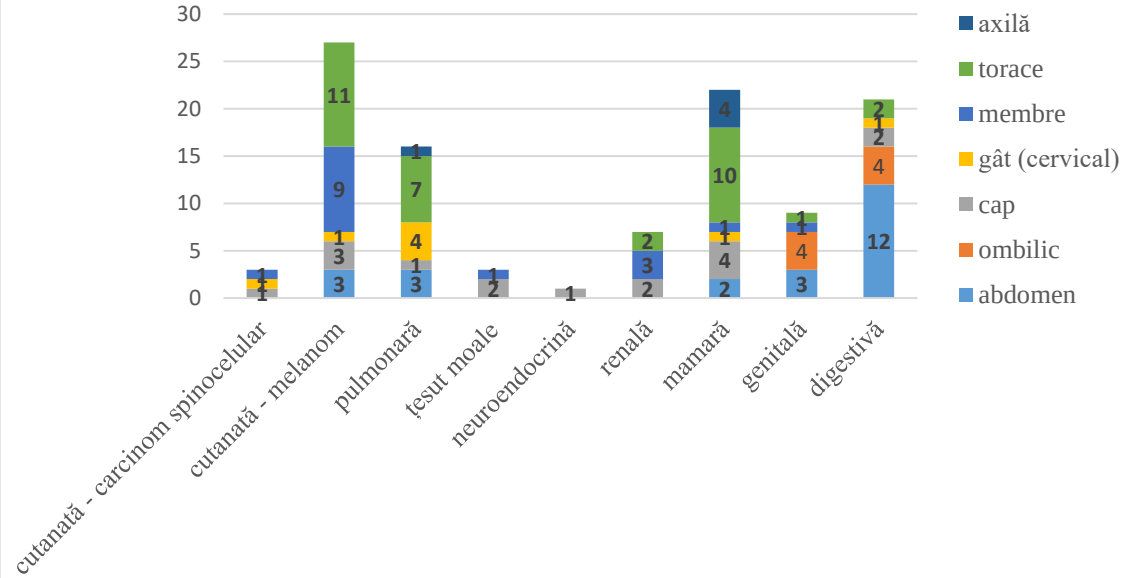
We analyzed the number of patients with cutaneous metastases according to the tissue of origin of the primary tumor, then according to gender and we observed that 28% of the cases (ranking first) were cancers of cutaneous origin (27 patients with melanoma, and 3 patients with spinocellular carcinoma), followed by breast cancers (22 women patients), digestive (21 patients), pulmonary (16 patients), genital (9 women patients), renal (7 patients), cancer of the soft tissues (3 patients) and neuroendocrine ones (1 patient), distribution graphically presented in the following figures.





As far as the location of metastases is concerned, most secondary malignant neoplasms with *a cutaneous* point of origin (melanomas and spinocellular carcinoma) appeared on the thorax and limbs, *breast and pulmonary ones* also affected especially the thorax, and the *digestive* cancers affected the abdomen, as it can be seen in the following figure.

The distribution of cutaneous metastases according to primary tumor origin and body part location

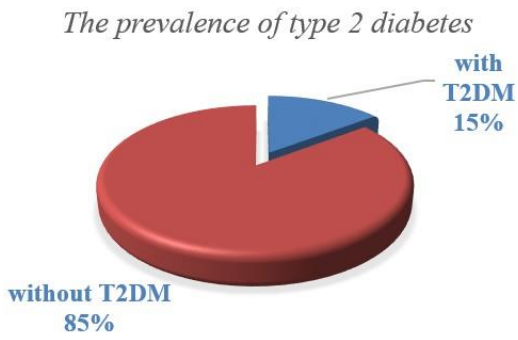


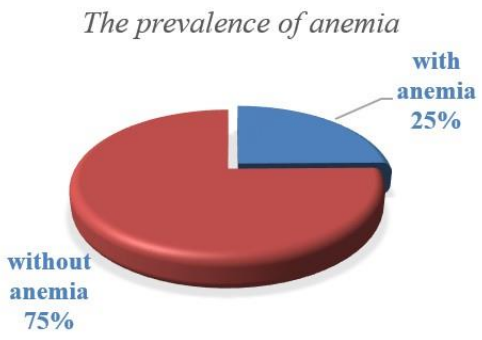
40 patients in the group (accounting for a percentage of 37%), presented *complications* at the level of the tissue in the form of superinfections, ulcerations or necrosis, but most of them (69 patients, representing 63%) had intact skin/ integument.

As far as comorbidities are concerned, only 48 out of the 109 patients suffered from *essential arterial hypertension*, 38 patients had *ischemic coronary disease*, 16 patients suffered from *type 2 diabetes*, 27 patients had *anemia* (defined as hemoglobin value lower than 11.9 g/dL in women and 13.6g/dL in men or hematocrit under 35% in women and 40% in men), as shown in the following pie charts.

The prevalence of hypertension

The prevalence of ischemic coronary disease





Chapter 7.1 of the present thesis brings a general view of the entire group of patients, 109 in number, and describes the charcteristics of each subgroup included in the study. It further encompasses information about the *characteristics of the subgroups of cutaneous metastases studied,* depending on the histopathological origin of each of the cases, with data on gender, metastases` localization, survival and distinctive characteristics.

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Chapter 7.2. presents a *descriptive statistical analysis* of the variables used in the study, with data included in the 8 tables in the chapter, and taking into account the total number of cutaneous metastases ”N=126”, some of which occured at different points in time and recorded on different dates, analyzed transversely in the study.

For the *interval variables* (e.g. age, size of metastases, values of laboratory tests) we evaluated: *the average, the median, the minimum, the maximum and the interval of distributions*, while for the *categorical variables* (such as gender, origin, localization, number, size, complications of metastases, the presence of integumentary lesions or visceral metastases) we evaluated: *the absolute frequencies* (number out of the toal number of cases included in the study) and *the relative frequencies* (presented as percentages %) of distributions.

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Chapter 7.3 of the thesis presents an *inferential-type survival analysis, the first half Kaplan-Meier* type; the second comprises two types of analysis: *the Cox regression model* and *the Cox-Aalen model*.

This chapter includes *109 unique patients* (”*N=109*”), unlike the previous analysis, which concerned all 126 cases of cutaneous metastases, some of which were metachronous.

It can be noticed that there is an inconsistency regarding the origin of the primary neoplasm, in this chapter, since the survival analysis did not depict any thyroid malignant neoplasm as the origin for cutaneous metastases. The finding is due to the fact that a patient had pulmonary cancer diagnosed prior to the thyroid cancer, and, according to the standards of the survival analysis, the survival period begins at the moment the primary neoplasm was diagnosed; the second patient with *thyroid cancer* didn`t have available data (a total of 3 patients out of the 112 were excluded from the database, as no information regarding survival was available) as such, 109 unique patients were included in the study.

The first part of the survival analysis was *Kaplan-Meier* type, which involved the following statistics:

- *median survival* defined as the estimated period of time in which half of the patients are expected to be still alive
- *restricted median survival time* (RMST), a statistical value characteristic for survival studies that are still ongoing (for example studies with patients for which the *event of interest – death* in the present study – didn`t happen) and which is defined as integral value beneath the survival curve, in which the intervention integral is on the time axis, between 0 and a point of interest
- *the number of patients at risk* (”number at risk”) – surviving patients, at risk of death

We also tested the influence of some demographic, clinical and paraclinical parameters on survival, using *log-rank and Peto tests (log-log-rank);* for the *categorical variables* their own categories were used, whereas two new categories were created for the continuous variables, using as a reference value (”cut-off”) the median of the distribution of the continuous variable (for homogeneity and in order to have enough patients in each category).

The survival curves, which indicate a patient's probability to be alive at a given time interval, were also graphically presented.

The second part of the survival analysis involved the use of the following models:

The model of Cox simple regression allowed the comparison of two or more hazard ratios (or the risk in time) for death to occur, a model which involves the fact that hazard ratios (HR) for predictors remain constant in time (the effect of predictors is constant in time) – the model being of multiplicative type. From a clinical point of view, the starting point of *Cox regression* is that at any one moment in time after diagnosis or onset of treatment, there are some demographic, clinical or paraclinical (i.e. predictors) factors that influence the patients' survival, the *Cox regression* model assuming that the action of these predictors does not change over the survival period; for example, if a predictor (such as type of location of primary cancer at pulmonary level versus location at breast level) doubles the death hazard (HR) 3 months after diagnosis, also at 12 months after diagnosis the pulmonary level location will double the death hazard, compared with the one at breast level. *The report of hazard ratios (HR)* was estimated for the simple Cox regression.

The second model used was the *Cox-Aalen model*, which, unlike the Cox model, estimates differently the effect of a predictor on patient's survival, an estimation resembling the one used in epidemiology; the *cumulative incidence of deaths* is estimated for each moment in time (number of deaths that happened until that moment, the *cumulative incidence* being calculated using a coefficient and an additive constant), using Kaplan Meier estimator to determine the survival curve. This model has the advantage that it can be used even when a constant influence of the predictor in time is not assumed. *The report of cumulative incidences* was estimated for the Cox-Aalen model.

V. CONCLUSIONS AND PERSONAL CONTRIBUIONS

1. The present study calls attention to pathology with varied clinical presentations, discussing the secondary malignant skin neoplasms caused by different types of cancer, a polymorphism that hinders early diagnosis and influences survival.
2. The cutaneous metastases are characterized by the distant spread of neoplastic cells, that can be located at one or several skin levels; these secondary malignant neoplasms occur during the development of certain malignant visceral and cutaneous neoplasms, and their frequency (compared to other locations) is very low.
3. The present dissertation quantifies the impact of the occurrence of secondary malignant neoplasms, using the cancer patients' date of death (and analyzing their survival as well) as a measuring instrument.
4. In the study we investigated the existent correlations between the location of the primary malignant tumor and the secondary site, between the origin of the primary tumor and the number of secondary malignant neoplasms and among the different demographic, clinical and paraclinical variables.
5. We included in the study metastases located on the epidermis, dermis and hypodermis caused by melanomas, carcinomas and adenocarcinomas, sarcomata, neuroendocrine tumors, and excluded cases found exclusively at the hypodermis level, those found in areas with epithelial mucosae, the cutaneous metastases caused by hematolymphoid malignant neoplasms and those recorded before November 2011 or after May 2018.
6. This doctoral study highlights important statistical data concerning the survival of patients with cutaneous metastases, from the moment of diagnosis to exitus.
7. The date of patients' death analyzed in January 2022) necessary to study survival was supplied by the *Directorate for Persons Recordand Database Management* (*Direcția pentru Evidența Persoanelor și Administrarea Bazelor de Date*), part of the Ministery of Internal Affairs; these data were processed according to the EU Regulation no. 2016/679 of the Parliament and Council of Europe.
8. This study was observational, retrospective non-randomized, which evaluated 126 cases of metachronous metastases, identified in 109 persons, recorded in the database obtained from the archives of the Department of Anatomical Pathology of the Emergency

University Hospital of Bucharest; the 126 samples processed histopathologically and immunohistochemically accounted for all the recordings of skin metastases analyzed between November 2011 and May 2018.

9. The doctoral research was performed after the patients consented to the use of biopsy and surgical samples to be utilized for clinical studies according to the ethical principles for medical research involving human subjects – Declaration of Helsinki 1975, revised in 2008 (5); the study received the Approval of the Ethics Committee of the Emergency University Hospital of Bucharest (registration no. 31673 on 07.01.2020).

10. In the study we concluded that the most frequent primitive malignant neoplasms that can cause cutaneous metastases were: melanoma, breast cancer, digestive malignant tumors and bronchial and lung cancers.

11. The patients' mean age was 64, with the youngest patient aged only 16 and the eldest 94 years of age.

12. We noticed that the feminine gender predominated slightly in the group.

13. More than half of the patients with cutaneous metastases also had visceral metastases.

14. Less than half of the patients with cutaneous metastases had multiple skin lesions.

15. The average size of the cutaneous metastases was approximately 26 mm, with lesions varying greatly in shape and surface; a third of them presented local complications as well.

16. Approximately one in ten patients had in his medical history another malignant neoplasia than the one that caused the skin metastases (thus associating two concomitant cancers).

17. A fourth of the 109 patients suffered from anemia at the time when the cutaneous metastases were diagnosed.

18. Less than half of the patients had dyslipidemia or essential hypertension.

19. In the group, 15% of the patients were previously diagnosed with type 2 diabetes, and a third of the 109 patients suffered from ischemic coronary disease.

20. The laboratory test showed normal mean values for NIR, fibrinogen, uric acid, total proteins, leukocytes, lymphocytes neutrophils, thrombocytes, and hemoglobin, while LDH and VSH had increased mean values.

21. We noticed an association between the localization of the primary tumor and that of the cutaneous metastases, meaning that the cutaneous metastases were found in the proximity of the primary malignant tumor; for example, melanomas frequently caused metastases on limbs and thorax; breast malignant tumors caused tumors on the head, neck

and thorax, a similar situation with the localization of metastases for bronchial and lung cancers, whereas the digestive and genital malignant tumors most commonly metastasized on the abdomen.

22. At the moment of the survival statistical analysis (January 2022), over 90% of the patients diagnosed with cutaneous metastases from 2011 until 2018 were deceased; over three-quarters of these died within the first two years after diagnosis.

23. The patients' age did not influence survival.

24. The death risk was similar both for patients under 64 years of age and for those over that age (the value was chosen because it represented the median of the group).

25. The global prognosis of the presence of cutaneous metastases was unfavorable, with a survival median of approximately 6-7 months and an integral under the survival curve (RMST) of 20 months, long survivals being extremely rare; in our study survival at 2 years was approximately 21.1%, at 5 years of approximately 5%, and at 100 months after the diagnosis there were only 2 survivors (under 2%) in our study.

26. After the statistical analysis of the general patient group, we noticed that women had a better evolution and a survival median over twice larger than that of men (the time estimated for 50% of the women to be still alive was 11 months versus 5 months in men), with lower mortality and a higher restricted median survival time.

27. The death risk was twice higher for men and remained constant over the entire period analyzed, their evolution being more severe and the survival likelihood sharply decreasing compared with that of women (possibly also connected with the origin of the primary tumor depending on gender).

28. Compared with other malignant tumors, longer survival rates, statistically significant were found only in the case of malignant breast tumors and melanoma in the patients in the study.

29. As it was previously mentioned, survival was better in women; the effect seemed to correlate with the favorable evolution of malignant breast tumors, found exclusively in women in our study (compared with men, who had a higher percentage of lung cancers, that are much more aggressive).

30. A better prognosis (with a lower percentage of deaths and longer survival) was noticed in cutaneous metastases on limbs, with a correlation between primary malignant neoplasia (melanoma in the present case) and the localization of cutaneous metastases on limbs.

31. We also noticed a correlation between the metastases on limbs and time; in the first 80 months (6-7 years) after diagnosis the death rate was up to 5 times lower compared with that of head and neck ones; in conclusion, the localization of cutaneous metastases on limbs has an undeniable better prognosis in time.

32. The development of metastases on the head and neck was associated with an unfavorable prognosis (with rapidly decreasing survival probability); cancers that metastasized most commonly in that area had different origins, and half of these patients died after only 4.5 months following diagnosis.

33. The death rate in patients with cutaneous metastases on the head and neck was more than twice higher, compared with that of patients with cutaneous metastases on the limbs.

34. The presence of concomitant metastases with different localizations from cutaneous ones was associated with high mortality, a survival median three times lower than that of patients who had only cutaneous metastases and 2 times lower average number of months between the diagnosis of cutaneous metastases and death.

35. The death rate was two times lower in patients without any concomitant metastases.

36. We noticed survival periods exceeding 20 months only in the patients who had no associated metastases in other organs, since secondary cutaneous metastases are not life-threatening, compared with visceral metastases.

37. We did not notice any statistically significant differences regarding the survival of patients with cutaneous metastases compared with those who associated other malignant neoplasms (except for those that generate cutaneous metastases); therefore, another concomitant cancer did not represent a prognostic factor;

38. The number of skin metastases (single or multiple) was not a factor that influenced the patients' prognosis.

39. The survival curves were similar, irrespective of the size smaller or larger than 20 mm) of the cutaneous metastases, the tests showing no statistical significance.

40. The anemia found at the time when cutaneous metastases were diagnosed was associated with serious prognosis and high mortality; half of the patients with anemia died approximately 2 months after the diagnosis; the survival median was 3 to 4 times lower than in patients without anemia, and the integral value under the survival curve being 4 times smaller.

41. The death rate was over 3 times higher in patients with anemia.

42. The presence or absence of type 2 diabetes or ischemic heart disease did not influence, from a statistical point of view, the patients' survival or prognosis.

43. The presence of any skin complications of metastases (such as fungal or bacterial superinfections, necrosis or ulceration) did not influence the patients' evolution.

44. The patients' survival, from a statistical point of view, was not influenced by the fibrinogen value.

45. A higher than 1.04 INR at the time the metastasis was diagnosed was associated with a more serious evolution, especially immediately after diagnosis (the death risk was 2.5 higher in patients with elevated INR in the first 10 months).

46. A lower or equal value of 7,16 g/dL of total proteins was an important negative predictive factor for a period of approximately 1 year after the time of diagnosis.

47. A total protein value over 7.16 g/dL was associated with a survival median and RMST 3 times higher, compared with the patients whose proteinemia was under 7.16 g/dL.

48. The erythrocyte sedimentation rate (ESR) did not statistically modify the survival period of patients with cutaneous metastases, irrespective of the value of this parameter (lower or higher than 30.5 mm/h).

49. A smaller number of leukocytes (under 7.710/μL) was associated with increased survival.

50. We also noticed a statistically significant time dependence of the coefficient in those with a higher number of leukocytes (over 7.710/μL) - the death rate in these patients was 2.8 times higher at 40 months.

51. A high number of thrombocytes was also associated with severe evolution.

52. The patients in our study whose thrombocyte value exceeded 259.000/μL had a 1.5 higher death risk compared with those who had a thrombocyte number under 259.000/μL, but no statistically significant time dependence was found in this situation.

53. Having analyzed survival in the entire patient group, the conclusion was that the most aggressive tumors were those with renal origin - in men, and genitals – in women, for which mortality was 100%; melanomas and breast cancers had most surviving patients, and their mortality was the lowest.

54. Our study had a series of limitations; the most important was, in our opinion, that not all patients survived the event of interest (death), so that certain statistics (for example RMST) could not be accurately evaluated.

55. Another important limitation was the fact that we could not follow the patients' evolution in progress (for example by 3 months, 6 months respectively follow-up visits), so we could not have an overall picture of the evolution of the predictors, since the available information for many patients concerned only the tests at the time of diagnosis and the date of the patient's death.

56. A further limitation of the study was that it described retrospectively a small number of cases – 109 unique patients with cutaneous metastases, and some subgroups (for example the subgroups created on the criterion of the histopathological origin of the primary malignant tumor) consisted of a very small number of patients, lending the study prone to bias.

57. The doctoral study, which is a retrospective type of research, could not include a control group of patients (patients with cancer, but with no cutaneous metastases) with the same characteristics and inclusion criteria. Therefore, we cannot supply a definite answer to the question of whether the analyzed clinical and biological parameters influence or not the occurrence of cutaneous metastases.

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List of published scientific articles

Articles published in extenso in indexed journals WEB of Science, Clarivate Analytics, without impact factor

1. **Belciu D**, Horodinschi RN, Costache M, Diaconu C. *An overview of skin metastases*. Proceedings of the 35th Balkan Medical Week, Atena, 25-27 septembrie 2018. FILOdiritto Editore, Italia. ISBN 978-88-85813-23-6 (see **Annex 1.** in the thesis) https://www.filodiritto.com/proceedings?field_cat_proc=&field_cat_proceedings_target_id=All&page=8

Studies published in the proceedings of international scientific manifestations with ISSN/ISBN

2. **Belciu** D, Costache M, Diaconu CC, Bodoarcă S. D2. *A case report and overview of recurrence in multiple skin metastases of malignant melanom*. Pg.S27. 22nd Balkan Medical Days, 26-29 septembrie 2019, Kyrenia, Cipru. Archives of the Balkan Medical Union 2019; 54(Suppl 1). ISSN 1584-9244 (print), 2558-815X (online) https://umbalk.org/supplement-1-2019/ (see **Annex 2.** in the thesis)

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